

Antibiotic Use Guidelines

for Companion Animal Practice (2nd ed.)



A guide to achieving the best possible clinical response
with the lowest risk of antibiotic resistance

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Foreword

The first edition of the Antibiotic Use Guidelines for Companion Animal Practice was published in autumn of 2012. The aim of the guidelines was to prevent increased antibiotic resistance. A questionnaire circulated to Danish veterinarians in 2015 (Jessen et al., DVT 10, 2016) indicated that the guidelines were well received, and particularly that active users had followed the recommendations. Despite a positive reception and the results of this survey, the actual quantity of antibiotics used is probably a better indicator of the effect of the first guidelines. Chapter two of these updated guidelines therefore details the pattern of developments in antibiotic use, as reported in DANMAP 2016 (www.danmap.org). Despite a number of assumptions regarding usage data, and uncertainties regarding the dog and cat population, it is evident that the total antibiotic consumption in companion animals fell by approximately 10% in the period 2012-2016. The use of broad-spectrum 3rd generation cephalosporins in particular fell dramatically. Challenges remain, in spite of these positive trends: the use of fluoroquinolones is unchanged and remains high, and a marked increase in the use of amoxicillin-clavulanate shows that there is still room for improvement.

One of the greatest challenges for changing antibiotic use in companion animals is the lack of information regarding optimal treatment lengths. In human medicine, treatment durations have been shortened progressively over recent years, while in veterinary medicine much longer treatment periods have been accepted without any scientific basis for their necessity. This is one of the changes to be found in this 2nd edition, where we have focused on treatment duration, using the somewhat limited veterinary evidence together with the experience from human medicine.

Underpinning this new version is a thorough revision of the chapters from the original guidelines. We are pleased that a completely new chapter on compassionate use permits and magistral (extemporaneous) preparations for medicines (Chapter 8) has been added, in response to the many queries received about the process to follow whenever a recommended preparation has not been approved for a given species or indication.

Identifying all the changes in individual chapters can be a challenge for the reader, and in that light the authors have planned various approaches to disseminate key points from the updated guidelines and to improve their implementation in practice. Prior to publication of the guidelines, a series of three articles in the Danish Veterinary Journal (DVT) covered changes in recommendations regarding the treatment of urinary, skin, ear and reproductive tract infections (DVT 3, 4 and 5, 2018).

The people behind the Antibiotic Use Guidelines for Companion Animal Practice:

Steering committee: Asger von Wenck and Helle Elkjær Johansen from the Companion Animal Group of the Danish Veterinary Association, and academic coordinators Lisbeth Rem Jessen and Peter Damborg (scientific editor) from the University of Copenhagen's Faculty of Health and Medical Sciences.

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Review: The updated text has been critically examined by Scott Weese (University of Guelph) and Luca Guardabassi, both internationally recognised experts in the field of rational veterinary antibiotic use.

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1 General principles for the rational use of antibiotics

In general, the following criteria should be fulfilled before antibiotic treatment commences:

- Proven presence of a bacterial infection, or well-grounded clinical suspicion of a bacterial infection. In other words, the presence of a viral, parasitic or fungal infection, which will not respond to antibiotic therapy, should be excluded or evaluated as being unlikely.
- It is considered unlikely that host immune defences will overcome the infection without the use of antibiotics.

These criteria do not apply to prophylactic antibiotic treatment in connection with certain surgical procedures (see Chapter 5).

Antibiotics play an important role in the clinic and choosing the most appropriate preparation is vital. When treating a bacterial infection, the choice of antibiotic should be based on an expectation of clinical efficacy, low toxicity and the least possible influence on the selection of multi-resistant bacteria. With regard to the choice of the most appropriate antibiotic, a distinction should be drawn between an empirical choice and one based on sensitivity testing.

Clinically, the initial choice of an antibiotic is usually made empirically. Especially when an infection is causing pain or discomfort, or for complicated or life-threatening infections, antibiotic treatment is usually started before results from culture and sensitivity testing are available. The welfare and survival of the patient can depend on selection of the optimal antibiotic.

In the following sections, general principles governing rational use of antibiotics are described with reference to factors influencing their clinical efficacy (bacterial sensitivity, penetration into and effectiveness within infected tissues, pharmacokinetics, pharmacodynamics, route of administration and treatment duration), toxicity, risk for development of resistance, and cost.

1.1 Bacterial sensitivity

Familiarity with the bacteria (Gram-positive, Gram-negative, aerobes and anaerobes) that commonly cause infections in different organ systems is a prerequisite for successful empirical antibiotic therapy. **Diagnostic cytology** should be performed whenever possible, since the information gained can be used to identify the involved microorganisms and thus guide the choice of antibiotic. When choosing a preparation, the veterinarian should be familiar with **typical pathogenic bacteria, local patterns of antibiotic resistance** in companion animals and with **typical bacterial sensitivities to particular antibiotics**. Some bacteria, for example *Pasteurella multocida* and *Streptococcus canis*, have predictable sensitivities and can be selectively treated with narrow-spectrum penicillins. Likewise, the majority of intracellular pathogens should be managed with tetracyclines, and the vast majority of anaerobes are sensitive to both penicillin and clindamycin. **Sensitivity testing** is recommended for bacterial pathogens whose sensitivity profile cannot be predicted. Variations in antibiotic sensitivity in different patient populations makes knowledge of local resistance patterns vital for these pathogens. This knowledge is kept current by regular sampling for culture and sensitivity testing.

When selecting an antibiotic, the veterinarian should be familiar with the specific patterns of bacterial antibiotic resistance in Danish companion animals. Tables 1 and 2 show the patterns of resistance in *Staphylococcus pseudintermedius* and *Escherichia coli* isolates from dogs and cats in the period just before publication of the first guidelines (2011-2012) and five years later (2016-2017).

Table 1: Antimicrobial resistance in clinical isolates of *Staphylococcus pseudintermedius* from dogs and cats in Denmark (source: SUND Vet Diagnostik, University of Copenhagen).

Antibiotic	2011-2012 (n=318)	2016-2017 (n=419)
Amoxicillin-clavulanate	10%	7%
Oxacillin	6%	6%
Cephazolin	6%	6%
Erythromycin	29%	26%
Clindamycin	30%	24%
Chloramphenicol	14%	17%
Doxycycline	- ^a	29%
Gentamicin	4%	3%
Amikacin	4%	1%
Enrofloxacin	3%	3%
Marbofloxacin	3%	4%
Sulfamethoxazole-trimethoprim	4%	5%

^aDoxycycline data from 2011-2012 using the latest cut-off values for the definition of resistance are not available.

For *S. pseudintermedius*, the overall pattern of resistance has remained largely unchanged over this period (Table 1). This is also true for oxacillin, for which 6% of isolates from both periods were resistant. Oxacillin is used as an indicator for methicillin-resistant *Staphylococcus pseudintermedius* (MRSP, see also Chapter 3), and these numbers suggest that the incidence of MRSP in Denmark is stable and relatively low. It should be noted that not all oxacillin-resistant isolates of *S. pseudintermedius* are MRSP, and the MRSP incidence is probably below 5%. Clindamycin is a narrow-spectrum antibiotic which is recommended as a first line systemic treatment for skin infections (see chapter 6 section 1). Despite a small fall in resistance, 25% of isolates from 2016-2017 were resistant to clindamycin. In the first edition of the guidelines, we attributed the high rate of resistance to the likelihood that many isolates were from recurrent and previously treated cases of pyoderma. This hypothesis is supported by recent research from the University of Copenhagen, which found

Table 2: Antimicrobial resistance in clinical isolates of *Escherichia coli* from dogs and cats in Denmark (source: SUND Vet Diagnostik, University of Copenhagen).

Antibiotic	2011-2012 (n=318)	2016-2017 (n=419)
Ampicillin	26%	14% ^a
Amoxicillin-clavulanate	7%	4% ^a
Cephazolin	5%	8%
Cefovecin	4%	-
Cefoxitin	4%	-
Cefpodoxim	4%	3%
Chloramphenicol	7%	3%
Doxycycline	7%	5%
Gentamicin	3%	2%
Amikacin	1%	1%
Enrofloxacin	9%	2%
Marbofloxacin	9%	1%
Imipenem	0%	0%
Sulfamethoxazole-trimethoprim	15%	6%

^aData for sensitivity to ampicillin and amoxicillin-clavulanate are solely from *E. coli* isolates from urinary tract infection, since *E. coli* isolates from other infections are almost always resistance to these two antibiotics.

clindamycin resistance in only 14% of *S. pseudintermedius* isolates from first presentations of canine pyoderma, which had not previously been treated with antibiotics (4).

Following publication of the guidelines, the level of resistance in *E. coli* was lower in 2016-2017 compared to 2011-2012 for several key antibiotics, such as amoxicillin, amoxicillin-clavulanate, sulfamethoxazole-trimethoprim and fluoroquinolones. For this last group, the decline in resistance was particularly marked (Table 2), which is encouraging given the clinical importance of these antibiotics. The general fall in resistance can be attributed to several factors including a change in isolation patterns between the two periods (in 2016-2017 65% of *E. coli* isolates were from urinary tract infections, compared to 41% in 2011-2012). At the same time, a larger than usual proportion of urinary tract isolates of *E. coli* originated in primary clinics compared to referral centres. Finally, it can be assumed that the guidelines have changed prescribing practice with regard to urinary tract infections. A questionnaire on this subject showed firstly, that the urinary tract chapter from the first version of the guidelines was the second most used after that covering skin infections, and secondly, that veterinarians who had read the chapter were more likely to follow its recommendations compared with those who had not (3).

1.2 Antibiotic penetration into infected tissue

Adequate tissue perfusion is necessary before diffusion of antibiotics into infected tissue can occur. Therefore, effective concentrations of antibiotics cannot be guaranteed in the extremities of patients with **hypovolaemic shock**. It can also be difficult to achieve effective concentrations of antibiotics in **abscesses and granulation tissue**, due to reduced perfusion. **Certain tissue types** do not permit ready diffusion of antibiotics from the blood to the tissue due to the presence of lipid membranes in the capillary walls. Such barriers exist in the CNS, eyes, prostate and the bronchi. A limited number of lipophilic antibiotics (see disease-specific chapters) are able to penetrate these barriers and in some instances may actually be concentrated in the tissues behind them. **Local tissue factors, for example the presence of pus or necrotic tissue**, can reduce an antibiotic's effect by binding and inactivating it. Production of **biofilm** on surgical implants can protect bacteria against antibiotics and phagocytosis. When choosing an antibiotic, account must be taken of these factors to ensure effective concentrations of the preparation at the site of infection.

1.3 Pharmacokinetics and pharmacodynamics

The pharmacology of antibiotic therapy can be divided into two main areas: pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetic factors such as dose, dosing interval, route of application, absorption, distribution and elimination in relation to time determine the preparation's serum concentration and thus its concentration in the tissues and extracellular fluids. Pharmacodynamics describes the relationship between serum concentrations and the pharmacologic effects of the preparation. For an antibiotic, the relationship between the serum concentration and the antibiotic effect is particularly interesting.

Antibiotics can be divided into three main groupings based on the parameters which best predict their clinical efficacy (Table 3):

- Concentration-dependent activity and prolonged duration of effect
- Time-dependent activity with limited duration of effect
- Concentration- and time-dependent activity with moderate duration of effect

For antibiotics in the first group (concentration-dependent antibiotics), such as the fluoroquinolones and aminoglycosides, the higher the antibiotic concentration is in relation to the pathogens minimal inhibitory concentration (C_{max}/MIC), the greater the effect. In practice, this means that the antibiotic should be given in high doses to maximise the clinical effect. **For antibiotics in the second group (time-dependent antibiotics)**, such as penicillins and cephalosporins, it is the length of time during which the antibiotic concentration at the site of infection exceeds MIC ($T>MIC$) which determines the clinical effect. It is important that these antibiotics are given at regular intervals. The clinical effect of **antibiotics in the third group**, for example clindamycin, exhibit a combination of concentration- and time-dependent efficacy, described by the area under the concentration curve (area under curve or AUC) in relation to the MIC (AUC/MIC). In these instances, both dose and dose interval are important in maximising the clinical effect (Table 3). The interested reader is referred to standard pharmacological texts for further discussion of these topics.

Table 3. Classification of antibiotics based on PK/PD parameters. MIC - minimal inhibitory concentration, C_{max} - maximum concentration, T - time, AUC - area under curve.

Antibiotic group	Examples	Pharmacological goal	PK/PD parameter
Concentration-dependent with prolonged duration of effect	Aminoglycosides Fluoroquinolones Metronidazole	Maximise concentration of antibiotic	C_{max}/MIC
Time-dependent with limited duration of effect	Cephalosporins Erythromycin Penicillins	Maximise time during which antibiotic concentration exceeds MIC	$T>MIC$
Time-dependent with moderate duration of effect	Azithromycin Clindamycin Tetracyclines	Maximise quantity of antibiotics over time	AUC/MIC

1.4 Route of application

The route of application should ensure active concentrations of antibiotic at the site of infection and, as far as possible, limit the exposure of other organ systems to the antibiotic in order to minimise the development of resistance in the normal bacterial flora. Local treatment of superficial pyoderma and otitis externa can achieve high concentrations of the active ingredient at the site of infection without affecting normal flora elsewhere. When high serum concentrations are desirable, intravenous treatment is recommended. Parenteral treatment will be necessary in diseases characterised by vomiting or regurgitation.

1.5 Treatment duration

There is little evidence regarding the optimal duration of antimicrobial treatment in animals. In general, antibiotic treatment should continue for 1-2 days beyond resolution of clinical signs. Chronic infections, skin infections, osteomyelitis, infections in immunosuppressed animals, and infections with intracellular pathogens often require longer treatment periods. Recommendations on treatment duration are given in more detail in the disease-specific chapters (Chapters 6.1-6.9). It

is important that treatment is not continued longer than necessary, in order to avoid unnecessary use of antibiotics. If prolonged treatment is employed, regular re-evaluations of the disease process and active decisions on extension of treatment are advised.

1.6 Antibiotic-related toxicity and side effects

In selecting an antibiotic, some consideration must also be given to potential toxicity or side effects. For example, nephrotoxicity is a well-known complication of aminoglycoside use, and these antibiotics are therefore not appropriate for patients with reduced renal function. Table 4 lists examples of antibiotic-related toxicity for the different classes of antibiotics.

Table 4. Examples of known antibiotic-related toxicities and side effects.

Class	Toxicity/side-effect	Remarks, warnings and interactions
Aminoglycosides	Renal tubular dysfunction. Neuromuscular blockade. Ototoxicity. Nystagmus.	Use with caution in patients with renal disease and hypovolaemia. Increased nephrotoxicity can occur when co-administered with first-generation cephalosporins, amphotericin B, loop diuretics and mannitol.
Beta-lactams (cephalosporins and penicillins)	Immune-mediated disease. Urticaria. Allergic reactions, especially with parenteral use, (rare). Acute renal tubular necrosis. Bleeding disorders with some products. Vomiting after oral administration (especially cephalixin).	Other medications with marked protein binding (furosemide, ketoconazole, NSAIDs) can compete with cephalosporins (especially cefovecin) leading to reduced efficacy (described in product literature). Certain cephalosporins can give false positive reactions for urine glucose.
Quinolones and fluoroquinolones	Cartilage damage in weight-bearing joints in growing animals. Retinal toxicity in cats (especially with high doses of enrofloxacin). Reduced seizure threshold.	Fluoroquinolones inhibit metabolism of some medications via cytochrome P450 inhibition (e.g. theophylline, propranolol).
Chloramphenicol	Bone marrow suppression/aplastic anaemia (higher risk in cats than in dogs). Reduced metabolism of other medications.	Chloramphenicol is a well-known P450 inhibitor, and can prevent metabolism of other medications (e.g. barbiturates). Aplastic anaemia can be induced in humans following contact (owners should be instructed to use gloves)
Lincosamides	Diarrhoea due to changes in gut flora. Oesophagitis and oesophageal stricture in cats after administration of clindamycin capsules (especially with high-dose treatment for toxoplasmosis).	Reduce dose in the presence of hepatic dysfunction or cholestasis. Erythromycin and chloramphenicol should not be

	Neuromuscular blockade.	co-administered with lincosamides (blocks effects).
Macrolides	Nausea, diarrhoea and abdominal pain. Vomiting and intestinal hypermotility (with erythromycin) due to cholinergic activity.	Erythromycin prevents metabolism of medicines via cytochrome P450 inhibition and can prevent breakdown of theophylline, benzodiazepines and digoxin. Co-administration of erythromycin with cyclosporin can result in nephrotoxicity. Caution: avoid co-administration with lincosamides (see above).
Nitroimidazoles	Neutropenia (metronidazole). CNS toxicity (metronidazole and ronidazole). Profuse salivation after oral dosing in cats	
Rifampicin	Hepatotoxicity. CNS symptoms. Pinnal erythema.	Rifampicin induces cytochrome P450 enzymes and glycoproteins and can result in reduced efficacy of other medicines. Causes orange discolouration of urine and tears
Sulphonamides and Sulfa/TMP	Cholestasis or acute hepatic necrosis (rare). Macrocytic anaemia (long-term treatment in cats). Dermatologic eruptions (Dobermann, Golden retriever and Labrador retriever). Thrombocytopenia. Suppurative non-septic polyarthritis (especially in Dobermann, Samoyed and miniature Schnauzer). Keratoconjunctivitis sicca with increased risk in dogs under 12kg (monitor under long-term treatment). Renal crystalluria (rare). Hyperkalaemia (TMP). Functional hypothyroidism. (induced, reversible on cessation of treatment).	There is no information regarding variations in the prevalence of side effects with different sulphonamides in dogs.
Tetracyclines	Renal tubular disease. Cholestasis. Fever (especially in cats). Inhibition of metabolism of medicines. Oesophagitis and stricture formation in cats after oral dosing (doxycycline).	

1.7 Risk for development of antibiotic resistance with clinical relevance to humans and companion animals

The regulatory authorities in Europe have licensed fluoroquinolones and cephalosporins for treatment of common infections of the urinary tract, skin and superficial wounds in companion animals. **However, it is well known from both human and veterinary medicine that the use of fluoroquinolones and third-generation cephalosporins, both of which are essential medicines, increases the development of extended spectrum beta-lactamase (ESBL)-producing *E. coli* and methicillin-resistant staphylococci.** MRSP and ESBL-producing *E. coli* are currently relatively rare amongst the canine and feline populations in Denmark (Chapters 1.1 and 3), but there is a real risk that these and other multi-resistant bacteria will spread if we do not limit the use of fluoroquinolones and cephalosporins. The antibiotic pyramid (Figure 1) ranks available antibiotics in order of their significance to human and veterinary medicine. This system can help the veterinarian choose an antibiotic based on the risk of spreading antibiotic resistance. Correct use of this prioritising system requires knowledge of both the clinical effect and pharmacological properties of the different antibiotics, including their abilities to concentrate at the site of infection. The antibiotic pyramid can also be used to choose amongst several preparations with the same expected clinical efficacy for empirical treatment of a given infection. This pyramid, together with data on expected clinical effects, forms the basis of the specific recommendations for empirical treatment of infections in the various organ systems (Chapter 6).

The authors have divided the antibiotics into five categories, based on how essential they are to human medicine, along with the risk for development and spread of resistance of high clinical relevance to both companion animals and humans. **The first category** comprises those antibiotics with a relatively narrow spectrum and limited risk for the development and spread of dangerous resistant bacteria in companion animals (dihydrostreptomycin and narrow-spectrum penicillins) and antibiotics which are not used for systemic treatment in humans in the European Union (e.g. chloramphenicol). **The second category** contains antibiotics with a somewhat broader spectrum and a limited risk for spreading resistance of high relevance to both companion animals and humans (aminopenicillins, lincosamides, macrolides, nitrofurantoin, sulphonamides with trimethoprim, and tetracyclines). First-generation cephalosporins and amoxicillin/clavulanate are placed in the **third category** due to their broader spectrum than the aminopenicillins and because their use can encourage selection of multi-resistant bacteria such as MRSP (Chapter 3). Rifampicin is increasingly used as an alternative medication for treatment of human MRSA infections in some countries. Gentamicin is also included in this group due to its importance in treating human infections such as endocarditis. The risk for spreading antibiotic resistance, which can lead to treatment failure, is even higher in the **fourth category**, which consists of amikacin, fluoroquinolones, metronidazole and third-generation cephalosporins. These antibiotics should be used with caution, both to preserve their clinical effect in veterinary medicine and to prevent the selection of resistant bacteria with high clinical relevance and zoonotic potential. Metronidazole has been placed in this group because it is critical in managing *Clostridium difficile* infections in human hospitals. **The fifth category** comprises the most essential drugs, namely the carbapenems, vancomycin and linezolid. Use of these should be restricted to rare instances of serious multi-resistant infections, which cannot be managed in any other way (Figure 1).

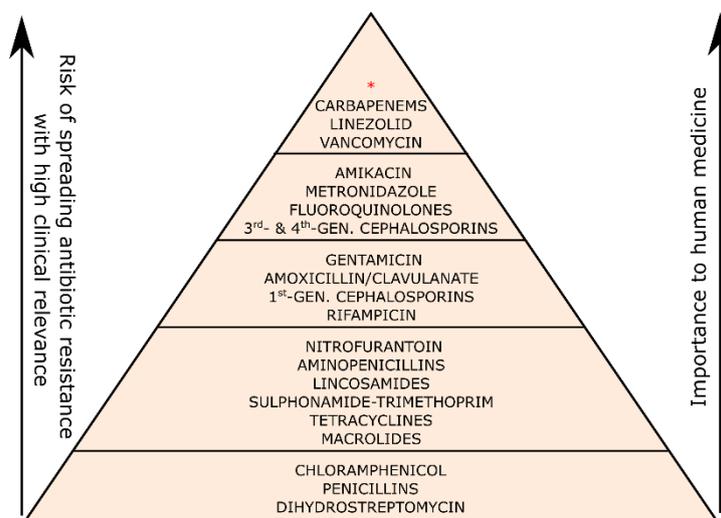


Figure 1. The authors' classification of systemic antibiotics based on clinical importance in human and veterinary medicine and the risk of spreading antibiotic resistance of high clinical relevance by their use in companion animals. Antibiotics with a particularly high risk for resistance, and with few or no therapeutic alternatives in humans, are placed in the top layer of the pyramid. Medications with a low risk of causing medically important antibiotic resistance are placed at the base of the pyramid. *Antibiotics from the uppermost layer should only be used if the criteria outlined in Section 1.7 are met.

Ideally, antibiotics from the top of the pyramid should not be used in companion animal practice.

Their use may be considered in the case of severe infections in animals of high economic or emotional value, but this use should be exceptional and follow careful consideration of the following criteria:

- The infection should be life-threatening or be causing severe suffering
- The infection should be documented by bacterial culture
- Resistance to all other available antibiotics lower in the pyramid should be documented by sensitivity testing at a recognised laboratory
- There should be a reasonable expectation of recovery after treatment
- Specialists in microbiology and internal medicine should be consulted with reference to alternative approaches to treatment

Use of carbapenems, linezolid and vancomycin will be minimised if the above criteria are followed. Restrictions in their use will preserve these antibiotics' effectiveness for use in human medicine against severe infections, and infections caused by multi-resistant bacteria.

1.8 Economic considerations

The choice of preparation, its route of application and the length of treatment all have an influence on the cost of treatment. Generally, the price of most antibiotics licensed for veterinary use does not have a deciding influence on product choice. Costs due to ineffective or wrongly-directed treatment can, however, be significant. It is usually the rational, well-planned treatment strategy, which will prove to be the most effective, and this is also true financially.

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2 Developments in antibiotic use in dogs and cats in Denmark

Background – registration of antibiotic use in animals

In Denmark, all sales of antibiotics for animal use are registered in the national database, VetStat, which is run by the Danish Veterinary and Food Administration agency of the Ministry of Environment and Food. The original focus of VetStat at its inception in 2000 was on production animals, in connection with the ban on use of antibiotics as growth promoters. VetStat's data from production animals remains far more detailed than that from companion animals and horses. For production animals, data includes species, age and indication for treatment, whereas for other animals (including horses), only a distinction between horses (code 11) and companion animals (code 90) is made. For companion animals, the species code is only registered for direct sales from pharmacies to owners – for sales or use in practice, the species code is only used for production animals. This means that much more detailed information regarding use of antibiotics in production animals is available, which is reported each year in DANMAP. The DANMAP reports show that by far the largest veterinary use of antibiotics is for pig production, which therefore has greatest significance for environmental antibiotic resistance. Usage figures need to be held up against population size (total number of animals or biomass) in order to assess selection pressure and the level of risk for development of antibiotic resistance (Figure 1).

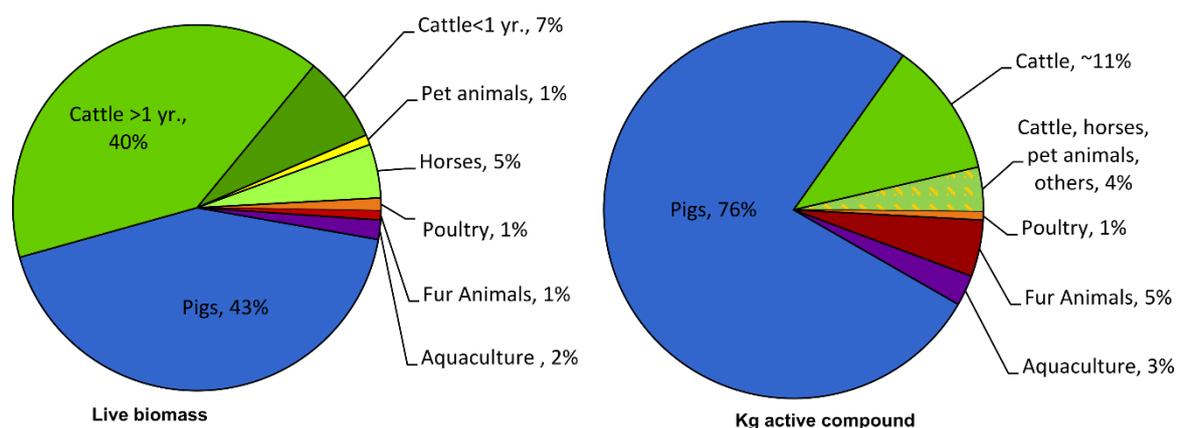


Figure 1. Estimated animal biomass and veterinary use of antibiotics in Denmark in 2012.
Source: DANMAP 2012

Antibiotic use in companion animals can be estimated from data on dispensing form and approvals for formulations for specific species, together with which types of clinic received human medicines. Estimates regarding use in companion animals and horses were released in DANMAP 2011, as Defined Animal Daily Dosages per 1000 Animal-Days (DAPD): in 2011, companion animal use amounted to 16-17 DAPD, equivalent to more than 1.6% of companion animals receiving treatment on any given day (2). Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600-2032.). This estimate far exceeds the values for cows (ca. 5 DAPD in 2011 (1)) and poultry (2.3 DAPD in 2012), but is lower than that for pigs (30 DAPD in 2012, decreasing to 27 in 2015). In comparison, medical use for patients in primary care practice was 18-19 DID (Defined Daily Doses per 1000 Inhabitant Days) in the period 2012-2015 (4). Veterinary use in companion animals is thus quantitatively similar to that for people, but broad-spectrum antibiotics make up a much larger proportion of veterinary use in companion animals. Since statistics for Danish dogs and cats are combined, use in dogs is

underestimated and that in cats overestimated – use in dogs may therefore be higher than use in humans.

Data validity and assumptions

Both mistakes in registration of species and failures to report data could occur. Even if this represents only a small fraction of use in production animals, it will have a significant effect on the remainder which otherwise is assumed to have been used in companion animals and horses, because use in these species makes up such a small part of total veterinary consumption (Figure 1). In addition, it is difficult to determine whether an antibiotic used in practice was intended for equine or companion animal treatment. Estimates of antibiotic use in companion animals is thus largely based on information about the preparation used. The estimates presented here use the following assumptions:

1. The following preparations for systemic treatment are assumed to be used exclusively in dogs and cats: all veterinary prescriptions for tablets and capsules (including human preparations), all formulations approved solely for use in dogs and/or cats, including oral pastes approved for dogs/cats and cefovecin for injection.
2. Oral pastes formulated for horses, and oral preparations formulated for production animals, are excluded, even if they have been registered as sold by pharmacies for use in companion animals, since this likely represents a data entry error¹. While it cannot be excluded that some dogs and cats are treated with sulphonamide-trimethoprim oral pastes intended for horses², dosing for companion animals is considered difficult.
3. Parenteral medicines are estimated separately. These are assumed to be used in companion animals and horses whenever they are not specifically registered as used in production animals. The proportions used in companion animals and horses is unknown. Cefovecin use is covered in assumption 1 (above), since under the veterinary medicine cascade regulations it is unlikely to be used in other species: in a similar vein, 3rd and 4th generation cephalosporins approved for production animals are excluded from these estimates.

Dosages used

Antibiotic use is reported as far as possible as the Defined Daily Dose for Animals (DDDA) in order to facilitate comparisons between different antibiotics. An exception is the use of topical preparations, reported as number of packages. Use is then adjusted for population size to produce a meaningful comparative unit (DDDA per 1000 animal days = DADD). Currently, the only reliable figures for dogs and cats date back to 2000, when a national census found that there were 546000 dogs and 646000 cats in Danish households. Due to an absence of data, it is assumed that populations of dogs and cats have remained stable in the period 2007-2016. Calculation of the standardised daily dose (DADD) assumes an average body mass of 10 kg for all dogs and cats. This was determined arbitrarily from the total numbers of cats, and small, medium and large breed dogs in 2000. This leads to uncertainty in the estimates for usage per 1000 animals, but probably does not have a significant impact on the observed trends in antibiotic use in dogs and cats, since the population composition changes fairly slowly due to the typical lifespan of companion animals.

¹ In the period 2012-2016 this consisted of approximately 1 DADD₁₀/1000 animal days, with a decreasing tendency which probably reflects better data registration.

² In the period 2012-2016, registrations of these products for species code 90 have been stable at approximately 1.5 DADD₁₀/1000 animal days.

2.1 Antibiotics for systemic use

Trends in the use of antibiotics for treatment of dogs and cats (oral preparations and cefovecin)

The sales trends for cefovecin and oral antibiotics for dogs and cats are shown in Figures 2 and 3. These primarily cover use in non-hospitalised patients, and can be compared to the human primary care sector. Sales made up an estimated 75% of all companion animal systemic use. Use of these antibiotics decreased by 14% from 2012 to 2015, from 12.4 DAPD to 10.7 DAPD. In 2016, usage increased to 11.2 DAPD, giving an overall reduction of 10% from 2012 (Figure 3).

