Antibiotic Use Guidelines for Companion Animal Practice

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

SvHKS

Antibiotic Use Guidelines for Companion Animal Practice

Authors of the guidelines:
Anette Spohr[c]
Birgitte Schjøth[d]
Bo Wiinberg[a]
Geoffrey Houser[a]
Jakob Willesen[a]
Lisbeth Rem Jessen[a]
Luca Guardabassi[b]
Mette Schjærff[a,e]
Thomas Eriksen[a]
Vibeke Frøkjær Jensen[f]
Danish Veterinary Ophthalmologic Association (DSVO), a division of SvHKS

[a]University Hospital for Companion Animals, Faculty of Health and Medical Sciences, Copenhagen University
[b]Department of Veterinary Disease Biology, Faculty of Health and Medical Sciences, Copenhagen University
[c]Faxe Veterinary Hospital
[d]Canicold International
[e]University of California
[f]National Food Institute, Technical University of Denmark

Foreword

This first set of Danish guidelines aimed at promoting rational veterinary use of antibiotics is the result of an initiative from the Danish Small Animal Veterinary Association (a division of the Danish Veterinary Association). The process was inspired by the Swedish antibiotic use guidelines, which were first produced in 2002 and revised in 2009.

The motivation for the Danish guidelines, in common with their Swedish counterparts, stems from the increasing resistance problems seen both in the medical and the veterinary fields, with an alarming rise in the number of infections caused by multiresistant bacteria in dogs, cats and other companion animals in Europe. With regulatory authorities increasing their focus on this problem, it is important that we both treat infections with as specific a choice of antibiotic as possible and limit the use of drugs that predispose to the development of multi-drug resistance if we as veterinarians are to continue to enjoy full prescribing privileges.

Currently, there is no significant development of novel antibiotics. Recent veterinary antibiotics are modifications of already established compounds. It is not cost-effective for pharmaceutical companies to develop new antibiotics, which makes it vital that we rationalise the use of those available to us in order to maintain their effectiveness.

The main goals of these guidelines are to give the practising veterinarian an update on rational antibiotic use and to act as a tool for rapidly selecting the optimal antibiotic for empirical treatment while minimising the risk for resistance development. With this in mind, the majority of the organ- or system-specific chapters conclude with a table summarising the recommended antibiotics.

Compared with their Swedish colleagues, Danish companion animal veterinarians less frequently perform bacterial culture and sensitivity testing, and the majority of diagnostic samples are sent to commercial laboratories outside Denmark. There is no national monitoring programme to follow the development of antibiotic resistance in companion animals, leading to a lack of data regarding its incidence. Another aim of these guidelines is to promote the use of culture and sensitivity testing. This will increase our overall knowledge regarding the development of antibiotic resistance as well as helping to guide therapy in practice. Special emphasis has been placed on infections of the skin and urinary tract, since these are the most common infections seen in practice and consequently where the majority of antibiotic use is directed. These organ systems are also the most common source of multiresistant bacterial cultures. A more rational use of antibiotics for these infections could lead to a significant reduction in the selection for, and spread of, multiresistant bacteria.

An association between the rates of antibiotic use and resistance problems has been demonstrated. In many other EU countries there is a significantly higher incidence of multiresistant bacteria, which correlates with the more liberal antibiotic prescribing policies in these countries. Very broad spectrum antibiotics, such as fluoroquinolones and third-generation cephalosporins, have good clinical efficacy against a wide range of pathogenic bacteria, but it is generally accepted that their use also predisposes to the development of multi-drug resistance. In order to maintain the clinical effectiveness of these antibiotics they should be reserved for the treatment of infections that will not respond to narrower spectrum antibiotics. As far as possible they should only be used based on sensitivity testing. Even more importantly, extremely judicious use should be made of antibiotics reserved for life-threatening infections in humans (e.g. the carbapenems). Should a need for these antibiotics arise, they should only be used following consultation with specialists in veterinary microbiology and veterinary internal medicine. Further information is given in chapter 1.7.

During development of these guidelines it became clear that there is a lack of controlled clinical studies regarding treatment of infections in companion animals. This guide is based on resistance

reports from the diagnostic laboratory at the Department of Veterinary Disease Biology and current knowledge in the fields of infectious diseases, antibiotic therapy, pharmacology and internal medicine.

We would like to emphasise that these guidelines are only recommendations to aid the management of the majority of common infections encountered in general practice. The authors are fully aware of the wide variety of clinical situations encountered in practice, and warn against misinterpretation of these guidelines as a set of rules to be rigidly followed in all circumstances.

The working group of authors for these guidelines comprised veterinarians in clinical practice and from the University Hospital for Companion Animals, Faculty of Health and Medical Sciences, Copenhagen University. The section relating to the eye was independently contributed by the Danish Veterinary Ophthalmologic Association.

The Authors

[a]Department of Veterinary Disease Biology, Faculty of Health and Medical Sciences, Copenhagen University
[b]University Hospital for Companion Animals, Faculty of Health and Medical Sciences, Copenhagen University
[c]National Veterinary Institute, Uppsala
[d]Hadsten Veterinary Clinic
[e]Helsingborg Veterinary Hospital
[f]Swedish University of Agricultural Sciences
[g]Dermatology Clinic for dogs and cats, Klampenborg
[h]Bagarmosen Veterinary Hospital
[i]North Carolina State University
[j]University of Glasgow
[k]University of California

Contents

List of Tables

List of Figures

1. General principles concerning 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 multiresistant 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. This important distinction has been largely ignored in the currently available guidelines for veterinary antibiotic use.

Clinically, the initial choice of an antibiotic is usually made empirically. 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 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 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 local patterns of bacterial 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 can not be predicted. Variations in antibiotic sensitivity in different bacterial populations makes knowledge of local resistance patterns vital. This knowledge needs to kept current by regular sampling for culture and sensitivity testing.

The largest Danish investigation of antibiotic resistance in clinical isolates from dogs reported sensitivity and resistance patterns for 449 *Escherichia coli*, 201 *Staphylococcus pseudintermedius*, 39

Pseudomonas aeruginosa, 37 *Streptococcus canis*, 29 *Proteus* spp. and 25 *Pasteurella multocida* isolates during the period 2000 to 2005.[1] Tables 1.1 and 1.2 compare the percentage prevalence of resistance reported in this study for *S. pseudintermedius* and *E. coli* to resistance noted at the diagnostic laboratory at the Department for Veterinary Disease Biology, University of Copenhagen (SUND VET DIAGNOSTIK) in 2011 to 2012. For comparison purposes, data from Sweden for 2011 are also shown.

Resistance characteristics for *S. pseudintermedius* are largely identical in Denmark and Sweden. With the exception of the emergence of methicillin resistant *S. pseudintermedius* (MRSP) and an increase in the prevalence of resistance to amoxicillin/clavulanate in Denmark, there have been no significant changes over the last 10 years (Table 1.1). Approximately 30% of isolates are resistant to clindamycin. This means that 7 out of 10 patients can theoretically be treated with this narrow spectrum lincosamide, whereas the broader spectrum preparations amoxicillin/clavulanate and cephalexin should be effective in 9 out of 10 patients. It must be added that the prevalence of resistance to clindamycin and other antibiotics is expected to be somewhat lower in practice. This is due to the fact that veterinarians tend to submit samples from recurrent or complicated[a] pyoderma cases more frequently than from uncomplicated first-time cases, which are often managed empirically without culture and sensitivity testing. A study of dogs in Sweden showed that the prevalence of bacterial resistance, including clindamycin resistance, was significantly higher in staphylococcal isolates from recurrent pyodermas compared with first-time pyodermas.[4]

The prevalence of resistance in *E. coli* to ampicillin, amoxicillin/clavulanate, cefpodoxime, enrofloxacin and sulpha/trimethoprim (all clinically relevant antibiotics in the treatment of *E. coli* infections) appears to have increased in Denmark over the last 10 years, and is roughly twice as high or more than rates in Sweden (Table 1.2). The vast majority of *E. coli* isolates were from the urinary tract and show a moderate level of resistance to antibiotics traditionally used against such

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[a]e.g. chronic pyoderma which is either refractory to treatment or which has recurred rapidly following cessation of treatment.

Table 1.1.: Antibiotic resistance in clinical *Staphylococcus pseudintermedius* isolates from companion animals in Denmark and Sweden.

Antibiotic	Denmark 2000-2005 (n=201)[a]	Denmark 2011-2012 (n=318)[b]	Sweden 2011 (n=388)[c]
Amoxicillin/clavulanate	0%	10%	-
Oxacillin	-	3%[d]	2%[d]
Cefalotin	<1%	6%[e]	2%
Erythromycin	30%	29%	30%
Clindamycin	27%	30%	24%
Chloramphenicol	13%	14%	-
Tetracycline	24%	0%[f]	26%
Gentamicin	-	4%	2%
Amikacin	-	4%	-
Enrofloxacin	1%	3%	2%[g]
Marbofloxacin	-	3%	-
Sulfamethoxazole/ trimethoprim	3%	4%	6%

[a] Clinical isolates from dogs only[1]

[b] Clinical isolates from dogs (97%) and cats (3%)[2]

[c] Skin isolates from dogs only[3]

[d] Cut-off values for resistance differ between Denmark and Sweden: results have been adjusted to reflect the number of oxacillin-resistant isolates confirmed as MRSP using *mecA* PCR

[e] Data refer to another first-generation cephalosporin (cefazolin)

[f] Data refer to another tetracycline (doxycycline)

[g] Data for enrofloxacin resistance have been corrected to the same breakpoint value to permit comparison between studies

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Table 1.2.: Antibiotic resistance in clinical *Escherichia coli* isolates from companion animals in Denmark and Sweden.

Antibiotic	Denmark 2000-2005 (n=449)[a]	Denmark 2011-2012 (n=163)[b]	Sweden 2011 (n=803)[c]
Ampicillin	26/19%	26%	16%[d]
Amoxicillin/clavulanate	4/4%	4%	-
Cefalotin	5/6%	5%[e]	-
Cefoxitin	-	4%	-
Cefpodoxime	-	4%	2%[f]
Chloramphenicol	5/6%	6%	-
Tetracycline	19/23%	7%[g]	7%
Gentamicin	3/2%	3%	1%
Amikacin	-	1%	-
Enrofloxacin	3/4%[h]	9%	2%[i]
Marbofloxacin	-	9%	-
Imipenem	-	0%	-
Sulfamethoxazole/ trimethoprim	-	15%	8%

[a] Clinical isolates (including urine samples) from dogs only [1]

[b] Clinical isolates from dogs (87%) and cats (13%) [2]

[c] Urinary isolates from dogs only [3]

[d] Although a lower breakpoint for ampicillin resistance is employed in Sweden than in Denmark ($\geq$16µg/ml versus $\geq$32µg/ml), the figures are comparable since most ampicillin-resistant *E. coli* have an MIC >32µg/ml

[e] Data refer to another first-generation cephalosporin (cefazolin)

[f] Data refer to another third-generation cephalosporin (cefotaxim)

[g] Data refer to another tetracycline (doxycycline)

[h] Data refer to another fluoroquinolone (ciprofloxacin)

[i] Data for enrofloxacin resistance have been corrected to the same breakpoint value to permit comparison between studies

infections. About 15% of *E. coli* isolates were resistant to sulpha/trimethoprim, while resistance to ampicillin was even more widespread (26%). However, just as mentioned for clindamycin resistance in pyoderma patients, the prevalence of resistance is likely to be lower in first-time or uncomplicated instances of urinary tract infection.

1.2. Antibiotic penetration into infected tissue

Adequate tissue perfusion is necessary before diffusion of antibiotics into infected tissue can occur. Effective concentrations of antibiotics cannot therefore 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. 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 be concentrated in the tissues behind them. Local 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 and possible toxicologic effects of the preparation. For an antibiotic the most interesting relationship is that between the serum concentration and the antibiotic effect.

Antibiotics can be divided into three main groupings based on the parameters which best predict their clinical efficacy (Table 1.3):

- those with concentration-dependent activity
- those with time-dependent activity
- those with both concentration- and time-dependent activity

For antibiotics in the **first group** (*concentration-dependent antibiotics*), such as the fluoroquinolones and aminoglycosides, an increase in effect is seen the higher the antibiotic concentration is in relation to the pathogens minimal inhibitory concentration (C_{max}/MIC). 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. For these antibiotics it is important that they are given at regular intervals. The **third group** of antibiotics, 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 (see Table 1.3). The interested reader is referred to standard pharmacological texts for further discussion of these topics.

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

Table 1.3.: 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	Aminoglycosides Fluoroquinolones Metronidazole	Maximise concentration of antibiotic	C_{max}/MIC
Time-dependent	Cephalosporins Carbapenems Penicillins Tetracyclines	Maximise time for which antibiotic concentration exceeds MIC	T>MIC
Concentration- and time-dependent	Azithromycin Clindamycin Erythromycin	Maximise the amount of antibiotic over time	AUC/MIC

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

Most first-time infections in immunocompetent animals respond adequately to 5–10 days of antibiotic therapy. 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 markedly longer treatment periods and as a general rule treatment should continue for 1–2 weeks beyond resolution of clinical signs. Recommendations on treatment duration are given in more detail in the disease-specific chapters (6.1–6.9). It is important that treatment is not continued longer than necessary to avoid unnecessary use of antibiotics. If prolonged treatment is employed, regular re-evaluations of the disease process and active extensions 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 1.4 shows examples of antibiotic related toxicity for the different classes of antibiotics.

Table 1.4.: Recognised toxicities and side-effects for selected antibiotics

Class	Toxicity/side-effect	Remarks, warnings and interactions
Aminoglycosides	Renal tubular dysfunction Neuromuscular blockade Ototoxicity Nystagmus	Caution: patients with renal disease and hypovolaemia Increased nephrotoxicity when co-administered with first-generation cephalosporins, amphotericin B, loop diuretics and mannitol
β-lactams (cephalosporins and penicillins)	Immune-mediated disease Urticaria Allergic reactions (rare) especially with parenteral use Acute renal tubular necrosis Bleeding disorders with some products Vomiting with oral administration (especially cephalexin)	Other medications with marked protein binding (frusemide, 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 weightbearing 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 (e.g. barbiturates)	Chloramphenicol is a well-known P450 inhibitor Aplastic anaemia can be induced in humans following contact (owners should apply with gloves)

Recognised toxicities and side-effects for selected antibiotics (*continued*).