Changes also occurred in the sales of individual antibiotics:

- Amoxicillin/clavulanate was by far the most often dispensed preparation for dogs and cats, making up 53% of all use in 2016. Use of amoxicillin/clavulanate has been sharply increasing in the last decade, albeit with a minor fall in use in 2013.
- First generation cephalosporins, lincosamides (clindamycin) and aminopenicillins (amoxicillin) are also frequently dispensed (Figure 2). From 2012 to 2016, there was a marked reduction in the use of 1st generation cephalosporins (from 16% to 9%) while use of clindamycin has increased consistently (to 13% in 2016). Use of aminopenicillin was slightly higher in 2016 (7%) compared to 2012 (5%).
- Of the critically important 3rd–4th generation cephalosporins, only cefovecin is used in companion animals: usage increased markedly from 2007 to 2009, but halved between 2010 and 2016 with a particularly sharp decrease from 2012 to 2013, consistent with the recommendations in the original guidelines.
- Use of oral fluoroquinolones also fell temporarily in 2013, but has since increased back to 2012 levels.
- Metronidazole (only approved for humans during this period) use dropped between 2012 and 2014, again consistent with previous recommendations.
- Similarly, the sale of nitrofurantoin tablets (human preparation) decreased by 99% from 2012 to 2013, and the use of sulphonamide-trimethoprim decreased significantly from 2013 to 2014. The low numbers for sulphonamide-trimethoprim are the result of the loss of the veterinary licensed preparation.
- Use of narrow-spectrum penicillins has also fallen gradually over the last decade, since only human preparations are available.

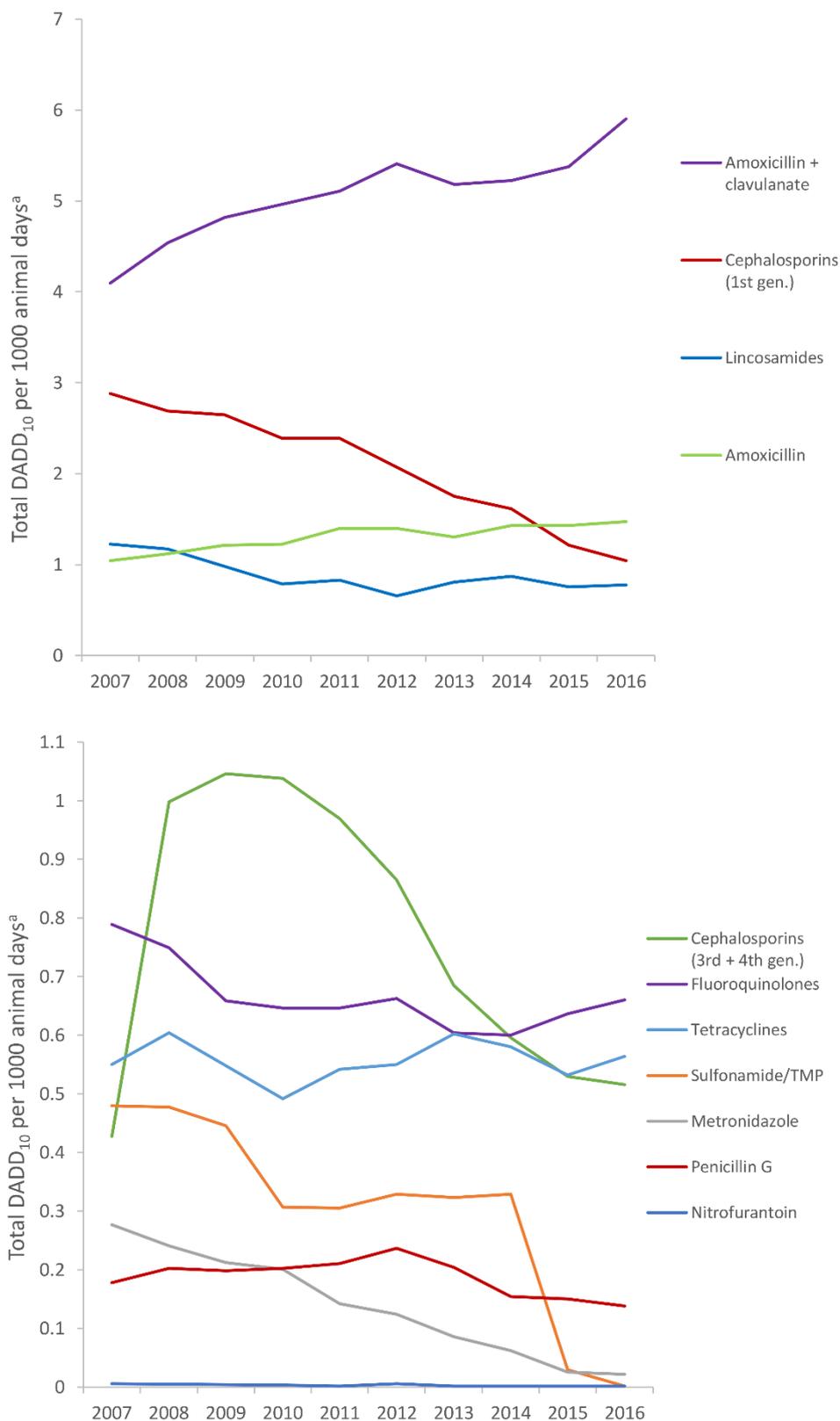


Figure 2. Changes in the use of various antibiotic classes for systemic treatment of companion animals. Totals cover all products formulated for use in companion animals (tablets, capsules and cefovecin injection). ^aThe companion animal population is assumed to remain constant at 1192000 dogs and cats over this period.

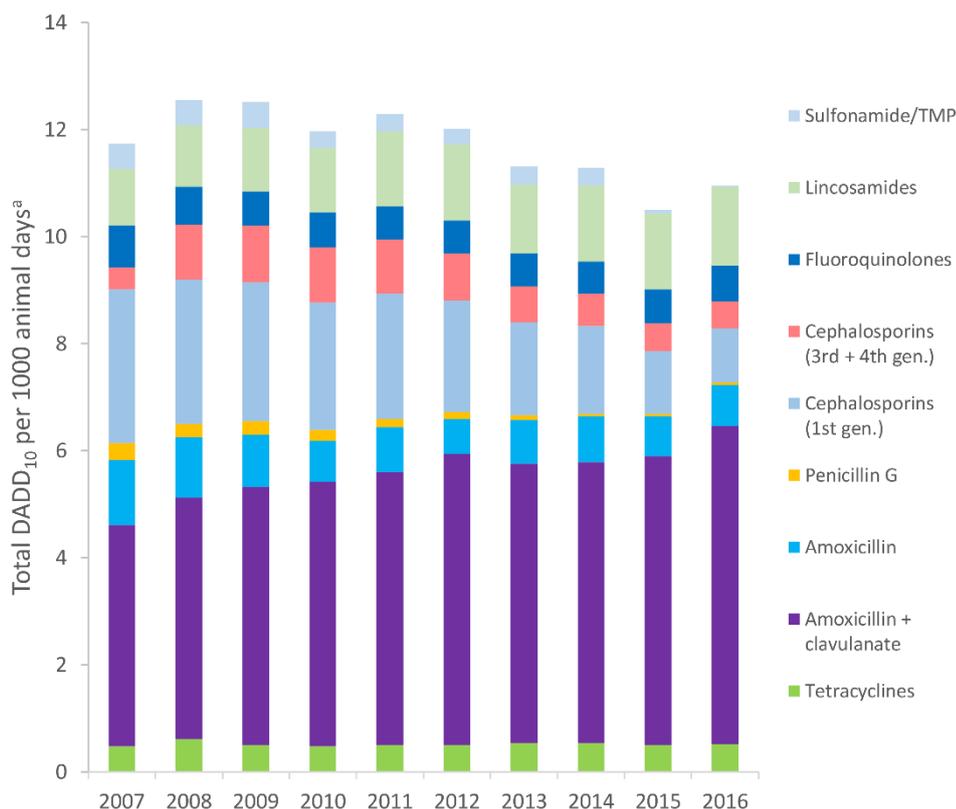


Figure 3. Developments in the use of systemic antibiotics for the treatment of companion animals, for the most commonly used antibiotic classes. Totals include medicines licensed for companion animal use and tablets and capsules intended for human use. Parenteral preparations, apart from cefovecin, are not included. ^aThe companion animal population is assumed to remain constant at 1192000 dogs and cats over this period.

Other parenteral medicines

Treatment with parenteral medicines can only be carried out by veterinarians and veterinary nurses, and therefore almost exclusively occurs in veterinary clinics, either during hospitalisation or at the start of a treatment course. Parenteral use is therefore relatively low compared to peroral use. In DANMAP 2011, parenteral use was estimated to be about 25% of the total systemic antibiotic use in companion animals, based on information regarding practice type. It is not possible to find exact quantities for systemic use in dogs and cats, since use in these species cannot be separated from use in horses. A significant proportion of narrow spectrum antibiotic use in these species probably can be attributed to equine practice, even allowing for perioperative antibiotic use in dogs and cats. The concentrations of different preparations can be used to roughly divide usage between horses and companion animals, since doses in excess of 0.1 ml/kg body mass are more likely to be intended for dogs and cats. Using this approach, tetracyclines and aminopenicillins may be used in larger quantities than cefovecin in companion animals. Estimates further indicate that parenteral use of fluoroquinolones is approximately 0.1 DAPD (see below), and remained at this level from 2012 to 2016.

Fluoroquinolones

Parenteral fluoroquinolones may only be administered by veterinarians, and use is therefore restricted to veterinary practices. The target species is only known for production animals, but use in

these is extremely limited due to legal restrictions. It is therefore a reasonable assumption that unattributed fluoroquinolones have been used in horses or companion animals. The changes in parenteral use of fluoroquinolones for various species is shown in Figure 4, with totals for oral antibiotics use for comparison. Compared to other antibiotics, parenteral fluoroquinolone use in horses and companion animals is low. It is impractical to use multiple preparations with different concentrations in practice, because overall use is so limited, and it is thus assumed that preparations with low concentrations have been used in companion animals, and those with high concentrations have been primarily used in horses. Consequently, use in companion animals appears to be slightly higher than in horses, based on kg active preparation. Use in companion animals made up the vast majority of all veterinary fluoroquinolone usage, with the proportion estimated at 82% in 2016.

2.2 Topical preparations

The majority of veterinary use of topical medications (such as ear and eye drops) are likely to be used in dogs and cats, although a certain proportion is used for horses. In this report, topical preparations are only excluded from the totals if specifically dispensed for use in horses or production animals. Since it is impossible to calculate a daily dose for these medications, use is

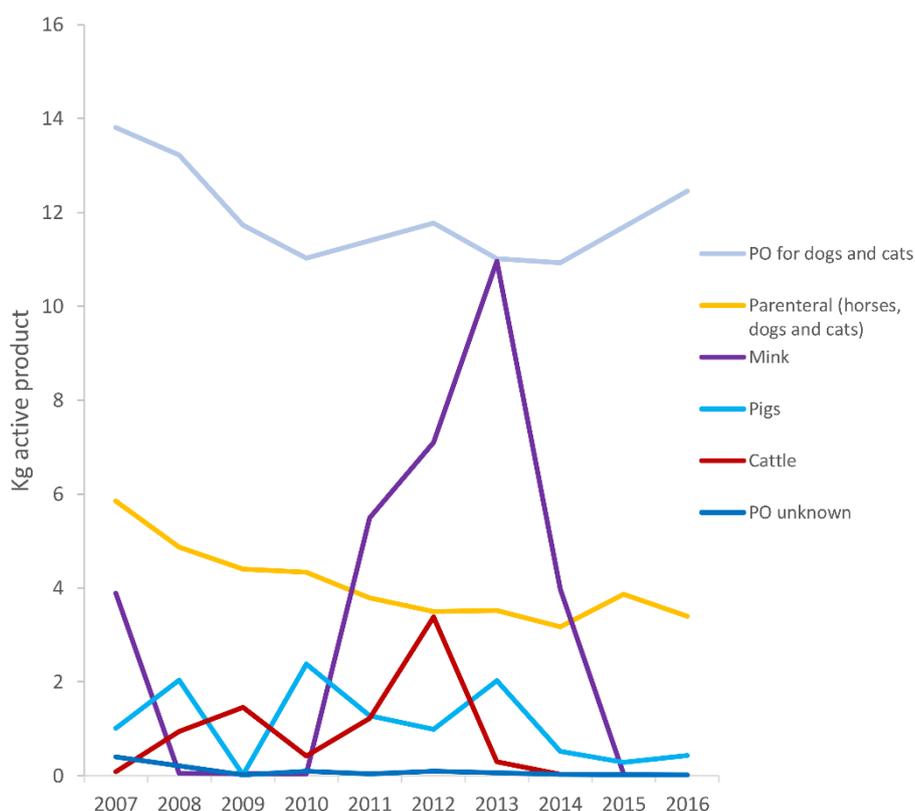


Figure 4: Development in the use of systemic fluoroquinolones for various animal species.

reported as total packages sold. Total packages can be used as a proxy for the number of treatment courses prescribed.

- Topical treatment of pyoderma consisted almost exclusively of fusidic acid (95% of all packages). Annual usage for pyoderma has remained fairly constant from 2012 to 2016, at between 25-29 packages per 1000 animals.

- Use of preparations for ear and/or eye infections has decreased by 8% from 2012 to 2016 (Figure 5), predominantly due to a decline in the use of eye preparations (22% fall). This decline mostly affected use of chloramphenicol, although fusidic acid use also decreased in this period.
- Topical treatment of ear infections typically involves three product groups: gentamicin (with antimycotics), polymyxin B (with miconazole) and fusidic acid, often combined with corticosteroids (Figure 5). Fluoroquinolones (with corticosteroids) made up 1% of the total packages sold for topical treatment of ear infections in 2016.
- Finally, some preparations can be used in both eyes and ears, accounting for circa 7% of sales for topical treatment (Figure 5). These preparations consist primarily of oxytetracycline in combination with polymyxin B.

2.3 Comparison with Sweden

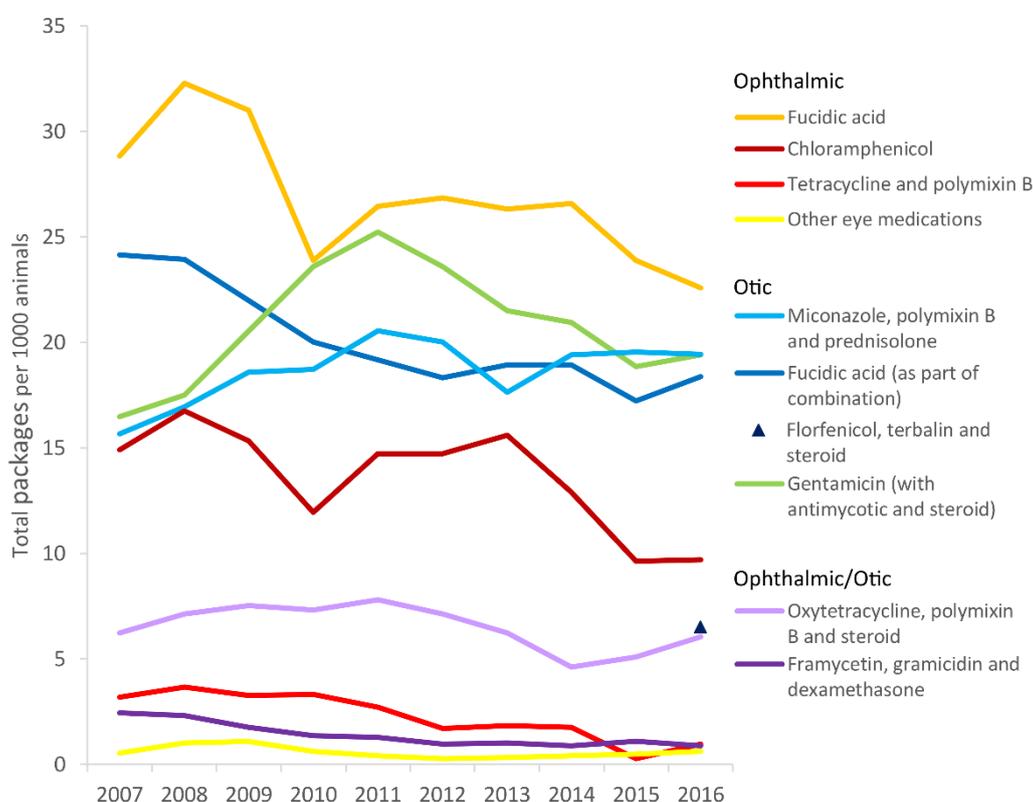


Figure 5: Changes in total topical treatment packages sold for companion animals and horses. The denominator used is the total population of dogs and cats, which has been assumed to be constant at 1192000 over the period shown.

In both Denmark and Sweden, antibiotic use is higher in dogs than in cats. Even though separate data on dispensing to dogs and cats do not exist for Denmark, it is possible to estimate the proportions, based on package sizes and population statistics (5).

In Sweden, antibiotic use is recorded separately for dogs and for cats, and the total packages per 1000 dogs is published in the Swedres-Svarm report. For dogs, there has been a consistent decline in

oral antibiotic use, with a decrease of 53% in the last 10 years from 593 packages/1000 dogs to 260 packages/1000 dogs in 2015 (7). In Denmark, the estimated use for dogs was 399 packages/1000 dogs in 2007, but this figure increased by 25% from 2007 to 2012 and then stabilised in the period up to 2015. This shows that currently the total antibiotic use in dogs is significantly higher in Denmark than in Sweden (approximately 50% higher, depending on changes in population statistics in Denmark and thus the division between dogs and cats). Interestingly, the average total DADD per package fell in this period, suggesting that it was particularly use in cats (or possibly small dogs) which drove the increase up to 2012. The differences between antibiotic use in Sweden and Denmark can be explained by the fact that even in 2006 there was considerable attention directed to antibiotic use in companion animals in Sweden, with media coverage, and local, regional and national workshops and national guidelines appearing in connection with the first case of MRSP in dogs in 2006 (6).

Data from the Swedish monitoring programme shows that the most commonly used oral antibiotics for dogs (7) are the same four groups which are most commonly used for treatment of dogs and cats in Denmark. However, there is a significant difference in their rankings. In Sweden, aminopenicillins (98 packages/1000 dogs) and lincosamides/macrolides (60 packages/1000 dogs) are the most commonly dispensed antibiotics, with aminopenicillin (plus inhibitor) the third most used at 40 packages/1000 dogs (7). In Denmark, use of an aminopenicillin plus inhibitor (amoxicillin/clavulanate) was estimated to be 143 packages/1000 dogs in 2006, and use in dogs and cats increased by 50% from 2006 to 2015 with a doubling in the total number of packages. In comparison, the Danish use of aminopenicillins without an inhibitor was only 17 packages/1000 dogs in 2007, and this has fallen since. The use of lincosamides/macrolides (predominantly clindamycin) is significantly lower in Denmark, with an estimated use of 15 packages/1000 dogs in 2007. In 2015 this had increased by 35% as measured in DADD₁₀, while clindamycin use measured in total packages dispensed had increased by 193%, indicating that use had increased primarily amongst cats and small dogs. This needs to be viewed in context of the use of cefovecin, since cefovecin can often be replaced by clindamycin for the treatment of staphylococcal infections. Since 2006 the use of fluoroquinolones has fallen by 79% in Sweden, to 15 packages/1000 dogs in 2015 (7). In Denmark, the estimated use of oral fluoroquinolones in dogs was 18 packages/1000 dogs in 2007. The combined total packages (and total DADD) of oral fluoroquinolones for dogs and cats fell by 20% from 2007 to 2015. This decrease is assumed to be divided equally between dogs and cats, and indicates that the use in dogs in 2015 was down to 14 packages/1000 dogs. This is a crude estimate, but suggests that the use of fluoroquinolones in dogs in Denmark and Sweden was roughly similar in 2015.

2.4 Discussion and conclusion

Investigations into changes in antibiotic use in companion animals in Denmark is complicated by the lack of information on which species medicines are dispensed for. In addition, the lack of data on trends in the size of the dog and cat populations is problematic. This makes comparisons to other species, to use in humans and to use in other countries difficult.

The total consumption of antibiotics which are only used in dogs and cats (in general practice) has fallen by 10% since 2012, following publication of the first guidelines. In Sweden, the dog population has increased by 8% over a 10-year period. Data from the Danish Dog Register does not suggest that there has been a similar increase in the number of dogs in Denmark.

As was recommended in the original antibiotic guidelines, the use of critically important 3rd and 4th generation cephalosporins fell drastically by 59% from 2012 to 2016. With regard to use of critically important fluoroquinolones, a temporary decline was seen in 2013 in association with publication of the guidelines. Oral use was 6% higher in 2016 compared with 2012, and use in companion animals continues to comprise the majority of veterinary use of fluoroquinolones. The use of metronidazole and nitrofurantoin also fell markedly since 2012: the fall in metronidazole use is likely related to a campaign in 2012 against their use for gastrointestinal problems.

Use of broad-spectrum antibiotics for dogs and cats has increased over this period. This is due to a marked increase in the use of amoxicillin/clavulanate from 2012 to 2016, which now accounts for 53% of use in the primary sector (oral preparations and cefovecin). This is in direct contradiction to the recommendations in the guidelines. Amoxicillin/clavulanate is broad spectrum, and thus should not be the first line choice for many infections in companion animals: in human medicine, there has also been a move away from use of aminopenicillins with enzyme inhibitors. In comparison, use of aminopenicillins with an inhibitor is much lower in Sweden, where use has been falling for the last 10 years, even though usage was lower in 2006 than in Denmark. In Sweden, aminopenicillins without an inhibitor are the most widely used antibiotics, while this group comprises only 5% of use in Denmark.

Use of 1st generation cephalosporins has been declining over the entire period. The primary indication has probably been dermatitis, and the decline in use probably is reflected in the increased use of amoxicillin/clavulanate. Conversely, the use of clindamycin has increased in compliance with the guidelines. Clindamycin is recommended as the first line antibiotic for systemic treatment of dermatitis, and even though its use has increased, it comprised only 13% of the total in 2016. This increase was primarily due to use in cats and small dogs, and is reflected in the decreasing consumption of cefovecin, which is probably primarily used in cats.

Overall, it can be concluded that there has been a positive development since 2012 in terms of a decline in the use of 3rd generation cephalosporins, metronidazole and nitrofurantoin in companion animals. Currently, there has also been a marked increase in the use of amoxicillin/clavulanate, and the use of fluoroquinolones has increased by 6%. Based on published data, the use of broad-spectrum antibiotics is much higher in Denmark than in Sweden, although it appears the level of use of fluoroquinolones in the two countries is comparable. Comparisons with Sweden indicate that it should be possible to reduce the use of amoxicillin/clavulanate significantly, and that lincosamides (clindamycin) and aminopenicillins could be used in its place for many indications.

The unavailability of sulphonamides for the treatment of companion animals has led to a decline in their use. Similarly, narrow spectrum penicillins are only available as human preparations, and according to the veterinary cascade regulations should not be used. This creates a problem in relation to the rational use of antibiotics with the aim of reducing antibiotic resistance.

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3 Multiresistant bacteria in companion animals

Within the last decade, a number of multiresistant bacteria have emerged in companion animals. The most important of these bacteria are extended spectrum beta-lactamase (ESBL) producing *Escherichia coli* and methicillin resistant *Staphylococcus pseudintermedius* (MRSP) (1). Both are resistant to beta-lactams (penicillins and cephalosporins), and frequently resistant to other antibiotic groups. They represent a serious threat to animal health due to the increased risk of treatment failure. These bacteria are recognised nosocomial pathogens, and can be spread between patients via contamination of the hospital environment, via invasive procedures and via veterinary personnel. From an owner's perspective these pathogens also represent an economic burden due to longer treatment times, extended hospitalisations and increased expenses for diagnostics. This chapter summarises the most important microbiological and clinical aspects of MRSP and ESBL-producing *E. coli*, focusing on diagnostics and treatment. Methicillin resistant *S. aureus* (MRSA) is not covered in this chapter, since it is rarely involved in companion animal infections in Denmark.

3.1 Definition of MRSP

MRSP is a *S. pseudintermedius* strain which has acquired the methicillin resistance gene *mecA*. This is the same gene found in MRSA. MRSP was first identified in Europe in 2006, and since then a specific clone (termed ST71) has spread rapidly and internationally (2). This clone, in addition to beta-lactam resistance, is typically also resistant to lincosamides, fluoroquinolones, sulpha/trimethoprim, macrolides, tetracyclines and gentamicin. In 2016-2017 the prevalence of MRSP in clinical isolates from Danish dogs was approximately 5% (Table 1, Chapter 1.1) which is markedly lower than that seen in many other European countries. Isolates from Danish dogs are unusual in that they often belong to clone ST258, which is characterised by being less multi-resistant than ST71 (3).

3.2 Diagnosis of MRSP

Resistance to oxacillin in *S. pseudintermedius* is characteristic of MRSP. Oxacillin should always be included in sensitivity testing of *S. pseudintermedius*. Absolute confirmation of MRSP requires identification of the *mecA* gene using PCR or of the protein PBP2a using a latex agglutination test. Until this confirmation is available, all oxacillin-resistant strains should be considered resistant to all beta-lactams, regardless of any apparent susceptibility to penicillins and cephalosporins in vitro.

3.3 Treatment of MRSP infections

Treatment of MRSP is complicated and should be customised to the individual patient based on factors such as type of infection, the patient's health status and the antibiotic resistance profile. MRSP is most commonly seen in skin and wound infections in dogs, and to a lesser degree in cats. **Whenever possible, employ treatment modalities which avoid use of antibiotics such as wound drainage and debridement, along with topical antiseptics.** Topical antiseptics containing chlorhexidine or benzoyl peroxide are very effective against superficial folliculitis. When antimicrobial treatment cannot be avoided, local application of e.g. fusidic acid is preferred to systemic use for localised skin infections. Systemic antibiotic therapy, when needed, should always be based on sensitivity testing and the cascade system described in Chapter 1.7.

The few antibiotics which can be effective against multiresistant bacterial strains may have significant side-effects, poor pharmacological profiles, or be essential to human medicine. Chloramphenicol, rifampicin and nitrofurantoin are examples of antibiotics to which a number of MRSP strains are sensitive. Chloramphenicol requires eight-hourly dosing, can occasionally cause bone marrow suppression and is difficult to source. Resistance to rifampicin is unusual in MRSP isolates but is readily acquired during treatment. For this reason, rifampicin should always be used in combination with another antibiotic, but finding another to which MRSP is sensitive can be difficult. Rifampicin is hepatotoxic and its use requires frequent monitoring of liver function. Nitrofurantoin is a useful antibiotic for uncomplicated urinary tract infections, but is unsuited to the treatment of other infections. Nitrofurantoin can produce gastrointestinal side-effects in dogs. Other products effective against MRSP are not licensed for veterinary use (e.g. amikacin, vancomycin and linezolid). Due to their status as drugs of last resort in human medicine their use should only be considered in rare instances (see Chapter 1.7).

Dogs and cats infected with MRSP must be isolated as far as possible from other hospital patients and from other animals in their household. The owner should inform veterinarians at subsequent consultations that their animal has previously been treated for MRSP. Further information on the control, prevention and treatment of MRSP has recently been published by the World Association for Veterinary Dermatology (WAVD) (4). See Chapter 6.1.5 for details on management of patients with skin infections caused by MRSP.

3.4 Definition of ESBL

ESBL stands for extended-spectrum beta-lactamase. This term covers enzymes produced by Gram-negative bacteria that can inactivate a range of beta-lactam antibiotics, and which can be inhibited by beta-lactamase inhibitors such as clavulanate. In companion animals, these enzymes are primarily associated with *E. coli*, but can also be produced by other Gram-negative pathogens such as *Proteus*, *Salmonella* and *Klebsiella*. The over 200 types of ESBL are divided into three main classes: CTX-M, SHV and TEM. All three classes have been reported in animals. CTX-M-15 is the most common ESBL form seen in humans and companion animals in Denmark. Isolates producing CTX-M-15 display a characteristic multi-resistance pattern which, in addition to beta-lactams, includes fluoroquinolones and sulpha/trimethoprim, amongst others.

In the period 2016-2017, approximately 3% of *E. coli* isolates from Danish dogs and cats were ESBL-producing, based on resistance to the 3rd generation cephalosporin, cefpodoxime (Table 2, Chapter 1.1).

3.5 Diagnosing ESBL

ESBL-producing bacteria can be difficult to identify because their *in vitro* activity against different cephalosporins is dependent on the ESBL-type. **Presence of ESBL should be suspected if Enterobacteriaceae show resistance to at least one of the third-generation cephalosporins recommended for demonstration of ESBL (cefpodoxime, ceftazidime and cefotaxime).** Final confirmation of ESBL requires demonstration of typical ESBL genes, for example with PCR. Based on international guidelines, isolates confirmed by PCR as ESBL-producers should be considered resistant to all cephalosporins, regardless of the results of sensitivity testing. If an isolate is not confirmed as

ESBL-producing by PCR, sensitivity test results should be interpreted individually for each beta-lactam antibiotic in the test panel.

3.6 Treatment of ESBL infections

ESBL-producing *E. coli* is frequently isolated from the urinary tract. The therapeutic challenge lies in the regular resistance of ESBL-producers to beta-lactams, sulpha/trimethoprim and fluoroquinolones, which are amongst the most commonly used antibiotics for urinary tract infections. The choice of antibiotic should be guided by sensitivity testing and the type of infection. If the isolate is resistant to all other veterinary licensed antibiotics than amoxicillin/clavulanate, then this antibiotic should be used at the highest possible dose (25 mg/kg PO TID) to maximise its clinical effect. Certain isolates are also sensitive to tetracyclines. In these cases, use of doxycycline can be considered even though this antibiotic is not well-suited to treatment of urinary tract infections, being primarily excreted via the intestines.

In situations where the isolate is resistant to amoxicillin/clavulanate, sulpha/trimethoprim, fluoroquinolones and tetracyclines, the clinician will be forced to use antibiotics which are not licensed for use in companion animals. Nitrofurantoin is extremely effective against ESBL-producing *E. coli*, but is best-suited to treating uncomplicated urinary tract infections due to its short plasma half-life and potential gastrointestinal side-effects. Alternative therapeutic options are chloramphenicol (which can cause bone marrow suppression) and the aminoglycosides gentamicin and amikacin (which are potentially nephrotoxic and should be avoided in patients with reduced renal function). It should be noted that while ESBL-producing *E. coli* isolates are generally sensitive to the carbapenems (e.g. imipenem), these products are not veterinary licensed, and use requires careful consideration as previously discussed (see Chapter 1.7)

3.7 Societal impact

The presence of ESBL-producing *E. coli* and MRSP in small animal hospitals has societal significance due to the risk of infecting owners and veterinarians. These multiresistant bacteria are still relatively rare in Denmark compared with some other countries (5), but it is nonetheless important to limit their advance through the use of increased microbiological monitoring and rational antibiotic use. Third-generation cephalosporins and fluoroquinolones are known to select for MRSP and ESBL-producing *E. coli*, and their use should be limited. **Use of laboratories with experience with these resistant strains, and the facilities for their detection, is recommended (6). This will ensure timely detection of multiresistant bacteria and appropriate guidance on treatment and prevention for clinicians.** In Denmark, specialist advice regarding the development and spread of antibiotic resistance in companion animals can be obtained from the Department of Veterinary and Animal Sciences (www.sundvetdiagnostik.ku.dk).

Because information regarding zoonotic transfer of MRSP and ESBL-producing *E. coli* from companion animals to humans is limited (7), there are no national guidelines to assist veterinarians in advising owners on measures to reduce this risk. Any risk assessment must therefore be based on an individual judgement of the situation, including assessment of the owner's immune status. Veterinarians must inform owners of the potential risks and encourage them in case of illness to inform the relevant health services that their household contains an animal carrying multiresistant bacteria.