Class	Toxicity/side-effect	Remarks, warnings and interactions
Lincosamides	Diarrhoea due to changes in gut flora Oesophagitis and stricture in cats after administration of clindamycin capsules (especially after high dose treatment for toxoplasmosis) Neuromuscular blockade	Reduce dose in the presence of hepatic dysfunction or cholestasis Erythromycin and chloramphenicol block action (avoid co-treatment)
Macrolides	Nausea, diarrhoea and abdominal pain Vomiting and intestinal hypermotility (erythromycin) due to cholinergic activity	Erythromycin prevents metabolism of medicines via cytochrome P450 inhibition and can prevent breakdown of theophylline, benzodiazepines and digoxin Co-treatment of erythromycin with cyclosporin can result in nephrotoxity Care: co-treatment with lincosamides (see above)
Nitroimidazoles	Neutropenia (metronidazole) CNS toxicity (metronidazole and ronidazole) Profuse salivation after oral dosing in cats	
Rifampicin	Hepatoxicity 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 Sulpha/trimethoprim	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 (trimethoprim) Functional hypothyroidism (induced, reversible on cessation of treatment)	Variations in the prevalence of side-effects with different sulphonamides is not known for 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 both fluoroquinolones and third-generation cephalosporins increases the development of extended spectrum β-lactamase (ESBL)-producing *E. coli* and methicillin-resistant staphylococci, both of which are highly clinically relevant. 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 multiresistant bacteria will spread if we do not limit the use of fluoroquinolones and cephalosporins now and in the future. Resistance to these drugs has already increased markedly in the last 10 years (Chapter 1.1), and the development of resistance to both is relatively high in companion animals when compared with other animal populations and with the human population in Denmark.[5] The antibiotic pyramid (Figure 1.1) 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 does require 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. The pyramid has, together with data on the expected clinical effect, formed the basis of the specific recommendations for empirical treatment of infections in the various organ systems (Chapter 6).

We have divided the antibiotics into five categories, based on their critical relevance to human medicine[6] along with the risk for development and spread of resistance of high clinical relevance from companion animals to 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 (e.g. penicillin, macrolides and streptomycin) 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 from companion animals to humans (aminopenicillins, lincosamides, tetracyclines, sulphonamides and nitrofurantoin). 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 multiresistant bacteria such as MRSP (Chapter 3). Rifampicin is increasingly used as an alternative medication for treatment of human MRSA infections in some countries (e.g. Sweden). 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 third-generation cephalosporins, fluoroquinolones, amikacin and metronidazole. 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 critical drugs, namely the carbapenems, vancomycin and linezolid. Use of these should be restricted to rare instances of serious multiresistant infections which cannot be managed in any other way (Figure 1.1).

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 these 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 multiresistant 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. Usually, a rational, well-planned treatment strategy will prove to be the most satisfactory, both in terms of efficacy and financially.
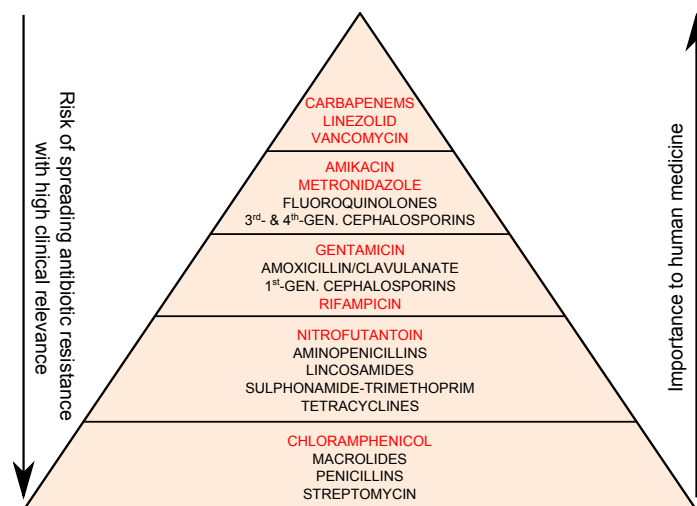
Figure 1.1.: Classification of systemic antibiotics based on clinical importance in human and veterinary medicine and the risk of spreading antibiotic resistance of high clinical relevance. Antibiotics with a particularly high risk for resistance and with few or no therapeutic alternatives in humans 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 not licensed for use in companion animals are highlighted in red.

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(http://ddd.dk/sektioner/hundkatsmaedyr/antibiotikavejledning/Documents/AntibioticGuidelines.pdf)

2. Antibiotic use in companion animals

In Denmark, veterinary antibiotic use is recorded in the national database Vetstat, which is run by the Ministry of Food, Agriculture and Fisheries. Vetstat collects data on total veterinary medicine sales from pharmacies and food mills, including quantities, date of sale, prescribing veterinarian and practice, and recipient. The species is also recorded for antibiotics supplied directly to animal owners, along with age group and a disease code in the case of production animals. Antibiotics supplied directly to veterinary practices are registered to a practice code: the veterinarian is responsible for recording information on antibiotics used in production animals, but not in companion animals (such as dogs, cats, rodents, reptiles and birds) or horses.

Veterinary use of antibiotics is published annually in the DANMAP report, which summarises results from the national surveillance programme for antibiotic use and resistance in animals, food products and humans. For companion animals, use is estimated from the following quantities:

- Antibiotics dispensed directly to companion animal owners via pharmacies
- Antibiotic preparations formulated for use solely in companion animals
- Human oral preparations supplied to veterinary practices (of which half goes to purely companion animal practices)
- Antibiotic preparations sold for use in purely companion animal practice

Developments in use need to be adjusted for changes in population size. Dogs and cats make up the majority of companion animals, and the calculations in this chapter are based on population numbers for cats and dogs of 650 000 and 550 000 individuals (Danmarks Statistic, 2000) and an average body mass for cats and dogs of 4kg and 20kg, respectively.[1] While the number of registered dogs has been fairly stable for many years (Danish Dog Register, 2012), the cat population has probably increased since the year 2000. This is assumed to have a minimal influence on the estimates and conclusions drawn below because cats both have a lower body mass and are treated less frequently than dogs, and thus account for <10% of antibiotic use in companion animals.

2.1. Total antibiotic use in companion animals in Denmark

Figure 2.1 shows the relative use of the different antibiotic classes in companion animals in Denmark in 2011. These estimates do not include parenteral and topical preparations (e.g. fusidic acid) prescribed for companion animals by mixed practices with the exception of the second-generation cephalosporin cefevocin, since the containing preparation is only licensed for use in companion animals.

Estimated antibiotic usage in companion animals in 2011 accounted for just under 2 tons out of a total veterinary consumption of 108 tons. Use of vital broad-spectrum antibiotics is currently relatively high in companion animals: 52% of all veterinary fluoroquinolones, and 72% of all veterinary cephalosporins used in 2011 were prescribed for companion animals. Of these cephalosporins only about 3kg of the medically important third- and fourth-generation cephalosporins were used in companion animals. Use of third-generation cephalosporins in companion animals amounted to 0.32 ADDkg[b] per kg live biomass: in comparison, use of third- and fourth-generation cephalosporins in cattle amounted to only 0.06 ADDkg/kg live biomass. These broad-spectrum cephalosporins were hardly used at all in swine and poultry production.[2] The relatively high use in companion animals

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[b]Defined Animal Daily Doses, a national veterinary equivalent to the human international Defined Daily Dose or DDD.
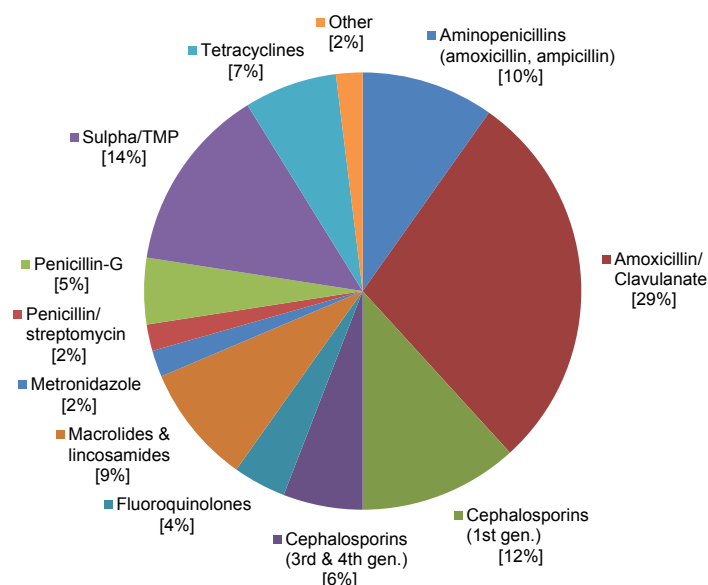
Figure 2.1.: Rates of use of different antibiotic classes relative to total antibiotic use in companion animals in Denmark in 2011

of fluoroquinolones and cephalosporins creates a potential risk for development of resistance to these antibiotics, which have been classified by WHO as 'critically important' to human treatment.

The most commonly used antibiotic in companion animal practice is amoxicillin/clavulanate. In 2011 its use accounted for 91% of the total veterinary consumption of aminopenicillins combined with a β-lactamase inhibitor. The resistance level in clinical isolates of *S. pseudintermedius* to this combination has increased markedly in recent years (Chapter 1.1). Additionally, dogs regularly yield *E. coli* isolates with CMY-2, an ESBL-like enzyme which mediates resistance to amoxicillin/clavulanate. These bacteria along with other examples of multiresistant bacteria of significance to the Danish companion animal sector are covered in more detail in Chapter 3.

Figure 2.2 illustrates the changes in oral antibiotic use in Denmark for treatment of dogs and cats. Since 2005 there has been a 36% increase in oral antibiotic use, which is almost entirely accounted for by the increased use of amoxicillin/clavulanate (88% increase). This largely reflects increased treatment of dogs.

The combined average total doses of antibiotics per dog or cat in Denmark is similar to that for humans. An important difference is that in humans narrower-spectrum preparations such as phenoxymethylpenicillin or cloxacillin are prescribed more often.[2]

2.2. Comparison with oral antibiotic use in dogs and cats in the rest of Scandinavia

In Norway and Sweden, oral antibiotics for companion animal use are primarily dispensed directly from pharmacies to owners, and the recipient species is recorded in the respective national pharmacy database. In Denmark, use in dogs and cats was estimated on the basis that all preparations formulated for treatment of patients exceeding 7kg body mass were intended for dogs. It was further assumed, based on data from Sweden and Norway, that small dogs (<7kg) were treated four times more often than cats (measured in total packs dispensed) and that this was true for all preparations.
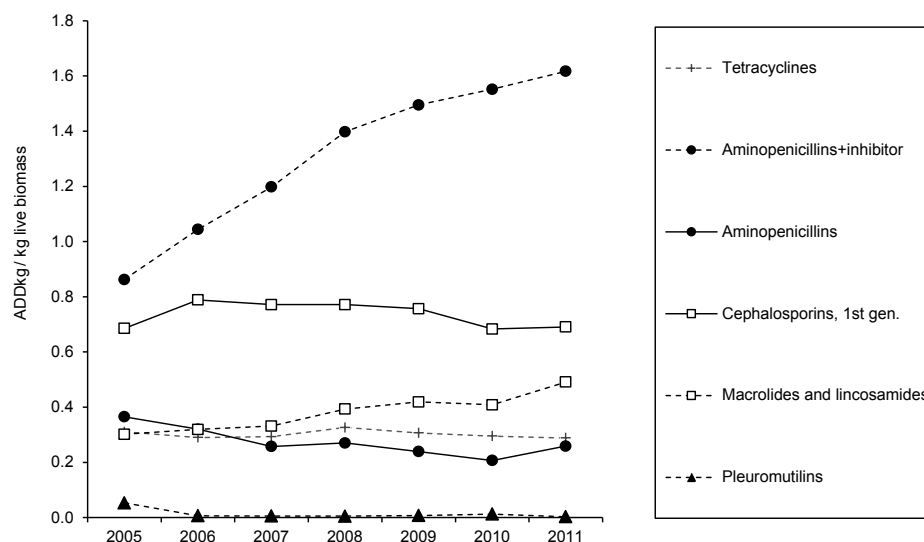
Figure 2.2.: Changes in oral antibiotic consumption for dogs and cats in Denmark between 2005 and 2011. Inhibitor refers to β-lactamase inhibitor such as clavulanate. Values are Defined Animal Daily Doses (ADD) per kg live biomass. Source: DANMAP 2011.[2]

Comparisons showed that consumption in 2005 was higher in Sweden than either Norway or Denmark. From 2005 to 2007, use in Norway and Denmark increased while use in Sweden fell.[3] The national statistics for antibiotic resistance and use (NORM-VET and SVARM) indicate these trends continued, such that use in Denmark after 2009 was higher than in Sweden and by 2011 was roughly equivalent to Swedish consumption in 2005. Norway, like Denmark, has experienced increased use of amoxicillin/clavulanate, with a roughly 70% increase between 2005 and 2010.[4] In contrast, total antibiotic usage in companion animals fell 21% from 2006 to 2010 in Sweden, with reduced consumption of cephalosporins (-51%), aminopenicillins with clavulanate (-33%) and fluoroquinolones (-32%).[5] The decline in antibiotic use in Sweden from 2006 to 2010 can be attributed to the use of national campaigns and guidelines over this period. There has been a particular focus on reducing the use of critically important broad-spectrum antibiotics. One of the concrete goals was a reduction in the use of first-generation cephalosporins, which are believed to encourage the spread of MRSA and MRSP. In Sweden, aminopenicillins (e.g. amoxicillin) and clindamycin comprised over 50% of companion animal use in 2010, reflecting the high market share of relatively narrow-spectrum antibiotics compared with Denmark (Figure 2.1).

2.3. Conclusions

Although the data for antibiotic use in Denmark are not complete for companion animals, it is clear that broad-spectrum antibiotics such as amoxicillin/clavulanate, third-generation cephalosporins and fluoroquinolones are used much more frequently in dogs and cats than in production animals. The Swedish experience clearly demonstrates that implementing national treatment guidelines and campaigns can result in marked reductions in the use of these antibiotics, while the developments in antibiotic use in Denmark plainly show that a similar approach is needed here.

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3. New multiresistant bacteria in companion animals

Within the past five years a number of multiresistant bacteria have emerged in companion animals, both in Denmark and in other countries. The most important of these bacteria are ESBL-producing *E. coli* and MRSP which are both resistant to most - and sometimes all - conventional veterinary antibiotics. Consequently, they represent a serious threat to animal health due to the increased risk of treatment failure. These multiresistant bacteria do not just impact the individual patient but are also recognised nosocomial pathogens, which can spread in the hospital environment via personnel and by other routes. 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. MRSP defined

MRSP is a *S. pseudintermedius* strain which has acquired the resistance gene *mecA*. This is the same gene as is seen in MRSA, and the presence of *mecA* confers resistance to β-lactam antibiotics. MRSP was first identified in Europe in 2006, and since then a specific clone (termed ST71) has spread rapidly internationally. This clone, in addition to β-lactam resistance, is typically also resistant to lincosamides, fluoroquinolones, sulpha/trimethoprim, macrolides, tetracyclines and gentamicin. In 2011 the prevalence of MRSP in clinical isolates from Danish dogs was approximately 3%,[1] which is markedly less than that seen in many other European countries and similar to the prevalence in Sweden (Chapter 1.1). Apart from the lower prevalence, the Danish isolates often do not belong to the European ST71 clone and are thus less multiresistant.

3.2. Diagnosing MRSP

Oxacillin and cefoxitin are the two antibiotics which are routinely employed to demonstrate methicillin resistance in staphylococci. While cefoxitin is the most effective marker for MRSA, oxacillin is the best antibiotic for identifying MRSP. Final confirmation of MRSP requires identification of *mecA* using PCR. Before this confirmation is available all oxacillin-resistant strains should be considered resistant to all β-lactams, regardless of any apparent susceptibility to penicillins and cephalosporins on sensitivity testing.

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, patient health status and 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 (e.g. wound drainage and debridement). When antimicrobial treatment cannot be avoided, local application is preferred to

systemic use. For example, topical antiseptics containing chlorhexidine or benzoyl peroxide can be employed. If these methods are not feasible or are ineffective then systemic treatment of MRSP using sensitivity testing and the antibiotic pyramid described in Chapter 1.7 is acceptable.

The few antibiotics which can be effective against multiresistant bacterial strains may have significant side-effects, poor pharmacological profiles, or be critically important to human medicine. Resistance to chloramphenicol and doxycycline is relatively common in MRSP ST71. Even if sensitive, chloramphenicol can be difficult to source, requires eight-hourly dosing and in rare cases can cause bone marrow suppression. 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, even though 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 MRSP occurs far more rarely in the urinary tract than in pyoderma, which nitrofurantoin is unsuitable for treating. Nitrofurantoin can produce gastrointestinal side-effects in dogs. Other products effective against MRSP are only available as injectables (amikacin, vancomycin, linezolid). Due to their status as drugs of last resort in human medicine their use should only be considered in rare instances (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.

3.4. ESBL defined

ESBL stands for *extended-spectrum β-lactamase*, which are enzymes produced by Gram-negative bacteria that can inactivate a range of β-lactam antibiotics. These enzymes can be themselves inhibited by clavulanate. The term 'extended-spectrum' is used because in addition to inactivating penicillins, aminopenicillins (ampicillin, amoxicillin) and first-generation cephalosporins (cefalexin, cefadroxil and cefazolin), they also affect third-generation cephalosporins (e.g. cefovecin). In companion animals these enzymes are primarily associated with *E. coli*, but can also be seen in other pathogenic bacteria such as *Proteus*, *Salmonella* and *Klebsiella*. The over 200 types of ESBL can be 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 *E. coli* from humans, and can also be seen in companion animals in Denmark. Isolates producing CTX-M-15 display a characteristic multi-resistance pattern which in addition to β-lactams includes fluoroquinolones and sulpha/trimethoprim amongst others.

In the period from 2010 to 2012 approximately 5% of all *E. coli* isolates at the diagnostic laboratory at the Department of Veterinary Disease Biology were resistant to third-generation cephalosporins. [1,2] Around half of these isolates had genes coding for CTX-M enzymes, including CTX-M-15. Other strains had the gene encoding the enzyme CMY-2. This so-called ampC β-lactamase is produced by bacteria which are usually sensitive to other antibiotic classes.

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 when sensitivity testing shows resistance to at least one of the third-generation cephalosporins recommended for demonstration of ESBL (cefpodoxime, ceftazidime and cefotaxime) together with sensitivity to

amoxicillin/clavulanate and the cefamycins (cefoxitin). CMY-2 β-lactamses can be distinguished by a lack of sensitivity to additional β-lactams including amoxicillin/clavulanate and cefoxitin.

This variation in ESBL activity and the fact that an isolate can possess more than one ESBL-type makes it important that any laboratory test-panel includes a broad range of β-lactam antibiotics. Final confirmation of ESBL requires PCR against typical ESBL genes. International recommendations are that isolates confirmed with PCR as ESBL-producers should be considered resistant to all cephalosporins regardless of the outcome of sensitivity testing. If an isolate is not confirmed to be ESBL-producing with PCR, then the resistance profile should be interpreted individually for each tested β-lactam antibiotic.

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 β-lactams, sulpha/trimethoprim and fluoroquinolones which are amongst the most commonly used antibiotics for urinary tract infections. In these cases, the choice of antibiotic should be guided by sensitivity testing and the infection type. If the isolate is sensitive to amoxicillin/clavulanate then this antibiotic should be used at the highest possible dose (25 mg/kg PO TID) to maximise the 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, fluoro-quinolones 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, veterinary use of preparations in this class (e.g. imipenem) requires careful consideration as previously discussed (Chapter 1.7).

3.7. Social consequences

The presence of ESBL-producing *E. coli* and MRSP in small animal hospitals has social significance due to the risk of infecting owners and veterinarians. These multiresistant bacteria are still relatively rare in Denmark compared with some other countries, but it is nonetheless important to limit their spread with the aid of increased microbiological monitoring and rational antibiotic use. Third-generation cephalosporins and fluoroquinolones are known for selecting MRSP and ESBL-producing *E. coli*, and care should be taken when using these antibiotics. It is recommended that laboratories with experience with these resistant strains be consulted and utilised, both so that multiresistant bacteria can be detected in a timely fashion and that the clinician can obtain guidance on treatment and containment. In Denmark, specialist advice regarding the development and spread of antibiotic resistance in companion animals can be obtained from the Department for Veterinary Disease Biology, Faculty of Health and Medical Sciences, University of Copenhagen (www.sundvetdiagnostik.ku.dk).

Because knowledge regarding zoonotic transfer of MRSP and ESBL-producing *E. coli* from companion animals to humans is limited, 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 the individual's 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 with multiresistant bacteria.

International guidelines for prevention and control of nosocomial infections and the spread of bacteria in veterinary practices are available online.[3]

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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. In the first, because the veterinarian decides when culture is indicated, what samples should be taken, how sampling should be performed and how these samples should be transported to the laboratory. In the second, because 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

Bacterial culture is always advisable but is of particular importance in the following situations:

- A complicated or life-threatening infection is suspected
- The patient fails to respond to the initial treatment
- The infection is recurrent or refractory
- The patient is immunosuppressed
- There is a need to monitor an established infection
- Infection with multiresistant bacteria is suspected

With regard to treatment failures, it is important that veterinarians both recommend and encourage regular check-ups of patients undergoing treatment. Educating the owner in identification of signs of problems or lack of improvement will also help avoid prolonged periods of unproductive treatment. Infection-specific indications for bacterial culture are outlined in Table 4.1. Because of the need to increase microbiological surveillance of antibiotic resistance, **culture and sensitivity testing is recommended for all instances of antibiotic-treated urinary tract infections and pyodermas**. These infections are the most common reasons for antibiotic prescription 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* (Chapter 3). Pyodermas in particular usually require prolonged treatment, and treatment failures can have negative consequences for both the patient's welfare and the owner's finances. Empirical antibiotic treatment pending results from the laboratory will always require individual assessment by the clinician based on infection type 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 recommended for demonstrating 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.*

Table 4.1.: Examples of infection-specific indications for bacterial culture and sensitivity testing

Infection	Comments
Recurrent infection	High risk of multiresistant bacteria
Deep pyoderma	Prolonged treatment required
Surgical wound infections	High risk of multiresistant bacteria
Lower airway infections	Life-threatening
Osteomyelitis	Life-threatening
Peritonitis	Life-threatening
Sepsis	Life-threatening
Urinary tract infection or pyoderma requiring antibiotic treatment	Need for microbiological surveillance of resistance patterns in dogs (see text)

4.2. Sampling and transport

As well as selecting the most suitable sample type for any given infection it is important to make sure that these 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 4.2 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 stored in this way, 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 as soon as possible 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). A urine culture dip paddle is a good alternative for transport of urine samples. These dip paddles, described in more detail in Chapter 6.3.1, can be sent either before or after incubation at 37℃. The latter option is particularly useful, since it can save unnecessary laboratory charges for sterile samples.

The diagnostic laboratory will normally supply the veterinarian with a test request form for completion and sending along with the sample. These forms should be completed thoroughly, because they provide the laboratory with important information regarding the patient and the sample. A request form should contain the following information:

- Name and contact information for the veterinarian sending the sample
- Patient's name or similar identification
- Patient's species, age and sex
- Sample type and where on the body it was obtained
- Time of sampling
- Clinical diagnosis and relevant history
- Cytological findings (if relevant)

- Information on current or recent antibiotic therapy
- Specific requests regarding culture

Table 4.2.: Recommended samples and sampling techniques for the most common bacterial infections in companion animals. In most cases commercially available transport media such as Amies or Stuarts will be appropriate.

System	Problem	Sampling technique and transport
	Wound	• 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 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	• 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	• 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	• 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)	Obtain skin biopsy: • Anaesthesia • Remove hair locally with sterile scissors • Disinfect the skin surface with 70% ethanol • Take biopsy using a punch with a diameter of 3-4mm • Place biopsy in sterile container moistened with one drop of sterile saline • Close biopsy site
External ear canal	Exudate	• Swab ear canal (horizontal canal preferred) with sterile culture swab • Place culture swab in transport medium
Urinary tract	Cystitis, pyelonephritis	• Ideally collect via cystocentesis and send immediately after collection in sterile container or on dip paddle (Chapters 4.2 and 6.3.1). Urine should be refrigerated if there is a delay before sending • Samples not collected via cystocentesis should be sent refrigerated to minimise growth of contaminants
Reproductive organs	Vaginitis, acute metritis, endometritis, pyometra	• Samples should be obtained from the cranial vagina or uterus, preferably via endoscopic biopsy port to minimise contamination from normal vaginal flora
	Mastitis	• After thorough cleaning of the gland surface and teat, samples should be milked into a sterile container
	Orchitis	• Second fraction of ejaculate and/or urine samples taken by cystocentesis should be placed in sterile containers • Consider testing for brucellosis

Samples and sampling techniques recommended for the most common bacterial infections in companion animals (*continued*).

System	Problem	Sampling technique and transport
	Prostatitis	• Mid-portion of third fraction of ejaculate and/or urine samples taken by cystocentesis should be placed in sterile containers
Respiratory tract	Upper airway	• Swabs and biopsies best obtained via rhinoscopy, avoiding contamination from the external nares • Place culture swab in transport medium
	Lower airway	• Samples best obtained via bronchoscopic-guided bronchoalveolar lavage with sterile saline - alternatively take brush samples via bronchoscopy • Transfer retrieved fluid to transport medium • Mycoplasma require specific media - contact laboratory for requirements before sampling
Gastrointestinal tract	Enteritis	• 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.	• Blood should be taken in EDTA tube • Other fluids should be collected into sterile containers or syringes (contact laboratory for specific requirements)

4.3. Culture 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 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 and so on can be found on the internet, including in the online atlas produced by the Department of Veterinary Disease Biology, Faculty of Health and Medical Sciences, University of Copenhagen (`http://pictures.life.ku.dk/atlas/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. This will result in optimal patient care and reduce the risk of misdirected therapy or overtreatment. Reporting accurate but 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 (as with β-lactams). This category also functions as a 'buffer zone' which can reduce the risk of misinterpretation based on technical errors in the sensitivity test. Resistant (R) bacteria are not inhibited by antibiotic concentrations achieved with standard dosing regimes. 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 particular bacteria. 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, cefoxitin and one or more third-generation cephalosporins (cefpodoxime, cefotaxime 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 4.3.

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. Some 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 (Table 4.3).

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. Although these two antibiotics have different chemical structures and belong to different classes (macrolides and lincosamides, respectively) resistance is coded 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 if an isolate is reported as resistant to erythromycin.

In addition to a diagnostic role, sensitivity testing can generate data which can be used in monitoring of bacterial resistance. The clinician can then adjust their choice of empirical therapies based on the

local resistance profile. 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 in the absence of prior antibiotic therapy. Bacterial culture of more uncomplicated or first-time infections will therefore improve monitoring quality and give a more realistic picture of general resistance development, thereby enabling better guidelines for empirical therapy. For this reason, it is recommended that all cases of urinary tract infection or pyoderma which require antibiotic treatment should undergo bacterial culture.

National data regarding resistance development would be extremely valuable for developing a sensible antibiotic policy. Currently there is no programme for monitoring resistance in companion animal practice in Denmark.

Table 4.3.: Guidelines for interpreting sensitivity tests for specific antibiotics

Antibiotic	Comments
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 β-lactamases. The 60-80% of staphylocci which produce β-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 β-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 β-lactams. Can be used to demonstrate MRSP although oxacillin is better. ESBL-producing *E. coli* are sensitive unless they also have another β-lactamase such as CMY-2.
Chloramphenicol	Inclusion in test panel recommended because it is often one of the few antibiotics effective against MRSP and ESBL-producing *E. coli.*
Clindamycin	Used to predict sensitivity to other lincosamides (e.g. lincomycin).
Doxycycline	Indicates sensitivity 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 (Chapter 4.4).
Fluoroquinolones	Even though extensive cross-resistance occurs for the different fluoroquinolones, drug-specific breakpoints exist for enrofloxacin, marbofloxacin, difloxacin and orbifloxacin.
Fucidic acid	Breakpoint is based on human systemic therapy: clinical relevance to companion animals is dubious since fucidic acid is used topically in these species.
Gentamicin	Important antibiotic used in human hospitals. Aminoglycoside resistance is 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 (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 *E. coli.*

Guidelines for interpreting sensivity tests for specific antibiotics (*continued*).

Antibiotic	Comments
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.
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.
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 (Chapter 1.7).

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5. Perioperative antibiotic therapy

5.1. Surgical infection risks

Surgical site infections (SSI) are common in humans. The precise prevalence in dogs and cats is uncertain, but complication rates of 0.8% to 29% and above have been reported depending on the type of surgery involved.[1–5] Occurrence of SSI increases the risk of wound breakdown, the need for reoperation, side-effects due to additional medical treatment, serious complications and death. In humans, and probably also in dogs and cats, the increasing prevalence of multiresistant bacteria is closely linked to the prevalence of SSI. Without effective preventive measures these bacteria can spread in the hospital environment and between patients. There appear to be four key factors which influence development of SSI, namely level of wound contamination, surgery time, host susceptibility and the presence of microorganisms.