International guidelines on the prevention and control of nosocomial infections and the spread of bacteria in veterinary practices are available online at the Danish Veterinary Association's website (www.ddd.dk/sektioner/familiedyr/infektionskontrol).

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4 Recommendations for performing and interpreting microbiological tests

This chapter provides basic information about bacterial culture and sensitivity testing in companion animal practice. The diagnostic process can be divided into two phases, sample handling and data handling. The clinician plays a vital role in both phases. Firstly, the veterinarian should be aware of when microbial culture is indicated, what samples should be taken, how sampling should be performed and how these samples should be transported to the laboratory. Subsequently, the veterinarian must have sufficient background knowledge to evaluate the quality of the laboratory report, interpret the resistance data, and select the right antibiotic for successful treatment. In both phases a close working relationship between the veterinarian and the laboratory is key to ensuring the quality of the diagnostic process and ultimately guaranteeing the best possible treatment for the patient.

4.1 Indications for bacterial culture

Performing bacterial culture is always a good idea, but it is particularly important in the following situations:

1. A complicated or life-threatening infection is suspected
2. The patient fails to respond to the initial treatment
3. The infection is recurrent or refractory
4. The patient is immunosuppressed
5. There is a need to monitor an established infection
6. Infection with multi-resistant bacteria is suspected
7. Any urinary tract infection or pyoderma which requires systemic antibiotic therapy

With regard to point 2 above, it is important that the clinician recommends and encourages regular follow-ups of their patients. In addition, the owner should be instructed in lesion identification and clinical signs, in order to avoid prolonged treatment courses in the absence of clinical improvement. As in the first version of the guidelines, **bacterial culture is recommended for all urinary tract infection or pyoderma which requires systemic antibiotic therapy** (point 7, above). These infections are the most common reasons for antibiotic dispensing in companion animal practice and are frequently associated with bacterial species which can have clinically significant antibiotic resistance, such as MRSP and ESBL-producing *E. coli* (see Chapter 3). Pyoderma, in particular, usually requires prolonged treatment, and treatment failures can have negative consequences for both the patient's welfare and the owner's finances. Empirical antibiotic treatment, pending laboratory results, will always require individual assessment by the clinician based on the type of infection and the condition of the patient.

For the vast majority of infections, aerobic culture is sufficient. Anaerobic culture may be indicated in soft-tissue infections where the presence of anaerobic bacteria is suspected based on clinical signs (e.g. purulent infection or gas production) or in cases of abdominal sepsis. Anaerobic culture results often have dubious clinical relevance, since these infections generally respond to appropriate antibiotics (penicillins, clindamycin or metronidazole) and because antibiotic resistance is not a great problem in anaerobic bacteria. Selective culture can be used to demonstrate certain pathogens in

non-sterile samples. For example, faecal samples from patients with diarrhoea can be analysed with selective procedures in order to demonstrate *Salmonella*, *Campylobacter* and *Clostridium difficile*.

4.2 Sampling and transport

As well as selecting the most appropriate sample type for any given infection, it is important to make sure that samples are obtained with a suitable technique. Samples should be taken from areas where the infection is active, and contamination from commensal flora should be avoided as far as possible. Particular attention should be given to sterile sampling techniques when contamination could adversely affect interpretation of the results (e.g. urine, blood and cerebrospinal fluid samples). Table 1 details the appropriate sample types and sampling techniques for diagnosing the most common bacterial infections in companion animal practice.

Most bacterial pathogens of companion animals are not adversely affected by the conditions under sample transport. Use of tubes containing transport medium is recommended for culture swabs which are to be sent by standard post or which for other reasons cannot be cultured within 24 hours of sampling. Samples for aerobic culture may be refrigerated in transport medium (e.g. Amies or Stuarts medium) if they cannot be immediately sent to the laboratory. Samples for anaerobic culture should never be refrigerated, and must be collected and sent using special transport tubes.

Urine samples require quantitative microbiology in order to estimate the bacterial load. For this reason, urine must be chilled immediately after collection and dispatched to the laboratory using refrigerated transport or boric acid tubes as soon as possible, so as to avoid potential changes in bacterial concentrations. If the duration of transport for urine samples without added preservatives exceeds 24 hours, international guidelines suggest that culture results should be interpreted with caution and that ideally the sampling process should be repeated (1). This problem can be partially overcome if urine is collected by cystocentesis, because samples obtained in this manner should either be sterile or considerably exceed the cut-off value for categorising the urine as infected ($>10^3$ CFU/ml). Culture media designed for in-clinic use are a good alternative for transport of urine samples. Examples of these products are described in Chapter 6.3.1, and they can be sent before or after incubation at 37°C. Waiting until after incubation can be particularly recommended, since it avoids unnecessary laboratory fees for sterile samples.

The diagnostic laboratory will normally supply the veterinarian with a submission form to be completed and sent with the sample. These forms should be completed thoroughly, because they provide the laboratory with important information regarding the patient and the sample. A submission form should contain the following information:

1. Name and contact information for the submitting clinician
5. Time of sampling
6. Clinical diagnosis and relevant history
2. Patient's name or similar identification
3. Patient's species, age and sex
4. Sample type and where on the body it was obtained
7. Cytological findings (if relevant)
8. Information on current or recent antibiotic therapy
9. Specific requests regarding culture

Table 1. Sample types and collection techniques, which are recommended for the commonest bacterial infections in companion animals. In most cases, commercial transport media consisting of Amies or Stuarts medium can be used.

System	Problem	Sampling technique and transport
	Wound	<ul style="list-style-type: none"> ➤ Cleaning of surface is unnecessary unless there is major contamination. ➤ Use sterile culture swab and place into transport medium. If a drain is removed, the tip can be sent for culture along with the swab in the culture medium. ➤ Pus can be aspirated with a syringe and needle and transferred to a sterile culture swab.
Skin	Pustule	<ul style="list-style-type: none"> ➤ Surface disinfection is unnecessary. ➤ Remove hair locally with sterile scissors. ➤ Puncture pustule with a sterile needle and transfer pus from the needle to the sterile culture swab. ➤ Place culture swab in transport medium.
	Crust	<ul style="list-style-type: none"> ➤ Surface disinfection is unnecessary. ➤ Lift edge of crust with sterile forceps and swab underlying skin with sterile culture swab. ➤ Place culture swab in transport medium.
	Epidermal collarette	<ul style="list-style-type: none"> ➤ Surface disinfection is unnecessary. ➤ Remove hair locally with sterile scissors. ➤ Swab the inner surface of collarette with sterile culture swab. ➤ Place culture swab in transport medium.
	Generalised pyoderma or focal deep pyoderma (e.g. closed furuncle)	<p>Obtain skin biopsy:</p> <ul style="list-style-type: none"> ➤ Anaesthesia or deep sedation. ➤ Remove hair locally with sterile scissors. ➤ Gently disinfect the skin surface with 70% ethanol – saturation of the skin should be avoided. ➤ Take biopsy using a punch with a diameter of 3-4mm. ➤ Place biopsy in sterile container moistened with one drop of sterile saline, and refrigerate until cultured. ➤ Close biopsy site with staple or suture.
External ear canal	Exudate or pus	<ul style="list-style-type: none"> ➤ Swab ear canal (horizontal canal preferred) with sterile culture swab. ➤ Place culture swab in transport medium.
Middle ear	Exudate or pus	<ul style="list-style-type: none"> ➤ Carefully perform myringotomy in the caudoventral aspect of the tympanic membrane (a stiff cat urinary catheter coupled to a syringe is suitable for this). ➤ Middle ear contents are gently aspirated and transferred to sterile culture swabs before placing in transport medium.
Urinary tract	Urine	<ul style="list-style-type: none"> ➤ Ideally collect via cystocentesis and send immediately after collection in a sterile container or on a dipslide (see Chapters 4.2 and 6.3.1). Urine should be refrigerated if sent to an external laboratory. ➤ Samples should be refrigerated during transport, or alternatively placed in boric acid tubes, to avoid false positives and negatives. This is particularly important

		<p>for samples not collected by cystocentesis, or if the transport time is expected to exceed 24 hours.</p> <ul style="list-style-type: none"> ➤ If cultured in-clinic, urine should be incubated at 37°C as soon as possible, and within 4 hours of sampling. ➤ Samples may also be sent to an external laboratory in the form of cultured colonies on agar (e.g. dipslide or chromogenic agar).
Reproductive organs	Vaginitis Endometritis Pyometra	<ul style="list-style-type: none"> ➤ Samples should be obtained from the cranial vagina or uterus, using a vaginoscope, proctoscope or endoscopic biopsy port to minimise contamination from normal vaginal flora.
	Acute metritis	<ul style="list-style-type: none"> ➤ Samples for bacterial culture should be obtained from the cranial vagina or uterus, using a vaginoscope, proctoscope or endoscopic biopsy port.
	Endometritis/ pyometra	<ul style="list-style-type: none"> ➤ Uterine washes or biopsies can be obtained for culture using a transcervical catheter. Note that pyometra can be induced by the sampling procedure!
	Mastitis	<ul style="list-style-type: none"> ➤ After thorough cleaning and disinfection of the gland surface and teat, samples should be milked into a sterile container under aseptic conditions.
	Orchitis	<ul style="list-style-type: none"> ➤ Second fraction of ejaculate and/or urine samples taken by cystocentesis should be placed in sterile containers. ➤ Consider testing for brucellosis.
	Prostatitis	<ul style="list-style-type: none"> ➤ Ideally, fine-needle aspirates or biopsies of the prostate should be transferred to sterile containers for culture. ➤ Alternatively, collect (1) the mid-portion of third fraction of ejaculate, (2) the mid-fraction collected by rectal prostatic massage, and/or (3) urine samples taken by cystocentesis, and place sample material in a sterile container.
Respiratory tract	Upper airway	<ul style="list-style-type: none"> ➤ Swabs and biopsies are best obtained via rhinoscopy, avoiding contamination from the external nares. ➤ Place culture swab or biopsies in transport medium.
	Lower airway	<ul style="list-style-type: none"> ➤ Samples are best obtained via bronchoscopy-guided bronchoalveolar lavage with sterile saline - alternatively take brush samples via bronchoscopy. ➤ Transfer retrieved fluid to transport medium. ➤ <i>Mycoplasma</i> require specific media - contact laboratory for requirements before sampling.
Gastrointestinal tract	Enteritis	<ul style="list-style-type: none"> ➤ Faecal samples or rectal swabs should be placed in sterile containers or transport medium, respectively.
Other localisations, including systemic infections	Vector-borne bacterial infections, meningitis, sepsis, arthritis, etc.	<ul style="list-style-type: none"> ➤ Blood should be collected in EDTA tubes. Other fluids should be collected into sterile containers or syringes (contact laboratory for specific requirements).

4.3 Culture results and interpretation

Bacterial culture should only be performed at laboratories with trained staff, suitable facilities and proper biosecurity measures including containment and waste disposal. Regardless of whether or not veterinary clinics have laboratory facilities, veterinarians should have some familiarity with the principles and techniques of bacterial culture in order to avoid mistakes in sampling (e.g. taking contaminated samples) or data analysis (e.g. use of antibiotics against contaminants instead of pathogens). This understanding can also assist an evaluation of the quality of services supplied by diagnostic laboratories.

Culture of the most frequently found bacterial pathogens of companion animals does not require special culture media. Primary culture is usually best performed on blood agar plates, since haemolytic pathogens such as *E. coli*, *S. pseudintermedius* or *Streptococcus canis* can be readily identified. For certain samples, such as urine, primary culture should be performed using selective indicator media such as MacConkey agar in order to more readily demonstrate *E. coli* and other Enterobacteriaceae. The entire process for bacterial culture and identification requires at least two days; primary culture on the first day, and identification and sensitivity testing on the second. Additional time may be required if there is a mixed infection, which can render isolation of single colonies from the primary culture problematic. Images and more detailed information about colony morphology, phenotypic tests etc. can be found on the Internet, including in the online atlas developed by the Department of Veterinary and Animal Sciences, University of Copenhagen (<http://atlas.sund.ku.dk/microatlas>).

Urine samples should be analysed quantitatively as described in Chapter 6.3.1. Certain infections can result in culture of multiple bacterial species. This is often the case for wound infections, otitis externa and, to a lesser extent, urinary tract infections. When this happens the clinical relevance of each organism should be decided based on its pathogenicity. For example, enterococci usually disappear from mixed urinary tract infections once the primary pathogen, such as *E. coli*, is successfully treated. The same is true for *Corynebacterium auriscanis*, which is often isolated in otitis externa but seldom found alone. Focusing antibiotic therapy against the bacterial species suspected to be the primary pathogen is a logical strategy, since antibiotics effective against multiple isolates may not exist. A good diagnostic service should therefore strive to identify which isolates are most likely to be pathogenic. Reporting accurate but clinically irrelevant results can be just as counterproductive as reporting inaccurate results, and have similarly serious consequences for patient care.

4.4 Performing and interpreting sensitivity tests

Sensitivity tests are an important part of the diagnostic workup for making a rational antibiotic selection. Bacteria may be classified as sensitive, intermediately sensitive or resistant based on standard breakpoint values, which are specific to the antibiotic, bacteria and host. **Sensitive (S)** bacteria are inhibited at antibiotic concentrations achieved in the plasma with correct dosing. **Intermediately sensitive (I)** isolates may be inhibited if the antibiotic is concentrated at the site of infection or can be administered at higher doses without side-effects. **Resistant (R)** bacteria are not inhibited by antibiotic concentrations achieved with standard dosing regimens. It should be emphasised that these categories only apply to systemic therapy. Topical therapy (e.g. in otitis externa) can result in successful treatment of apparently resistant isolates because the local antibiotic concentration far exceeds that which could be achieved systemically.

The most widespread sensitivity tests are the disc diffusion and dilution methods. Although the dilution method is more precise, comparable results can be achieved with disc diffusion provided it is performed and interpreted according to recognised standards, for example those published by the Clinical Laboratory Standards Institute (2). Assembly of the antibiotic panel for sensitivity testing should take account of the bacterial species to be tested and the possibility of demonstrating clinically-relevant antibiotic resistance. Some antibiotics are only relevant for specific bacterial species. For example, penicillins and macrolides (e.g. erythromycin) are only effective against Gram-positive bacteria, while oxacillin is only relevant for demonstrating methicillin-resistant staphylococci. Inclusion of amoxicillin/clavulanate, ceftazidime and one or more third-generation cephalosporins (cefepime, ceftazidime or ceftazidime) is recommended for demonstrating ESBL-producing *E. coli*. A list of antibiotics, which should be considered for carrying out sensitivity tests of bacteria from companion animals, is shown in Table 2.

Interpretation of sensitivity results is not as simple as it might appear. Certain antibiotics are used as indicators of sensitivity to chemically related antibiotics in the same class or subclass. **A familiarity with antibiotic classification and an understanding of why certain antibiotics are included in the sensitivity test despite not being used in practice is therefore vital** (see Table 2). The interpretation of results involving erythromycin and clindamycin deserves discussion in its own right, given the status of clindamycin as the empirical therapy of choice for pyoderma in Denmark. Even though these two antibiotics have different chemical structures and belong to different classes (macrolides and lincosamides, respectively) resistance is encoded by the same gene, *ermB*. In some cases, expression of *ermB* can be induced by the presence of macrolides but not by lincosamides. A special disc diffusion test (D test) should be utilised to demonstrate inducible resistance to clindamycin. In the absence of this information, use of clindamycin should be avoided whenever an isolate is reported as resistant to erythromycin.

In addition to a diagnostic role, sensitivity testing can generate data for the monitoring of bacterial resistance. Clinicians can then adjust their choice of empirical therapies based on local resistance profiles. Raw data collected over a longer period can identify increases or decreases in resistance, with one important caveat: sensitivity testing in general practice tends to be restricted to more difficult cases, which are often associated with resistant bacteria due to prior treatment. This results in both an overestimation of resistance levels and difficulties in extrapolating these resistance data to cases of uncomplicated infections without prior antibiotic therapy. Bacterial culture of a larger number of uncomplicated or first-time infections will therefore improve monitoring quality and give a more realistic picture of resistance development generally, enabling better guidelines for empirical therapy. This is one of the reasons why all cases of urinary tract infection or pyoderma, which require systemic antibiotic treatment, should undergo bacterial culture.

National data regarding resistance development is extremely valuable for developing a sensible antibiotic policy. Currently, only the Department of Veterinary and Animals Sciences at the University of Copenhagen has a monitoring programme for resistance in bacteria from companion animal practice in Denmark (see Chapter 1.1, Tables 1 and 2).

Table 2. Antibiotic-specific guide to interpretation of sensitivity testing.

Antibiotic	Comment
Amikacin	Important antibiotic used in human hospitals. Aminoglycoside resistance is drug-specific. Resistance to amikacin is less common than to gentamicin.
Ampicillin	Used to predict sensitivity to aminopenicillins including amoxicillin. Inactivated by most beta-lactamases. The 60-80% of staphylococci which produce beta-lactamase are resistant to penicillin and aminopenicillins, but sensitive to first-generation cephalosporins (cefalexin, cefadroxil and cefazolin) and amoxicillin/clavulanate.
Amoxicillin/ clavulanate	Important in demonstrating ESBL-producing bacteria, which are sensitive to this combination but resistant to most other beta-lactams.
Cefalothin	Predicts sensitivity to other first-generation cephalosporins (cefalexin, cefadroxil, cefazolin) even though cross-resistance is not 100%.
Cefoxitin	Used to demonstrate MRSA and ESBL-producing bacteria. Staphylococci resistant to cefoxitin should be considered methicillin-resistant, i.e.: resistant to all beta-lactams. Can be used to demonstrate MRSP although oxacillin is preferred. ESBL-producing <i>E. coli</i> are sensitive unless they also have another beta-lactamase such as CMY-2.
Third-generation cephalosporins	Cefpodoxime, ceftazidime and/or cefotaxime are all suitable for demonstration of ESBL-producing bacteria. Cefovecin is the only third-generation cephalosporin licensed for use in dogs and cats in Denmark.
Clindamycin	Used to predict sensitivity to other lincosamides (e.g. lincomycin).
Chloramphenicol	Inclusion in test panel is recommended because it is often one of the few antibiotics effective against MRSP and ESBL-producing <i>E. coli</i> .
Doxycycline	Indicates resistance to other tetracyclines, but has better pharmacologic properties. Staphylococci, which show intermediate sensitivity to tetracycline, can be sensitive to doxycycline.
Erythromycin	Indicates resistance to lincosamides (lincomycin and clindamycin) and newer macrolides (azithromycin and clarithromycin). Can be used to demonstrate inducible resistance to lincosamides via the D-test (see Chapter 4.4).
Fusidic acid	Breakpoint is based on human systemic therapy: clinical relevance to companion animals is dubious, since fusidic acid is used topically in these species.
Fluoroquinolones	Even though extensive cross-resistance occurs for the different fluoroquinolones, drug-specific breakpoints exist for enrofloxacin, marbofloxacin, difloxacin, orbifloxacin and pradofloxacin.
Gentamicin	Important antibiotic used in human hospitals. Aminoglycoside resistance is often drug-specific. Resistance to gentamicin is more widespread than to amikacin.
Imipenem	Treatment of last resort for Gram-negative infections in humans. Use of carbapenems such as imipenem in companion animals cannot be justified unless stringent requirements are met (see Chapter 1.7).
Nitrofurantoin	Used exclusively for urinary tract infections, where it is a good second choice for treatment of uncomplicated cystitis caused by MRSP or ESBL-producing <i>E. coli</i> .
Oxacillin	Used solely to demonstrate methicillin resistance in staphylococci. The most effective drug for demonstrating MRSP.
Rifampicin	No specific breakpoints exist for companion animals, but rifampicin should be included in test panels, since it is often effective against MRSP. Should only be used in combination with other antibiotics because resistance rapidly develops during treatment.
Sulfamethoxazole/ trimethoprim	Can predict general sensitivity to sulphonamides in combination with trimethoprim.
Vancomycin	Treatment of last resort for Gram-positive infections in humans. Use of glycopeptides such as vancomycin in companion animals cannot be justified unless stringent requirements are met (see Chapter 1.7).

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5 Perioperative antibiotic therapy

5.1 Risk assessment for surgical site infection

Surgical site infections (SSI) are common in humans. The prevalence in dogs and cats is less well documented, but the average rate of SSI in small animal surgery is around 3-5%. The incidence of complications is affected by both wound classification and the type of surgery (1,2,3,4,5).

Occurrence of SSI increases the risk of poor outcomes, the need for reoperation, side-effects due to additional medical treatment, and increased risk of death. In humans the increasing prevalence of multiresistant bacteria is closely linked to the prevalence of SSI, since without effective preventive measures these bacteria can spread in the hospital environment and between patients. The same is probably true for dogs and cats. There appear to be four key factors which influence development of SSI: 1) level of wound contamination, 2) surgery time, 3) host susceptibility and 4) presence of microorganisms. Adhering to the principles for asepsis, atraumatic surgery, tissue handling and hygiene, as well as monitoring the incidence of wound infections, are clearly important.

Level of wound contamination

Surgical wounds can be classified according to the level of contamination in order to assess their infection risk (see Table 1).

Surgery time

The duration of surgery together with the total anaesthesia time is one of the most important factors in the development of SSI. Clean orthopaedic procedures exceeding 90 minutes have an increased prevalence of SSI (2,6). Experience from clinical practice suggests this also holds true for soft-tissue procedures (1).

Host susceptibility

A number of patient factors have been described as indicative of SSI risk. These include age, clinical factors (such as obesity) and paraclinical factors (such as blood glucose and serum protein levels, and elevated infection markers). The American Society of Anesthesiologists (ASA) classification scheme (3) permits a uniform evaluation of patients' pre-anaesthetic physical status and provides a simple, validated method to determine the risk of intra- and postoperative cardiopulmonary complications. ASA classification has subsequently been shown to be an indicator of SSI development in humans, and it is assumed to function similarly in dogs and cats (Table 2).

Table 1. Wound classification and associated infection risk

Wound type	Description	Examples	Infection risk
Clean	<ul style="list-style-type: none"> ➢ Elective, non-emergency, non-traumatic ➢ No acute inflammation ➢ No break in aseptic technique ➢ Respiratory, gastrointestinal, biliary and genitourinary tracts not entered (excluding routine sterilisation operations) ➢ Primary closure (± active drainage) 	<ul style="list-style-type: none"> ➢ Explorative laparotomy ➢ Castration ➢ Ovariectomy/ ovariohysterectomy ➢ Orthopaedic operations ➢ Salivary mucocoele 	2.0-4.8%
Clean-contaminated	<ul style="list-style-type: none"> ➢ Elective entry into respiratory, gastrointestinal, biliary or 	<ul style="list-style-type: none"> ➢ Enterotomy ➢ Intestinal anastomosis 	3.5-5.0%

	<ul style="list-style-type: none"> genitourinary tracts with minimal spillage and without evidence of infected urine, bile or secretions ➤ Minor break in technique ➤ Emergency operations that are otherwise clean 	<ul style="list-style-type: none"> ➤ Cystotomy ➤ Cholecystectomy ➤ Pyometra ➤ Emergency operations are by definition <i>at least</i> clean-contaminated 	
Contaminated	<ul style="list-style-type: none"> ➤ Surgery of respiratory, gastrointestinal, biliary or genitourinary tracts with gross spillage or evidence of infected urine, bile or secretions ➤ Major break in aseptic technique ➤ Acute, non-purulent inflammation ➤ Traumatic wounds <4 hours old ➤ Chronic open wounds for grafting or covering 	<ul style="list-style-type: none"> ➤ Enterotomy ➤ Intestinal anastomosis ➤ Cystotomy ➤ Cholecystectomy ➤ Pyometra with leakage 	4.6-12%
Dirty	<ul style="list-style-type: none"> ➤ Pre-existing perforation of respiratory, gastrointestinal, biliary or genitourinary tracts with minimal spillage and without evidence of infected urine, bile or secretions ➤ Purulent infections ➤ Traumatic wounds >4 hours old ➤ Wounds with necrosis, foreign material or faecal contamination 	<ul style="list-style-type: none"> ➤ Leakage from perforated viscera ➤ Infected operation sites ➤ Septic peritonitis ➤ Abscesses ➤ Open fractures 	6.7-18%

5.2 Prevention and management of infections

SSI cannot be completely prevented, but strategies such as atraumatic surgical technique, aseptic operating room procedures, identification of at-risk patients, postoperative protection of surgical incisions and perioperative use of antibiotics in a limited and focused fashion are the most effective and practical methods to reduce SSI prevalence.

Atraumatic surgical technique

Atraumatic tissue handling, in order to prevent ischaemia and subsequent necrosis, is important for good wound healing. Preservation of vascularity, limited use of retractors, prevention of tissue desiccation, careful haemostasis and good tissue approximation are all ways to reduce the risk of SSI.

Table 2. ASA classification

ASA classification	Description	Examples
1	Healthy individuals without known disease.	Castration, sterilisation, uncomplicated hernia closure, patellar luxation, cruciate ligament rupture.
2	Localised disease or mild systemic illness (afebrile patients which are clinically unaffected).	Deformities, uncomplicated diabetes mellitus, skin tumours, trauma without hypovolaemia, mild infections without fever.
3	Serious systemic illness (febrile patients with clinical signs of disease).	Fever, anaemia, complicated diabetes mellitus, diabetic ketoacidosis, cardiac murmurs, moderate trauma, pneumonia.
4	Serious, life-threatening illness.	Severe trauma with hypovolaemia, cardiac failure, renal failure, hepatic failure.
5	Moribund, not expected to survive >24 hours without surgical intervention.	Polytrauma, multi-organ failure, terminal neoplasia, Addisonian crisis, gastric dilation-volvulus.

Aseptic operating room procedures

Behaviour in the operating room has a major impact on both the prevalence and the prevention of SSI. Patient preparation and dental procedures should not be performed in the operating room. More specifically, attention should be paid to: 1) minimising the number of personnel in the room; 2) good ventilation; 3) clipping of patient hair immediately prior to the operation; 4) cleaning and disinfection of the skin with soap, antiseptic (chlorhexidine) and alcohol; 5) use of waterproof drapes; 6) hand-disinfection using mild soap and alcohol, with the use of a soft sponge instead of a brush. Within the operation room, personnel should wear surgical clothing and hats which completely cover the hair. Surgical clothing should have close-fitting, elasticated openings at the arms, waist and legs. Surgeons and personnel working within one metre of the surgical area should also wear a facemask.

Postoperative protection of the surgical incision

Whenever practical, protection of the incision for the first 24-48 hours with a suitable bandage is recommended. Wound coverings should permit gaseous exchange without trapping excessive moisture around the incision. Dressing changes and all wound care should only be performed after general hand disinfection and with the use of gloves.

Identification of at-risk patients

The ASA and wound classification schemes can be combined to identify a patient's risk of developing SSI. Patients which have already been hospitalised for at least four days and patients under treatment with fluoroquinolones have an increased risk of colonisation with multiresistant *E. coli* which can cause SSI (REF 4). Hospitalisation should therefore be considered an additional risk factor for SSI.

Perioperative use of antibiotics

Perioperative antibiotic prophylaxis cannot replace proper aseptic surgical technique. It should be used based on an individual evaluation of the patient's status (ASA classification) and expected surgery (wound classification). Perioperative antibiotics should be given immediately prior to surgery and normally are not continued beyond closure of the surgical incision. The initial dose should ideally be given intravenously 30-60 minutes **before** incising the skin and repeated at intervals of twice the plasma half-life. For ampicillin, this means redosing every 2 hours, and for cephazolin, every 4 hours.

As a general rule:

- **Low-risk patients** ASA 1-2 with clean procedures, and afebrile ASA 3 patients undergoing a clean or clean-contaminated procedure **do not require** antibiotic prophylaxis.
- **High-risk patients** ASA 3 with contaminated or infected wounds, patients with purulent infections, febrile patients and ASA 4-5 **should** receive antibiotics perioperatively.
- **Patients in which SSI would be catastrophic** (e.g. orthopaedic implantation, CNS surgery) **should** receive antibiotics perioperatively.

Choice of antibiotic

For perioperative use, the ideal preparation should have the following attributes:

1. Can be given intravenously to ensure a high plasma concentration
2. Effective against pathogens typically involved in SSI
3. Does not encourage the development of resistance
4. Has few or no side-effects

Table 3. Rational perioperative antibiotic selection based on likely sources of infection.

Source	Typical microorganisms	First-choice antibiotics
Skin flora	Staphylococci, <i>Pasteurella</i> spp.	Cefazolin (20 mg/kg) given IV preoperatively and repeated at 4 hour intervals until completion of surgery.
Gastrointestinal tract or uterus	All enteric bacteria, including <i>E. coli</i> , enterococci, and anaerobes.	Ampicillin (20 mg/kg) given IV preoperatively and repeated at 2 hour intervals until completion of surgery. In high-risk, critical patients (ASA-4 or 5), or with spillage of intestinal contents or pus into the abdomen, ampicillin or penicillin G can be combined with enrofloxacin (5 mg/kg) IV to provide enhanced cover against Gram-negative bacteria.

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6 Organ and system specific guidelines

6.1 The skin

6.1.1 Overview

Aetiology, prevalence and definitions

Bacterial skin infection (pyoderma) is common in companion animals. It has been estimated that around 20% of dogs and cats presenting in general practice have a skin condition, and that about 25% of these are due to bacterial infections (1). Generalised pyoderma occurs commonly in dogs and typically involves the hair follicles (2). Canine pyoderma is usually secondary to an underlying primary condition, especially allergies (3). In cats, generalised pyoderma is less common and usually due to the patient being immunocompromised, even though it can also be seen with allergies. Subcutaneous abscesses following bite wounds occur frequently in cats (3). Over 90% of bacterial pyodermas in dogs are due to *S. pseudintermedius* (4). *S. pseudintermedius* (in dogs and cats) and *S. aureus* (primarily in cats) are considered commensal organisms, and normally are found predominantly on the oral, nasal and anal mucosa (3, 5). Other bacteria which can be involved in pyoderma, especially in dogs, include *S. aureus*, *S. schleiferi*, coagulase-negative staphylococci, *Streptococcus canis* (5, 6), and Gram-negative bacteria such as *E. coli*, *Proteus mirabilis* and *Pseudomonas* spp. (3).

Clinically, skin infections are categorised by their depth (Figure 1), as this determines the choice of antimicrobial therapy. The most common type of canine pyoderma is superficial bacterial folliculitis (7).