Level of wound contamination

Surgical wounds can be classified according to the level of contamination in order to assess their infection risk (Table 5.1). The overall mean infection rate for surgical wounds is around 5%. Despite its subjectivity, classification of wounds in this manner has been shown to be a fairly reliable means to predict the risk of developing SSI.

Table 5.1.: Surgical wound classifications and associated infection risks.

Wound type	Description	Examples	Infection risk
Clean	• Elective, non-emergency, non-traumatic • No acute inflammation • No break in technique • Respiratory, gastrointestinal, biliary and genitourinary tracts not entered (excluding routine sterilisation operations) • Primary closure (± active drainage)	• Explorative laparotomy • Castration • Ovariectomy/ ovariohysterectomy • Orthopaedic procedures	2.5–6%
Clean-contaminated	• Elective entry into respiratory, gastrointestinal, biliary or genitourinary tracts with minimal spillage and without evidence of infected urine, bile or secretions • Minor break in technique • Emergency operations that are otherwise clean	• Enterotomy • Intestinal anastamosis • Cystotomy • Cholecystectomy • Pyometra	2.5–9.5%

Surgical wound classifications and their associated infection risks (*continued*).

Wound type	Description	Examples	Infection risk
Contaminated	• Surgery of respiratory, gastrointestinal, biliary or genitourinary tracts with gross spillage or evidence of infected urine, bile or secretions • Major break in technique • Acute non-purulent inflammation • Traumatic wounds ≤4 hours old • Chronic open wounds for grafting or covering	• Enterotomy • Intestinal anastamosis • Cystotomy • Cholecystectomy • Pyometra with leakage	5.5–28%
Dirty	• 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	• Leakage from perforated viscera • Infected operation sites • Septic peritonitis • Abscesses • Open fractures	18–25%

Surgery time

The duration of surgery is one of the most important factors in the development of SSI. Orthopaedic procedures exceeding 90 minutes have an increased prevalence of SSI.[6] Experience from clinical practice suggests this also holds true for soft-tissue procedures.

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 Anesthiologists (ASA) classification scheme was originally intended to permit uniform evaluation of a patients pre-anaesthetic physical status and provide a simple, validated method to determine the risk of intra- and postoperative cardiopulmonary complications.[7] It 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 5.2).[3]

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.

Table 5.2.: ASA classification of pre-anaesthetic status.

ASA class	Description	Examples
1	Healthy individual without pre-existing disease	Neutering operations, uncomplicated hernia, patella luxation, cruciate ligament rupture
2	Localised disease or mild systemic disease (afebrile patients that appear well)	Malformations, uncomplicated diabetes mellitus, skin tumours, trauma without circulatory shock, mild infections without fever
3	Serious systemic disease (febrile patients that appear ill)	Fever, anaemia, complicated diabetes mellitus and diabetic ketoacidosis, heart murmur, trauma with circulatory shock, pneumonia
4	Life-threatening systemic disease	Severe trauma with circulatory shock, heart failure, renal failure, hepatic failure
5	Moribund, not expected to survive 24 hours without surgery	Polytrauma, multiple organ failure, terminal cancer, Addisonian crisis, gastric torsion

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 dessication, careful haemostasis and good tissue approximation are all ways to reduce the risk of SSI.

Aseptic operating room procedures

Behaviour in the operating room has an major impact on both the prevalence and the prevention of SSI. Proper behaviour includes: minimising the number of personnel in the room; good ventilation; clipping of patient hair immediately prior to the operation; cleaning and disinfection of the skin with soap, antiseptic (chlorhexidine) and alcohol; use of waterproof drapes; 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. Adhesive, semi-permeable wound plasters permit oxygen exchange without allowing the incision to completely dessicate. Necessary bandage changes should 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. Hospitalisation should therefore be considered an additional risk factor for SSI.

Perioperative use of antibiotics

Perioperative antibiotic prophylaxis should be used based on an individual evaluation of the patient's status (ASA class) 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 be given not more than 60, and ideally 0–30, minutes before incising the skin. Prophylactic antibiotics must be given before starting surgery and should be administered intravenously to ensure high plasma concentrations.

As a general rule:

- **Low-risk patients** (ASA class 1–2 with clean procedures) do not require antibiotic prophylaxis
- **High-risk patients** (ASA class 3–5, patients with systemic infections, infected wounds or undergoing orthopaedic surgery) should receive antibiotics perioperatively

Choice of antibiotic

Recommended antibiotics are listed in Table 5.3. For perioperative use, the ideal preparation should have the following attributes:

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

Table 5.3.: Rational antibiotic selections for perioperative use, based on likely pathogens

Source	Likely pathogens	Recommended antibiotics
Skin	Staphylococci and *Pasteurella* spp.	Cefazolin (20 mg/kg IV preoperatively and repeated at 90 minute intervals until closure of the incision)
Gastrointestinal tract or uterus	Enteric bacteria, including *E. coli*, enterococci and anaerobic bacteria	Ampicillin (20 mg/kg IV preoperatively and repeated at 90 minute intervals until closure of the incision) Note: in critical patients (ASA class 4–5) or if peritoneal spillage of intestinal contents or pus occurs, ampicillin or penicillin G can be supplemented by enrofloxacin (5 mg/kg IV) to provide better coverage of Gram-negative bacteria

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6. Organ- and disease-specific recommendations

Contents

6.1. The skin

6.1.1. Overview

Aetiology, prevalence and definitions

Bacterial skin infections are 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 most commonly in dogs and is almost always secondary to an underlying primary condition.[2] In cats, generalised pyoderma is uncommon and usually due to the patient being immunocompromised. Subcutaneous abscesses following bite wounds occur frequently in cats[3]. Over 90% of bacterial pyodermas in dogs are due to *S. pseudintermedius* (formerly *S. intermedius*), a commensal organism of both dogs and cats.[4] In common with *S. aureus*, which is mostly found on cats, *S. pseudintermedius* is primarily isolated from the oral, nasal and anal mucosa.[3;5] Other bacteria which can be involved in pyoderma (especially in dogs) include *S. aureus*, *S. schleiferi*, other coagulase-negative staphylococci,[5;6] *E. coli*, *Proteus mirabilis* and *Pseudomonas* spp.[3]

Skin infections are categorised by their depth (Figure 6.1) as this determines the choice of therapy to a large extent.

Diagnosis, culture and sensitivity testing

A cytological evaluation is needed to identify 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 stain such as 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 such as Hemacolor® or Diff-Quick®. Microscopy typically reveals cocci (and occasionally rods) plus degenerative neutrophils with or without phagocytosed bacteria. Overgrowth of bacteria without a neutrophilic response may also be seen.

Culture and sensitivity testing is recommended in all cases of bacterial pyoderma for which systemic antibiotic therapy is considered. In addition to aiding selection of the correct antibiotic, it also yields information on resistance patterns in pathogenic bacteria both in first-time pyoderma and in chronic infections (Chapter 4.1). Clinicians are therefore strongly encouraged to perform culture and sensitivity testing in all pyoderma cases. It is of particular importance when intracellular rods are observed, when there is a lack of response to antibiotic therapy, when new lesions develop during treatment or in chronic or recurrent pyoderma. Sampling techniques are described in more detail in Chapter 4.2 and in Table 4.2.

Overview of pyoderma treatment

Topical treatment should be prioritised in the management of pyoderma, especially in dogs. Surface, superficial and localised deep pyodermas can be treated effectively with topical preparations in many cases.[7] Topical treatment can also complement systemic therapy. Topical preparations include shampoos, ointments, gels, creams and wipes. Fusidic acid is available in Denmark as a topical antibiotic in the form of a gel for dogs. Wipes are available which contain 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

Surface pyoderma
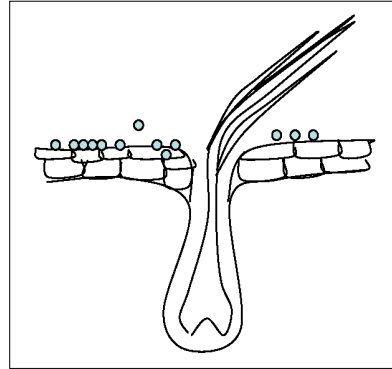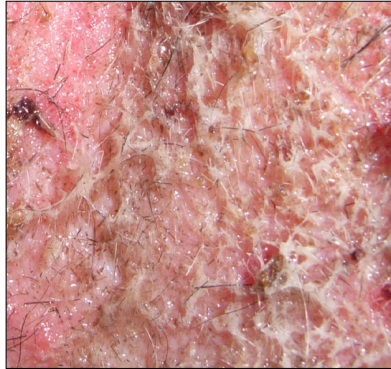
Superficial pyoderma
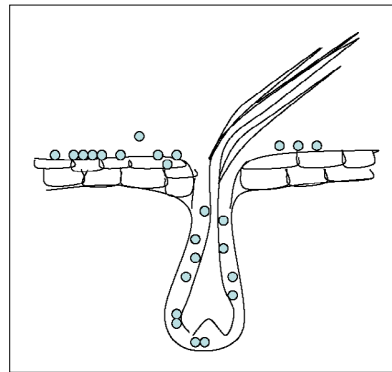
Deep pyoderma
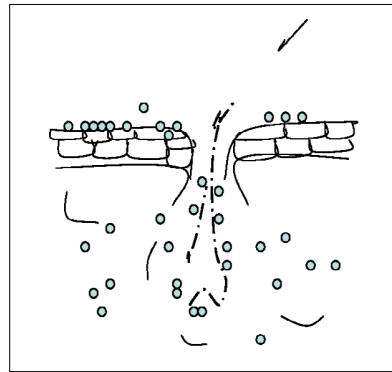
Figure 6.1.: Clinical categories of pyoderma. For each category a representative photographic example is shown along with a line drawing to highlight the level of infection . The blue dots represent bacteria.

to antimicrobial agents (Table 6.1) shampoos also contain delivery vehicles which help distribute the active ingredients more widely over the body.[3] Normally a frequency of up to 2–3 times weekly is recommended for whole-body shampooing, but this can be varied according to the patient and the severity of the pyoderma. If applied locally (for example, to the axilla) 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 it is rinsed off. The most common side-effect of shampoo therapy is drying of the skin, so washes should be followed by a moisturising agent. The use of topical therapy against bacterial and yeast skin infections has been reviewed.[8]

Systemic antibiotic therapy (Table 6.2) should be considered on a case-by-case basis. It is essential to identify and address any underlying primary disorder to achieve optimal results. Antibiotic therapy should be supported by culture and sensitivity testing. 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 intersitial space and adnexa.[12] The extent, depth and chronicity of the pyoderma will determine the duration of therapy. The effect of treatment can be evaluated by examining the extent of lesions, using cytology, and taking bacterial cultures both during and at the end of treatment. Cessation of therapy should not occur without discussion with the veterinarian in charge of the patient. As a general rule, superficial pyoderma should be treated for at least one week after cessation of clinical signs, whereas in deep pyoderma treatment should continue at least two weeks beyond apparent resolution. Use of antimicrobial shampoos alongside systemic therapy is recommended.

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. When these occur, papules, pustules or furuncles will be evident at the edges of the lesion as satellite lesions.

Table 6.1.: Selected shampoo ingredients with an antimicrobial effect.

Ingredient	Mechanism of action	Comments
Chlorhexidine	• Destroys the bacterial cell membrane leading to a loss of osmotic regulation and cell death • Broad-spectrum bacteriocide [9;10]	Moderate effect against *Malassezia*
Ethyl lactate	• Hydrolysed to lactic acid, lowering skin pH and inhibiting bacterial lipases • Bacteriostatic effect [11]	Good penetration of hair follicles and sebaceous glands
Benzoyl peroxide	• Releases oxygen radicals leading to bacteria cell membrane rupture • Broad-spectrum bacteriocide [10]	Has a follicle-cleansing effect but can dry or irritate the skin

Table 6.2.: Antibiotic recommendations for systemic treatment of pyoderma. The priority system applies both to empirical therapy and to selection of an antibiotic following culture and sensitivity testing.

Priority	Comments	Examples
First	• As narrow-spectrum as possible • Uncomplicated and/or first-time pyoderma	• Lincosamides ◦ Clindamycin

Second	• When resistance to first-line antibiotics confirmed
	• May be needed for chronic, recurrent pyoderma
		• 1st-generation cephalosporins
		  ◦ Cefalexin
		  ◦ Cefadroxil
		• Amoxicillin/clavulanate
		• Sulpha/trimethoprim
		• Doxycycline

Third	• Only when resistance to first and second line antibiotics is demonstrated
	• Typically used for *Pseudomonas* infections
		• Fluoroquinolones
		  ◦ Enrofloxacin
		  ◦ Marbofloxacin
		  ◦ Pradofloxacin
		• 3rd-generation cephalosporins
		  ◦ Cefovecin

Diagnosis

The diagnosis is based on clinical signs and the techniques described in Chapter 6.1.1.

Treatment

Treatment options are outlined in Table 6.3. Topical therapy is normally sufficient for management of surface pyoderma.

Table 6.3.: Treatment options for surface pyoderma. Prioritisation of the treatments is valid both for empirical therapy and subsequent adjustments based on culture and sensitivity testing.

Problem	Antibiotics	Comments
Intertrigo (skin fold dermatitis)	• Systemic antibiotics are not necessary	• Clip fur • Topical disinfectant (chlorhexidine) $\pm$ 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')	• Systemic antibiotics are not usually necessary
	• Reserve systemic antibiotics (Tables 6.4 and 6.5) for concurrent folliculitis or furunculosis
		• Clip fur
		• Topical disinfectant (chlorhexidine) $\pm$ drying agent (boric or acetic acid) as required
		• Topical antibiotics (fusidic acid BID, 5–10 days) if bacterial overgrowth is present
		• Prevent further trauma
		  ◦ Elizabethan collar
		  ◦ NSAIDs *or*
		  ◦ Glucocorticoids (topical or systemic)

6.1.3. Superficial pyoderma

Aetiology and prevalence

Superficial folliculitis is the most commmon form of pyoderma seen in dogs. 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 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, bacterial overgrowth syndrome and mucocutaneous pyoderma. These typically exhibit more crusting, collarettes and erosions than purulent hair follicle infections. Superficial pyodermas are also noted in cats, although less frequently than in dogs.[13] Underlying allergies or immunosuppressive diseases such as FIV, FeLV, diabetes mellitus or neoplasia should be ruled out in these cases.

Diagnosis

The diagnosis is based on clinical signs and the techniques described in Chapter 6.1.1. Efforts to identify the underlying cause are strongly recommended with recurrent pyodermas.

Treatment

Treatment options are outlined in Table 6.4. Topical therapy with shampoos should be the first choice, since many superficial pyodermas can be effectively management with shampoos alone. , shampoos can function prophylactically to reduce recurrence. When using systemic therapy, combination with a topical management will increase efficacy. Systemic therapy should extend at least one week beyond resolution of clinical signs.

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 leading to inflammation and infection in the surrounding dermis. Localised furunculosis may be seen interdigitally, at the carpus, on the chin, at calluses or as a lick granuloma. If infection spreads throughout the whole dermal layer, it is termed cellulitis. German shepherd dogs can suffer from a form of deep pyoderma characterised by fistulous reactions and deep ulcerations of the skin. In cats, deep pyoderma is rare but can be seen focally as chin furunculosis 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 typically can be treated topically.

Diagnosis

The diagnosis is based on clinical signs and the techniques described in Chapter 6.1.1. Histopathology, culture, and sensitivity testing of surgical biopsies is recommended. Chronic or recurrent deep pyodermas should always prompt investigation for an underlying cause.

Table 6.4.: Treatment options for superficial pyoderma. Prioritisation of the treatments is valid both for empirical therapy and subsequent adjustments based on culture and sensitivity testing.

Problem	Antibiotics	Comments

Canine
• Impetigo
• Superficial folliculitis
  ◦ Juvenile
  ◦ Secondary
  ◦ Pyotraumatic
• Superficial spreading dermatitis
• Bacterial overgrowth syndrome
• Mucocutaneous pyoderma[a]
	• Try topical therapy first[a]
	
	• If no response:
	  ◦ Clindamycin (5.5–11 mg/kg PO BID)
	  ◦ Amoxicillin/clavulanate (12.5 mg/kg PO BID)
	  ◦ 1st-generation cephalosporin such as cephalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID)
		• Shampoo **locally**
		  ◦ Wash affected area daily for one week
		  ◦ Continue on every other day basis for one week
		  ◦ Use as needed thereafter
		
		• Shampoo **whole body**
		  ◦ Wash twice weekly for 2–3 weeks
		  ◦ Continue once weekly for two weeks
		  ◦ Use as needed thereafter

Feline superficial pyoderma	• If infection confirmed:
	  ◦ Clindamycin (5.5–11 mg/kg PO BID)
	  ◦ Amoxicillin/clavulanate (12.5 mg/kg PO BID)
	  ◦ 1st-generation cephalosporin such as cephalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID)
		• Rare in cats: exclude other causes of pustular reactions and rule out underlying causes

[a] Topical therapy is not recommended for mucocutaneous pyoderma

Treatment

Treatment options are outlined in Table 6.5. Focal deep pyoderma can be managed with topical therapies with a follicle cleansing effect. Systemic antibiotics should be chosen when lesions are widespread, and can be combined with topical therapy. Therapy should continue for at least two weeks beyond resolution of clinical signs.

6.1.5. Cellulitis, abscesses and traumatic wounds

Aetiology and prevalence

Cellulitis is a 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., β-haemolytic *Streptococcus* spp., *E. coli*, *Pasteurella canis* (in dogs) and *Pasteurella multocida* subsp. *multocida* and *septica* (in cats).[14] Anaerobic bacteria such as *Fusobacterium* spp. and *Clostridium* spp. can also be involved.[3;15] Persistent fistulous and draining nodules may be associated with *Actinomyces*, *Nocardia* or mycobacteria. Traumatic wounds, which includes thermal and chemical burns, have a high risk of secondary bacterial contamination.

Diagnosis

The diagnosis can usually be made based on the history, clinical presentation and cytological evaluation. Culture and sensitivity testing is recommended if the response to treatment is poor, there

Table 6.5.: Treatment options for deep pyoderma. Prioritisation of the treatments is valid both for empirical therapy and subsequent adjustments based on culture and sensitivity testing.

Problem	Antibiotics	Comments

• Furunculosis
  ◦ Interdigital
  ◦ Carpal
  ◦ Chin
  ◦ Callus
  ◦ Pyotraumatic
  ◦ Deep generalised
• Lick granuloma
• Cellulitis
	• Clindamycin (5.5–11 mg/kg PO BID)
	• Amoxicillin/clavulanate (12.5 mg/kg PO BID)
	• 1st-generation cephalosporin such as cephalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID)
		• Supplement with antimicrobial shampoo with follicle cleanser
		  ◦ Use 2–3 times weekly for 2–3 weeks
		  ◦ Once weekly for two weeks
		  ◦ Thereafter as needed
		
		  ◦ Localised treatment can be performed more frequently

• Feline chin furunculosis	• Clindamycin (5.5–11 mg/kg PO BID) • Amoxicillin/clavulanate (12.5 mg/kg PO BID)	• Local rinses with chlorhexidine once or twice daily • Distinguish from feline acne which does not require systemic treatment

is systemic illness, draining fistulae develop or if wound healing is poor. 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 6.6. 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. 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. Pathogens such as *Pasteurella* are sensitive to penicillins, and bite wounds can often be effectively treated with ampicillin or amoxicillin.[16] Clindamycin is particularly effective against anaerobes and intracellular bacteria, but less so against Gram-negative bacteria.[16] Treatment durations of 5–10 days are sufficient for uncomplicated abscesses. Burn injuries can require intensive treatment and monitoring for tissue necrosis and circulatory shock.

Table 6.6.: Treatment options for cellulitis and abscesses. Prioritisation of the treatments is valid both for empirical therapy and subsequent adjustments based on culture and sensitivity testing.

Problem	Antibiotics	Comments
Cellulitis or abscess	• If antibiotics are required: ◦ Clindamycin (5.5 mg/kg PO BID) ◦ Amoxicillin (20 mg/kg PO BID) ◦ Amoxicillin/clavulanate (12.5 mg/kg PO BID)	• Can often be managed by drainage and flushing alone • Use cytology to guide antibiotic choice (cocci - clindamycin, rods - amoxicillin) • Rinse cavity with diluted disinfectant such as chlorhexidine
Burns (thermal or chemical)	• Amoxicillin/clavulanate (12.5 mg/kg PO BID) • 1st-generation cephalosporin such as cephalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID) • Enrofloxacin (5–20 mg/kg PO SID) • Marbofloxacin (2 mg/kg PO SID)	• Antibiotics recommended particularly for poorly healing wounds • Clip surrounding area to facilitate monitoring • Rinse thoroughly • Apply cold compresses • Systemic analgesia • Avoid use of steroids • Administer IV fluids • Severely infected burns will require systemic and topical antibiotics ◦ Fusidic acid (without steroid) ◦ Gentamicin ◦ Neomycin ◦ Bacitracin ◦ Silver sulphadiazine

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6.2. The ear

Otitis externa and otitis media

Primary causes of otitis externa in dogs include parasites, allergies, medicine reactions and autoimmune disease, which can be aggravated by bacteria, *Malassezia*, canal stenosis and otitis media. Factors which can predispose the ear to otitis externa include temperature, anatomic conformation, excess hair growth in or around the ear canal and underlying allergic or endocrine disorders. Primary allergic disease is the most common cause of ear infections in dogs.[1;2] It is important that any underlying cause(s) 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.[1] Otitis externa is seen somewhat less often in cats (around 2–10%) and is frequently secondary to parasites (*Otodectes*) or nasopharyngeal polyps in the ear canal.[3] 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., *Bacillus* spp. and *Pseudomonas* spp.[4–6]

Pseudomonas infections account for between 20–35% of ear infections in dogs and are often associated with chronic otitis externa and/or otitis media.[3;7] Risk factors for *Pseudomonas* infections include exposure of the ear canal to water and recurrent otitis which has been repeatedly treated with antibiotics.[4] *Pseudomonas* infections can predispose to otitis interna.

Diagnosis

Cytology should always be performed to look for pathogens and inflammatory cells. Culture and sensitivity testing should primarily be performed when rods are identified on cytology, in cases of chronic otitis externa or if the response to treatment is poor. Visualisation of the typmanic membrane and assessment of its integrity is important before selecting further treatment, because many topical ear preparations are potentially ototoxic.[8] Visualisation is not always possible due to the presence of cerumen, exudate or severe pain which prevents otoscopy. Ear flushing under anaesthesia can thus be useful both in the diagnosis and management of otitis externa. Cytology and culture samples should be obtained before flushing.

Treatment

Treatment recommendations are outlined in Table 6.7. 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 exudate which could reduce the efficacy of topical antibiotics. 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] Patients with intact tympanic membranes and moderate amounts of ear wax can also be managed with ear cleaning at home following suitable owner instruction. Ear cleaning preparations typically include ceruminolytics, drying agents and antimicrobial agents (Table 6.8). 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 either pure yeast infections or bacterial otitis. As an alternative the clinician can choose to use an ear cleaner containing an antimicrobial component. [10]

Systemic anti-inflammatories in the form of corticosteroids are particularly useful when chronic changes (such as fibrosis, oedema and glandular hyperplasia) are present in the ear canal 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 due to ear canal ulceration, risk of toxicity or if patient or owner compliance is poor. Systemic therapy should always be based on culture and sensitivity testing, and the treatment response evaluated with repeated clinical and cytological evaluations.

Care should be taken with the use of topical preparations when the tympanic membrane is ruptured. Repeated flushing with warm sterile saline, possibly in combination with non-ototoxic antimicrobial compounds such as chlorhexidine or Tris-EDTA, is preferable. Polymixin B and the aminoglycosides gentamicin and neomycin are often found in topical ear preparations and are known to be ototoxic. [4;11] The fluoroquinolones marbofloxacin and ciprofloxacin are thought to be less ototoxic [4;11] but care should still be taken with topical use. Complete healing of the ruptured tympanic membrane can take 3 weeks to 3 months. [12]

Table 6.7.: Recommended treatment options for infectious otitis.

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 an alternative to antibiotic therapy	• Intact tympanic membrane: ◦ Ear flushing is recommended if excessive cerumen ◦ Ear cleaners alone are sufficient if moderate cerumen • Treatment example: ◦ Chlorhexidine gluconate 0.15% with Tris-EDTA BID for at least 14 days
Pronounced otitis externa caused by cocci or otitis externa with mixed infections of cocci and rods	• Intact tympanic membrane but ear flushing and use of antimicrobial cleaners are insufficient: ◦ Fucidic acid and framycetin combination (5–10 drops BID for 10–14 days) ◦ Gentamicin (4–8 drops BID or 1ml/ear/day for 10 days)	• Intact tympanic membrane: ◦ Ear flushing ◦ Ear cleaners can complement topical antibiotic therapy 　• Chlorhexidine gluconate 0.15% with Tris-EDTA BID for at least 14 days 　• Use at least 10–15 minutes before antibiotics • Perforated tympanic membrane: ◦ Avoid topical antibiotics ◦ Ear flushing and non-ototoxic cleaners should be used

Recommended treatment options for bacterial otitis (*continued*).

Problem	Antibiotic therapy	Comments

Otitis externa caused by rods (but not *Pseudomonas*)	• Intact tympanic membrane:
	◦ Polymixin B (3–5 drops BID for 14 days)
	◦ Gentamicin (4–8 drops BID or 1ml/ear/day for 10 days)
	◦ Marbofloxacin (10 drops SID for 14 days)
		• Intact tympanic membrane:
		◦ Ear flushing
		◦ Ear cleaners or Tris-EDTA can be used to enhance antibiotic efficacy
		  • Chlorhexidine gluconate 0.15% with Tris-EDTA BID or Tris-EDTA alone BID for at least 14 days
		  • Use at least 10–15 minutes before antibiotics
		• Perforated tympanic membrane:
		◦ Avoid topical antibiotics
		◦ Ear flushing and non-ototoxic cleaners should be used

Otitis externa caused by *Pseudomonas* spp.	• Frequently multiresistant - treatment must be guided by sensitivity testing • Local therapy is preferred • Intact tympanic membrane: ◦ Polymixin B (3–5 drops BID for 14 days) ◦ Gentamicin (4–8 drops BID or 1ml/ear/day for 10 days) ◦ Marbofloxacin (10 drops SID for 14 days) ◦ Silver sulphadiazine 1% salve (non-veterinary) dissolved in Tris-EDTA (SID for 10–14 days) • Perforated tympanic membrane: ◦ Ciprofloxacin (human ear preparation) (4 drops BID for 14 days) • In severe infections and when topical therapy is impossible, systemic therapy based on sensitivity testing may be employed ◦ Enrofloxacin (5 mg/kg PO SID) ◦ Marbofloxacin (2 mg/kg PO SID) ◦ Use of gentamicin or amikacin is discouraged due to the risks of nephro- and ototoxicity	• Ear flushing is essential prior to and during treatment • Intact tympanic membrane: ◦ Use Tris-EDTA and chlorhexidine as described above ◦ Acetic acid and lactic acid can also be effective [13] • Perforated tympanic membrane: ◦ Use Tris-EDTA and chlorhexidine as described above • Anti-inflammatory treatment ◦ Use of systemic glucocorticoids is often beneficial
Malassezia infection	• Avoid antibiotics if there is no bacterial component • All veterinary licensed ear preparations with antifungals include antibiotics • Ear cleaners with antimicrobial effects are preferred	• Ear cleaner components effective against *Malassezia* ◦ Chlorhexidine 0.15% ◦ Tris-EDTA ◦ Salicylic acid ◦ Lactic acid ◦ Acetic acid
Otitis media	• Topical antibiotics should be avoided • Some cases can be managed with ear flushing alone • Systemic therapy should be guided by sensitivity testing ◦ Amoxicillin/clavulanate (12.5 mg/kg PO BID) ◦ 1st-generation cephalosporins [cephalexin (25 mg/kg PO BID) or cefadroxil (20 mg/kg PO BID)] ◦ Enrofloxacin (5 mg/kg PO SID) or marbofloxacin (2 mg/kg PO SID)	• Image bullae with radiography or CT • Obtain culture samples from middle ear • Flushing of bulla with warm sterile saline is essential in treatment • Tris-EDTA and/or chlorhexidine can be combined with saline flushing • Systemic glucocorticoid therapy can help prevent further hyperplasia and stenosis of the ear canal

Table 6.8.: Common ingredients of ear cleaning products.