Diagnosis, culture and sensitivity testing

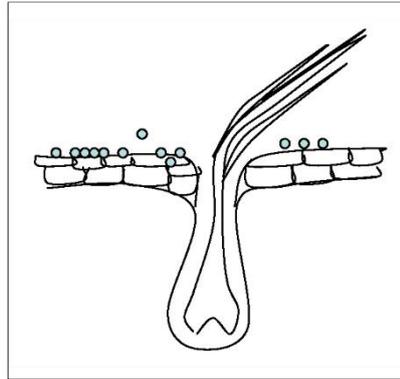
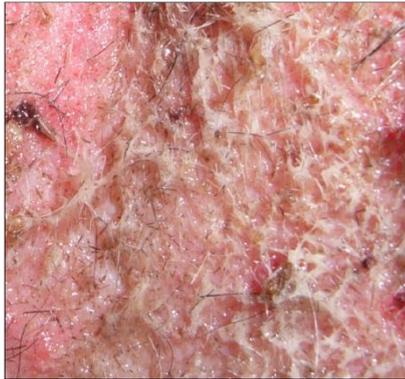
Cytological evaluation is necessary to confirm the existence of a bacterial pyoderma. This examination can be performed using a tape-test, direct smear or fine-needle aspirate. When performing a tape-test, a drop of a blue stain (Azure B or methylene blue) can be placed on the microscope slide before carefully lying the tape over the drop. In this way the tape acts as a cover slip for microscopy. Fine-needle aspirates should only be performed from intact pustules or nodular lesions. Once the sample has been transferred to a slide it should be allowed to dry or be heat-fixed before staining with a modified Romanovsky stain (e.g. Hemacolor® or Diff-Quik®). Microscopy findings include cocci and/or rods, depending on the cause, often alongside degenerative neutrophils which typically contain phagocytosed bacteria. Overgrowth of bacteria without a neutrophilic response may also be seen in superficial pyoderma.

Culture and sensitivity testing is essential with bacterial pyoderma and is recommended for all cases for which systemic antibiotic therapy is considered. Clinicians are encouraged to perform culture and sensitivity testing with both primary and recurrent pyoderma, and to minimise the use of empirical therapy. Culture and sensitivity testing can be sometimes be neglected either from an economic perspective or based on the opinion that empirical therapy is usually effective. However, due to the frequency with which canine pyoderma is seen in general practice, a more targeted approach to selecting antibiotics could significantly aid the fight against multidrug resistance. It is important that veterinarians do not take the currently low prevalence of MRSP in Denmark for granted (see Chapter 3). **Culture and sensitivity testing should become an integrated part of the clinical examination.** This will help ensure a high quality of treatment and promote the correct use of antibiotics. In addition to identifying an appropriate antibiotic, testing contributes to the knowledge base regarding national resistance patterns for initial presentations as well as for chronic skin infections.

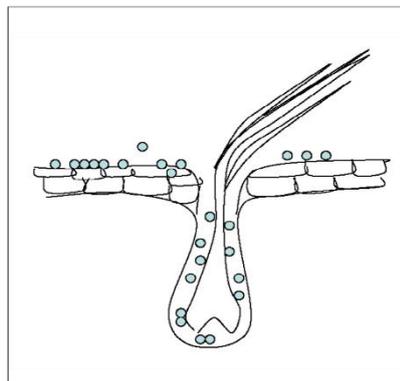
Bacterial culture is particularly important when 1) intracellular bacteria are seen on cytology; 2) there is a poor response to current antibiotic therapy; 3) new lesions appear during treatment; or 4) pyoderma is chronic or recurrent. Suitable sampling techniques are described in Table 1 in Chapter 4.2.

Underlying causes for recurrent pyoderma, especially allergies, should be identified and managed in order to optimise the response to therapy and reduce the risk of recurrence.

Surface pyoderma



Superficial pyoderma



Deep pyoderma

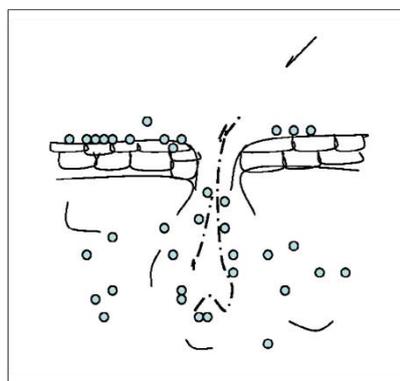


Figure 1: Clinical categories of pyoderma, based on the depth of infection.

Overview of pyoderma treatment

Topical treatment should be prioritised in the management of pyoderma, especially in dogs. Surface, superficial and localised deep pyodermas can, in many cases, be treated effectively with topical preparations (8, 9). Topical treatment can also complement systemic therapy. Topical antibacterial preparations include shampoos, ointments, gels, creams and wipes. Fusidic acid is licensed in Denmark as a topical antibiotic in the form of a gel for dogs. Wipes are available which contain antiseptic ingredients such as chlorhexidine and drying agents. These preparations can be efficacious for surface pyoderma but are of limited use in more widespread disease. Use of shampoos is more appropriate for these patients. In addition to antimicrobial agents (see Table 1), shampoos also contain delivery vehicles which help distribute the active ingredients more widely over the body (10). Normally a frequency of up to 2-3 times weekly is recommended for whole-body shampooing in order to avoid excessive drying, with a reduction in frequency once control is achieved. If applied locally (for example, to the axilla or inguinal area) then the number of applications per week can be higher, since a smaller area is under treatment. The shampoo should be allowed to sit in contact with the skin for 5--10 minutes to attain an optimal antimicrobial effect before thoroughly rinsing off. The most common side-effect of shampoo therapy is drying of the skin, so washes can be supplemented by a moisturising agent (e.g. conditioner). The use of topical therapy against bacterial and yeast skin infections has been reviewed (11).

Table 1. Selected shampoo ingredients with antimicrobial actions

Ingredient(s)	Mechanism of action	Comments
Acetic acid (2%) and boric acid (2%)	Reduces skin pH, which limits bacterial surface growth (12). Bactericidal effect (12).	Has an additional preventative effect against <i>Malassezia</i> .
Chlorhexidine (typically 2%-4%)	Destroys the bacterial cell membrane leading to a loss of osmotic regulation. Broad-spectrum bactericide (12,13).	Moderate effect against <i>Malassezia</i> (12).
Ethyl lactate (10%)	Hydrolysed to lactic acid, lowering skin pH and inhibiting bacterial lipases. Bacteriostatic and bacteriocidal (14).	Good penetration in to hair follicles and sebaceous glands.
Benzoyl peroxide (3%)	Releases oxygen radicals causing rupture of bacterial cell membranes. Broad-spectrum bactericide (10,11).	Has a follicle-cleansing effect and is keratolytic and degreasing. Can dry and irritate skin.

Systemic antibiotic therapy (see Table 2) should be considered on a case-by-case basis. It is essential to identify and address any underlying primary disorder to achieve optimal results, and treatment should be backed up by culture and sensitivity testing. Concurrent use of antimicrobial shampoo is recommended, and it should be considered whether topical management alone would be sufficient.

Systemic therapy is usually indicated for skin infections which cover large areas of the body and where the hair follicle and surrounding skin is involved. The antibiotic concentration which is achieved in the skin is dependent on the rate of diffusion from the dermal capillaries into the interstitial space and adnexa (15). For this reason, pyoderma often requires much longer courses of treatment than other systemic infections, in which a therapeutic concentration is reached more rapidly. The extent, depth and chronicity of the pyoderma will determine the duration of therapy, but there is still inadequate data to determine the optimal duration due to a lack of controlled studies. Currently, general recommendations are that superficial pyoderma should be treated for

one week after resolution of clinical signs, and deep pyoderma for two weeks after resolution. The effect of treatment should always be determined by a veterinarian, and follow-up examination before the end of antibiotic therapy is critical. The effect of treatment can be evaluated by examining the extent of lesions and cytologically. This decision can potentially be supported by repeated bacterial culture prior to the end of treatment.

Table 2. Recommendations for systemic treatment of pyoderma.

Priority	Comments	Examples
First	Should be as narrow-spectrum as possible. Typically used for uncomplicated or first-presentation pyoderma	Lincosamides (e.g. clindamycin). NB: Good for first-presentation pyoderma but resistance to lincosamides increases in recurrent cases due to increased antibiotic exposure (16).
Second	Should be reserved for patients with confirmed resistance to narrow-spectrum antibiotics. Typically used for recurrent pyoderma.	<ul style="list-style-type: none"> ➤ 1st generation cephalosporins (e.g. cefalexin, cefadroxil). ➤ Amoxicillin/clavulanate. ➤ Sulfa-TMP. ➤ Doxycycline.
Third	Should be restricted to patients with resistance to the previous two groups, e.g. with <i>Pseudomonas</i> spp. infection.	<ul style="list-style-type: none"> ➤ Fluoroquinolones (e.g. enrofloxacin, marbofloxacin, pradofloxacin). ➤ 3rd generation cephalosporins (e.g. ceftiofur).

6.1.2 Surface pyoderma

Aetiology and prevalence

Surface pyoderma occurs commonly in dogs. Skin fold pyoderma (intertrigo) can be seen in brachycephalic breeds or obese dogs in which folds of skin create a warm, moist environment (for example in the muzzle, lip, tail base or vulval folds). Pyotraumatic dermatitis ('hotspot'), a pruritic inflammation of the skin surface, occurs following self-trauma. In some patients, pyotraumatic dermatitis can invade the deeper layers of the skin resulting in a pyotraumatic folliculitis or furunculosis, in which the hair follicles are involved.

Diagnosis

Diagnostics are performed as described in the overview section.

Treatment

See Table 3.

6.1.3 Superficial pyoderma

Aetiology and prevalence

Superficial bacterial folliculitis is by far the most common form of pyoderma seen in dogs. It is characterised by purulent infection of the hair follicles in the absence of follicular rupture. Superficial pyoderma is typically secondary to an underlying disorder (allergies, ectoparasites or endocrine disease). Some short-haired breeds may develop a primary idiopathic bacterial folliculitis (3). Impetigo, another purulent skin infection, is not associated with the follicles but instead with

relatively superficial epidermal pustules. **Impetigo** is a type of superficial bacterial pyoderma characterised by pustules which are not connected to the hair follicles. These pustules lie under the stratum corneum, and impetigo is therefore a more superficial infection than a classic folliculitis. It is common in young dogs, and in some patients may be complicated by juvenile folliculitis (not to be confused with juvenile cellulitis). Other forms of superficial pyoderma include **superficial spreading pyoderma and bacterial overgrowth syndrome**, which typically exhibit more diffuse erythema, alopecia, hyperpigmentation and lichenification combined with a seborrheic odour from the skin, as opposed to a suppurative infection of the hair follicles. Mucocutaneous pyoderma is a distinct disease characterised by erosions, ulcerations and crusting at the mucocutaneous junctions, especially around the lips and nose. Superficial pyodermas are also noted in cats, although less frequently than in dogs (17). Underlying allergies or immunosuppressive diseases (FIV/FelV, diabetes mellitus, neoplasia) should be suspected in cats.

Diagnosis

Diagnostics are performed as described in the overview section. Investigation and identification of underlying causes is recommended with recurrent episodes.

Treatment

See Table 3.

6.1.4 Deep pyoderma

Aetiology and prevalence

Deep pyodermas are less commonly seen. **Furunculosis** is a development of folliculitis in which the hair follicle ruptures, and the contents provoke inflammation in the surrounding dermis. Localised disease may be seen as **interdigital furunculosis, carpal furunculosis, muzzle furunculosis, callus pyoderma** (over bony prominences) or **lick granuloma**. Diffuse spread of infection through the whole dermal layer is termed **cellulitis**. German shepherd dogs can suffer from a form of deep pyoderma characterised by fistulous reactions and deep ulcerations of the skin (18). In cats, deep pyoderma is rare but can be seen focally as furunculosis on the chin where a primary problem with follicular blockage leads to secondary infection and furunculosis. This should be distinguished from feline acne which is more common and which usually can be treated topically.

Diagnosis

Diagnostics are performed as described in the overview section. Histopathology and bacterial culture of surgical biopsies is recommended. Chronic or recurrent deep pyodermas should always prompt investigation for an underlying cause.

Treatment

See Table 3.

6.1.5 Skin infections with methicillin-resistant staphylococci (MRSP)

MRSP (methicillin-resistant *Staphylococcus pseudintermedius*) and other multiresistant bacteria should be suspected whenever the response to antibiotic treatment is inadequate. Bacterial culture and sensitivity testing should be performed as described earlier. Patients suspected of or confirmed to have MRSP should be isolated from other patients, particularly those which are immunocompromised. Use of gloves and frequent hand disinfection are recommended to reduce spread.

Treatment

In general, **antibiotic therapy should be discontinued** in patients with MRSP, and treatment restricted to topical antiseptics (typically with a concentration of at least 2-4%). In dogs, shampooing with products containing chlorhexidine, benzoyl peroxide or ethyl lactate is recommended. Topical antibiotic therapy with mupirocin ointment 2% (human preparation) can sometimes be useful for localised infections. However, mupirocin should only be used in situations in which antiseptics have proved inadequate, since it is an important human antibiotic. Resistance patterns should be carefully evaluated for each patient, if systemic antibiosis is being considered due to a lack of effect of shampooing. MRSP is, by definition, resistant to all beta-lactams (even when combined with clavulanate). Frequently, MRSP is also less sensitive to clindamycin, sulfa/TMP and fluoroquinolones, but this depends on the particular MRSP clone (21). The reader is referred to the section on systemic treatment of MRSP infections (see Chapter 3.3).

Table 3. Choice of antibiotic for surface, superficial and deep skin infections. Priorities given in the table apply to both initial empirical treatment and any adjustment made following culture and sensitivity testing.

Problem	Antibiotics	Comments
Surface pyodermas – limited to the stratum corneum. Topical treatment is usually sufficient.		
Intertrigo (skin fold dermatitis)	Systemic antibiotics are not necessary	<ul style="list-style-type: none"> ➤ Clip fur (e.g. around lip fold). ➤ Topical disinfectant (chlorhexidine) and/or drying agent (boric or acetic acid) as required. ➤ Topical antibiotics (fusidic acid BID, 5-7 days) if bacterial overgrowth is present. ➤ Disinfectant wipes containing drying agent may be useful for prophylactic management.
Pyotraumatic dermatitis ('hot spot')	<p>Systemic antibiotics are not usually necessary.</p> <p>Reserve systemic antibiotics (see examples below) for concurrent pyotraumatic folliculitis or furunculosis, in which satellite lesions (papules, pustules or furuncles) will be visible at the periphery of the main lesion.</p>	<ul style="list-style-type: none"> ➤ Clip fur. ➤ Topical disinfectant (chlorhexidine) and/or drying agent (boric or acetic acid) as required. ➤ Topical antibiotics (fusidic acid with betamethasone BID, 5-7 days) may be useful. ➤ Prevent further trauma with a protection collar. <p>In addition:</p> <ul style="list-style-type: none"> ➤ Anti-pruritics (glucocorticoids as spray, ointment or systemic treatment), or; ➤ Analgesics (e.g. NSAIDs).
Superficial pyodermas – involve the epidermis and/or hair follicle. There is no penetration of the basal membrane or hair follicle rupture. Shampoo therapy should be the first choice, since many superficial pyodermas respond well to shampooing alone. Equally, shampooing can be an effective prophylactic measure for preventing recurrence. If systemic treatment is used, this should be combined with an antimicrobial topical therapy. Shampoo must be applied thoroughly to the skin		

and left in contact for 5-10 minutes before rinsing. A moisturising conditioner can be added to reduce drying of the skin. Current recommendations for the duration of systemic treatment are to continue 1 week beyond resolution of clinical signs.

Canine Impetigo	If there is no response to topical therapy alone, see the section below on superficial folliculitis.	<ul style="list-style-type: none"> ➤ Shampoo <p>Suggested treatment regime:</p> <ul style="list-style-type: none"> ➤ Wash affected area daily for one week ➤ Continue on every other day basis for one week, and thereafter as needed.
Superficial folliculitis Examples: <ul style="list-style-type: none"> ➤ Juvenile folliculitis ➤ Superficial bacterial folliculitis (most common, often secondary to e.g. allergy, hypothyroidism, etc.) ➤ Pyotraumatic folliculitis 	<p>If there is no response to topical therapy alone:</p> <ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID) or 11 mg/kg PO SID). 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation cephalosporin, e.g. cefalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID). 	<ul style="list-style-type: none"> ➤ Shampoo <p>Suggested treatment regime:</p> <ul style="list-style-type: none"> ➤ Wash twice weekly for 2-3 weeks ➤ Continue once weekly for two weeks, and thereafter as needed.
Superficial spreading pyoderma		
Bacterial overgrowth syndrome		
Mucocutaneous pyoderma		<ul style="list-style-type: none"> ➤ Topical therapy is not recommended.
Feline superficial pyoderma	<p>If true infection confirmed:</p> <ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID) or 11 mg/kg PO SID). 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation cephalosporin, e.g. cefalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID). 	<ul style="list-style-type: none"> ➤ Superficial pyoderma is rarer in cats than in dogs. Underlying causes such as allergies or immunosuppression should be excluded. ➤ Topical treatments are not recommended for cats.
<p>Deep pyodermas – involve the hair follicle and surrounding dermis due to rupture of the hair follicle wall. Focal deep pyoderma can be managed topically, e.g. with a preparation with a follicle-cleansing effect. Systemic antibiotics should be used for widespread lesions and can be combined with topical therapy. Current recommendations for the duration of systemic treatment are to continue 2 weeks beyond resolution of clinical signs.</p>		
Interdigital, carpal and chin furunculosis	<ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID) or 11 mg/kg PO SID). 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation cephalosporin, e.g. cefalexin (25 	<ul style="list-style-type: none"> ➤ Supplement with antimicrobial shampoo, ideally with follicle-cleansing effect. <p>Suggested treatment regime:</p>
Callus pyoderma	cephalosporin, e.g. cefalexin (25	

Lick granuloma (traumatic furunculosis)	mg/kg PO BID) or cefadroxil (20 mg/kg PO BID).	<ul style="list-style-type: none"> ➤ Use 2-3 times weekly for 2-3 weeks. ➤ Then once weekly for two weeks. ➤ Thereafter as needed ➤ Focal treatment can be performed more frequently
Pyotraumatic furunculosis		
Deep generalised furunculosis		
Cellulitis		
Feline chin furunculosis	<ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID) or 11 mg/kg PO SID). 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation cephalosporin, e.g. cefadroxil (20 mg/kg PO BID). 	<ul style="list-style-type: none"> ➤ Local rinses with chlorhexidine once or twice daily ➤ Distinguish from feline acne (build-up of keratin without bacterial infection) which does not require systemic treatment

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) pyoderma – resistant to all beta-lactams and is often associated with multi-resistance. Culture and sensitivity should always be performed and evaluated for each patient.

MRSP pyoderma	<p>All systemic therapy should be stopped and topical therapy prioritised.</p> <p>If systemic antibiotics are necessary: Avoid beta-lactams. The resistance profile should be used to individualise treatment (see Chapter 3).</p>	<ul style="list-style-type: none"> ➤ Antiseptic shampoos recommended (chlorhexidine, benzoyl peroxide, or ethyl lactate). ➤ Mupirocin 2% ointment can be used for focal pyoderma which does not respond to antiseptic treatment. ➤ As far as is possible, affected animals should be isolated from other patients (especially immune-compromised ones) to avoid transmission. ➤ Avoid spreading of infection on hands and clothes of personnel who handle MRSP patients. ➤ Disinfection of rooms and cages is recommended.
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6.1.6 Cellulitis, abscesses, anal sac and nail bed infections, and traumatic wounds

Aetiology and prevalence

Cellulitis is an acute, diffuse inflammatory process in the subcutaneous tissues, in contrast to an **abscess** which is a localised collection of pus. The most common causes of both cellulitis and abscesses are bite or scratch wounds, which are particularly common in cats. Bacteria seen in association with bite wounds include *Staphylococcus* spp., beta-haemolytic *Streptococcus* spp., *E. coli*, *Pasteurella canis* (in dogs) and *Pasteurella multocida* subsp. *multocida* and *septica* (in cats) (22). Anaerobic bacteria such as *Fusobacterium* spp. and *Clostridium* spp. can also be involved (3, 23). Persistent fistulous and draining nodules should raise suspicion of infection with *Actinomyces*, *Nocardia* or mycobacteria.

Anal sac infection (and abscessation) can arise following repeated impaction of the anal sacs, or be secondary to an underlying disease (e.g. allergy or endocrine disease). **Perianal fistulae** are painful and characterised by prominent ulceration and/or fistulous outbreaks of the rectal mucosa and perineum, which predispose to localised secondary bacterial infection. The condition is most probably immune-mediated, and German shepherd dogs are predisposed. **Bacterial onychitis** can occur secondary to trauma to the nail (usually restricted to a single digit) or to an underlying condition such as endocrine disease (in which case multiple digits may be involved). Purulent exudate from the nail fold, lameness and/or discolouration of the coat due to licking (especially in dogs) are often seen. Traumatic wounds such as burns, classified as either thermal (heat, solar) or chemical (caustic), have a high risk of secondary bacterial infection, because the epidermis is either severely damaged or destroyed.

Diagnosis

The diagnosis can usually be made based on the history, clinical presentation and cytological evaluation. Bacterial culture is recommended if the response to treatment is poor, there is systemic illness, draining fistulae develop or if wound healing is poor (e.g. burns). If acid-fast bacteria (mycobacteria) are suspected, specific diagnostic investigations should be performed to confirm their presence: these investigations are not covered in this section.

Treatment

Treatment options are outlined in Table 4. Treatment of abscesses can consist solely of draining and flushing of the cavity with a dilute antiseptic (such as chlorhexidine) without systemic antibiotic therapy. This can be sufficient in well-defined abscesses in otherwise healthy animals (i.e. afebrile and with no systemic illness). Antibiotics should only be used if there is evidence of systemic effects, diffuse tissue involvement or potential joint involvement, or in immunosuppressed individuals. Culture and sensitivity testing should always be performed before starting treatment. Pathogens such as *Pasteurella* are sensitive to penicillins, and bite wounds can often be effectively treated with ampicillin or amoxicillin (23). Clindamycin is particularly effective against Gram-positive aerobes, anaerobes and intracellular bacteria, but less so against Gram-negative bacteria (24). Prior to receiving culture results, cytology can help guide the choice of antibiotic (e.g. clindamycin if cocci are seen, or amoxicillin if rods are found). Treatment durations of 5-10 days are sufficient for uncomplicated abscesses. Burn injuries can require intensive treatment including fluid therapy, and monitoring for tissue necrosis and circulatory shock.

Table 4. Choice of antibiotics for treatment of cellulitis, abscesses, anal sac infections, nail bed infections and burns. Priorities given in the table apply to both initial empirical treatment and any adjustment made following culture and sensitivity testing.

Problem	Antibiotics	Comments
Cellulitis or abscess (e.g. following bite wound)	If antibiotics are required: 1. Clindamycin (5.5 mg/kg PO BID or 11 mg/kg PO SID) or amoxicillin (20 mg/kg PO BID). 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID).	<ul style="list-style-type: none"> ➤ Can often be managed by drainage, flushing and debridement alone ➤ Rinse cavity with diluted, non-irritating disinfectant e.g. 0.05-0.2% chlorhexidine. ➤ If systemic therapy is needed, culture and sensitivity testing should be performed.
Anal sac infections and abscesses	Suggested systemic therapy:	➤ Mild cases can be managed by drainage and flushing (e.g. with dilute chlorhexidine) under anaesthesia.

	<ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID or 11 mg/kg PO SID) 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation cephalosporin (e.g. cefalexin 25 mg/kg PO BID or cefadroxil 20 mg/kg PO BID). 	<ul style="list-style-type: none"> ➢ If systemic therapy is indicated, culture and sensitivity should be performed. ➢ Duration of therapy is typically for 1 week beyond resolution of clinical signs. ➢ Recurrent episodes of anal sac infection should prompt investigation of underlying causes. ➢ Surgical extirpation of the anal sacs can be beneficial in recurrent cases.
Perianal fistulae (immune-mediated process in which T-cells attack circumanal (hepatoid), sebaceous and apocrine glands in the perianal region)	<p>The underlying cause requires immunomodulating therapy such as cyclosporine or topical tacrolimus.</p> <p>Suggested systemic antibiotic therapy for secondary infection:</p> <ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID or 11 mg/kg PO SID) – for coccoid infections, less effective against rods. 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation cephalosporin (e.g. cefalexin 25 mg/kg PO BID or cefadroxil 20 mg/kg PO BID). 	<ul style="list-style-type: none"> ➢ Wash the area daily with 0.05-0.2% chlorhexidine. ➢ Culture and sensitivity testing should be performed before systemic antibiotics. ➢ Duration of treatment varies, and is dependent on how rapidly immunomodulating therapy begins to take effect (healing of fistulae and ulceration).
Nail bed infections (paronychia, bacterial infection of the skin around the nail)	<p>Topical therapy should be prioritised.</p> <p>Suggested systemic therapy:</p> <ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID or 11 mg/kg PO SID) 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation cephalosporin (e.g. cefalexin 25 mg/kg PO BID or cefadroxil 20 mg/kg PO BID). 	<p>Simple bacterial nail bed infection:</p> <ul style="list-style-type: none"> ➢ Repeated soaks with solutions containing antiseptic shampoos such as chlorhexidine or ethyl lactate. <p>Nail bed infections in multiple digits:</p> <ul style="list-style-type: none"> ➢ Systemic antibiotics is often required. Culture and sensitivity testing should be performed. <p>Nail bed infections secondary to other disease:</p> <ul style="list-style-type: none"> ➢ Identify and treat the underlying cause. ➢ If the nail (keratin) is also involved, fungal infections should be excluded (e.g. dermatophytosis). ➢ If multiple nails are deformed, investigate for immune-mediated lupoid onychitis (SLO).
Burns (thermal or chemical)	<ol style="list-style-type: none"> 1. Amoxicillin/clavulanate (12.5 mg/kg PO BID) or 1st generation 	<ul style="list-style-type: none"> ➢ Antibiotics recommended particularly for poorly healing wounds ➢ Clip surrounding area to facilitate monitoring

cephalosporin e.g. cefalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID).	<ul style="list-style-type: none"> ➤ Rinse thoroughly ➤ Apply cold compresses ➤ Provide systemic analgesia ➤ Avoid use of steroids
2. Enrofloxacin (5--20 mg/kg PO SID), marbofloxacin (2 mg/kg PO SID) or pradofloxacin (3-4.5 mg/kg PO SID).	<ul style="list-style-type: none"> ➤ Administer IV fluids ➤ Severely infected burns will require systemic and topical antibiotics ➤ No Danish licensed topical veterinary antibiotics are available, so cascade regulations should be applied: <ul style="list-style-type: none"> ➤ Fusidic acid (without steroid) ➤ Gentamicin ➤ Neomycin ➤ Mupirocin (primarily effective against staphylococci) ➤ Silver sulfadiazine

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6.2 The ear

6.2.1 Otitis externa and otitis media

Overview

When considering causes of canine otitis externa, attention must be paid to **predisposing factors** (temperature, anatomy conformation, excess hair growth in the ear canal, underlying allergic or endocrine disease), **primary factors** (parasites, allergens, reactions to medicines, autoimmune disease), and **complicating factors** (bacteria, yeasts, canal stenosis, otitis media) (1, 2). Primary allergic disease is one of the most common causes of ear infections in dog (1, 2). It is important that any underlying cause(s) for otitis externa are identified and managed in order to optimise the response to treatment of otitis.

Aetiology and prevalence

Otitis externa is a common clinical presentation in general practice, seen in about 10-20% of canine patients (3). Otitis externa has an estimated prevalence in cats of around 2-10%, and is frequently secondary to parasites (*Otodectes*) or nasopharyngeal polyps in the ear canal (2). The normal microbial flora in the ear includes *Staphylococcus* spp., *Micrococcus* spp., *Streptococcus* spp., *Corynebacterium* and *Malassezia* (4). Bacteria which commonly contribute to otitis externa are *S. pseudintermedius*, *Proteus* spp., *Corynebacterium* spp., *E. coli*, *Pasteurella* spp., *Streptococcus canis* and *Pseudomonas* spp. (4-6).

Pseudomonas is isolated from between 20-35% of ear infections in dogs and is often associated with more severe cases of otitis externa and/or otitis media (2, 7). Risk factors for *Pseudomonas* infections include exposure of the ear canal to water, breed conformation (e.g. Cocker spaniels and Bassett hounds) and recurrent otitis that has been repeatedly treated with antibiotics (4).

Pseudomonas infections can predispose to severe inflammation of the ear canal, including perforation and rupture of the tympanic membrane leading to otitis media and interna (2, 4).

Diagnosis

Cytology should always be performed to look for pathogens and inflammatory cells. In many cases, a biofilm of thick, slimy and often dark-coloured material can be recognised. This biofilm is a protein- and polysaccharide-rich matrix which is produced by bacteria and aids them in avoiding the host immune response and resisting the effects of topical antibiotics (8). Culture and sensitivity testing should primarily be performed when rods are identified on cytology, and in cases of chronic otitis externa and/or if the response to treatment is poor. Visualisation of the tympanic membrane and assessment of its integrity is important before selecting further treatment, because many topical ear preparations are potentially ototoxic (9). Visualisation is not always possible due to the presence of cerumen, exudate or severe pain which prevents otoscopy. Ear flushing under anaesthesia is beneficial both for diagnosis and for management of otitis externa. Cytology and culture samples should be obtained before flushing.

Treatment

Flushing the ear canal is an important component of therapy, since it facilitates examination of the tympanic membrane. It also enables removal of any excess wax and biofilm which could reduce the efficacy of topical antibiotics (8). Ear flushing should be performed under general anaesthesia, using warmed sterile saline under controlled pressure. Overaggressive flushing should be avoided since there is a risk of inducing vestibular disease, Horner's syndrome, facial nerve paralysis and deafness (9, 10). Patients with intact tympanic membranes and only moderate amounts of earwax can also be managed with an **ear rinse** at home, following suitable owner instruction. Ear rinses typically include cerumenolytics, drying agents and antimicrobial agents (see Table 1). All licensed topical ear treatments in Denmark consist of broad-spectrum antibiotics combined with antifungal and anti-inflammatory products. This makes it difficult to use focused narrow-spectrum antibiotic therapy for pure yeast infections or for mild coccoid bacterial otitides. As an alternative the clinician can choose to use an ear rinse containing an antimicrobial component, e.g. chlorhexidine and Tris-EDTA (11). It is important that chlorhexidine/Tris-EDTA rinses are used in combination with another that has a cerumenolytic effect whenever there are increased amounts of cerumen in the ear canal, since chlorhexidine/Tris-EDTA rinses lack this property (11).

Systemic anti-inflammatories in the form of corticosteroids are particularly useful when chronic, hyperplastic changes of the ear canal (e.g. fibrosis, epithelial oedema, glandular hyperplasia) are present or when the ear is very painful.

Systemic antibiotics are frequently ineffective and usually only indicated if the middle or inner ear is involved or if topical treatment is impossible (e.g. ear canal ulceration, risk of toxicity or poor owner compliance). Systemic therapy should always be based on culture and sensitivity testing, and the treatment response evaluated with repeated clinical and cytological evaluations.

If the tympanic membrane is perforated, care should be taken with the use of topical preparations.

Repeated flushing with warm sterile saline, possibly in combination with non-ototoxic antimicrobial compounds (e.g. 0.15% chlorhexidine or Tris-EDTA), is preferable. Polymixin B and aminoglycosides (e.g. gentamicin and neomycin – the latter licensed for use in humans) are often found in topical ear preparations and can be ototoxic (4, 12). Fluoroquinolones (e.g. marbofloxacin and ciprofloxacin – the latter water soluble and licensed for use in humans) are thought to be less ototoxic (4, 12) and may be needed for *Pseudomonas* infections, but care should still be taken with topical use. Complete healing of the ruptured tympanic membrane can take 3 weeks to 3 months (13).

Table 1. Common ingredients in ear cleaning products.

Agent type	Examples	Mode of action	Ototoxicity
Ceruminolytics	➤ Calcium sulfosuccinate, urea peroxide, squalene, hexamethyl tetracosane, propylene glycol, glycerine, mineral oils.	<ul style="list-style-type: none"> ➤ Soften and dissolve cerumen. ➤ Require 10–15 minutes for effect. 	<ul style="list-style-type: none"> ➤ Most ceruminolytics, with the exception of squalene, are ototoxic (propylene glycol >10%, sulfosuccinate, glycerol, urea peroxide, ethanolamine (14, 15)), and should not be used if the tympanic membrane is perforated.
Drying agents	➤ Salicylic acid, boric acid 2%, acetic acid 2%, lactic acid, benzoic acid, isopropyl alcohol, aluminium acetate.	<ul style="list-style-type: none"> ➤ Dry the ear canal, preventing maceration of the epithelium. 	<ul style="list-style-type: none"> ➤ Can irritate the ear canal and should not be used to excess, or if the ear canal is ulcerated. ➤ Acetic acid, aluminium acetate, isopropyl alcohol and salicylic acid are potentially ototoxic (16–18), and care should be taken if the tympanic membrane is damaged. Dilution with sterile saline may be beneficial (10).
Antimicrobial	➤ Chlorhexidine, lactic acid, boric acid 2%, acetic acid 2%, salicylic acid, lysozyme, antimicrobial peptides, Tris-EDTA (usually in combination with other products).	<ul style="list-style-type: none"> ➤ Direct bacteriostatic and/or bacteriocidal actions (primarily chlorhexidine) (11). ➤ Also effective against <i>Malassezia pachydermatis</i> (19, 20). 	<ul style="list-style-type: none"> ➤ Chlorhexidine is not ototoxic at low concentrations (0.05% and 0.15%) but can be ototoxic at > 2% (11). ➤ Tris-EDTA is safe to use if the tympanic membrane is ruptured (21).

Table 2. Suggested treatment regimes for bacterial ear infections. Removal of excess cerumen before antimicrobial administration is essential for successful management of otitis. Chlorhexidine and Tris-EDTA, for example, are not directly ceruminolytic alone, and their antimicrobial effect is greatly reduced in the presence of cerumen in the ear canal. Topical glucocorticoids are often necessary for managing ear canal inflammation. Recurrent ear infections should prompt investigation and management of underlying primary causes.

Problem	Antibiotic therapy	Comments
Mild otitis externa caused by cocci	➤ Ear cleaning products with antimicrobial effect (e.g. chlorhexidine, Tris-EDTA, acetic acid or isopropyl alcohol) are recommended as an alternative to antibiotic therapy	<p>Intact tympanic membrane:</p> <ul style="list-style-type: none"> ➤ Ear flushing is recommended if excessive cerumen. ➤ Ear cleaners alone are sufficient if only moderate cerumen. <p>Suggested treatment regime:</p> <ul style="list-style-type: none"> ➤ Chlorhexidine gluconate 0.15% with Tris-EDTA BID for 8–10 days.

Topical glucocorticoid, if there is inflammation or hyperplasia of the ear canal:

- Triamcinolone acetonide with salicylic acid SID for 8-10 days.
- Hydrocortisone aceponate (1ml in each ear SID for 8 days) [product is available only in spray form, and must be drawn up in to a disposable syringe before dosing].
- Betamethasone (lotion, human preparation) SID for 8-10 days.

Pronounced otitis externa caused by cocci or otitis externa with mixed infections of cocci and rods

Intact tympanic membrane:

1. Fucidic acid and framycetin combination (5-10 drops BID for 1-2 weeks).
2. Gentamicin (4--8 drops BID or 1ml/ear/day for 10 days).

Intact tympanic membrane:

- Ear flushing under anaesthesia
- Ear cleaners will complement topical antibiotic therapy

Suggested treatment regime:

- Chlorhexidine gluconate 0.15% with Tris-EDTA BID for 8-10 days Use at least 10--15 minutes before antibiotics to increase the effect of antibiotic treatment.

Perforated tympanic membrane:

- Ear flushing and non-ototoxic products should be used (e.g. chlorhexidine with Tris-EDTA in low concentrations, 0.05-0.15%).
- Topical antibiotics should ideally be avoided. If necessary, use with caution and warn the owner of the risk of ototoxicity.
- Topical antibiotics should be aqueous solutions.
- Oil-based preparations must not be used.

Otitis externa caused by rods (but not *Pseudomonas* –see below)

Intact tympanic membrane:

1. Polymixin B (3--5 drops BID for 10-14 days).
2. Gentamicin (4--8 drops BID or 1ml/ear/day for 10-14 days).
3. Marbofloxacin (10 drops SID for 10-14 days)

Intact tympanic membrane:

- Ear flushing
- Ear cleaners will complement topical antibiotic therapy.

Suggested treatment regime:

- Chlorhexidine gluconate 0.15% with Tris-EDTA (BID for 1-2 weeks).
- Tris-EDTA alone (BID for 1-2 weeks).
- Use at least 10--15 minutes before administration of antibiotics.

Perforated tympanic membrane:

- Ear flushing and non-ototoxic products should be used (e.g. chlorhexidine with Tris-EDTA in low concentrations, 0.05-0.15%).
-

Otitis externa
caused by
Pseudomonas spp.

1. Frequently multi-resistant. Treatment must be guided by sensitivity testing
2. Local therapy is preferred, since it improves the response to therapy.

Intact tympanic membrane:

1. Polymixin B (3--5 drops BID for 14 days).
2. Gentamicin (4--8 drops BID or 1ml/ear/day for 14 days).
3. Marbofloxacin (10 drops SID for 14 days).
4. Ciprofloxacin with hydrocortisone (human ear preparation) (4-10 drops BID until clinical resolution and negative cytology).
5. Silver sulphadiazine 1% salve (human product) dissolved in Tris-EDTA (SID for 10--14 days).

Perforated tympanic membrane:

- Ciprofloxacin with hydrocortisone (human ear preparation) (4-10 drops BID until clinical resolution and negative cytology).
- Marbofloxacin may be considered (aqueous veterinary product) (10 drops SID until clinical resolution and negative cytology).
- In cases with severe infection and if topical therapy is impossible, systemic therapy (based on sensitivity testing) may be used:
- Enrofloxacin (5 mg/kg PO SID), marbofloxacin (2 mg/kg PO SID), or pradofloxacin (3-4.5 mg/kg PO SID).

- Topical antibiotics should ideally be avoided. If necessary, use with caution and warn the owner of the risk of ototoxicity.
- Topical antibiotics should be aqueous solutions.
- Oil-based preparations must not be used.

General recommendations:

- Ear flushing is essential before starting treatment, and repeated flushing is often necessary.
- Use non-ototoxic products (e.g. chlorhexidine with Tris-EDTA in low concentrations, 0.05-0.15%).

Anti-inflammatory treatment:

- Glucocorticoids topically (see treatment suggestions above), and possibly systemically, are essential components of treatment for *Pseudomonas* due to the massive inflammation that accompanies infection.
- Management of biofilm:
- Biofilm reduces the effectiveness of antimicrobial products.
- Tris-EDTA dissolves biofilm (pure Tris-EDTA or chlorhexidine with Tris-EDTA combinations can be given 10 minutes before treatment with topical antibiotics until the biofilm problem has been eliminated).

Antimicrobial ear cleaners with effect against *Pseudomonas*:

- Acetic acid, boric acid and lactic acid have proven efficacy (22) but are irritant and are usually preferred as preventative treatments following healing of ear canal lesions.

	<ul style="list-style-type: none"> ➤ Use of gentamicin or amikacin is discouraged due to the risks of nephro- and ototoxicity. 	
<i>Malassezia</i> infection	<ul style="list-style-type: none"> ➤ Avoid antibiotics if there is no bacterial component. ➤ All veterinary licensed ear preparations with antifungals include antibiotics. Ear cleaners with antimicrobial effects are therefore preferred over these. 	<p>Ear cleaner components effective against <i>Malassezia</i>:</p> <ul style="list-style-type: none"> ➤ Chlorhexidine. ➤ Tris-EDTA. ➤ Salicylic acid. ➤ Lactic acid. ➤ Acetic acid.
Otitis media	<ul style="list-style-type: none"> ➤ Topical antibiotics should be used with caution. Owners should be informed of the risk of ototoxicity if topical therapy is used. ➤ Topical antibiotics should be aqueous solutions. ➤ Oil-based preparations must not be used. ➤ Some cases can be managed with ear flushing alone ➤ Systemic therapy should be guided by culture and sensitivity testing. ➤ <p>Suggested treatment regimes:</p> <ol style="list-style-type: none"> 1. Clindamycin (5.5 mg/kg PO BID or 11 mg/kg PO SID) (only for Gram-positive cocci). 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID) 3. 1st generation cephalosporins, e.g. cefalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID). 4. Enrofloxacin (5 mg/kg PO SID), marbofloxacin (2 mg/kg PO SID), or pradofloxacin (3-4.5 mg/kg PO SID). 	<ul style="list-style-type: none"> ➤ Image bullae with radiography or CT in order to identify filling. ➤ Myringotomy, performed caudoventrally in the tympanic membrane, to drain middle ear contents, obtain samples for culture, and permit flushing of the bulla with warmed sterile saline is an essential treatment step. ➤ Tris-EDTA and/or chlorhexidine can be used in combination with sterile saline for flushing. ➤ Systemic glucocorticoid therapy can help prevent further hyperplasia and stenosis of the ear canal. ➤ Secondary neurological complications, including vestibular syndrome and facial nerve deficits, should be managed with supportive treatments such as anti-emetics and ocular lubricants.

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6.3 The urinary tract

6.3.1 Overview

Bacterial causes

Escherichia coli is the most common cause of urinary tract infections and accounts for 30-50% of all infectious cystitis cases in dogs and cats. Other common canine and feline pathogens include *Staphylococcus*, *Proteus* and *Enterococcus* (1, 2). Bacteria such as *Klebsiella*, *Pseudomonas*, *Streptococcus*, *Enterobacter* and *Pasteurella* may also be seen, but in general are less common and in dogs are usually found in mixed infections.

Diagnosis

Urinalysis and sediment examination

Urinalysis comprises refractometer measurement of specific gravity, urine dipstick tests and microscopic evaluation of unstained and stained urine sediment (using Wright's stain or Hemacolor®). The leukocyte and nitrite results on dipsticks are not reliable for veterinary use, so pyuria can only be diagnosed via microscopy. Ideally, urine should be collected by cystocentesis and examined within 60 minutes of sampling. The combination of an inflammatory sediment and intracellular bacteria in neutrophils indicates urinary tract infection, but the absence of bacteria on microscopy does not rule it out. Leukocyte casts in the urine are rare and indicate pyelonephritis.

Culture

Bacterial culture is the only method for definitively diagnosing urinary tract infection and is **recommended in all suspected cases**. Urine for culture should always be collected by cystocentesis unless there are specific contra-indications such as coagulopathy. If the correct cut-off values are used, there is little difference between samples collected by catheter or mid-flow. Both can be contaminated and difficult to interpret. Since catheterisation is more invasive, its use cannot be recommended over collection of mid-flow samples.

Samples should be cultured within 24 hours of collection. Mid-flow and catheter samples should be cultured as quickly as possible, ideally within 4 hours (3). If samples are sent to an external laboratory, the urine should be placed in a sterile container and refrigerated for transportation: alternatively, a suitable transport medium such as boric acid can be used. Refrigeration or the use of transport medium is particularly important if the expected time in transit will exceed 24 hours.

Interpretation of culture results depends on the urine sampling method. Mid-flow samples must always be interpreted quantitatively, using a high cut-off value of 100 000 colony forming units (CFU) per ml. If the bacterial concentration is below this level, the culture is interpreted as representing contamination. Growth of more than two pathogens is also typical of contamination with one or more types of bacteria. Cut-off levels for different urine sampling methods are given in Table 1.

Table 1. Cut-off values for infection, based on Sørensen et al., 2016 (3) and Bartges et al, 2004 (4).

Sampling method	Dog	Cat
Cystocentesis	>1000 CFU/ml ^a	>1000 CFU/ml ^a
Free-catch and catheter-obtained urine (bitches)	>100 000 CFU/ml ^b	>10 000 CFU/ml ^b

^aLower bacterial counts in samples obtained by cystocentesis can be significant and represent infection.

^bThere is a risk of false-positives and false-negatives when interpreting bacterial counts for free-catch urine.

In-house culture

Point of care or in-house culture, which produces results within 24 hours, can be used for sporadic cases of cystitis in dogs and cats. The results are used to determine if antibiotics are needed or not. Agar plates with colonies can be refrigerated and sent to an external laboratory for bacterial identification and sensitivity testing. It can be advantageous for clinics to send in-house media to a laboratory after an initial incubation at 37°C – this avoids sending sterile samples, and the risk of false positive or false negative culture results is minimised. Only culture media which have been validated for canine and feline urine should be used. Several commercial products are available, including urine culture dipslides (5) (see Figure 1a) and chromogenic agar with a combined sensitivity test (6) (see Figure 1b). The bacterial concentration can be estimated visually after incubation based on the inter-colony spacing.



Figure 1a. Urine culture dipslide (Uricult®). The dipslide consists of a thin piece of plastic coated with non-selective agar medium on one side and selective/indicator MacConkey agar medium on the other. Urine is poured over the media and the dipslide incubated at 37°C overnight. This dipslide demonstrates growth of coliform bacteria on the side with MacConkey agar.

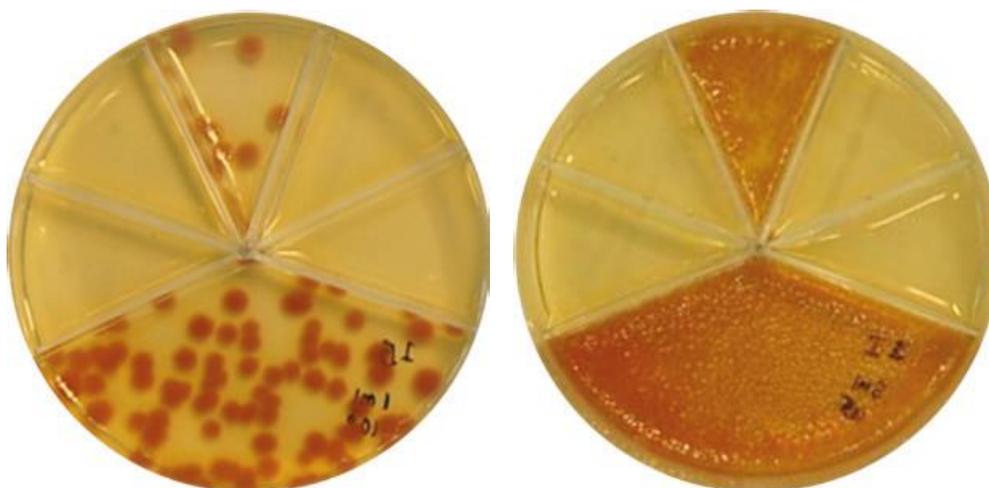


Figure 1b. Combined culture and sensitivity testing using chromogenic agar (Flexicult Vet). Urine is poured over the media which is then incubated for 18-24 hours at 37°C. Growth of 1000 CFU/ml and 100 000 CFU/ml E. coli can be seen, sensitive to 4 out of the 5 antibiotics tested for in the small compartments.

Sensitivity testing and choice of antibiotic

Routine use of sensitivity testing is recommended. Provided validated in-house tests are used, sensitivity testing can be performed in-house for patients with first presentations of sporadic cystitis

(see Chapter 6.3.2). For patients with more complicated disease, such as recurrent cystitis, when precise bacterial identification and sensitivity testing will be vital for management, urine or agar should always be sent to an external microbiological laboratory.

Many antibiotics are concentrated in the urine, such that standard dosing regimens will produce a urine concentration far in excess of that in the plasma or renal parenchyma. Because of this, bacteria in the bladder may be sensitive to a specific antibiotic, while the same bacteria in the renal parenchyma will be resistant. In order to avoid misinterpretation of test results, the clinician should **always indicate on the request form whether the infection is suspected of being in the upper or lower urinary tract.**

The following sections cover empirical antibiotic therapy for the various presentations of urinary tract infection in dogs and cats. Treatment recommendations are summarised in Table 2.

6.3.2 Lower urinary tract

Sporadic cystitis in dogs

Definition

Cystitis is a bacterial infection of the urinary bladder which produces clinical signs. Sporadic cystitis is defined as a single episode of cystitis, and replaces the term simple urinary tract infection. Sporadic cystitis can occur with or without underlying systemic, neurological or urogenital disease. Patients with underlying disease are at risk for developing recurrent cystitis and/or subclinical bacteriuria, which are described later.

Prevalence

The true prevalence of canine sporadic cystitis is unknown but it has been previously estimated that 1 in 7 dogs will have a sporadic urinary tract infection at some point in their life (7).

Diagnosis

Symptoms of cystitis include pollakiuria, stranguria, dysuria and haematuria. These are not specific and only localise to the lower urinary tract. Recent studies in Danish general practice indicate that 50% of dogs with clinical signs localised to the lower urinary tract had sporadic cystitis: for bitches, the figure was 65% (8). The remaining dogs did not have infection.

Diagnostic tests comprise urinalysis and bacterial culture and sensitivity as described in Chapter 6.3.1. **In dogs with an isolated first presentation of cystitis, quantitative culture without sensitivity testing is acceptable.** In-house culture media with bacterial colonies can be refrigerated and subsequently sent for sensitivity testing if the response to empirical treatment is poor. In-house sensitivity tests which indicate the presence of multidrug resistant bacterial (such as ESBL, see Chapter 3.4) should always be confirmed at an external laboratory.

Treatment

The empirical antibiotics of choice for sporadic cystitis are aminopenicillins (amoxicillin without clavulanate) or sulfa/trimethoprim (see Chapter 8 regarding availability). Recent studies of dogs with sporadic cystitis in Danish general practice showed that 87% and 94% of all bacterial isolates from urine are sensitive to amoxicillin and sulfa/trimethoprim, respectively, at the concentrations achieved in urine. 95% of isolates of the most common urinary tract pathogen (*E. coli*) were sensitive to these two antibiotics (8).

Limited evidence is available regarding optimal treatment length for canine sporadic cystitis, but recent studies have shown that 3-day therapy is as effective as one lasting 10-14 days (9-11). Sulfa/TMP was one of the antibiotics trialled as 3-day therapy (10), but not amoxicillin. In humans there is overwhelming evidence of the efficacy of treatment durations of 3-5 days with both sulphonamides and pivmecillinam (12). Based on human studies and the initial evidence from dogs, treatment durations of 3-5 days for sulfa/TMP and 5 days for amoxicillin are recommended (Table 2).

Antibiotics should ideally be withheld until initial culture results are available, provided this is possible within 24 hours. Analgesic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) can start immediately, and should continue for a few days unless contra-indicated. In dogs in which sediment microscopy shows clear evidence of bacterial infection (intracellular bacteria in neutrophils), or in dogs with marked pain, it is acceptable to start antibiotic therapy immediately. One option is to use injectable beta-lactam preparations with 24 hours duration until infection is confirmed by culture.

Delaying antibiotic treatment until infection is confirmed by culture is recommended, provided results will be available within 24 hours. Start analgesic treatment with NSAIDs immediately.

Sporadic cystitis in intact male dogs

Sporadic cystitis is rarely seen in intact male dogs, and underlying prostatitis should be suspected and investigated for (13). Diagnosis and management of prostatitis is described in Chapter 6.5.11. Intact male dogs without evidence of prostatitis can be treated as described above.

Sporadic cystitis in cats

Definition

Sporadic cystitis in cats is defined as for dogs. This represents a major change in thinking, since traditionally urinary tract infection in cats has been considered to be complicated due to the high prevalence of underlying disease (14, 15). Even though cats with cystitis often have a more complex disease profile than dogs, there is currently no evidence that urinary tract infections per se are more complex or more complicated to treat.

Aetiology and prevalence

Studies show a prevalence of symptomatic feline bacterial cystitis of 1-19%, and an increased prevalence in older cats. The large majority of cats with symptoms localised to the lower urinary tract have **idiopathic cystitis**. This is not caused by bacterial infection and should **not** be managed with antibiotics (16, 17).

Diagnosis

The clinical signs are the same as for dogs, but cats also exhibit periuria (urinating in inappropriate places). The diagnostic approach is largely the same as for canine sporadic cystitis. Cats should also be investigated for predisposing underlying conditions.

Treatment

The first-choice antibiotics are amoxicillin or sulfa/TMP given for 5 days (see Table 2). There are no studies on optimal treatment duration in cats, so recommendations are based on human and canine studies.

Recurrent cystitis in dogs and cats

Definition

Recurrent cystitis is characterised by 3 or more episodes of cystitis within a one-year period. Infections which occur within 6 months of previous treatment are also considered recurrent.

Recurrent cystitis can be due to:

1. Reinfection (new occurrence of bacterial infection)
2. Recidivism due to incomplete elimination of the original infection
3. Persistent infection, in which persistent bacteriuria is seen under treatment and between symptomatic episodes (in contrast to recidivism)

Aetiology and prevalence

Recurrent urinary tract infection is often due to a local or systemic abnormality or disease which either predisposes the patient to recurrent infection (see Table 3) or hinders complete elimination of bacteria. The latter can be caused by an untreated bacterial nidus (deep dormant infection in the urinary bladder wall, uroliths, urinary bladder polyps or tumours, prostatitis, pyelonephritis), immune-incompetence or inadequate treatment of the previous infection. The time interval between infections has not been investigated in dogs and cats. As a rule of thumb, recurrent cystitis typically appears soon (within weeks) after the end of treatment, whereas an interval of several months may be seen between reinfections. Reinfections can also occur rapidly (within weeks).

Diagnosis

The diagnostic workup comprises urinalysis and bacterial culture, and sensitivity testing should always be performed as described in Chapter 6.3.1. Use of the same laboratory for repeated testing is advantageous. The isolation of different bacteria from episode to episode is indicative of reinfection, as is the repeated isolation of the same bacteria with a markedly different sensitivity profile. When the same bacteria with identical or similar resistance profiles are isolated, it is difficult to distinguish between reinfection or recurrence, since intestinal flora could be the source of repeated reinfection.

It is vitally important to investigate for underlying factors and diseases, since treatment success is dependent on identification and management of these. The choice of antibiotic, dose and compliance should be factored in to the patient evaluation with recidivistic or persistent infections. Investigations can require the use of advanced diagnostic imaging and cystoscopy. Referral to colleagues with expertise in these fields may be necessary.

Treatment

Treatment should always be based on sensitivity testing. If treatment must be started before this is available, amoxicillin or sulfa/TMP are suitable choices. Adjunctive use of NSAIDs should be considered. The optimal treatment duration has not been investigated, but there is no reason to believe that patients with reinfection benefit from prolonged therapy. Reinfection should therefore be managed as for sporadic cystitis, with 3-5 days of treatment. The recommended treatment duration for recidivistic cystitis (incomplete elimination) depends on the cause. Short durations (3-5 days) are suitable after inadequate management of a previous infection, whereas deep infections of the urinary bladder wall may benefit from longer treatment (1-2 weeks). If urolithiasis, prostatitis or pyelonephritis are identified, treatment protocols for these conditions should be followed.

Monitoring

The aim of treatment is resolution of clinical signs, and repeat bacterial culture is only indicated if the clinical response to treatment is inadequate.

Subclinical bacteriuria in dogs and cats

Definition

Subclinical bacteriuria is defined as the presence of significant numbers of bacteria in the urine without concurrent clinical signs of lower urinary tract disease.

Aetiology and prevalence

Subclinical bacteriuria is seen in both dogs and cats. Studies suggest a prevalence in healthy dogs of 2-9% (18). A much higher prevalence (15-30%) is reported in dogs with underlying disease or immunosuppression (19, 20, 21, 22, 23). In healthy cats, the reported prevalence is only 1% (24), but in cats with systemic disease it is not uncommon to find subclinical bacteriuria (2, 14, 15).

Diagnosis

A positive bacterial culture (as described in Chapter 6.3) confirms the diagnosis. Sediment microscopy findings can vary from normal to active. Any suspicion of underlying disease (see Table 3) should be addressed.

Animals with subclinical bacteriuria do *not* necessarily require antibiotics

Treatment

Antibiotic treatment of subclinical bacteriuria is not recommended. This represents a major change in thinking, since previously the focus has been on eliminating bacteria without considering whether or not there was evidence of urinary tract disease. In humans with subclinical bacteriuria there is good evidence that treatment is unnecessary, even if they have underlying disease (12). On the contrary, treatment of these patients can lead to increased antibiotic resistance and increase the incidence of symptomatic infections (25, 26). There are only a few longitudinal studies of dogs and cats with subclinical bacteriuria, but complications have not been identified in untreated animals (18, 27). In a few cases, treatment may be indicated (e.g. if there is urolithiasis, or in renal patients in which pyelonephritis cannot be excluded, or in severely immunocompromised animals). Only uncontrolled diabetic patients, in which bacteriuria might be contributing to poor control, should receive antibiotics: well-controlled diabetics do not require antibiotic treatment.

Monitoring

Routine monitoring of patients with subclinical bacteriuria is not required.

Urolithiasis-associated infections

Aetiology and prevalence

Cystitis caused by urease-producing bacteria (usually staphylococci and *Proteus*) can lead to struvite urolithiasis in dogs.

Diagnosis

The clinical signs are as described for sporadic cystitis. Bacterial culture and sensitivity testing should be performed as described in Chapter 6.3. An external laboratory should always be used for bacterial identification and sensitivity testing.

Treatment

Dogs with struvite urolithiasis and infection with urease-producing bacteria should be treated with antibiotics regardless of whether or not they have clinical signs of cystitis. Antibiotic choice is guided by sensitivity testing. Many staphylococci are resistant to amoxicillin, and for these patients

amoxicillin/clavulanate is a good choice. Dogs with struvite urolithiasis and bacteria which are not urease-producers (such as *E. coli*), are only treated if there are clinical signs of cystitis. If there are no clinical signs, these patients are managed as for subclinical bacteriuria.

There is little evidence regarding optimal treatment durations in dogs with cystitis and struvite urolithiasis, and historically antibiotic therapy throughout the period of urolith dissolution has been recommended. There is no evidence that this is necessary. A small study in dogs showed that 7 days of treatment was effective (28). Based on this, initial treatment durations of 7 days are recommended.

6.3.3 Upper urinary tract

Pyelonephritis

Aetiology and prevalence

Prevalence data for upper urinary tract infections in dogs and cats do not exist. Ascending infection from the urinary bladder to the kidney is assumed to be the most common cause of pyelonephritis.

Diagnosis

Pyelonephritis causes acute, systemic clinical signs including dehydration, fever, polyuria/polydipsia, depression and anorexia. Abdominal or renal pain may also be seen. The disease can also present in a slowly progressive form with a less obvious clinical picture. Numerous paraclinical abnormalities may be found, including azotaemia, low urinary specific gravity and a dilated renal pelvis. Sampling for bacterial culture from the renal pelvis is necessary to confirm the diagnosis. Pyelocentesis is not routinely performed, and in practice the diagnosis is often made presumptively on the basis of clinical and paraclinical findings in combination with urinalysis, bacterial culture and sensitivity testing performed on urine obtained by cystocentesis, as described in Chapter 6.3.1. Urine from the urinary bladder can be sterile, which makes diagnosis of pyelonephritis challenging. It may be necessary to refer to colleagues with expertise in this field.

Treatment

There are no evidence-based recommendations regarding treatment of pyelonephritis in dogs and cats. The choice of antibiotic should be based on sensitivity testing, and as mentioned in Chapter 6.3.1, it is important to inform the laboratory of the infection's localisation. Empirical antibiotic therapy should be started before culture results are available, due to the risk of compromised renal function. Due to the seriousness of this condition, there is little margin for error in antibiotic choice. Based on Danish resistance profiles for *E. coli* isolated from the urinary tract, fluoroquinolones are recommended as the first line treatment for pyelonephritis. Sulfa/TMP is an alternative, and is recommended in Sweden as first line therapy at a dose of 30 mg/kg. Clinical experience with the use of Sulfa/TMP for pyelonephritis is currently limited. General recommendations are to use the highest possible dose, in order to maximise antibiotic concentrations in the renal parenchyma. Use of internationally recommended doses (29) at the upper end of the dose interval can require off-label use with respect to the licensed recommendations in Denmark, and the owner should be informed of this. Off-label doses should not be used in patients with reduced renal function. Patients with pyelonephritis often require hospitalisation, parenteral antibiotics, and supportive fluid and analgesic therapy. If there is evidence of sepsis, the protocols detailed in Chapter 6.8 should be followed. There are no canine or feline studies on optimal treatment duration for pyelonephritis. Based on established human practice, a treatment duration of 10-14 days is recommended.

Monitoring

Treatment efficacy should be monitored during therapy, and an improvement in clinical and paraclinical signs is expected within 72 hours. Bacterial culture should be repeated 7-14 days following completion of treatment.

6.3.4 Dog and cats with urinary catheters

There is no evidence to support use of prophylactic antibiotics either before, during or after removal of indwelling urinary catheters in dogs or cats. On the contrary, studies suggest that prophylactic antibiotics encourage the development of resistant bacteria (30). Bacterial culture and sensitivity testing should be performed if clinical signs of urinary tract disease develop. Urine should be obtained by cystocentesis and not via the catheter or catheter tip. Treatment durations are as detailed for sporadic cystitis in Chapter 6.3.2.

Table 2. Recommendations for antibiotic treatment of urinary tract infections in dogs and cats.

Infection	Diagnostics	Antibiotic	Comments
Sporadic cystitis in dogs and cats	Urinalysis, culture and sensitivity testing. In-clinic culture can be used.	Amoxicillin (10 mg/kg PO BID for 5 days) [11-15 mg/kg PO TID (10) ^a]. Sulfa/TMP ^b (15 mg/kg PO BID for 3-5 days).	Delay antibiotic treatment until culture results are available (although maximum 24 hours) ^c . Amoxicillin is a time-dependent antibiotic, so TID administration is preferred to ensure a persistent high urine concentration. Analgesic treatment can be started immediately ^d . Check intact male dogs for evidence of prostatitis.
Recurrent cystitis in dogs and cats	Urinalysis, culture and sensitivity testing. Use an external laboratory.	Amoxicillin (10 mg/kg PO BID) [11-15 mg/kg PO TID (10) ^a]. Sulfa/TMP ^b (15 mg/kg PO BID). Treatment durations: Reinfection – 3-5 days, as for sporadic cystitis; Incomplete elimination – 3-14 days, depending on cause (see text).	Potential underlying or predisposing conditions should be investigated. Monitoring: culture should be repeated if no clinical response is seen.
Subclinical bacteriuria in dogs and cats	Urinalysis and culture.	Antibiotic treatment is not normally recommended if there are no clinical signs.	See text for exceptions.
Infections associated with struvite urolithiasis in dogs	Urinalysis, culture and sensitivity testing.	Amoxicillin (10 mg/kg PO BID) [11-15 mg/kg PO TID (10) ^a]. Amoxicillin/clavulanate [if staphylococci] (12.5 mg/kg IM, SC or PO BID) [12.5-25 mg/kg PO TID (10) ^a]. Treatment duration: 7 days.	Dogs without clinical signs of cystitis should only be treated if urease-producing bacteria are present, such as staphylococci or <i>Proteus</i> .