Agent type	Examples	Mode of action	Safety and ototoxicity
Ceruminolytics	• Calcium sulfosuccinate* • Urea peroxide* • Squalene • Hexamethyltetra-cosan • Propylene glycol* • Glycerine* • Ethanolamine* • Mineral oils	• Soften and dissolve cerumen • Require 10–15 minutes for effect	• Ceruminolytics marked (*) are ototoxic [14;15] and should not be used if the tympanic membrane is ruptured • Propylene glycol >10% is ototoxic • Squalene has been shown not to be ototoxic [15]
Drying agents	• Salicylic acid* • Boric acid • Acetic acid* • Lactic acid • Benzoic acid • Isopropyl alcohol* • Aluminium acetate	• Dry the ear canal, preventing maceration of the epithelium	• Can irritate the ear canal and should not be used to excess • Drying agents marked (*) are potentially ototoxic [16–18] and care should be taken if the tympanic membrane is damaged. Dilution with sterile saline may be sufficient
• Antimicrobial	• Chlorhexidine • Lactic acid • Boric acid • Acetic acid • Salicylic acid • Lysozyme • Tris-EDTA *Listed products are often mixed*	• Direct bacteriostatic or bacteriocidal action (chlorhexidine) [10] • Inhibit bacteria by reducing pH • Effective against *Malassezia* [19]	• Chlorhexidine is not ototoxic at low concentrations (0.05% and 0.15%) but can be ototoxic at >2% • Tris-EDTA is safe to use if the tympanic membrane is ruptured [20]

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6.3. The urinary tract

6.3.1. Overview

Bacterial causes

E. 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* spp., *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 usually found in mixed infections. Mixed infections make up about 20% of all urinary tract infections.[1]

Diagnosis and culture

A thorough urinalysis comprises refractometer measurement of specific gravity, urine dipstick tests and microscopic evaluation of stained and unstained urine sediment. Suitable stains include Wright's and 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 30 minutes of sampling. The combination of an inflammatory sediment and bacteria (often intracellular) strongly indicates urinary tract infection: the absence of bacteria on microscopy does not, however, exclude the possibility of infection. Leukocyte casts in the urine indicate pyelonephritis. Chronic upper urinary tract infections and those secondary to other diseases (particulary systemic diseases) may present without abnormal urinalysis findings.[2;3]

The diagnosis of urinary tract infection is based on bacterial culture. Urine for culture should always be collected by cystocentesis unless there are specific contra-indications (e.g. thrombocyte count $<50 \times 10^3$). If the bladder is insufficiently full to permit cystocentesis, urine may be collected by sterile catheterisation (males) or from mid-stream during urination (females). Cultures from urine collected by these alternatives should always be interpreted quantitatively in order to distinguish contamination from true infection (Table 6.9). In patients with urolithiasis the chances of positive culture are increased significantly by sampling directly from the urolith or from bladder biopsies.[4]

Use of urine culture dip paddles (Figure 6.2), as described in Chapter 4.2, can be advantageous because the dip paddles are ideal for use as transport medium and do not need to be sent refridgerated. Furthermore, sending of sterile samples can be avoided by performing the initial incubation in-house. It should be noted that this method is not suitable for quantitative analysis.

Table 6.9.: Cut-off values for quantitative determination of urinary tract infection (modified from Bartges et al. 2004[5]). CFU - colony forming unit.

Sampling method	Dog	Cat
Cystocentesis[a]	$>10^3$ CFU/ml	$>10^3$ CFU/ml
Catheterisation (males)	$>10^4$ CFU/ml	$>10^3$ CFU/ml
Catheterisation or spontaneous urination (females)[b]	$>10^5$ CFU/ml	$>10^4$ CFU/ml

[a] Lower bacterial counts from cystocentesis samples can still be significant and represent infection
[b] Even with these higher cut-offs there is a risk of false positives: culturing spontaneously voided urine is not generally recommended

Figure 6.2.: Urine culture dip paddle (Uricult®). The thin plastic paddle is covered on one side by non-selective agar medium and on the other by the selective and indicative MacConkey agar medium. The paddle is dipped or wetted with urine and incubated overnight at 37°C. The MacConkey agar shown here is covered with red colonies of coliform bacteria.

Treatment

For many antibiotics, standard dosing regimes achieve much higher antibiotic concentrations in the urine than in the plasma. In practice this often means that bacteria can be effectively treated with antibiotics to which they only appear to be intermediately sensitive. Upper urinary tract infections are the exception because antibiotics are not concentrated in the renal parenchyma or pelvices. The following sections describe empirical antibiotic selections for various urinary tract infections in dogs and cats, and are summarised in Table 6.10. **It is strongly recommended that all treatments for urinary tract infections are based on sensitivity testing.** The empirical treatment recommendations should be seen as a guide to treatment pending culture results.

6.3.2. Lower urinary tract

Uncomplicated urinary tract infections in dogs

Aetiology and prevalence Approximately 14% of all dogs will suffer an uncomplicated urinary tract infection at some point in their lives.[6] Uncomplicated urinary tract infections are characterised as single episodes which do not recur after treatment and in which no underlying systemic, anatomic, neurologic or functional cause is present.

Diagnosis Symptoms of uncomplicated urinary tract infection include polliakuria, stranguria, dysuria and haematuria. These are not specific and only localise to the lower urinary tract. Diagnostics should be performed as described in Chapter 6.3.1.

Treatment The final choice of antibiotic should be based on culture and sensitivity testing. For empirical therapy, pending sensitivity results, the use of aminopenicillins or sulpha/trimethoprim is recommended. In Denmark, approximately 74% and 85% of *E. coli* isolates from dogs and cats are sensitive to either aminopenicillins or sulpha/trimethoprim respectively.[7] These figures are likely higher for uncomplicated infections. In addition, both of these antibiotics are concentrated in the urine such that even intermediately sensitive isolates can be effectively eliminated. In the absence of evidence-based recommendations for antibiotic treatment durations, adoption of the established Scandinavian practice of one week's treatment is suggested.[8]

Complicated urinary tract infections in dogs

Aetiology and prevalence Only 4–5% of lower urinary tract infections in dogs can be characterised as complicated. Complicated infections result from an underlying local or systemic disease which predisposes for recurrent or persistent infection. Anatomic examples include ectopic ureters, tumours, urolithiasis and sphincter mechanism incompetence. Systemic diseases which can result in urinary tract infection include hyperadrenocorticism, renal failure, diabetes mellitus and immunosuppression.[3] Infections of the upper urinary tract or prostate can similarly act as sources of complicated lower urinary tract infection.

Diagnosis Similar symptoms as for uncomplicated urinary tract infection may be observed. It is worth noting that not all complicated urinary tract infections are symptomatic. In particular, urinary tract infections secondary to systemic disease can be entirely symptom-free.[3] Diagnostics should be performed as described in Chapter 6.3.1. In addition, it is important to perform a thorough work-up for potential underlying diseases in these patients, since treatment success is dependent on identification and management of the initiating factors. Intact male dogs should be specifically checked for prostatitis.

Treatment Treatment should be based on culture and sensitivity testing. Pending results, empirical therapy with aminopenicillins or sulpha/trimethoprim is recommended. The latter is the drug of choice for intact male dogs, in which prostatitis could be an underlying cause.[9] Specific treatment recommendations for prostatitis are given in Chapter 6.5.11. Sulpha/trimethoprim is not usually recommended for longterm treatment due to the side-effect profile of this combination (Table 1.4). There are no evidence-based recommendations for treatment duration in dogs with complicated cystitis. International practice suggests a treatment period of four weeks,[10] while established Scandinavian practice prefers a shorter period of two to three weeks. Since this patient population is quite varied, treatment durations should be decided individually. Dogs with well-controlled systemic disease or dogs with first-time cystitis in combination with a systemic disease may be adequately treated with one week of antibiotics, whereas treatment durations of four weeks or more may be needed in patients with struvite urolithiasis.

Common to all complicated urinary tract infection patients is the need for ongoing monitoring. Urine culture should always be performed 7 days after cessation of treatment both to confirm the success of treatment and to check for recurrence. Urine cultures performed at 5–7 day intervals are recommended in patients with a history of persistent or recurrent infections.

Urinary tract infections in cats

Aetiology and prevalence Studies suggest that only 2–12% of younger cats with urinary tract symptoms have bacterial cystitis. The vast majority of younger cats with symptoms referable to the

lower urinary tract have *idiopathic cystitis*.[11] This does not have an infectious cause and should not therefore be treated with antibiotics. In older cats and cats with predisposing diseases the prevalence of bacterial cystitis increases to 10–22%.[2;12]

Diagnosis The symptoms of urinary tract infection are as described for dogs. Cats may also start to urinate in other places than their litter tray. Infections secondary to systemic diseases in particular can be asymptomatic.[2] Diagnostics should be performed as described in Chapter 6.3.1. Cats should always be investigated for underlying disease due to the rarity of primary urinary tract infection.

Treatment Treatment should always be based on culture and sensitivity testing. Aminopenicillins are recommended for treatment initiated before results are available. Treatment duration depends on the underlying cause, as described for dogs above.

The response to therapy should be confirmed at the end of treatment and, in selected patients, during treatment, as described for dogs.

6.3.3. Upper urinary tract

Pyelonephritis

Aetiology and prevalence There are no data available on the prevalence of upper urinary tract infections in dogs and cats. Ascending infection from the bladder to the kidneys is the most common cause of pyelonephritis. Haematogenous spread to the renal parenchyma occurs rarely.

Diagnosis Acute pyelonephritis causes signs of systemic disease such as hypovolaemia, pyrexia, depression and anorexia. Abdominal or renal pain may be present. Chronic pyelonephritis on the other hand is slowly progressive and the symptoms can be less marked: some patients can be asymptomatic. Diagnostics should be performed as described in Chapter 6.3.1. Culture of urine from the bladder can be negative and sediment examination unremarkable in cases of chronic pyelonephritis, making this condition a diagnostic challenge. Culture of urine from the renal pelvices is necessary to confirm the diagnosis. However, pyelocentesis is rarely performed and the diagnosis of pyelonephritis is therefore often presumptive, based on positive bladder urine culture along with compatible clinical and paraclinical findings.

Treatment Antibiotic therapy should be selected based on sensitivity testing, but because renal function remains at risk pending results empirical treatment should be initiated as soon as possible. Due to the severity of this disease there is little margin for error. In Denmark, 96% of *E. coli* isolates are sensitive to amoxicillin/clavulanate, and 91% are sensitive to enrofloxacin.[7] Amoxicillin/clavulanate is therefore a good first choice whilst enrofloxacin is a suitable alternative. Patients with acute pyelonephritis often require hospitalisation, parenteral antibiosis, supportive fluid therapy and analgesics. If there is evidence of sepsis, the protocol for septic patients given in Chapter 6.8 should be followed. In the absence of data regarding treatment duration for pyelonephritis in dogs and cats, established veterinary guidelines of 4–6 weeks treatment regardless of chronicity should be followed.[10] It is important that the effect of therapy is monitored during treatment, for example 5–7 days following commencement and 7, 30 and 60 days following cessation of therapy.

Table 6.10.: Empirical antibiotic therapy for urinary tract infections. Prioritisation of antibiotics applies to both initial treatment and subsequent adjustment based on sensitivity testing. The stated doses are the licensed doses in Denmark - recommendations from international guidelines published in 2010 are shown in italics. [10]

Infection	Antibiotic	Comments
Uncomplicated lower urinary tract infections in dogs	• Amoxicillin (10 mg/kg PO BID ≤7 days)*[11–15 mg/kg PO TID]* • Sulpha/trimethoprim (15 mg/kg PO BID ≤7 days)	
Complicated lower urinary tract infections in dogs and lower urinary tract infections in cats	• Amoxicillin (10 mg/kg PO BID ≤7 days) *[11–15 mg/kg PO TID]* • Sulpha/trimethoprim (15 mg/kg PO BID ≤7 days) Duration: from 1–4 weeks (usually 2–3) depending on the underlying cause	• Evaluate patient for underlying disease • Confirm response to therapy with culture 7 days after cessation of treatment and in selected cases 5–7 days after commencing treatment • Sulpha/trimethoprim is first-line therapy for intact male dogs

Upper urinary tract infection (pyelonephritis)	• Amoxicillin/clavulanate (12.5 mg/kg IM/SC/PO BID for 4–6 weeks) *[11-15 mg/kg PO TID]*
	• Enrofloxacin (5 mg/kg IM/SC/PO SID for 4–6 weeks) *[dogs: 20 mg/kg]*
		• Parenteral antibiotics and supportive therapies necessary for acute pyelonephritis
		• Monitor response to therapy with culture
		  ◦ 5–7 days after commencing therapy
		  ◦ 7, 30 and 60 days after cessation

6.3.4. Indwelling 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 suggests that prophylactic antibiotics encourage the development of resistant bacteria. [13] Monitoring of urinary sediment of catheterised animals during and after catheterisation for development of inflammation is recommended. If inflammatory sediment or signs of lower urinary tract infection are recognised, or in critical patients in which infection must be avoided, urine culture must be performed and treatment initiated according to sensitivity testing.

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6.4. The oral cavity and gastrointestinal tract

Overview

The gastrointestinal (GI) tract is a complex ecosystem consisting of a large population of primarily anaerobic bacteria. Bacterial numbers vary throughout the GI tract, with the lowest numbers in the stomach (10^1–10^6 CFU/g) and greater numbers in the small intestine (10^1–10^9 CFU/g) and colon (10^9–10^{11} CFU/g). The makeup of the GI flora is affected by many factors, amongst others motility, available substrates, pH, bile acids and pancreatic secretions.

Diagnosis

Patients with GI problems should undergo a routine clinical examination which 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.

Faecal investigations include culture for enteropathogens and identification of possible enterotoxins. Before culture is performed a parasitological examination including flotation and investigation for protozoa (e.g. *Giardia*) 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 relationship in many cases, and because most bacteria can also be isolated from healthy animals.** Bacteriologic investigations of faeces are frequently overinterpreted, resulting either in treatment for normal flora or treatment of infections which should be self-limiting in immunocompetent animals.

6.4.1. Oral infections

Oral infections comprise a diverse mix of Gram-positive and Gram-negative anaerobes and aerobes. All oral interventions will induce a temporary bacteraemia which under normal circumstances will be 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 and calculus. Predisposing factors for gingival infections are viral infections and immunosuppression. Parodontitis is defined as inflammation of the periodontium 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

Diagnosis of oral infections is based on presenting symptoms and oral investigations. Radiography is indicated 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:

- The first choice medication is clindamycin and the second choice is amoxicillin/clavulanate, based on studies showing their efficacy against oral infections
- Culture and sensitivity testing is recommended
- Combination therapy should be reserved for severe infections
- 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. Parodontitis does not require antibiotic therapy but instead demands professional periodontal treatment and ongoing monitoring.

Oral surgery and dental extractions

Periodontal treatments such as extraction or surgical interventions in the oral cavity induces a bacteraemia which is usually eliminated by the immune system after approximately 20 minutes. Prophylactic antibiotic treatment should be reserved for patients which can not 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. This dose 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 frequently self-limiting and resolves within 1–2 weeks.