Upper urinary tract infection (pyelonephritis) in dogs and cats	Urinalysis, culture and sensitivity testing.	<p>Fluoroquinolones: Enrofloxacin (5 mg/kg, IM, SC or PO SID) [dog: 20 mg/kg (10)]^a, pradofloxacin (3-4.5 mg/kg PO SID), or marbofloxacin (2 mg/kg PO SID) [2.5-5.5 mg/kg PO SID]^a.</p> <p>Alternative to fluoroquinolones: Sulfa/TMP (30 mg/kg IV, IM, SC or PO BID).</p> <p>Treatment duration: 10-14 days.</p>	<ul style="list-style-type: none"> ➤ Parenteral antibiotics and supportive therapies necessary for acute pyelonephritis. ➤ Monitor response to therapy with culture 7-14 days after cessation of therapy. ➤ Use of the highest possible doses are recommended (international recommendations are given in brackets []), except in patients with reduced renal function. ➤ Enrofloxacin and marbofloxacin are not recommended for cats with reduced renal function.
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^aRefers to the licensed dose for use in Denmark. International recommended doses are given in square brackets where these differ from the licensed dose.

^bAmoxicillin and sulfa/TMP can both be considered first-choice antibiotics for cystitis.

^cStart antibiotic therapy immediately in dogs with obvious signs of pain or with evidence of infection on urine sediment examination. Consider using an injectable product with 24-hour duration until culture results confirm infection.

^dCaution should be exercised with the use of NSAIDs in patients with unknown renal status.

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6.4 The oral cavity and gastrointestinal tract

Overview

The gastrointestinal (GI) tract contains a complex ecosystem, termed the gut microbiota, which includes the bacteria, virus, fungi and protozoa which live in the gastrointestinal tract. Bacterial numbers vary throughout the GI tract, with the lowest numbers in the stomach (10^1 - 10^6 CFU/g) and with numbers increasing along the small intestine (10^1 - 10^9 CFU/g) and colon (10^9 - 10^{11} CFU/g). The GI microbiota is affected by many factors, including gut motility, available substrates, pH, bile acids and pancreatic secretions.

Diagnosis

Patients with GI problems should undergo a routine clinical examination that can be supplemented as needed with additional investigations such as blood, urine and faecal tests, ultrasonography, radiography and endoscopy (including biopsies for histopathology) depending on the severity and duration of the condition.

Evaluation of faecal samples includes culture for enteropathogens and identification of possible enterotoxins. Before culture is performed a parasitological examination including flotation and investigation for protozoa (e.g. *Giardia* and *Cryptosporidium*) should be performed. In relevant cases (primarily puppies), testing for parvovirus may be indicated. **As will be emphasised in the following sections, culture results should be interpreted with caution due to unproven causative relationships in many cases, and because most bacteria can also be isolated from healthy animals.** Bacteriologic investigations of faeces are, unfortunately, frequently overinterpreted, resulting in either treatment for normal flora or treatment of infections that should be self-limiting in immunocompetent animals.

6.4.1 Oral infections

The oral cavity contains a diverse mix of Gram-positive and Gram-negative anaerobes and aerobes. All oral interventions induce a temporary bacteraemia that under normal circumstances is eliminated by the immune system. The most common inflammatory conditions of the oral cavity are gingivitis, parodontitis, stomatitis and root abscesses. **Gingivitis** is a local inflammation of the gingiva often caused by dental plaque. Predisposing factors for gingival infections are viral infections and immunosuppression. **Periodontitis** is inflammation of the periodontal tissues, leading to irreversible tissue loss around the tooth. **Stomatitis** is inflammation of the oral mucosa, often accompanied by secondary bacterial infection. Chronic stomatitis is more often seen in cats than in dogs and is frequently idiopathic. **Root abscesses** and open fractures both involve the bony structures of the upper or lower jaws.

Diagnosis

The diagnosis of oral infections is based on clinical signs together with oral investigations. Radiography is required to confirm the presence of root abscesses.

Treatment

In many cases, treatment and prevention of oral infections can be achieved with antiseptic preparations, e.g. chlorhexidine. Gingivitis and plaque formation can be prevented by daily use of liquid or gel chlorhexidine formulations, although pre-existing plaque must be removed mechanically. Antibiotics are generally reserved for patients with local or systemic signs of infection,

for example prominent swelling, pus, fever, lymphadenopathy or raised leukocyte count. Before initiating empirical antibiotic therapy, the following points should be considered:

1. Empirical therapy should be based on evidence which has shown that clindamycin (first choice) and amoxicillin/clavulanate (second choice) are effective against oral infections in dogs and cats.
2. Bacterial culture and sensitivity testing are recommended.
3. Combination therapy should be reserved for severe infections.
4. A treatment duration of 7 days is recommended, although osteomyelitis warrants 21-28 days treatment

In the case of gingivitis, thorough dental cleaning is usually sufficient to treat the inflammation. Cleaning can be supplemented with antiseptic preparations as described earlier. Routine treatment of gingivitis with antibiotics is unwarranted. Periodontitis does not require antibiotic therapy but instead demands professional periodontal treatment and ongoing monitoring of plaque build-up.

Oral surgery and dental extractions

Periodontal treatments such as extraction or surgical interventions in the oral cavity induce a bacteraemia that is usually eliminated by the immune system within approximately 20 minutes. Prophylactic antibiotic treatment should be reserved for patients that cannot tolerate this bacteraemia, such as geriatric patients and patients with heart disease, systemic illness or immunosuppression. In addition to topical antiseptic preparations, these patients can receive clindamycin (5.5-11 mg/kg PO) or amoxicillin (20 mg/kg IM) 20-30 minutes prior to surgery. Dosing can be repeated approximately 6 hours later if necessary.

6.4.2 Acute gastroenteritis

Acute gastroenteritis is defined as the appearance of clinical signs referable to the GI tract (vomiting, anorexia and diarrhoea) within the previous few hours to days. Acute gastroenteritis is often self-limiting and resolves within 1-2 weeks. In most cases, antibiotic treatment is unnecessary.

Aetiology and prevalence

Acute gastroenteritis is common in dogs and cats and can be related to feeding (food intolerance, sudden dietary changes, and toxins), infectious agents (bacteria, viruses, and parasites), acute pancreatitis, or physical problems (such as foreign bodies or intussusceptions). Important information to collect when considering possible aetiologies includes the patient's age, duration of symptoms (acute, chronic or recurrent), general condition, vaccination status, feeding (commercial diet, bones and raw food (BARF), etc.), likelihood of dietary indiscretion, the presence of haematemesis, haematochezia or melena, and the presence of similar cases locally together with the possibility of enteropathogens in the household (either from other animals or humans).

A recent study showed that marked changes in the gut microbiota occur during acute gastroenteritis, including a decrease in the numbers of 'good bacteria' that produce short-chain fatty acids in the lumen (*Blautia* spp., *Faecalibacterium* spp. and *Turicibacter* spp.) (27). Bacteria previously categorised as pathogens, such as *Salmonella* spp., *Campylobacter jejuni*, *Clostridium perfringens*, *Clostridium difficile* and enteroinvasive/enteropathogenic *E. coli*, are now classified as opportunistic pathogens (22). A large study of cases of canine acute diarrhoea found these opportunistic pathogens in only 10% of affected dogs (3).

Campylobacter

The prevalence of *Campylobacter* is roughly the same in both healthy and clinically affected animals. *C. jejuni* and *C. upsaliensis* are seen most commonly, with a prevalence of 0-53% (22).

Campylobacter infection rarely produces clinical signs. In one study, the prevalence of *C. jejuni* and *C. upsaliensis* was twice as high in young dogs (under one year old) with diarrhoea, compared to healthy young dogs. A similar correlation has not been found in older dogs, indicating that *Campylobacter* infection is mostly relevant in young dogs (2). Clinical signs include mucoid or watery diarrhoea (occasionally bloody), fever for 3-7 days, vomiting and anorexia. Concurrent infection with other enteropathogens such as parvovirus, *Giardia*, endoparasites or *Salmonella* can worsen these signs. *Campylobacter* infection is zoonotic, and owners should be counselled on hygiene precautions to reduce the risk of transferring infection at home.

Salmonella

Clinical salmonellosis is rare in companion animal practice. International studies have shown a prevalence of 0-4% in healthy dogs and 0-9% in dogs with diarrhoea (22). The prevalence of *Salmonella* has been shown to be much higher in dogs and cats fed raw food diets such as BARF (17, 20). Infection is often asymptomatic, but can give symptoms such as fever, depression, vomiting and diarrhoea. Affected patients require supportive treatment and should be monitored for signs of sepsis. *Salmonella* infection is zoonotic, and owners should be counselled on hygiene precautions to reduce the risk of transferring infection at home.

Clostridium difficile

C. difficile is a common enteropathogenic bacteria in humans and in horses. The clinical significance of toxigenic *C. difficile* in dogs and cats is unknown. The bacteria can be isolated in the faeces of 0-58% of healthy dogs, most commonly in younger dogs (22). In dogs with diarrhoea, *C. difficile* was found in 10-21% of patients (3, 33).

Clostridium perfringens

C. perfringens is an opportunistic pathogen that has been found in 11-100% of healthy dogs and 43-63% of healthy cats. In dogs with diarrhoea, the prevalence is 27-86% (22, 24, 27, 30). Clinical signs of *C. perfringens* infection range from acute to chronic small and large bowel diarrhoea to acute haemorrhagic diarrhoea syndrome (AHDS, see later) (22, 23, 30). Strains of *C. perfringens* are classified into biotypes A-E based on toxin production. The most common strain in dogs and cats is biotype A. Recently, 2 subtypes of enterotoxin A have been identified, termed NetE and NetF. These could in the future aid identification of more serious infections for which antibiotic therapy could be needed (23).

Escherichia coli

The significance of enteropathogenic or enterotoxin-producing *E. coli* in the development of acute and chronic diarrhoea in dogs and cats is still uncertain. Enteroinvasive *E. coli* has been shown to influence the development of the rare condition histiocytic colitis in Boxers and French bulldogs (4, 21). This condition is covered in more detail later, and should not be confused with inflammatory bowel disease (IBD), which is also seen in these breeds (18).

Faecal culture reports should always be interpreted cautiously, since most bacteria can also be recovered from healthy animals.

Treatment

The primary aim of therapy is to prevent and replace fluid losses. Surgery is indicated for the removal of foreign bodies and treatment of intussusception. Historically, antibiotics have often been used in acute gastroenteritis, but the fact that the majority of infections are self-limiting means that supportive treatment will be sufficient in most cases.

Gastrointestinal infections are often self-limiting and antibiotic therapy is rarely required.

Use of antibiotics for GI problems requires careful consideration, since unnecessary use will disturb the normal flora and select for resistant strains. Antibiotics should be reserved for patients with severe mucosal damage secondary to parvovirus, which are severely ill, or which show signs of sepsis (see Chapter 6.8). The choice of antibiotic should as far as possible be based on sensitivity testing.

Table 1. Antibiotics with effect against specific enteropathogens.

Infection	Antibiotic	Comments
<i>Campylobacter</i> spp.	Erythromycin (10-15 mg/kg) PO, BID for 5-10 days.	Note that these infections are often self-limiting in nature. Antibiotic treatment is only recommended in patients which are severely clinically affected. If signs of sepsis are seen, refer to Chapter 6.8.
<i>Clostridium perfringens</i>	1. Amoxicillin 10 mg/kg BID for 5-7 days. 2. Metronidazole (10-20 mg/kg in dogs and 62.5 mg total dose in cats) PO, BID for 5-7 days.	
<i>Salmonella</i> spp.	Select according to sensitivity profile.	

Acute haemorrhagic diarrhoea syndrome (AHDS)

AHDS, formerly known as haemorrhagic gastroenteritis (HGE), is a specific disease characterised by a necrotising enteritis with an acute presentation of bloody diarrhoea and high risk for serious dehydration. AHDS can rapidly become life-threatening. It should be noted that the majority of dogs with acute gastroenteritis and mildly bloody faeces do not have AHDS. Patients with AHDS exhibit reduced numbers of important bacteria of the gut microbiota (*Blautia* spp., *Faecalibacterium* spp., and *Turicibacter* spp.). This facilitates sporulation and growth of, for example, toxigenic *Clostridium perfringens*. A relationship between AHDS and *C. perfringens* enterotoxin has been found (22, 23, 30).

Patients with AHDS represent a group in which empirical antibiotic therapy can be necessary for some, although far from all patients require it. **Most cases are self-limiting with supportive therapy.** Studies have shown that treatment with amoxicillin/clavulanate does not shorten the duration of vomiting and diarrhoea in patients without sepsis (29). Bacterial culture is always indicated in these patients, but clinical signs can worsen rapidly, and treatment may be needed before culture results are available. AHDS causes a breakdown of the mucosal barrier and patients are at risk of rapid deterioration and development of sepsis. If this happens, the disease can prove fatal and hospitalisation with intensive care is required. Close monitoring for signs of sepsis is recommended in these patients, and if seen, treatment should be instituted as described below.

Patients with bloody diarrhoea can be divided into three groups:

1. Mild bloody diarrhoea, without clinical dehydration or systemic illness.
2. Severe bloody diarrhoea with clinical dehydration, but no evidence of sepsis.
3. Severe bloody diarrhoea with clinical dehydration and evidence of sepsis.

Signs of sepsis include elevated pulse frequency, increased or decreased respiratory frequency, fever or hypothermia, and leukocytosis or leukopaenia (see Chapter 6.8).

Recommended treatment

- Group 1: Patients should be managed at home with supportive therapy (e.g. pre- or probiotics, and dietary management). The owner should be advised to contact the clinic immediately if the condition worsens.
- Group 2: Patients should be hospitalised for fluid therapy and monitoring for sepsis. Supportive treatments such as antiemetics, analgesia, pre- and probiotics and assisted enteral feeding are indicated.
- Group 3: Patients should be hospitalised for intensive fluid therapy and parenteral antibiotics. Most patients respond to ampicillin (10-20 mg/kg IV q6-8 hours). If the patient fails to respond or worsens, add enrofloxacin (5 mg/kg IV q24 hours). Enrofloxacin is contra-indicated in growing animals. Further information on the management of sepsis can be found later (see Chapter 6.8).

Acute haemorrhagic diarrhoea syndrome should only be treated with antibiotics if there is evidence of sepsis.

6.4.3 Gastritis

Aetiology

It is rare that the cause of gastritis is identified, but the following conditions should be considered: systemic disease, foreign bodies, food allergies or intolerances, drug side-effects and infections. *Helicobacter* spp. have been shown to be important pathogens in human gastritis patients, but their significance in dogs and cats is less clear. A range of different *Helicobacter* species have been isolated in recent years from both dogs and cats, including *H. felis*, *H. bizzozeronii*, *H. salmonis* and *Candidatus Helicobacter heilmannii*. These bacteria occur commonly in the gastric mucosa of both healthy animals and patients with chronic gastritis. In some studies, certain species have been assumed to be pathogenic whereas other studies have concluded that there is no significant relationship between infection and clinical signs.

Diagnosis

Symptoms of gastritis include anorexia, melena, haematemesis and vomiting of gastric contents or bile. *Helicobacter* spp. can often be identified on histology of gastric biopsies where these spiral bacteria can be localised to the mucous, crypts or parietal cells. Although species identification can be performed using PCR, this is currently a research tool rather than a diagnostic aid.

Treatment

Gastritis is an inflammatory condition, and treatment with antibiotics is **not** indicated, given the uncertain significance of *Helicobacter* or other bacteria in the development of gastritis. Patients with

gastric ulcers should be treated with proton-pump inhibitors initially, and supplemented with antibiotics only if sepsis develops as a sequel to perforation and peritonitis. Omeprazole and pantoprazole are the most potent proton-pump inhibitors.

6.4.4 Inflammatory bowel disease

Aetiology, prevalence and diagnosis

The term inflammatory bowel disease (IBD) covers a group of chronic inflammatory disorders of the GI tract that produce chronic anorexia, vomiting and diarrhoea with a duration exceeding 4 weeks. The diagnosis is based on gastrointestinal biopsies. Several types of IBD have been defined:

1. Lymphoplasmocytic enteritis/colitis.
2. Eosinophilic enteritis/colitis.
3. Lymphangiectasia.
4. Histiocytic (granulomatous) colitis.

Treatment

Prednisolone alone has been demonstrated to be as effective for treatment of IBD as combining prednisolone with metronidazole. The recommended strategy for managing IBD is therefore use of prednisolone, and/or other immunosuppressives, in combination with dietary management.

Histiocytic/granulomatous ulcerative colitis in Boxers and French bulldogs is caused by an enteroinvasive *E. coli* (Adherent and Invasive *E. coli*, or AIEC) attacking the colonocytes, and is the only IBD subtype for which antibiotic therapy is indicated. The diagnosis is confirmed by routine histopathologic examination, along with a fluorescence in situ hybridisation (FISH) test, of colonic biopsies. Further information can be found at the Cornell University College of Veterinary Medicine website (www.cornell.edu/labs/simpson). A clinical response is seen with long-term antibiotic therapy, for example using enrofloxacin (5 mg/mg PO SID) for 4-6 weeks (5).

Patients with inflammatory bowel disease should be treated with immunosuppressives and dietary management. Antibiotics should not be used unless a diagnosis of histiocytic/granulomatous colitis has been made.

6.4.5 Intestinal dysbiosis

Intestinal dysbiosis refers to an imbalance in the gut microbiome. There is frequently a reduction in microbiome diversity. This is also seen in a group of patients which previously have been characterised as suffering from small intestinal bacterial overgrowth (SIBO), but in which it is more appropriate to describe as a loss of intestinal bacterial diversity rather than bacterial overgrowth.

Intestinal dysbiosis is common in, but not exclusive to, chronic gastroenteritis in dogs and cats. There are currently no validated tests for dysbiosis, and the diagnosis is therefore usually tentative.

Treatment

To reverse the dysbiosis, treatment should focus on limiting the disease process in the intestines by reducing exposure to elements that can trigger the sensitive gastrointestinal immune defences. **Use of antibiotics should be avoided as far as possible**, because they reduce intestinal bacterial diversity and thus have the potential to worsen the situation. Patients suspected to have dysbiosis should be

investigated for underlying gastrointestinal disease. In dogs with chronic gastrointestinal signs, the following approach is recommended:

1. Investigate for intestinal parasites, and perform blood tests for B12, folate, and possibly cPLI and TLI.
2. See if the disease is diet-responsive by trialling a hypoallergenic diet for 4 weeks.
3. If there is no response to the diet, consider adding a pre- or probiotic supplement.
4. Take intestinal biopsies (endoscopic or full-thickness) for histopathology.
5. If treatment so far has been ineffective, and based on histopathology, assess if the condition is steroid-responsive.
6. If the response is inadequate, add an additional immunosuppressives, such as cyclosporine.
7. If there is no response to these approaches, test the response to antibiotic therapy.

There is very little evidence for the efficacy of antibiotics in dysbiosis, and treatment runs the risk of worsening the condition. The following recommendations reflect the results of various studies that have shown a beneficial effect. The first-choice antibiotic is tylosin (10-15 mg/kg PO q8-12 hours): tylosin is not licensed for use in companion animals, making its use problematic. The second-choice antibiotic is metronidazole (10 mg/kg PO q8-12 hours): it should be noted that metronidazole is an important human antibiotic and positioned high on the antibiotic pyramid (see Figure 1, Chapter 1.7). Treatment duration is dependent on the clinical response.

Patients which do not respond to any of the treatment steps, or in which recurrence is seen following the end of treatment, should be thoroughly investigated again, rather than repeatedly treated with antibiotics.

6.4.6 Giardiasis

Giardiasis is caused by the protozoan *Giardia intestinalis* (also called *G. duodenalis* and *G. lamblia*), and is included here because antibiotics are commonly employed in its treatment, even though as a rule this is unnecessary.

Diagnosis

Due to intermittent shedding of *G. intestinalis*, single faecal tests have a sensitivity of only 70%. Collection of faecal samples over 3-5 days can improve test sensitivity (1, 14, ESCCAP guidelines). The following methods may be used to diagnose Giardia:

1. *Giardia* IDEXX ELISA snap-test (sensitivity 89%, specificity 100%) is a widely available in-house test.
2. Immunofluorescence staining or PCR (available at diagnostic laboratories).
3. Zinc sulphate concentration test (available at diagnostic laboratories) permits identification of cysts, and has the same sensitivity as the IDEXX snap-test.
4. Microscopic examination of fresh faecal smears to reveal ovoid cysts or motile pear-shaped trophozoites.

Salt flotation tests, commonly used in-clinic for diagnosis of roundworm infestation, causes deformation of the *Giardia* cysts and this method should not be used for *Giardia* diagnosis.

Treatment

Treatment of *Giardia* with one of the preparations described below should be combined with intensive hygiene measures.

- First choice is fenbendazole (50 mg/kg PO q24 hours for 5 days). Treatment can be repeated if clinical signs and oocyst shedding persist.
- An alternative is use of a combination tablet containing febantel, pyrantel and praziquantel (5 mg/kg febantel, 14.4 mg/kg pyrantel and 5 mg/kg praziquantel PO q24 hours for 3 days) (see ESCCAP guidelines).
- Metronidazole (25 mg/kg q12 hours for 5 days) is also effective but its use should be restricted to refractory cases.

The patient should be washed using a shampoo containing chlorhexidine digluconate at the start and end of treatment in order to reduce the risk of reinfection. Thorough cleaning and disinfection of the patient's home environment (including baskets, bedding, feeding bowls and litter trays) is recommended alongside collection and disposal of faeces.

Further information on preventative measures and on other protozoans (e.g. *Cryptosporidium*) can be found on the website of the European Scientific Counsel Companion Animal Parasites (ESCCAP) at www.ESCCAP.org.

Table 2. General recommendations for antibiotic use in gastrointestinal disease (adapted from (15)). Refer to the disease-specific section for details on products, doses and treatment duration.

Antibiotic therapy is *not* indicated for:

- Acute non-haemorrhagic and haemorrhagic enteritis without evidence of sepsis
- Findings of specific enteropathogens unless there is concurrent severe clinical illness and/or evidence of sepsis
- Acute haemorrhagic diarrhoea syndrome (AHDS) without evidence of sepsis
- Intestinal dysbiosis, except in exceptional cases (see text).
- Giardia infection – this should be initially treated with fenbendazole.
- Inflammatory bowel disease (IBD), unless granulomatous/histiocytic colitis is demonstrated.

Antibiotic therapy *is* indicated for:

- Acute haemorrhagic diarrhoea syndrome (AHDS) with evidence of sepsis
- Granulomatous/histiocytic colitis
- Findings of specific enteropathogens with concurrent severe clinical illness and/or evidence of sepsis
- Parvovirus infections

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6.5 The reproductive system

6.5.1 Overview

The vagina, vestibule and prepuce of normal dogs and cats normally contain a mixed bacterial flora (1, 2). This flora is similar to the bacteria found on the perineum. The vaginal flora varies somewhat during the oestrous cycle, with a more extensive bacterial population (qualitatively and quantitatively) during oestrous compared to anoestrous. It is now known that the uterus is not sterile and normally contains a limited mixed population of bacteria at all stages of the oestrous cycle, primarily in dioestrus. The vaginal flora does not reflect the uterine flora in healthy bitches (3).

Mating and pregnancy

The presence of bacteria in the reproductive tract is normal, and antibiotic therapy can disturb the vaginal flora and result in reduced fertility as well as selection for resistant strains (4). Only a combination of clinical signs and either pure bacterial culture or moderate to vigorous growth of especially *E. coli*, beta-haemolytic streptococci such as *S. canis*, or *Mycoplasma canis* is indicative of inflammation and the need for antibiotic treatment.

Because of the risk for foetal abnormalities, treatment of pregnant bitches and queens with antibiotics and other medications should be restricted to those that are necessary for the treatment of serious disease in these patients (5). Aminopenicillins such as amoxicillin (with or without clavulanate) are the first-choice antibiotics for infections in pregnant animals.

Spermatogenesis

Data on reproductive toxicity of antibiotics are generally lacking, but aminopenicillins such as amoxicillin (with or without clavulanate) and fluoroquinolones such as enrofloxacin can often be used in males without apparent adverse effects on spermatogenesis. As for females, antibiotic treatment of male breeding animals should be restricted to that required for management of illness. Antibiotic use in healthy breeding animals is not recommended because it can disturb the normal genital bacterial flora.

6.5.2 Juvenile vaginitis

Juvenile vaginitis causes a yellow vaginal exudate in otherwise healthy immature bitches. The symptoms normally disappear with the first oestrous cycle. Topical treatment with chlorhexidine or another mild disinfectant, or with a short acting oestrogen ointment can be considered. Juvenile vaginitis should only be treated with systemic antibiotics if there is concurrent urinary tract infection (see Chapter 6.3).

6.5.3 Vaginitis in adult bitches

Aetiology and prevalence

Vaginitis is nearly always a secondary problem, and can be caused by urine pooling, strictures, foreign bodies, tumours or an enlarged clitoris/penis if the animal is a hermaphrodite or pseudohermaphrodite.

Diagnosis

Digital and vaginoscopic examination of the vagina, and vaginal cytology should be supplemented by bacterial culture in animals with characteristic symptoms (vaginal discharge). Sampling should always be done with a speculum. If there has been prior antibiotic therapy, fungal culture should also be performed.

Treatment

The underlying cause should be treated, if possible. Topical treatment consists of washing/flushing with mild antiseptics. This can be supplemented, if necessary, by antibiotic treatment based on sensitivity testing. Human Lactobacillus preparations are not effective, as the canine vagina is not naturally acidic, but rather neutral or mildly alkaline.

6.5.4 Acute metritis

Aetiology and prevalence

Acute metritis is a bacterial infection of the uterus. Metritis typically occurs following abortion, dystocia, contamination from assisted parturition, or retained placenta. Reduced uterine tone predisposes to metritis. Usually, the cause is an ascending infection by bacteria such as *E. coli*, *Staphylococcus* spp., *Streptococcus* spp., *Proteus* spp. and *Corynebacterium* sp. (4).

Diagnosis

Typical signs include a foul purulent vulvar discharge, depression, agalactia, fever and anorexia in the dam, and restless and noisy pups. Samples should be obtained from the cranial vagina for bacterial culture. If the signs are associated with abortion in the last third of pregnancy or with the birth of weak puppies, serological testing for *Brucella canis* should be considered. *Brucella canis* is a zoonosis.

Treatment

Treatment should be initiated immediately with aminopenicillins such as amoxicillin (with or without clavulanate), which is well tolerated by puppies and kittens, if present. If blood samples indicate low ionised calcium levels then supplemental calcium should be given (IV, SC or PO). Acute metritis can be life-threatening and treatment for sepsis may be necessary (see Chapter 6.8). In peracute presentations, the clinician should consider the possibility of peritonitis or uterine rupture. Local intrauterine antibiotic therapy administered transcervically is a potential alternative or supplement to systemic antibiotics. Aglepristone is not effective for uterine emptying after parturition due to low progesterone concentrations: suitable ecbolic agents include oxytocin and PGF_{2α} or PGF_{2α}-analogues.

6.5.5 Endometritis and cystic endometrial hyperplasia (CEH)

Aetiology and prevalence

Endometritis, and in particular breeding-induced endometritis (BIE), is a significant problem in bitches (7-10). Bitches with cystic endometrial hyperplasia have a prolonged uterine clearance and are predisposed to BIE (8, 9, 11).

Diagnosis

Reaching a diagnosis can be difficult without taking uterine biopsies (12, 13). Uterine lavage for cytology and bacterial culture is an alternative diagnostic procedure, but has a lower sensitivity and specificity than uterine biopsies. Sampling is associated with a risk of inducing pyometra. Considerable experience with histopathological interpretation of uterine biopsies is essential (7, 12), and an expert should be consulted. Acute endometritis is often associated with an eosinophilic infiltration, whereas chronic endometritis exhibits a lymphocytic or lymphoplasmocytic infiltration (12). Most affected bitches are infertile, but are otherwise clinically normal. Occasionally, there may be vulvar discharge or depression. A prolonged uterine clearance after mating is indicative of BIE: this can be demonstrated by ultrasonography, which can also give an indication of the extent of inflammation, especially in acute cases (13, 14). Vaginal cytology or bacterial cultures are rarely helpful (3); in addition, haematologic parameters are typically within reference ranges for healthy dogs. Before commencing treatment, samples from the uterus should be sent for bacterial culture.

Treatment

Acute endometritis is most often treated systemically with either amoxicillin/clavulanate for 5-7 days or TMP/sulpha for 7-10 days. Intrauterine treatment with penicillins or cephalosporins, either in combination with or instead of systemic antibiotics, can be considered once bacterial culture results are available. Intrauterine antibiotic treatment requires transcervical catheterisation. Concurrent use of aglepristone and possibly PGF₂α or PGF₂α-analogues is recommended, particularly if there is fluid in the uterus. Clinicians should bear in mind the side-effects of PGF₂α and PGF₂α-analogues (anorexia, vomiting and diarrhoea), and only use them if the cervix is open. Side-effects can be minimised by using low doses. Follow-up ultrasonography is essential to confirm the effect of treatment. Patients with **prolonged uterine clearance or BIE**, can be managed empirically with TMP/sulpha for 4 days PO. If **chronic changes** are seen on histopathology, a 2-week course of either TMP/sulpha (first-choice) or a fluoroquinolone (e.g. enrofloxacin, only if indicated by culture and sensitivity testing) is recommended to increase the chances of pregnancy (11). If there is fluid in the uterus, use of aglepristone and possibly PGF₂α or PGF₂α-analogues is again recommended. Recurrent disease is usually managed by ovariohysterectomy.

6.5.6 Pyometra

Aetiology and prevalence

Pyometra usually occurs in dioestrus (>60% of cases). The precise aetiology and pathogenesis are still unclear. Classically, CEH-associated degenerative changes are believed to create optimal conditions for uterine infection with opportunistic bacteria, primarily *E. coli*, which ascend from the vagina (10). Progesterone mediates the disease, and oestrogens exacerbate progesterone's effects. Alternatively, local uterine irritation (e.g. due to foreign material) could lead to a trophoblastic reaction and bacterial proliferation, which induces pyometra. Pyometra can be fatal if sepsis develops or complications occur.

Diagnosis

If the cervix is open, a (muco-)purulent vulvar discharge is seen. Depression, loss of appetite, vomiting, polyuria and polydipsia are common clinical signs. No discharge will be seen, if the cervix is closed. Consequently, pyometra is a differential diagnosis in all intact bitches with non-specific illness. Ultrasonography, or radiography, can confirm the diagnosis. The severity of clinical signs, the presence of an open or closed cervix, and uterine diameter do not necessarily correlate with the degree of systemic compromise. Samples for bacterial culture and sensitivity testing should be taken immediately, and blood samples to look for systemic inflammatory response syndrome (SIRS) and to evaluate renal function.