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 when considering the possible aetiology includes the patient's age, duration of symptoms (acute, chronic or recurrent), vaccination status, feeding (commercial, bones and raw food (BARF), etc.), likelihood of dietary indiscretion, the presence of haematemesis, haematochezia or melena, fever, clinical signs of sepsis, the presence of similar cases locally and possibility of enteropathogens in the household (both from other animals and humans). The most important bacterial causes of acute gastroenteritis are described in more detail below.

Campylobacter Infection with *Campylobacter* rarely produces clinical signs, but gastroenteritis due to *C. jejuni* and *C. upsaliensis* has been described, despite the fact that both bacteria can be isolated from healthy animals. 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* spp. can worsen these signs.

Salmonella Clinical salmonellosis is rare in companion animal practice. Asymptomatic carriers occur commonly, and in international studies *Salmonella* has been isolated from up to 30% of healthy dogs and 17% of healthy cats. Infection can in some cases produce severe haemorrhagic gastroenteritis, and if bacterial translocation from the GI tract occurs this can lead to septicaemia, endotoxaemia and disseminated intravascular coagulation.

Clostridium difficile Clinical signs of *C. difficile* infection range from mild self-limiting small or large intestinal diarrhoea to mixed diarrhoea to the potentially fatal acute haemorrhagic diarrhoea syndrome (AHDS). The clinical significance of toxigenic *C. difficile* is well described in humans and horses, but remains less clear in dogs and cats.

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 histiocytic colitis in young Boxers (Chapter 6.4.4).

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 is usually sufficient.

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, signs of sepsis and/or in the presence of specific bacterial enteropathogens (Table 6.11). The choice of antibiotic should as far as possible be based on sensitivity testing.

Empirical antibiotic therapy for acute haemorrhagic diarrhoea syndrome (AHDS)

Empirical antibiotic therapy is frequently considered for patients with acute haemorrhagic diarrhoea since the symptoms can worsen rapidly and treatment can be necessary before culture results are available. Bacterial culture is always indicated. In AHDS the mucosal barrier is breached and there is a significant risk for developing sepsis. Recent research has shown that treatment with amoxicillin/clavulanate does not apparently reduce the duration of diarrhoea and vomiting in cases of aseptic haemorrhagic gastroenteritis. Instead, close monitoring of patients for signs of sepsis and subsequent treatment according to their clinical status is recommended. Patients can be divided into three groups based on their presenting signs:

1. Mild bloody diarrhoea with no evidence of hypovolaemia or other systemic effects
2. Severe bloody diarrhoea with hypovolaemia but no evidence of sepsis
3. Severe bloody diarrhoea with hypovolaemia and evidence of sepsis

Table 6.11.: Antibiotics typically effective against specific enteropathogens.

Infection	Antibiotics	Comments
Campylobacter spp.	• Erythromycin (10 mg/kg PO BID for 10 days) • Tylosin (10–20 mg/kg PO BID for 10 days)	• Reserve treatment for puppies and kittens
Clostridium difficile	• Metronidazole (10-20 mg/kg [dogs] or 62.5 mg [cats, total dose] PO BID for 5–7 days)	• Treatment is not recommended in otherwise healthy animals
Clostridium perfringens	• Tylosin (10–20 mg/kg PO BID for 10 days) • Metronidazole (10-20 mg/kg [dogs] or 62.5 mg [cats, total dose] PO BID for 5–7 days)	• Treatment is not recommended in otherwise healthy animals
Salmonella spp.	• Base on sensitivity testing • Treat for 10 days	• Reserve treatment for patients with severe bloody diarrhoea, hypovolaemia, fever or signs of sepsis • Culture should be repeated after treatment

Signs of sepsis can include elevated pulse frequency, slow or rapid respiration, hypothermia or fever, and leukocytosis or leukopaenia (Chapter 6.8). Patients in the **first group** should be managed at home without antibiotics. The owner should be instructed to contact the clinic if the condition worsens. Patients from the **second group** should be admitted for fluid therapy and monitoring for sepsis. Patients in the **third group** should be admitted for fluid therapy and parenteral antibiotic treatment. Most patients respond to ampicillin (10–20 mg/mg IV every 6–8 hours). In the absence of a response, or if the clinical condition worsens, supplement therapy with metronidazole (10–20 mg/kg IV every 12 hours) or enrofloxacin (5 mg/kg IV every 24 hours). Enrofloxacin should not be used in growing animals. Further information on the management of sepsis is given in Chapter 6.8.

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. bizzeronii*, *H. salmonis* and '*Candidatus* Helicobacter heilmanii'. 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

Routine therapy with antibiotics is probably not indicated given the uncertain significance of *Helicobacter* in the development of gastritis. In patients with gastric ulcers which respond poorly to conventional therapy and in which *Helicobacter* can be demonstrated in gastric biopsies, combination therapy for 14 days using a proton pump inhibitor (e.g. omeprazole), amoxicillin (20 mg/kg PO BID) and metronidazole (10-15 mg/kg PO BID) is recommended. Both of these antibiotics can be administered concurrently with clarithromycin (7.5 mg/kg PO BID) if necessary. Additional treatment protocols have been described in the literature.

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 which produce chronic anorexia, vomiting and diarrhoea of more than 4 weeks duration. The diagnosis is based on GI biopsies. Several types of IBD have been defined:

- Lymphoplasmocytic enteritis/colitis
- Eosinophilic enteritis/colitis
- Lymphangectasia
- Histiocytic (granulomatous) colitis

Treatment

It has been demonstrated that prednisolone alone is as effective for treatment of IBD as combining prednisolone with metronidazole. Assessment of the response to sole therapy with prednisolone is therefore recommended before supplementing with antibiotics. The first-choice antibiotic for IBD is tylosin (20 mg/kg PO BID or TID). If there is no response, or if tylosin is unavailable, alternatives are oxytetracycline (10–20 mg/kg PO BID or TID) as a second choice or metronidazole (10 mg/kg PO BID or TID) as a third choice. Treatment durations of 14 days to 8 weeks have been described depending on the diagnosis.

Histiocytic ulcerative colitis (granulomatous colitis) in Boxers Histiocytic ulcerative colitis in Boxers is caused by an invasive *E. coli* infection of the colonocytes. The diagnosis is confirmed by routine histopathologic examination and a fluorescence *in situ* hybridisation (FISH) test of colonic biopsies. A clinical response can be seen after long-term antibiotic therapy, for example using enrofloxacin (5 mg/mg PO SID) for 28 days or longer. Recent studies have shown that resistance development is widespread and it is recommended that treatment is instituted based on sensitivity testing rather than empirically.

6.4.5. Bacterial overgrowth and antibiotic-responsive diarrhoea

Small intestinal bacterial overgrowth (SIBO) is defined as unusually high numbers of aerobes and anaerobes in the small intestine. This can be caused by an underlying GI disease (e.g. exocrine pancreatic insufficiency or IBD) and it is therefore important that any primary disorder is identified and managed before starting antibiotic treatment. Antibiotic responsive diarrhoea (ARD) is a condition in which diarrhoea resolves with antibiotic therapy but recurs on cessation of treatment. This condition is rare but can be seen in young large-breed dogs, and the diagnosis is made by exclusion of all other causes. A thorough investigation for potential underlying disease is required.

Both SIBO and ARD can be managed with tylosin (20 mg/kg PO BID or TID) for 2–4 weeks (SIBO) or 4–6 weeks (ARD). As a second choice use oxytetracycline (10–20 mg/kg PO TID) or as third choice use metronidazole (10 mg/kg PO BID or TID).

6.4.6. Giardiasis

Giardiasis is caused by the protozoan *Giardia lamblia*, but is included here because antibiotics are commonly employed in its treatment even though as a rule this is unnecessary. The first-choice preparation for management of giardiasis in dogs and cats is fenbendazole (50 mg/mg PO SID for 5 days), and treatment can be repeated if clinical signs and oocyst shedding persist. Another treatment option is the combination of febantel, pyrantel and praziquantel (5 mg/kg febantel, 14.4 mg/kg pyrantel and 5 mg/kg praziquantel PO SID for 3 days). For preventive strategies the reader is referred to the European Scientific Counsel Companion Animal Parasites (ESCCAP) guidelines (`www.ESCCAP.org`).

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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 around the vulva and anus. The vaginal flora varies somewhat during the oestrous cycle, with a more extensive bacterial population in animals in heat compared to those in anoestrous. The uterus is sterile except at mating and parturition.

Mating and pregnancy

The presence of bacteria in the outer reproductive tract is normal and antibiotic therapy can result in selection for resistant strains. Despite a paucity of data, because of the risk of foetal abnormalities treatment of pregnant bitches and queens should be restricted to antibiotics and other medications which are absolutely necessary for the treatment of serious disease in these patients.[3] Amoxicillin is the first-choice antibiotic for infections in pregnant animals.

Spermatogenesis

Spermatogenesis can be adversely affected by several antibiotics, although amoxicillin/clavulanate appears not to have negative effects. Generally, treatment of healthy breeding animals with antibiotics cannot be recommended since this will upset the normal bacterial balance of the genital system.

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 and should only be treated if there is concurrent urinary tract infection (Chapter 6.3).

6.5.3. Vaginitis in adult bitches

Aetiology and prevalence

Vaginitis can be caused by strictures, hermaphroditism, foreign bodies and tumours. Primary vaginitis is rare.

Diagnosis

Vaginoscopy and vaginal cytology in animals with vaginal discharge can be supplemented with bacteriological and mycological investigations.

Treatment

The underlying cause should be removed if possible. Local treatment consists of washing/flushing with acidic antiseptics. This can be supplemented if necessary by antibiotic treatment based on sensitivity testing.

6.5.4. Acute metritis

Aetiology and prevalence

Acute metritis is a bacterial infection of the uterus, usually following dystocia or abortion. The cause is generally ascending infection by bacteria such as *E. coli*, *Staphylococcus* spp., *Streptococcus* spp., *Proteus* spp. and corynebacteria.[4]

Diagnosis

A persistent foul purulent vulval discharge, depression, agalactia, fever and anorexia in the dam and restless and noisy pups are typical signs. Uterine contractions may be observed. Samples should be obtained without delay for bacterial culture. If the signs are associated with abortion, serological testing for *Brucella canis* should be considered.

Treatment

Treatment should be initiated with calcium and amoxicillin/clavulanate, which is well-tolerated by puppies and kittens, if present. Acute metritis can be life-threatening and treatment for sepsis may be necessary (Chapter 6.8). With peracute presentations, the clinician should consider the possibility of peritonitis or uterine rupture.

6.5.5. Endometritis

Aetiology and prevalence

Cystic endometrial hyperplasia and endometritis are seen in metoestrous and dioestrous due to the interaction of the progesterone-influenced endometrium and the normal bacterial flora.[5]

Diagnosis

The clinical signs are variable and include depression, reduced or absent fertility, and vaginal discharge. Vaginal cytology, vaginoscopy, ultrasonography and blood work can indicate the extent of the inflammatory process. Uterine biopsies will confirm the diagnosis. Culture samples should be obtained from the cranial vagina or, if possible, the uterus prior to treatment.

Treatment

Before using aglepristone and prostaglandins, start empirical antibiotic therapy with sulpha/trimethoprim (first choice) or enrofloxacin (second choice). In chronic cases, treatment duration should extend to 3 weeks. Ongoing monitoring is necessary to confirm treatment efficacy. In recurrent cases, ovariohysterectomy is the treatment of choice.

6.5.6. Pyometra

Aetiology and prevalence

Pyometra results from the interaction of the progesterone-influenced endometrium and the normal bacterial flora. *E. coli* is the dominant bacteria in dogs and cats. Pyometra occurs predominantly during metoestrous.

Diagnosis

In most cases a serous or mucopurulent vaginal discharge is noted along with depression, anorexia, vomiting, polyuria and polydipsia. Ultrasonography or radiology can confirm the diagnosis. Samples for bacterial culture should be obtained without delay.

Treatment

If the patient is in otherwise good health and relatively young (≤5 years) or is a valuable breeding animal then medical therapy with aglepriston and prostaglandins together with antibiotics can be initiated. The antibiotic should be effective against Gram-negative bacteria - for example, enrofloxacin.[6] Alternatively ovariohysterectomy can be performed, using perioperative antibiotics as described in Chapter 5.

6.5.7. Mastitis

Aetiology and prevalence

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

Diagnosis

Acute mastitis can be life-threatening, with systemic symptoms. The affected mammary gland becomes hot, painful and tense: abscessation may occur, and the bitch will be febrile and depressed. Milk from the affected gland is typically yellowish, brown or blood-tinged. Following cleaning of the teat and surrounding skin, milk should be expressed for bacterial culture and sensitivity testing.

Treatment

Infected glands should be milked out several times daily. Abscesses should be opened and drained. Any nursing pups should be fed with milk replacement. The first-choice antibiotics for these patients are the aminopenicillins (e.g. amoxicillin) since these appear safe for use during lactation. Treatment should continue for 7–10 days.[7]

6.5.8. Caesarian section

Antibiotic therapy should not be needed in uncomplicated cases. If the uterus is damaged, if there is foetal decomposition 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) are a suitable choice.

6.5.9. Balanoposthitis

Preputial infections are common in the dog but are rarely seen in cats. Causes include overgrowth of normal flora, anatomical abnormalities, foreign bodies and infection with herpesvirus. A purulent discharge is characteristic. Antibiotic therapy is rarely indicated since the condition can be readily managed with daily washes with chlorhexidine rinse, for example.[8]

6.5.10. Orchitis and epididymitis

Aetiology and prevalence

Causes include blunt trauma, wounds and haematogenous spread. Due to the increased international transport of breeding animals in particular, clinicians should be aware of the possibility of infection with *Brucella canis* in dogs. An uncommon potential causative agent in cats is the coronavirus causing feline infectious peritonitis.

Diagnosis

The testis and/or epididymis becomes swollen and painful. The patient commonly begins to lick the affected area. Chronic orchitis is not painful and over time causes atrophy of the affected testis. Ultrasonography along with culture of ejaculate and urine samples can confirm the diagnosis. Serology for brucellosis may be considered.

Treatment

Uni- or bilateral castration is recommended, depending on whether or not breeding potential is to be preserved. The first-choice antibiotics are amoxicillin/clavulanate and sulpha/trimethoprim.[8] Treatment should continue for 2–3 weeks. Antibiotic treatment alone is rarely sufficient, and the affected testis frequently atrophies following infection.

6.5.11. Prostatitis

Aetiology and prevalence

Benign prostatic hyperplasia predisposes to infection in older dogs. Prostatitis has been reported in the cat, but is unusual.[9] Infections are most commonly caused by *E. coli*, *S. pseudintermedius* and *S. aureus*.[10]

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 may reveal hypertrophy and permit fine needle aspirates from the prostatic parenchyma for bacterial culture. Alternatively trans-rectal prostatic massage can be performed, and ejaculate sent for culture along with urine samples.