Treatment

Medical treatment with aglepristone and possibly PGF₂α or PGF₂α-analogues can be used if the owner is unwilling to neuter the patient because of an intended later use for breeding, and if the patient is otherwise in good health and relatively young (ideally <5 years old). Oestrogen-producing ovarian tumours or cysts should be ruled out before medical treatment, as these will increase the risk of recurrence. Progesterone levels must be over 1 ng/ml so that aglepristone is effective. Antibiotic therapy should be effective against Gram-negative bacteria. Depending on the severity of the disease, a fluoroquinolone (e.g. enrofloxacin) is recommended as first choice. Amoxicillin/clavulanate is also an option, but its efficacy against *E. coli* is less certain. Antibiotic treatment should be continued for 5-6 days. A new protocol for aglepristone consisting of injections on days 0, 2, 5, and 8 may be more effective than the standard protocol of injections on days 0, 1, and 7. Uterine emptying during treatment should be confirmed using ultrasonography. Alternatively, **ovariohysterectomy** may be performed – see Chapter 5.2 for guidelines on perioperative antibiotic use.

6.5.7 Mastitis

Aetiology and prevalence

Infections of the mammary glands can occur during lactation post-partum, but may also be seen during canine pseudopregnancy. The most common bacterial causes are *E. coli* and staphylococci.

Diagnosis

Acute mastitis can be life-threatening. The affected mammary gland becomes hot, painful and tense: abscessation may occur, the skin may become discoloured, and fever and depression may be seen. Milk from the affected gland is typically yellowish, brown or blood-tinged. Following cleaning and disinfection of the teat and surrounding skin, milk should be pressed from the teat for bacterial culture and sensitivity testing.

Treatment

Infected glands should be milked out several times daily. In severe cases and when the bitch is systemically ill, the puppies should be removed and fed with milk-replacer. If only one gland is affected, and the condition is relatively mild, access to the gland can be prevented with adhesive tape to avoid intake of infected milk by the puppies. If the mastitis is gangrenous or abscesses

develop, these should be opened and drained. In these cases, specific treatment to prevent sepsis can be necessary. The first-choice antibiotic for these patients is amoxicillin/clavulanate, since it is safe for both the bitch and puppies. Treatment should be continued for 7-10 days (16).

6.5.8 Caesarean section

Antibiotic therapy is not needed in uncomplicated cases. If the uterus is damaged, or if parturition has been prolonged and difficult, it may be appropriate to use antibiotics prophylactically to prevent spread of infectious agents into the bloodstream. Aminopenicillins (e.g. amoxicillin/clavulanate) are a suitable choice.

6.5.9 Balanoposthitis

A mucoid to pus-like discharge from the prepuce is often seen in dogs and is usually not a sign of inflammation, but rather preputial smegma (epithelial cell debris and accumulations of fluids such as urine or semen). Smegma can bother owners, but is not dangerous for the dog, and does not require antibiotic treatment. Castration (surgical or using a GnRH implant) will stop excessive smegma production. Preputial flushing will reduce the severity markedly.

Balanoposthitis is characterised by inflammatory changes (reddening, thickening, warmth, pain and disturbed function) of the penile and/or preputial mucosa, and is seen rarely in dogs and cats. Causes include overgrowth of normal preputial flora, anatomical abnormalities, foreign bodies and herpesvirus infection. Topical antibiotic therapy can be used if inflammation is severe and bacterial culture confirms the presence of infection. Systemic antibiotic therapy is rarely indicated. Daily preputial flushing with 0.9% saline or 0.2% chlorhexidine increases the chances of treatment success (17).

6.5.10 Orchitis and epididymitis

Aetiology and prevalence

Causes include blunt trauma, wounds, haematogenous or lymphatic spread of opportunistic bacteria, and autoimmune disease (with or without concurrent thyroiditis). Typically, young dogs are affected, and most often the vaginal process is also involved (periorchiepididymitis). Due to increased international transportation of animals (in particular, breeding animals) clinicians should be aware of the possibility of infection with *Brucella canis* in dogs. An uncommon potential causative agent in cats is feline coronavirus, which also causes Feline Infectious Peritonitis.

Diagnosis

In acute cases, the testis and/or epididymis becomes swollen, warm and painful. Hind limb lameness, purulent discharge and increasing licking of the affected area are common clinical signs. Chronic orchitis is not painful and over time causes atrophy of the affected testis. Ultrasonography along with culture of the second fraction of ejaculate (and urine samples, if there is concurrent cystitis) can confirm the diagnosis. Serology for brucellosis should be considered.

Treatment

Antibiotic therapy alone is rarely successful, and testicular atrophy frequently occurs following infection. Uni- or bilateral castration is recommended, depending on whether or not breeding potential is to be preserved. The first-choice antibiotic is TMP/sulpha and the second-choice is a fluoroquinolone. Treatment should continue for at least 4 weeks. Recurrence is common, especially with shorter treatment durations. Clinical examination and follow-up bacterial culture is recommended at the end of therapy to confirm treatment success.

6.5.11 Prostatitis

Aetiology and prevalence

Benign prostatic hyperplasia, often seen together with prostatic cysts, predisposes to infection in older dogs (18, 19, 20). Prostatitis is unusual in the cat, but has been reported. Infections are most commonly caused by *E. coli*, *Staphylococcus pseudintermedius* and *Staphylococcus aureus* (18, 19, 20).

Diagnosis

Clinical signs include fever, pain on prostatic palpation, bloody or purulent discharge from the urethra, and oedema of the prepuce, scrotum or hind limbs. Finding blood, bacteria and leukocytes in the third fraction of the ejaculate strongly indicates prostatic infection. Ultrasonography can demonstrate prostatic hypertrophy and permit fine needle aspirates from the prostatic parenchyma for cytology and bacterial culture. Alternatively, trans-rectal prostatic massage can be performed, and prostatic fluid sent for culture along with urine samples. Prostatic fluid from the third fraction of the ejaculate can also be used for bacterial culture. Semen collection is usually only possible in chronic prostatitis, since the acute form is too painful: in these cases, fine needle aspirates should be taken to confirm the diagnosis.

Treatment and prognosis

The first-choice antibiotic for prostatitis is TMP/sulpha (18, 19, 20, 21). In severe or life-threatening cases, fluoroquinolones (such as enrofloxacin, marbofloxacin or pradofloxacin) may be used. Treatment is thereafter adjusted based on the results of culture and sensitivity testing and the potential for each medication to cross the blood-prostate barrier (18, 19, 22). There are no data concerning required treatment durations for canine prostatitis. Established practice is up to 4 weeks treatment for acute cases and 4-6 weeks treatment for chronic cases. Shorter treatment durations can be considered in acute presentations, when castration results in a more rapid resolution of clinical disease. Prolonged therapy (up to 12 weeks) may be necessary in exceptional cases, especially if there are prostatic abscesses or if the owner initially declines castration (see notes below) (19). The various risks associated with long-term antibiotic therapy should be considered, including development of drug resistance, liver and kidney damage, and anaemia (see Table 4 in Chapter 1.6). Long-term use of TMP/sulpha can be associated with hypothyroidism, keratoconjunctivitis sicca and non-regenerative anaemia (all dose-dependent), as well as fever, skin eruptions, aseptic polyarthritis and blood dyscrasias such as thrombocytopenia, neutropenia and haemolytic anaemia (all idiosyncratic). Surgical castration, or medical castration using anti-androgens (possibly combined with GnRH agonist implants), can increase the chances of successful treatment.

Table 1. Empirical antibiotic treatment for reproductive tract infections.

Infection	Antibiotic	Comments
Juvenile vaginitis	Usually unnecessary.	Topical therapy with chlorhexidine or similar mild antiseptic can be considered. Oestrogen creams with a short duration of effect can be applied locally.
Adult vaginitis	Wait for culture and sensitivity results.	Topical therapy with chlorhexidine or similar mild antiseptic can be sufficient. Identification and management of the primary cause is important for treatment success in the long term.
Acute metritis	<ol style="list-style-type: none"> 1. Amoxicillin/clavulanate (12.5 mg/kg PO BID for 5-7 days). 2. TMP/sulpha (15 mg/kg PO BID for 5-7 days). 3. Enrofloxacin (5 mg/kg IV SID for 5-7 days) for life-threatening infections. <p><u>Intra-uterine</u> antibiotic therapy with penicillins or cephalosporins can be considered instead of or in addition to systemic therapy.</p>	<p>Supportive treatment with intravenous fluid therapy should be given along with uterotonics (oxytocin, PGF-2α, PGF-2α analogues) and, if needed, calcium.</p> <p>Note that kittens or puppies should be removed from the dam and fed milk replacer if antibiotics which are potentially toxic to them are used (e.g. enrofloxacin, TMP/sulpha).</p>
Endometritis/ cystic endometrial hyperplasia	<p>Acute endometritis:</p> <ol style="list-style-type: none"> 1. Amoxicillin/clavulanate (12.5 mg/kg PO BID for 5-7 days). 2. TMP/sulpha (15 mg/kg PO BID for 5-7 days). <p><u>Intra-uterine</u> antibiotic therapy with penicillins or cephalosporins can be considered instead of or in addition to systemic therapy.</p> <p>Prolonged uterine clearance and suspicion of breeding induced endometritis (BIE):</p> <ol style="list-style-type: none"> 1. TMP/sulpha (15 mg/kg PO BID for 4 days). <p>Chronic endometritis:</p> <ol style="list-style-type: none"> 1. TMP/sulpha (15 mg/kg PO BID for up to 2 weeks). 2. Enrofloxacin (5 mg/kg PO SID for up to 2 weeks – only after culture and sensitivity testing)¹. <p><u>Intra-uterine</u> antibiotic therapy with penicillins or cephalosporins can be considered instead of or in addition to systemic therapy.</p>	<p>Acute/chronic endometritis: if there is fluid in the uterus, treatment can be supplemented with aglepristone (10 mg/kg SC, two doses 24 hours apart) or PGF-2α/PGF-2α analogues (e.g. cloprostenol 1 μg/kg SC).</p>
Pyometra	<p>Medical management:</p> <ol style="list-style-type: none"> 1. Enrofloxacin (5 mg/kg PO SID for 5-6 days)¹. 2. Amoxicillin/clavulanate (12.5 mg/kg PO BID for 5-6 days). 	<p>Aglepristone (10 mg/kg SC) on days 0, 2, 5 and 8 (or days 0, 1 and 7). If necessary, supplement with PGF-2α/PGF-2α analogues (e.g. cloprostenol 1 μg/kg SC on days 2-6).</p>

Note that amoxicillin/ clavulanate may not be effective against *E.coli* in the uterus.

Ovariohysterectomy:

Antibiotics are only needed if there is moderate to severe systemic illness or with sepsis (see Chapter 6.8).

Mastitis

1. Amoxicillin/clavulanate (12.5 mg/kg PO BID for 5-7 days).

Milk out several times a day, open and drain any abscesses.

Note that kittens or puppies should be removed from the dam and fed milk replacer if the mother is severely affected, or if other antibiotics are used.

Caesarean section

Antibiotics are only necessary in cases of uterine rupture or dystocia.

1. Amoxicillin/clavulanate (12.5 mg/kg PO BID for 5 days).

See also Chapter 5.2 regarding perioperative use of antibiotics.

Balanoposthitis

Systemic antibiotics are rarely necessary, and should only be used based on culture and sensitivity testing.

Topical therapy with 0.2% chlorhexidine, a similar mild antiseptic, or sterile saline can be considered if there is marked inflammation or if infection is demonstrated on culture.

Note that discharge from the prepuce is usually smegma rather than balanoposthitis. Smegma usually **does not** require treatment. If quantities are excessive or if it bothers the owner, topical flushing solutions can be used. Castration can also reduce smegma production.

Orchitis and epididymitis

1. TMP/sulpha (15 mg/kg PO BID for at least 4 weeks).
2. Enrofloxacin (5 mg/kg PO SID for at least 4 weeks).

Bi- or unilateral castration recommended, particularly in chronic cases.

Prostatitis

1. TMP/sulpha (15-30 mg/kg PO BID for 4 weeks for acute cases, 4-6 weeks for chronic cases).
2. Enrofloxacin (5-15 mg/kg PO SID for 4 weeks for acute cases, 4-6 weeks for chronic cases) – use after culture and sensitivity testing¹.

Note that treatment should be extended to 8-12 weeks if abscessation is seen or if castration is not performed.

Surgical castration or medical management with antiandrogens, possibly in combination with GnRH-agonist implants for medical castration, increase the chances of successful antibiotic therapy. Manage abscesses surgically. Note that the prolonged courses of TMP/sulpha needed here can cause side-effects (see Chapter 1.6).

¹Alternatively, use marbofloxacin (2 mg/kg PO SID) or pradofloxacin (3 mg/kg PO SID).

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6.6 The respiratory tract

6.6.1 Overview

The clinical manifestations of airway disease are variable and include nasal discharge, productive or non-productive coughing, increased respiratory noise, tachypnoea, dyspnoea and exercise intolerance. The first steps in investigating a patient with airway problems consist of localisation of the signs to the upper or lower respiratory tract, followed by more specific localisation to the nasal passages, pharynx, trachea, bronchi, lung parenchyma or pleura.

Causes of respiratory disease include trauma, neoplasia, allergies, parasites and fungal, viral or bacterial infections. A thorough examination will lay the groundwork for the choice of empirical therapy, which often is started before test results are available. Bacterial infections in dogs and cats are frequently secondary to viral or fungal infections. A wide variety of bacterial species can be involved including *E. coli*, streptococci, staphylococci, *Bordetella* and *Pasteurella*.

The results of bacterial cultures from airway samples should always be interpreted cautiously, since even in healthy dogs and cats a multitude of bacteria can be isolated that have no clinical significance. Concurrent cytology can aid interpretation of the microbiological investigations. For example, the presence of *Simonsiella* bacteria along with cornified squamous cells on cytology indicates oral contamination (1). In this situation, cultures are likely to contain one or more aerobic bacterial species. Conversely, cytological samples containing intracellular bacteria strengthen the confidence in a positive culture result, since they are more indicative of a true bacterial infection. Detailed information on bacterial infections of the canine and feline respiratory tracts in Denmark is unfortunately not widely available.

6.6.2 Rhinitis

Aetiology and prevalence

Primary bacterial rhinitis is rare in dogs and cats (2, 3). Primary viral rhinitis due to feline herpesvirus (FHV-1) or calicivirus is seen frequently in the cat in association with a secondary bacterial infection. Even though the cause is viral, antibiotic treatment may be needed if the infection does not improve within 7-10 days or if the patient is clinically compromised. In addition to bacterial and viral causes, fungal infections can occur. Since rhinitis is often lymphoplasmocytic in nature, prednisolone may be a more relevant treatment option than antibiotics.

Diagnosis

CT scans, rhinoscopy and cytology can be used to confirm the diagnosis and rule out conditions such as dental disease, polyps and fungal infection. Culture samples can be obtained with a swab or by flushing the caudal nasal passages, or taken in conjunction with rhinoscopy. Results should be interpreted cautiously since there is a high risk of contamination with normal flora. Culture from tissue samples can be considered as an alternative.

Treatment

Antibiotic choice is based on the expected causative agents which include aerobes (*Pasteurella multocida*, *E. coli*, *Bordetella bronchiseptica*, *Streptococcus* spp., *Pseudomonas* spp.), anaerobes

Bacteroides fragilis, *Fusobacterium nucleatum*, *Peptostreptococcus anaerobias*) and *Mycoplasma felis* (4). Doxycycline is recommended as the empirical first-choice antibiotic with amoxicillin as a second choice (see Table 1).

6.6.3 Tracheitis and bronchitis

Aetiology and prevalence

Infectious tracheobronchitis or 'kennel cough' is a common, multifactorial condition in dogs. A combination of parainfluenza virus (PIV), adenovirus (CAV-2) and *B. bronchiseptica* is frequently responsible but other viruses, including herpesvirus (CHV-1) and influenza virus (CIV), have also been isolated. Primary respiratory pathogens such as *Mycoplasma* spp. can also be involved. The clinical course varies depending on the pathogens present.

Diagnosis

Diagnosis is based on clinical examination and history. Viral isolation and bacterial culture can be performed, but are rarely indicated unless there is either significant lower airway involvement or systemic illness.

Treatment

Infectious tracheobronchitis is frequently self-limiting. Antibiotics are indicated in cases complicated by involvement of the lower airways or the presence of fever. Doxycycline is the first choice due to its efficacy against *Mycoplasma* spp., and the limited occurrence of resistance in *Bordetella bronchiseptica* (see Table 1).

6.6.4 Pneumonia

Aetiology and prevalence

Bacterial pneumonia is more common in dogs than in cats. It is frequently caused by opportunistic infections in immunocompromised patients. Enterobacteria are the most commonly isolated bacteria, but primary respiratory pathogens such as *Mycoplasma* spp., *Bordetella bronchiseptica* and *Streptococcus equi* subsp. *zooepidemicus* may also be found.

Diagnosis

Appropriate clinical signs and the results of thoracic auscultation and radiography are indicative. Bronchoalveolar lavage (BAL) using a bronchoscope or transtracheal washing is recommended in stable patients in order to obtain fluid and/or brush samples for culture and cytology. Culture of *Mycoplasma* spp. requires special transport medium (check with diagnostic laboratory). Cytology should always be performed. Studies indicate that C-reactive protein (CRP) is a good marker for bacterial pneumonia, with a sensitivity of 100% when CRP levels exceed 100 mg/L and a specificity of 100% when CRP levels are below 20 mg/L.

Treatment

In stable patients, which can be managed on an out-patient basis, amoxicillin/clavulanate is an appropriate first choice. Doxycycline is an excellent second choice, especially in milder cases where *Mycoplasma* or *Bordetella bronchiseptica* are suspected (see Table 1) (5). For most pneumonia patients, hospitalisation and more intensive treatment is necessary. Intravenous ampicillin is the empirical first choice antibiotic for **hospitalised patients without signs of sepsis. Unstable patients (e.g. those with sepsis)**, or those which fail to respond to monotherapy, can be treated with a combination of enrofloxacin and ampicillin. Intravenous clindamycin can be used as an alternative to ampicillin in this combination therapy. If a positive response to treatment is not seen within 2-3 days, a change of antibiotic should be considered. Treatment should continue until there are clear signs of improvement radiographically and the inflammatory haemogram has resolved, along with normalisation of biochemistry changes (particularly CRP). Re-evaluate these tests regularly, and not more than 10-14 days after starting treatment.

6.6.5 Aspiration pneumonia

Lung injury can result from inhalation of stomach contents with a low pH, which cause chemical burns to the lung epithelium and a marked inflammatory response with the potential for secondary bacterial infection. Aspiration pneumonia is seen most often in dogs. The significance of bacterial infection in aspiration pneumonia is contentious, but the use of broad-spectrum antibiotics for 2-4 weeks is recommended. Therapy is usually initiated with the combination of IV ampicillin and enrofloxacin. Once the patient is stabilised, therapy may be continued with oral amoxicillin/clavulanate for the remainder of the treatment duration (see Table 1).

6.6.6 Pyothorax

Aetiology and prevalence

Purulent pleuritis (pyothorax) can be caused by viruses, bacteria and fungi. For bacterial infections the most common causes are penetrating thoracic trauma, bite wounds (particularly in cats) and foreign bodies (particularly in dogs). As a result, a wide range of bacteria may be isolated in cases of pyothorax. Anaerobes such as *Fusobacterium* and *Nocardium asteroides* are often seen in dogs, whereas *Pasteurella multocida* along with anaerobes are often found in cats (6-9).

Diagnosis

Thoracic radiographs (both before and after pleural drainage), pleurocentesis and pleural lavage, microbial culture and sensitivity testing, and routine haematology and biochemistry are indicated in the work-up of these patients. Cytology of the pleural fluid typically indicates a septic exudate with a high specific gravity, neutrophilia and intra- and extracellular bacteria.

Treatment

Placement of chest drains and flushing of the pleural cavity is central to the management of patients with pyothorax. A combination of ampicillin and enrofloxacin is recommended for initial antibiotic therapy (6-8), pending results of culture and sensitivity testing. Treatment durations of 4-6 weeks (and up to 16 weeks) are not unusual, but should be tailored to the individual by consideration of clinical signs, reduction in exudate production, and resolution of radiographic changes (see Table 1). The effect of

treatment should be evaluated daily using fluid production, fluid cytology, a haemogram, and inflammatory biomarkers (C-reactive protein in the dog and serum amyloid A in the cat) as guides. If the response to 2-3 days treatment is poor, or if the condition worsens, a change in antibiotics or surgical exploration (using thoracoscopy or thoracotomy) should be considered.

Table 1. Empirical antibiotic treatments for respiratory tract infections.

Infection	Antibiotic	Comments
Rhinitis	<ol style="list-style-type: none"> 1. Doxycycline (10 mg/kg PO SID for 7-14 days). 2. Amoxicillin (10 mg/kg PO SID for 7-14 days). 	Antibiotics are often unnecessary. In chronic cases longer treatment durations may be needed.
Tracheitis and bronchitis	<ol style="list-style-type: none"> 1. Doxycycline (10 mg/kg PO SID for 7-14 days). 2. Amoxicillin (10 mg/kg PO SID for 7-14 days). 	Antibiotics are often unnecessary.
Pneumonia	<p>A.</p> <ol style="list-style-type: none"> 1. Amoxicillin/clavulanate (12.5 mg/kg PO BID). 2. Doxycycline (10 mg/kg PO SID). <p>B. Ampicillin (20 mg/kg IV TID).</p> <p>C. Ampicillin (20 mg/kg IV TID) with enrofloxacin (5 mg/kg SC). Clindamycin (5-10 mg/kg IV BID) may be used as an alternative to ampicillin.</p> <p>Treatment duration is dependent on the clinical and radiographic response (see Chapter 6.6.4).</p>	<p>A. Oral treatment is for stable, out-patient cases only. Note that doxycycline is primarily for milder cases in which Mycoplasma or Bordetella are suspected.</p> <p>B. Stable hospitalised patients.</p> <p>C. Combination therapy for patients which are unstable, at risk of sepsis, require oxygen, or following sensitivity testing.</p>
Aspiration pneumonia	<ol style="list-style-type: none"> 1. Amoxicillin/clavulanate (12.5 mg/kg PO BID). 2. Ampicillin (20 mg/kg IV TID) with enrofloxacin (5 mg/kg SC or PO SID). <p>Treatment duration often 4-6 weeks.</p>	<p>Start treatment IV if possible, switching to oral treatment once stable. Combination therapy should be reserved for patients at risk of sepsis or following sensitivity testing.</p>
Pyothorax	<ol style="list-style-type: none"> 1. Ampicillin (20 mg/kg IV TID) with enrofloxacin (5 mg/kg SC or PO SID). <p>Treatment duration often 4-6 weeks (but may be significantly longer, depending on clinical signs.)</p>	<p>Start treatment IV if possible, switching to oral treatment once stable. Culture and sensitivity testing and cytology of pleural fluid should be performed following thoracocentesis.</p>

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6.7 Tick-borne disease

6.7.1 Overview

The deer tick *Ixodes ricinus* is the vector for endemic tick-borne diseases in Denmark. Occasionally, infections due to other vector tick species can be seen in animals coming from abroad. For example, in dogs and cats which have travelled from southern Europe or from North America where other tick species such as *Rhipicephalus sanguineus*, *Dermacentor* spp. and *Amblyomma* spp. are found in addition to *Ixodes ricinus*. The most important tick-borne bacterial infections are outlined in Table 1. In general, culture and sensitivity testing is not performed in cases of tick-borne disease, since results take several weeks to obtain and only a few laboratories offer this service.

Table 1. Important tick-borne bacterial diseases in Denmark

Infection	Tick vector	Endemic in Denmark?
<i>Anaplasma phagocytophilum</i>	<i>Ixodes ricinus</i>	Yes
<i>Borrelia burgdorferi</i>	<i>Ixodes ricinus</i>	Yes
<i>Ehrlichia canis</i>	<i>Rhipicephalus sanguineus</i>	No

The clinician should consider the possibility of co-infection with multiple agents when a diagnosis of tick-borne disease is suspected. Co-infection with *A. phagocytophilum* and *B. burgdorferi* results in more complex and serious clinical signs in both dogs and humans. Compared to single-agent infections, co-infection results in a more pronounced thrombocytopaenia in dogs.

Although the following sections focus on treatment, preventive measures against tick-borne disease are still important, especially when patients travel abroad - for example, to southern Europe. Tick repellants and daily removal of ticks from the skin and coat can prevent transmission of these diseases. Use of an appropriate tick-removing tool is recommended, along with the use of gloves and subsequent hand disinfection when handling ticks.

6.7.2 Granulocytic anaplasmosis

Aetiology and prevalence

Canine granulocytic anaplasmosis is caused by *Anaplasma phagocytophilum* (formerly *Ehrlichia equi*), an obligate intracellular Gram-negative coccus. In Denmark, it is transmitted via the bite of infected deer ticks. It primarily attacks the host's neutrophils but can also infect eosinophils, within which it reproduces inside structures called morulae. Clinical disease can occur in dogs, humans and other animals. In rare instances it may also be seen in cats.

Diagnosis

The clinical signs are non-specific, typically including fever, depression, anorexia, and muscle or joint pain, with or without associated lymphadenopathy and splenomegaly. The diagnosis is based on clinical suspicion, a history of possible tick-exposure, haemogram and serum biochemistry and specific laboratory investigations. In the acute phase, the causative agent can be demonstrated in the blood, bone marrow or splenic tissue using PCR, prior to treatment. This technique is both sensitive and specific, and can confirm infection one week before morulae can be seen in

granulocytes (1, 2). Serological confirmation requires demonstration of a four-fold rise in paired IgG titres over a 2-3-week period.

Treatment

When the clinical picture and diagnostic tests indicate infection with *A. phagocytophilum*, treatment with doxycycline for 10 days is the treatment of choice (see Table 2) (1). Doxycycline's lipid-solubility characteristics ensure high intracellular concentrations. Doxycycline can also be used for treatment of infected puppies since the risk of enamel hypoplasia and dental discolouration is lower than for other tetracyclines. If the response to treatment is poor, rifampicin and enrofloxacin may be used (3-5). Data regarding the optimal treatment duration are lacking, but 10 days treatment appears to be sufficient given that chronic infection has not been reported.

6.7.3 Ehrlichiosis

Aetiology and prevalence

Ehrlichiosis is caused by *Ehrlichia canis*, an obligate intracellular Gram-negative bacterium which infects monocytes and macrophages in dogs. *E. canis* is **not** endemic in Denmark and infections are therefore seen exclusively in dogs which have travelled from areas in which the brown dog tick (*R. sanguineus*) is found.

Diagnosis

E. canis infection can cause multisystemic disease with acute, subclinical and chronic forms. Clinical suspicion is based on an appropriate history, clinical signs, and laboratory investigations. Platelet counts, serum protein electrophoresis and serological studies are good screening methods, but confirming the diagnosis requires PCR and DNA sequencing (6). PCR can be performed on blood, bone marrow, splenic aspirates or conjunctival scrapes prior to initiation of therapy.

Treatment

Doxycycline is the drug of choice for treatment of ehrlichiosis (3, 4). Data regarding the optimal treatment duration are lacking, but the American College of Veterinary Medicine Consensus study group (7) recommends 28 days treatment (see Table 2). Ehrlichiosis can also be treated using the antiprotozoal compound imidocarb dipropionate. After initiating treatment with doxycycline, a dramatic clinical improvement is typically observed within 24-48 hours in dogs with acute or mild chronic ehrlichiosis, and the thrombocytopenia generally resolves within 14 days (7). Platelet counts should be monitored weekly during treatment and for 1-3 months following cessation of treatment. Quantitative PCR can also be used to assess the adequacy of treatment in the post-treatment period (7).

6.7.4 Borreliosis

Aetiology and prevalence

Borreliosis is caused by the Gram-negative spirochaete *Borrelia burgdorferi*, which in Denmark is transmitted by the bite of the deer tick. A study found that around 15% of *Ixodes ricinus* in Denmark were infected with *Borrelia*, and that 64% of these carried more than one *B. burgdorferi*

genospecies. The most common genospecies were *B. afzelli* (64%) and *B. garinii* (57%), while *B. sensu stricto* was less common (3.6%) (8). Danish and Swedish surveys of asymptomatic dogs have shown seroprevalences of 6% and 4%, respectively (9, 10). These dogs were not suspected of having borreliosis. In humans, *B. sensu stricto* is associated with joint and nervous system signs, *B. afzelli* with chronic skin changes and *B. garinii* with neurological signs. **The majority of infected dogs do not develop clinical signs.** In an American study that investigated both seropositive and seronegative dogs, 4.8% (6/125) and 4.6% (5/109) in each group had signs compatible with borreliosis (11).

The majority of the literature pertaining to *Borrelia* infections in dogs is from North American experimental studies using *B. sensu stricto*. Clinical signs of *B. sensu stricto* infection are fever, depression, lymphadenopathy and shifting lameness due to polyarthritis (12). **There are no published data regarding the clinical signs associated with the *Borrelia* genospecies typical in Denmark.** A Swedish study concluded that it was unlikely that infection with *Borrelia* and *Anaplasma* would produce CNS signs in dogs, and that the presence of antibodies alone was insufficient to diagnosis CNS disease caused by these organisms (13). There are several reports from North America of nephropathy in dogs positive for antibodies to *B. burgdorferi* (14, 15, 16). There is insufficient evidence that *B. burgdorferi* occurs in renal tissue in dogs with 'borrelia-associated nephritis' (17). Instead, the disease is suspected to have an immune-mediated aspect (16).

Diagnosis

As a rule, diagnosis of borreliosis is difficult due to the non-specific clinical picture (fever, depression, lymphadenopathy, shifting lameness, neurological signs). There is no single test to confirm a diagnosis, which instead must be based on a history of tick contact in an endemic area and signs compatible with borreliosis, clinical suspicion, positive serology, elimination of differential diagnoses and a rapid response to treatment. PCR can be used to demonstrate *Borrelia* DNA in the synovium of affected joints, the skin adjacent to affected joints or the skin around tick bites. A positive PCR result cannot distinguish between living or dead organisms. Serological investigations using paired titres is useless since the titre increase occurs before clinical signs appear (in contrast to anaplasmosis). Serology and PCR results must therefore be interpreted in light of the clinical signs and history.

Treatment

Around 95% of seropositive dogs never develop signs of infection. A solid evidence base for treatment must therefore be established before initiating therapy. Antibiotics are frequently employed as a diagnostic tool since confirming the diagnosis is so difficult. Doxycycline for 28 days is the treatment of choice (see Table 2). Doxycycline is usually also selected for treatment of possible co-infection with *Anaplasma*, other rickettsial organisms and *Leptospira* spp. Dogs with nephropathy may require extended treatment with doxycycline plus adjunctive treatment with an ACE-inhibitor, low-dose aspirin, omega-3 fatty acids and dietary modification. If doxycycline hypersensitivity occurs, amoxicillin can be substituted. It should be noted that treatment guidelines are based on American medical guidelines, since there is a lack of data regarding treatment of canine borreliosis.

Table 2. Treatment guidelines for tick-borne diseases.

Agent	Antibiotic	Comments
<i>Anaplasma phagocytophilum</i>	1. Doxycycline (10 mg/kg PO SID for 10 days).	*Note that rifampicin can cause hepatotoxicity, CNS symptoms and orange discolouration of urine, saliva and tears (see Chapter 1.6, Table 4).
	2. Enrofloxacin (10 mg/kg PO SID for 10 days).	
	3. Rifampicin* (10 mg/kg PO SID for 10-14 days).	
<i>Ehrlichia canis</i>	1. Doxycycline (10 mg/kg PO SID for 28 days).	*Note that use requires permission from the Danish Medicines Agency. Can be nephrotoxic and ototoxic.
	2. Imidocarb dipropionate* (5 mg/kg IM, two doses 14 days apart).	
<i>Borrelia burgdorferi</i>	1. Doxycycline (10 mg/kg PO SID for at least 28 days).	
	2. Amoxicillin (20 mg/kg PO TID for 30 days).	

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6.8 Sepsis

Sepsis can be caused by bacterial, viral, fungal or protozoal disease. This section focuses exclusively on bacterial sepsis.

Definition

Sepsis is a complex clinical syndrome with a high morbidity and mortality, which is now defined in human medicine as a life-threatening organ dysfunction caused by a dysregulated host response to infection. This updated definition was published in 2016 (1) and represents a break with the previous understanding of the condition and its diagnosis. Previously, sepsis had been defined as an infection that caused a systemic inflammatory response syndrome (SIRS), characterised by changes in clinical and paraclinical parameters such as temperature, pulse rate, respiration rate and white blood cell count. The increasing recognition of the role of organ dysfunction in sepsis indicated a more complex pathophysiology than a purely systemic inflammatory response in the presence of infection. As the SIRS criteria had also been shown to have suboptimal sensitivity and poor specificity, this concept became redundant and is no longer used in human medicine.

Bacteria contain potent inflammatory activators, such as the lipopolysaccharide (LPS) of Gram-negative bacteria. The subsequent host response consists primarily of activation of pro- and anti-inflammatory cytokines, and it is the balance between these two groups of cytokines that is primarily responsible for the clinical picture. A particularly severe form of sepsis is termed septic shock, and is characterised by profound hypotension that requires vasopressor treatment.

Aetiology and prevalence

Sepsis and/or septic shock are common causes of morbidity and mortality in critically ill patients. The veterinary incidence is unknown, but the mortality rate is comparable to that in humans at 20-65% (2, 3). Of the many potential septic foci, infection of the GI tract is the most common and accounts for about 50% of cases. Other less frequent causes include trauma, septic abdomen, pyelonephritis, pneumonia, endocarditis and prostatitis. Gram-negative bacteria (primarily *E. coli*) are most commonly isolated from septic dogs and cats, but both mixed infections and pure Gram-positive infections (usually enterococci or streptococci) may be seen.

Diagnosis

The clinical signs of sepsis are relatively non-specific and can include haemodynamic instability, fever, respiratory abnormalities, abdominal pain and vomiting. Clinical suspicion should prompt a search for a possible septic focus and sepsis-induced organ dysfunction. It is extremely important to identify the septic focus and, if possible, obtain tissue, blood or fluid samples for bacterial culture and sensitivity testing. Cytology or pathology can be used to replace or complement culture in some cases. If a focus cannot be identified, blood culture is recommended.

Protocol for blood culture (4)

Bacteraemia is frequently mild, which makes it important to collect a relatively large volume of blood for culture. Multiple samples over a 24-hour period are recommended to reduce the risk of false negatives due to intermittent bacteraemia as well as false positives due to contamination (usually from skin commensals). Samples should be obtained before starting antibiotics, but in critically-ill animals treatment should not be delayed until culture results are available.

Sampling is performed at least twice and preferably 3 times within 24 hours, with an interval of at least 30-60 minutes. Venepuncture is performed at a new location each time. If it is impossible to delay administration of antibiotics due to the critical clinical status of the patient, two simultaneous samples should be obtained from different locations. Blood must not be taken through an intravenous cannula.

Sampling must be performed aseptically, with cleaning and disinfection of the skin as for surgery, along with hand disinfection and the use of sterile gloves. Each blood sample should be 5 ml for cats and small dogs and 10 ml for medium to large dogs. These are divided equally between aerobic and anaerobic blood culture media using fresh sterile needles. Fresh culture media are used for each sample. Media are incubated at 37°C until all samples have been obtained, and then transported as rapidly as possible to a microbiological laboratory.

Treatment

Rapid diagnosis and commencement of treatment is essential in sepsis. Delayed antibiotic treatment in septic patients increases the risk for bacterial spread and a more potent inflammatory response. Empirical antibiotic therapy, prior to culture results, is based on the following considerations (5, 6):

1. The most common pathogens associated with the identified or suspected focus of infection
2. The chosen antibiotics ability to penetrate the relevant tissues
3. Local resistance patterns
4. Effect of recent antibiotic treatment, and the potential for drug resistance in relation to this
5. The suspected source of infection (hospital-acquired vs community-acquired)

Once infection is confirmed, and pending culture results, treatment with IV antibiotics is indicated. **If the septic focus is known**, treatment is based on likely infectious agents and antibiotic penetration into the infected tissue. **If the septic focus is unknown**, treatment should address the 'four quadrants', i.e. be simultaneously effective against Gram-positive, Gram-negative, aerobic and anaerobic bacteria (see Table 1). As soon as culture results are available, treatment is de-escalated (i.e. the treatment spectrum is narrowed) in accordance with the sensitivity profile. If no agent is isolated, but sepsis is still considered likely, de-escalation is carried out based on regular clinical re-evaluations of the patient.

There is an increasing focus on tailoring the treatment strategy to the infections origin and type, the patient's clinical status, immune status and duration of illness, along with the results of bacterial culture. Human studies have shown that de-escalation of sepsis treatment based on culture results and daily clinical evaluations does not increase mortality compared with patients treated with broad-spectrum antibiotics throughout (7, 8). One study showed that de-escalation could in fact reduce mortality in these patients (8).

Short-term treatment (<7 days) is normally sufficient. Recent human studies have revealed that shorter treatment durations are not associated with increased mortality rates (9-11). The duration of treatment should be determined on a patient-by-patient basis using daily clinical evaluations supported by measurement of inflammatory biomarkers (leukogram, C-reactive protein), and monitoring of the underlying infectious focus (e.g. prostatitis, pneumonia). Chronic treatment (weeks) may be indicated for infections which involve particular structures (endocarditis, discospondylitis).

Table 1. Choice of antibiotics for sepsis of unknown origin.

Infection	Antibiotic	Comments
Sepsis of unknown origin	Ampicillin (22 mg/kg IV TID-QID) OR clindamycin (12 mg/kg IV BID).	Treatment should be de-escalated as soon as culture and sensitivity results are available (see text).
	In combination with: Enrofloxacin (5 mg/kg IV SID) OR gentamicin (5-10 mg/kg slow IV SID).	Enrofloxacin should not be used in growing animals. Gentamicin should not be used in patients with reduced renal function, and IV crystalloids should always be administered simultaneously with it.

Sepsis prophylaxis

Only a few situations justify the use of prophylactic sepsis treatment. This is limited to patients which have developed neutropaenia due to viral infections (e.g. parvovirus) or chemotherapy, and which have a clinical picture indistinguishable from bacterial sepsis (12). Sepsis prophylaxis employs ampicillin or amoxicillin/clavulanate IV as the initial empirical therapy. If the patient's condition worsens, this is supplemented by enrofloxacin or gentamicin IV (see Table 1 for contra-indications). The guidance above on de-escalation should be followed.

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6.9 The eye

6.9.1 Conjunctivitis in dogs

Aetiology and prevalence

Primary infectious conjunctivitis is rare in dogs. Underlying causes such as decreased or low tear production, eyelid abnormalities, distichiasis, trichiasis, foreign bodies, draughts, smoke irritation and allergies should be considered when evaluating the patient with conjunctivitis (1-3). Hyperaemia and oedema of the conjunctiva can also indicate diseases of the adnexa or globe. Follicular conjunctivitis is not a symptom of bacterial or viral infection (3-5).

Diagnosis

Potential underlying causes, as outlined above, should be checked for. Cytology and/or histopathology, possibly supplemented with bacterial culture and sensitivity testing, should be performed. Symptomatic bacterial conjunctivitis is often associated with staphylococci and other Gram-positive bacteria (6,7). The normal conjunctiva is rarely sterile, with various studies demonstrating positive cultures in up to 90% of healthy dogs. Typical isolates are coagulase-positive *Staphylococcus* spp., other staphylococci and *Streptococcus* spp. (8-9). Gram-negative bacteria can be found in 7-8% of samples from normal dogs; however, anaerobes are rarely seen (8-12). When sampling from the conjunctival sac for bacterial culture, it is vital to avoid contamination from the eyelid skin. Interpretation of both the bacteriology report and the composition of the isolated flora should always be informed by the clinical signs.

Treatment

Any underlying cause should be addressed, possibly in combination with topical flushing (using sterile isotonic saline or an eye flushing solution). Management of **follicular conjunctivitis** in young dogs with topical flushing will often result in significant improvement. Further reduction in follicular swelling and associated signs can be achieved using topical steroids (3). **Neonatal conjunctivitis** (ophthalmia neonatorum) requires opening/separation of the eyelids so that flushing can be performed. In addition, topical antibiotics and artificial tear drops should be used until the puppy's own tear production is sufficient (3). For treatment of **confirmed bacterial infections** of the conjunctiva, topical fusidic acid is the first-line antibiotic. If the response is poor, side-effects are seen, or if the infection is not sensitive to fusidic acid, then chloramphenicol or tetracycline may be used. Flushing is recommended as a supplement to antibiotic therapy, and should be performed prior to antibiotic administration. Topical therapy is always sufficient (6).

6.9.2 Conjunctivitis in cats

Aetiology and prevalence

Primary bacterial conjunctivitis in cats may be seen due to *Chlamydophila felis* and *Mycoplasma* spp. Ocular infections and conjunctivitis can also result from infection with feline herpesvirus type 1 (FHV-1) (2).

Diagnosis

Bacterial culture of the conjunctival sac of healthy cats is negative 65% of the time: when positive, typical isolates are *Staphylococcus aureus* and *Staphylococcus epidermidis* (26%) and *Mycoplasma* spp. (5%) (14). PCR tests for *Chlamydophila felis*, *Mycoplasma felis*, and FHV-1 are offered by several laboratories. Negative tests do not exclude the possibility of infection. Optimal results are obtained from sampling early in the course of the disease. Infection with *Chlamydophila felis* is suspected to be zoonotic, but transmission from cats to humans is rare (15-17).

Treatment

Infection with ***Chlamydophila felis*** in cats is treated most effectively with oral tetracycline or doxycycline. A treatment period of at least 4 weeks is recommended to eliminate the infection (15). If the patient lives with other cats, these should be treated concurrently because asymptomatic carriers do occur. Cats which live alone can be rendered asymptomatic using topical tetracycline or chloramphenicol (4-5 times daily for 2 weeks), but this does not eliminate the infection. If recurrence occurs then 4 weeks of systemic therapy is recommended (15-17, 19). Infection with ***Mycoplasma felis*** is usually self-limiting and resolves within a month: however, the patient remains potentially infectious for a further month. It may be treated in similar fashion to *Chlamydophila* infection. Before treating younger patients with doxycycline or tetracycline, the risk of damage to dental enamel should be considered (18, 20). Cats vaccinated against *Chlamydophila felis* experience less severe signs but are not completely protected against infection, and are therefore a potential source of infection (2).

6.9.3 Blepharitis

Aetiology and prevalence

Blepharitis refers to inflammation of the eyelid margin and may be focal (nodular) on a single eyelid or affect one or more eyelids in their entirety (confluent). This condition may be seen in isolation or as part of a generalised dermatopathy. Infectious blepharitis is usually caused by staphylococci or streptococci with an associated immunological reaction. Blepharitis can also be seen due to parasites such as *Demodex*, *Sarcoptes* and *Leishmania* (2, 3).

Diagnosis

The diagnosis can usually be reached based on the clinical signs. Secretions from inflamed or infected meibomian glands or from pyogranulomata can be sent for culture and/or cytology (2, 3).

Treatment

Eyedrops containing fusidic acid are the first-line treatment, with chloramphenicol or tetracycline as alternatives. Eye flushing in combination with antibiotics is advisable. If the condition consists of more than just a few nodules, systemic therapy with amoxicillin/clavulanate is recommended. Additional anti-inflammatory therapy to reduce irritation should be considered (3).

6.9.4 Non-ulcerative keratitis

Aetiology and prevalence

Keratitis is rarely caused by bacterial infection, but more commonly by mechanical or immunological factors. In cats, keratitis may be seen due to FHV-1 infection (2, 21).

Diagnosis

A focused clinical examination should be performed, including measurement of tear production. Samples for cytology, histopathology and/or bacterial culture can be obtained.

Treatment

Patients with distichiasis, trichiasis, ectopic cilia or anatomic abnormalities of the eyelids should be managed surgically. Patients with keratoconjunctivitis sicca (KCS) due to low tear production should be treated topically with cyclosporin. Lubricating eyedrops should be used concurrently until the cyclosporin has achieved maximal effect (21). Topical steroids can also be used during this period, if there is no evidence of either corneal ulceration or infection. Topical antibiotics and frequent lubrication may be necessary if there is corneal ulceration or secondary bacterial infection, and it is usually advisable to delay immunomodulating treatment until any corneal ulcer is healed (21). Eyedrops containing fusidic acid are the first-line treatment, with chloramphenicol as an alternative. Flushing is recommended as a supplement to antibiotic therapy, and should be performed prior to antibiotic administration.

6.9.5 Ulcerative keratitis

Aetiology and prevalence

Acute corneal ulceration may result from trauma, ectopic cilia or eyelid abnormalities, particularly in younger patients. Chronic ulcers, in which the corneal epithelium heals poorly and with reduced adherence to the underlying stroma, are seen more commonly in older patients. Corneal ulcers infected with *Pseudomonas* spp. or beta-haemolytic streptococci can develop into 'melting' ulcers due to production of proteinases and collagenases by these bacteria (22).

Diagnosis

Corneal ulcers are classified by their depth. Relevant investigations include biomicroscopy (slit-lamp examination) and fluorescein staining. Bacteriology and cytology should be undertaken for chronic ulcers, for ulcers which increase in depth or for ulcers which respond poorly to treatment. Samples should be taken from the edge of suspected melting ulcers. Therapy should be initiated pending the culture and sensitivity results (see below) (22).

Treatment

If the patient exhibits miosis and pain then topical atropine is indicated, possibly supplemented by systemic analgesics. **Primary superficial ulcers** can be managed with prophylactic topical antibiotics during healing. Eyedrops containing fusidic acid are the first-line treatment, with chloramphenicol and tetracycline as alternatives. **Chronic ulcers or poorly healing ulcers** often require mechanical debridement of any loose epithelial edges. Keratotomy may be performed in dogs. Lubricating

eyedrops should be used as a supplement to antibiotic treatment. Ointments should not be used with deep stromal lesions where there is a risk of perforation: in this situation, chloramphenicol eyedrops are the treatment of choice. Oral amoxicillin/clavulanate is used for **perforated corneas**, or if perforation is suspected. The lesion is treated surgically according to best practice. **Melting ulcers** should be treated intensively with topical broad-spectrum antibiotics, of which ciprofloxacin is the treatment of choice until culture and sensitivity results are available. Oral antibiotic with amoxicillin/clavulanate should be started immediately, along with frequent topical application of a collagenase inhibitor (22). Antibiotic therapy is subsequently adjusted in light of culture results.

6.9.6 Uveitis

Aetiology and prevalence

Although uveitis has many potential causes, local bacterial infection is rarely to blame unless there is perforation of the cornea or sclera. Toxaemia, systemic disease, glaucoma, trauma, bleeding, neoplasia, lens protein leakage and immunological conditions can all cause uveitis. Idiopathic uveitis accounts for a large proportion of cases. Infection with *Borrelia*, *Anaplasma*, *Leptospira*, herpesvirus, canine distemper, *Leishmania*, *Toxocara*, *Toxoplasma*, or septicaemia of any cause, can result in uveitis (23, 24). In cats, uveitis may be seen due to FIP, FeLV and toxoplasmosis. Idiopathic lymphoplasmocytic uveitis is commonly seen (25, 26).

Diagnosis

Classic signs of uveitis include blepharospasm, miosis, opacity of the anterior chamber (due to cells and protein), vascular injection of the ciliary body, conjunctival hyperaemia, corneal oedema, hypopyon, hyphaema, iridal oedema and cataracts. Hypotonia will be observed provided that the corneal oedema permits intraocular pressure measurement. Laboratory investigations can be useful and include haematology, urinalysis, serology and bacterial culture, possibly in combination with diagnostic imaging (26).

Treatment

Therapy should be directed at the primary cause, if identified, and topical and systemic analgesics administered. Systemic antibiotics should be given if infection, perforation or systemic infection can be demonstrated. The choice of antibiotic depends on the diagnosis. Mydriatics (atropine) should be considered if blepharospasm, miosis and/or photophobia are observed, provided there are no contra-indications (e.g. glaucoma) (2, 26).

6.9.7 Retrobulbar abscesses and orbital cellulitis

Aetiology and prevalence

The cause is frequently difficult to identify, but foreign bodies, haematogenous spread and local spread of infection from the nasal cavity or dental roots are likely causes. Typical bacteria include *Staphylococcus* spp., *E. coli*, *Pasteurella* spp. and anaerobes (27).

Diagnosis

The patient usually presents acutely with unilateral exophthalmos, protrusion of the nictitating membrane, conjunctival hyperaemia and pain on opening the mouth. Ultrasound-guided fine-needle aspirates or biopsies can recover material for cytology and bacterial culture (27, 28).

Ultrasonography and/or CT scanning can be useful (27).

Treatment

Drainage should be established, if possible. Systemic analgesics should be given along with antibiotics. Amoxicillin/clavulanate may be used until sensitivity results are available (27).

6.9.8 Dacryocystitis

Aetiology and prevalence

The most common cause of nasolacrimal sac infection is a foreign body, typically plant material. Trauma or extension of infection from surrounding structures can also cause dacryocystitis. Bacteria isolated in these patients usually reflect opportunistic infection by normal conjunctival flora, including staphylococci and streptococci (29).

Diagnosis

The diagnosis is based on clinical signs of mucoid or mucopurulent discharge from the medial canthus with or without swelling over the nasolacrimal sac. Passage of fluorescein from the conjunctival sac to the nasal passages will be reduced or absent. Cytology and culture should be performed.

Treatment

If possible, the inciting cause should be removed and the lacrimal punctae flushed daily until normal tear flow is re-established. Topical antibiotics, for which chloramphenicol is the first choice, should be used: systemic antibiotic therapy (e.g. amoxicillin/clavulanate) is also recommended. The choice of preparation can be adjusted based on sensitivity results. Topical and systemic anti-inflammatory treatment is recommended unless contra-indicated (29).

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7 Handling of antibiotics and other medicines

7.1 Overview

Medicines should be handled in such a way that ensures that unnecessary contact with pharmaceuticals, including antibiotics, is avoided. Various studies have shown that veterinarians have a greater risk of being MRSA carriers than the general population (1-4). This remains the case in countries with a low prevalence of MRSA in companion animals, which suggests that other causative factors than contact with animals (e.g. handling of antibiotics) are more significant for carrier status. *Staphylococcus aureus* is part of the normal human skin flora, and repeated exposure to antibiotics can contribute to selection of MRSA. With this in mind, it should be noted that handling of antibiotics without using gloves appears to be normal practice amongst veterinarians in Denmark (3).

In general, with regard to handling of any pharmaceutical (including antibiotics), it is important to avoid both contamination of the product and unnecessary contact with the product, as far as is possible. Gloves should be worn when handling tablets, creams and ointments. Tablets should only be crushed in a sealed mortar or fume cupboard. When dissolving powders for injection, procedures which minimise possible spread of aerosols and fumes should be employed (see workplace health and safety guidelines for veterinary hospitals and clinics). With regard to Parliamentary Act 1353 of 29th November 2017 on the veterinary use, supply and prescription of medicines for animals, veterinarians are required to ensure that medicines stored at the practice address are kept in appropriate conditions and are not accessible by unauthorised people. When a veterinarian supplies medicines for use in animals other than production animals, the package must include the following information:

1. Owner's name
2. Species
3. Diagnosis
4. Dose, route of administration, and treatment period
5. Dispensing date
6. Veterinarian's authorisation number

A label including this information should be affixed to the medicine's packaging. If the packaging consists of several layers, the label should, if possible, be placed on the inner packaging. Medicines should be stored as recommended by the manufacturer to maximise product longevity, and thereby its efficacy. A number of factors including temperature, humidity and sunlight can have negative effects on product quality. Medicines must be stored in the original packaging and may not be repackaged. Certain products have a limited shelf life following opening of the package or after making into a solution. In these cases, the dates of opening and expiry should be written on the packaging. Medicines should not be used after their expiry date.

7.2 Leftover medicine

Medicines are categorised as hazardous waste, because they can be harmful to health and to the environment. Medicines should therefore be disposed of safely. Danish Parliamentary Act 855 of 4th August 2008 requires pharmacies to collect leftover or expired medicines from patients and medical personnel for disposal, and such items should therefore be delivered to a pharmacy.

Clinical waste disposal schemes are available in all regions of Denmark. Veterinary hospitals and clinics must subscribe to these schemes. Special containers are available for specific forms of waste, such as needles and medicine residues.

7.3 Client information regarding antibiotic therapy

To ensure the continued efficacy of antibiotic preparations in both humans and animals, owners must be informed of the importance of following treatment instructions. In some cases, it may be beneficial to use alternative treatment options and possibly avoid the use of antibiotics, even though this could prolong recovery, since this will reduce the risk of developing bacterial resistance. When prescribing antibiotics, it is important that owners are aware of the risks of unsatisfactory outcomes and possible side-effects. The owner should understand the treatment plan and the importance of correct dosing intervals and treatment lengths. In many cases antibiotic treatment will produce such a rapid improvement in clinical signs that the owner may feel disposed to stop treatment early, increasing the risk of recurrence. The clinician should ensure that the owner is capable of administering the medicine as directed. Even simple topical medications (such as for otitis externa) can be difficult for some owners to administer. Cats can be awkward to medicate orally. Demonstrating administration of medications is therefore recommended, particularly when the owner is inexperienced. The clinician may have to seek alternative treatment options if the owner finds they are unable to administer the medication as advised. Information regarding alternative dosing protocols and routes can be obtained from manufacturers and pharmacies. Finally, the owner should be advised to use gloves and to wash their hands after product administration, and informed of special storage requirements if these are relevant.

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8 Applying for compassionate use permits and magistral (extemporaneous) preparations

It can be challenging to combine a rational antibiotic policy and avoidance of resistance development with the cascade regulations (paragraph 4 of Parliamentary Act 1353 of 29th November 2017, (1)), since the range of antibiotics licensed for veterinary use in Denmark is limited. Based on specific resistance results, or a desire for rational use of antibiotics, it is possible to obtain permission to import and prescribe foreign or magistral (extemporaneous) preparations.

A thorough overview of the cascade regulations and how to apply for permission has been published in the *Dansk Veterinærtidsskrift* (2). Figure 1 outlines the necessary steps to determine if it is necessary to make an application, and if so, which agency it should be addressed to.

Medicines licensed abroad

Contacting a local pharmacy is recommended in order to explore the availability of foreign medicines, as they may be able to provide information on which products are available via their importers. Alternatively, medical databases of individual countries may be useful, if publicly accessible. Products from EU countries, Switzerland and Canada are preferable, since the information required by the Danish Medicines Agency is publicly available there. An example would be the possibility of obtaining a general import licence for foreign potentiated sulphonamides following the loss of the Danish licence for Tribissen® Vet in tablet form.

For products licensed in the USA it is necessary to request this information from the manufacturer, which is often not interested in supplying it.

As a rule, start with applying for a general compassionate use permit. This can often be successful, if you frequently treat patient groups which have need of a product that is not available in Denmark, or if it is for a product to treat a condition which has an acute onset.

Magistral preparations

A number of magistral preparations can be produced in accordance with the cascade regulations without specific permission. These are listed in appendix 2 of Act 1353 (1) together with the target species and indications which the product can be prescribed for. The appendix is updated regularly, and can be accessed at <https://www.retsinfo.dk>. If a need for a magistral preparation not on this list can be documented, an application for a permit can be made to the Danish Veterinary and Food Administration. As a rule, it is only possible to get permission for magistral preparations for individual animals.

General requirements for applications

All applications should be made via the relevant agencies website. The Medicines Agency prefers that applications are made and signed digitally using an employee's NemID. Alternatively, an application can be completed online, printed, signed and e-mailed to the relevant authority. Applications made using outdated form versions are rejected automatically.

Veterinarians in practice must be registered as employees of their clinic in VetReg (<https://www.vetreg.dk/dypra/startside.jsp>) in order to apply for an import licence, which can then be used by any veterinarian in that clinic.

Before completing an application, certain information should be prepared:

- Product name
- Composition of the product
- Form, route of administration and strength
- Summary of product characteristics
- Indication (clear statement of which condition(s) or clinical sign(s) the requested product is required to treat)
- Comprehensive explanation why licensed alternatives in Denmark and/or abroad cannot be used. Results of bacterial resistance testing can be useful here. Previous attempts at treatment and the results thereof should be detailed (and can be sent as an attachment).
- The expected effect of the product on the indication given above, preferably with documentation.
- For compassionate use permits, the importer responsible for bringing the product into Denmark should also be identified.

8.1.2 Processing time and use of permits

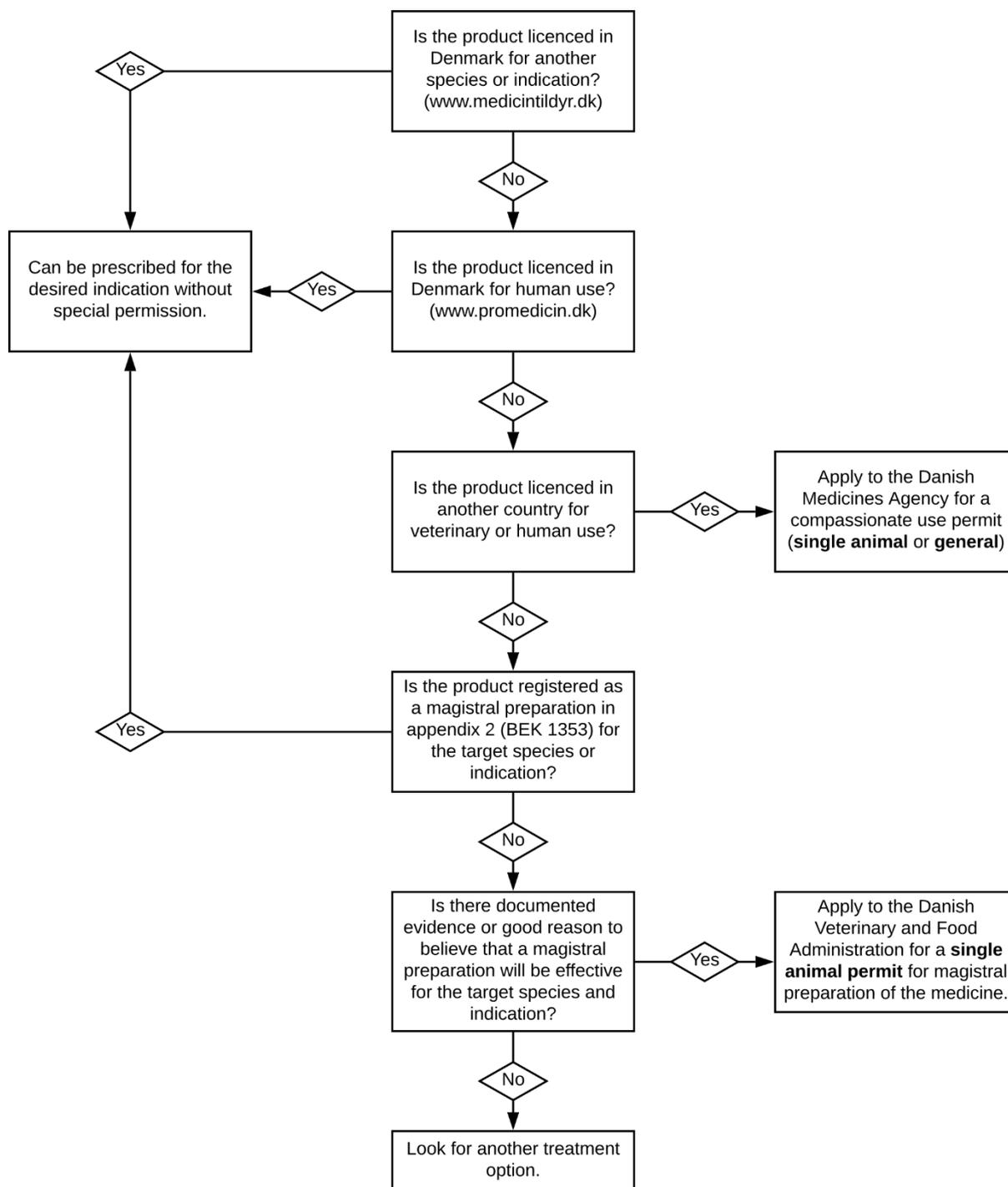
It can take up to 4 weeks for an application to be processed. In acute cases, the application can be rushed through within 24 hours Monday-Friday, by adding “HASTER”³ after the applicant’s name. It should be noted that replies from the Danish Medicines Agency are sent to the electronic post-box registered to the CVR (VAT) number of the clinic.

The dispensing pharmacy must have a copy of the necessary permit before a medicine for which a compassionate use permit has been granted can be dispensed. The owner can, for example, take the permit with them to the pharmacy.

³ URGENT

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Figure 1. Overview of the cascade regulation decision tree for treatments which are not licensed for the target species or indication.



^aFor example, for large dogs it is possible to combine the human medicines Lucosil and Trimopan to produce a Sulfa/TMP preparation with 500+100 mg, suitable for treatment of a 40 kg dog.

^bFor example, permission can be sought for single animal or general compassionate use permits for the sulfa/TMP preparation Bactrim (Roche) as a 200+40 mg/5ml oral suspension for use in smaller animals including exotics.

^cFor example, the current version of appendix 2 contains Tylosin 50 mg and 300 mg tablets for gastrointestinal infections in dogs and cats.

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Additional resources

Danish Medicines Agency Application form – Treatment of a single animal (*enkelttilladelse*):

<https://laegemiddelstyrelsen.dk/da/godkendelse/udleveringstilladelser/dyr/ansoegning-om-veterinaer-enkelt-udleveringstilladelse-e-blanket,-digital-signatur/>.

Danish Medicines Agency Application form – Treatment of multiple animals (*generel tilladelse*):

<https://laegemiddelstyrelsen.dk/da/godkendelse/udleveringstilladelser/dyr/ansoegning-om-veterinaer-generel-udleveringstilladelse-e-blanket,-digital-signatur/>.

Danish Veterinary and Food Administration Application form:

https://www.foedevarestyrelsen.dk/_layouts/15/Netcompany.FVS0001/Pages/FormView.aspx?XsnLocation=/FormServerTemplates/Ansoegning_ProduktionsdyrUdelukketFraKonsum.xsn.