Treatment

The first-choice antibiotics for prostatitis are enrofloxacin and sulpha/trimethoprim, subsequently adjusted based on the results of culture and sensitivity testing and the potential for any medication to cross the blood-prostate barrier.[11] The risks of long-term sulpha/trimethoprim treatment should be noted (Table 1.4). There are no data concerning required treatment durations for canine prostatitis. Established practice is up to 4 weeks treatment in acute cases and 6–8 weeks treatment for chronic cases. Generally the response to antibiotic treatment is good but recurrence is not uncommon. For this reason, castration should be considered.

Table 6.12.: Empirical antibiotic treatment of reproductive system infections.

Infection	Antibiotic	Comments
Juvenile vaginitis	Usually unnecessary	Topical therapy with chlorhexidine or similar mild antiseptic can be considered
Adult vaginitis	Wait for culture results	Topical therapy with acidic solutions can be sufficient
Acute metritis	• Amoxicillin/clavulanate (12.5 mg/kg PO BID for 5–7 days) • Sulpha/trimethoprim (15 mg/kg PO BID for 5–7 days - puppies or kittens should be removed)	Supportive treatment with calcium, fluid therapy and uterotonics
Endometritis	• Sulpha/trimethoprim (15 mg/kg PO BID for up to 2 weeks) • Enrofloxacin (5 mg/kg PO SID for up to 2 weeks)	Concurrent treatment with aglepristone or prostaglandins
Pyometra	• Medical management ◦ Enrofloxacin (5 mg/kg PO SID for 1–2 weeks) • Ovariohysterectomy ◦ see Chapter 5	Give aglepristone on days 1,2 and 7, possibly in combination with prostaglandins
Mastitis	• Amoxicillin (10 mg/kg PO BID for 7–10 days)	Milk out several times a day, open and drain any abscesses
Caesarian section	See Chapter 5	
Balanoposthitis	Usually unnecessary	Topical therapy with chlorhexidine or similar mild antiseptic can be considered
Orchitis and epidydimitis	• Amoxicillin/clavulanate (12.5 mg/kg PO BID for 2–3 weeks) • Sulpha/trimethoprim (15 mg/kg PO BID for 2–3 weeks)	Bi- or unilateral castration recommended particularly in chronic cases
Prostatitis	• Enrofloxacin (5 mg/kg PO SID for 4–8 weeks) • Sulpha/trimethoprim (15 mg/kg PO BID for 4–8 weeks)	Manage abscesses surgically. Note that long-term use of sulpha/trimethoprim can cause side-effects (Table 1.4)

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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 stages of investigating a patient with airway problems consist of general 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 commences 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 which 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] Cultures are likely to contain one or more aerobic bacterial species. Conversely, cytological samples which show 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.

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 connection 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 (Table 6.13).

6.6.3. Tracheitis and bronchitis

Aetiology and prevalence

Infectious tracheobronchitis or 'kennel cough' is a common, multifactorial condition of 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 picture can vary depending on the pathogens present.

Diagnosis

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

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. (Table 6.13).

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. and *B. bronchiseptica* may also be found.

Diagnosis

Appropriate clinical signs and the results of thoracic auscultation and radiography are indicative. Bronchoalveolar lavage (BAL) performed using a bronchoscope or transtracheally 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 and should be discussed in advance with the laboratory. Concurrent cytology should always be performed.

Treatment

In stable patients, which are expected to be managed on an out-patient basis, amoxicillin/clavulanate is an appropriate first choice (Table 6.13). Most pneumonia patients benefit from hospitalisation and more intensive treatment. 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 the combination of enrofloxacin and ampicillin. If a positive response to treatment is not seen within 2–3 days, a change of antibiotic should be considered. Treatment durations can be prolonged, from a minimum of 2–3 weeks extending up to 6

weeks, or one week beyond resolution of clinical signs. Antibiotic therapy should not be withdrawn before radiological signs of pneumonia have resolved and the haemogram has returned to normal. Monitoring of C-reactive protein levels may also be useful.

6.6.5. Aspiration pneumonia

Severe lung injury can result from inhalation of stomach contents with a low pH resulting in chemical burns to the lung epithelium and the subsequent, marked inflammatory response along 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 in place of ampicillin (Table 6.13). If there is an adequate response to treatment over 10–14 days, removal of one of the combination antibiotics and conversion to monotherapy can be considered.

6.6.6. Pyothorax

Aetiology and prevalence

Purulent pleuritis or pyothorax can be caused by viruses, bacteria and fungi. In 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.[5–8]

Diagnosis

Thoracic radiographs (both before and after pleural drainage), pleurocentesis, culture and sensitivitiy 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 antibiosis (Table 6.13). The effect of treatment should be evaluated daily using fluid production, fluid cytology, haemograms 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 6.13.: Empirical antibiotic treatment of respiratory tract infections.

Infection	Antibiotic	Comments
Rhinitis	• Doxycycline (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	• Doxycycline (10 mg/kg PO SID for 7–14 days) • Amoxicillin (10 mg/kg PO BID for 7–14 days)	• Antibiotics are often unnecessary
Pneumonia	• Amoxicillin/clavulanate (12.5 mg/kg PO BID) • Ampicillin (20 mg/kg IV TID) • Ampicillin (20 mg/kg IV TID) with enrofloxacin (5 mg/kg SC SID) Treatment duration 2–4 weeks or one week beyond resolution of clinical signs	• Oral treatment for stable, out-patient cases only • Ampicillin IV monotherapy for stable hospitalised patients • Combination therapy for patients which are unstable, septic or on oxygen therapy or following sensitivity testing
Aspiration pneumonia	• Amoxicillin/clavulanate (12.5 mg/kg PO BID) • Ampicillin (20 mg/kg IV TID) with enrofloxacin (5 mg/kg SC or PO SID) Treatment duration often 4–6 weeks	• Start treatment IV if possible, switching to oral treatment once stable • Combination therapy for patients with sepsis or following sensitivity testing
Pyothorax	• Ampicillin (20 mg/kg IV TID) with enrofloxacin (5 mg/kg SC or PO SID) Treatment duration often 4–6 weeks (up to 16 weeks depending on severity)	• Start treatment IV if possible, switching to oral treatment once stable • Culture and sensitivity testing and cytology of pleural fluid should be performed following pleurocentesis

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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. 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 6.14. 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.

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 pronouced 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 and 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, testing positive a week before morulae can be seen in granulocytes.[1;2]

Table 6.14.: Important tick-borne bacterial infections seen in Denmark.

Infection	Vector	Endemic
Anaplasma phagocytophilum	*Ixodes ricinus*	✔
Ehrlichia canis	*Rhipicephalus sanguineus*	✘
Borrelia burgdorferi	*Ixodes ricinus*	✔

Serological confirmation requires demonstration of a four-fold rise in 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 (Table 6.15).[1] Doxycycline's lipid-solubulity characteristics ensure high intracellular concentrations. Doxycycline can also be recommended 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 raised by an appropriate history, 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 may 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 recommends 28 days treatment (Table 6.15).[7] 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.

6.7.4. Borreliosis

Aetiology and prevalence

Borreliosis is caused by the Gram-negative spirochaete *B. burgdorferi*, which in Denmark is transmitted by the bite of the deer tick. A study found that around 15% of Danish *Ixodes ricinus* were infected with *Borrelia*, and 64% of these had more than one *B. burgdorferi* genospecies. The most common genospecies were *B. afzelli* (64%) and *B. garinii* (57%), while *B. burgdorferi* 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. *B. burgdorferi* sensu stricto is associated with joint and nervous system signs, *B. afzelli* with chronic skin changes and *B. garinii* with neurological signs in humans. The majority of infected dogs do not develop clinical signs. In an American study which investigated both seropositive and seronegative dogs, 4.8% (6/125) and 4.6% (5/109), respectively, 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. burgdorferi* sensu stricto. Clinical signs of *B. burgdorferi* 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* could 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 regarding nephropathy in dogs positive for antibodies to *B. burgdorferi*.[14–16] There is insufficient evidence that *B. burgdorferi* can be found in renal tissue in dogs with 'borrelia-associated nephritis'.[17] 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 can not distinguish between living or dead organisms. Serological investigations using paired titres (as for anaplasmosis) is useless since the titre increase occurs before clinical signs appear. Interpretation of PCR and serology results must therefore be performed 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 (Table 6.15). 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. It should be noted that treatment guidelines are based on American guidelines for treating humans, since there is a lack of data regarding borreliosis in dogs.

Table 6.15.: Empirical antibiotic treatment of tick-borne diseases.

Agent	Antibiotic	Comments
Anaplasma phagocytophilum	• Doxycycline (10 mg/kg PO SID for 10 days) • Enrofloxacin (10 mg/kg PO SID for 10 days) • Rifampicin (10 mg/kg PO BID for 10–14 days)	Rifampicin can cause hepatotoxicity, CNS signs, orange discolouration of urine, saliva and tears (Table 1.4)
Ehrlichia canis	• Doxycycline (10 mg/kg PO SID for 28 days) • Imidocarb diproprionate (5 mg/kg IM two doses 14 days apart)	Imidocard treatment requires approval from the Danish Medicines Agency, and can be nephrotoxic and ototoxic
Borrelia burgdorferi	• Doxycycline (10 mg/kg PO SID for ≥28 days) • Amoxicillin (20 mg/kg PO TID for 30 days)	

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6.8. Sepsis

6.8.1. Definition

This section covers clinical treatment of sepsis and is not intended as a guide to prophylactic treatment. Sepsis is a clinical syndrome characterised by a systemic inflammatory response (SIRS) in connection with an infection (bacterial, viral, fungal or protozoal). This section focuses exclusively on bacterial sepsis.

Lipopolysaccharide (LPS) from Gram-negative bacteria elicits a potent inflammatory response which in combination with the effects of the bacteria themselves results in the high morbidity and mortality associated with sepsis. The host response consists primarily of activation of pro- and anti-inflammatory cytokines and the balance between these two groups is what determines the clinical picture. Gram-positive bacteria can also provoke a powerful inflammatory response. Untreated sepsis can lead to the development of septic shock, characterised by low blood pressure, microvascular leakage and endothelial damage. Circulatory failure ultimately results in reduced perfusion, organ failure and death.

Aetiology and prevalence

Sepsis and/or septic shock are common causes of morbidity and mortality in critically ill patients. The veterinary prevalence is unknown but the mortality rate is comparable to that in humans at 20–60%.[1–3] Of the many potential septic foci, infection of the GI tract is the most common and accounts for about 50% of cases.[3–5] 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 (Table 6.16). Culture from infected tissue should always be performed if the patient is stable because rapid initiation of therapy with the appropriate antibiotic is essential to minimise further bacterial growth and to stop the host inflammatory response.

Table 6.16.: Bacterial causes of sepsis in dogs and cats reported in five veterinary studies. Infections are categorised as either pure Gram-positive or Gram-negative or as mixed Gram-positive and Gram-negative.

Species (n)	Frequency of infection with:			Common isolates (n)
	Gram +	Gram -	Mixed	
Dog and cat (14)[6]	Unknown	Unknown	43%	• *E. coli* (7) • Enterococci (4)
Cat (12)[4]	28%	38%	34%	• *E. coli* (7) • β-haemolytic streptococci (3) • *Pseudomonas* (2)
Cat (31)[5]	Unknown	Unknown	54%	• *E. coli* (17) • Enterococci (14) • *Clostridium* (9)
Dog (20)[1]	37%	26%	37%	• *E. coli* (13) • Streptococci (8) • Enterococci (4)
Dog and cat (19)[3]	16%	5%	79%	• *E. coli* (14) • Enterococci (13) • *Clostridium* (4) • α-haemolytic streptococci (4)

Diagnosis

The clinical signs of sepsis are relatively non-specific and can include an elevated pulse rate, increased or decreased respiratory rate, fever or hypothermia and leukocytosis or leukopaenia. It is vital to identify the septic focus and if possible obtain tissue, blood or fluid samples for bacterial culture and sensitivity testing. Sometimes it will not be possible to take samples due to cardiovascular instability or increased bleeding tendencies. Cytology or pathology can be used to replace or complement culture in these cases.

Treatment

Empirical antibiotic therapy should be based on the following information:

- Location of the infectious focus and the expected flora at this site
- The ability of a given antibiotic to penetrate the focus of infection
- The effect of recent antibiotic treatment and the possibility of resistance in connection with this (if appropriate)
- The likely source of infection (hospital- or community-acquired)

The importance of choosing the optimum antibiotic has been demonstrated.[3] For the 5 cases in which a sub-optimal selection was made, the mortality rate was 80%. Delayed treatment of septic patients risks further bacterial spread and an increased inflammatory response. Septic patients require broad-spectrum antibiotic therapy. Once infection is confirmed, and pending culture results, treatment with IV antbiotics is indicated. This treatment should address the 'four quadrants', i.e. be effective against Gram-positive, Gram-negative, aerobic and anaerobic bacteria. The first-choice combination is the use of ampicillin (22 mg/kg every 8 hours) with enrofloxacin (5 mg/kg once daily) until sensitivity testing is available. The treatment duration can vary from days to weeks depending on the cause.

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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. 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.

Diagnosis

Potential underlying causes should be evaluated. Cytology, possibly supplemented with bacterial culture and sensitivity testing, should be performed. Symptomatic bacterial conjunctivitis is often associated with staphylococci and other Gram-positive bacteria. The normal conjunctiva is rarely sterile, with various studies demonstrating positive cultures in up to 90% of healthy dogs. Typical isolates are staphylococci and *Streptococcus* spp. Gram-negative bacteria can be found in 7–8% of samples from normal dogs, whereas anaerobes are rarely seen. When sampling from the conjunctival sac for bacterial culture it is vital to avoid contamination from either the skin or eyelids. Interpretation of the culture report should always be performed in light of the observed signs.

Treatment

Any underlying cause should be addressed, possibly in combination with topical flushing using sterile isotonic saline or eye flushing solutions containing boric acid.

Management of follicular conjunctivitis in young dogs using topical flushing will often result in significant improvement. Further reduction in follicular swelling and associated signs can be achieved using topical steroids. Neonatal conjunctivitis (ophthalmia neonatorum) requires opening and separation of the eyelids so that flushing can be performed. Topical antibiotics and artificial tear drops should be used until the puppy's own tear production is sufficient. 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 is an excellent alternative. Flushing is a recommended supplement to antibiotic therapy. Local therapy is always sufficient.

6.9.2. Conjunctivitis in cats

Aetiology and prevalence

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

Diagnosis

Bacterial culture of the conjunctival sac of healthy cats is negative 65% of the time: typical isolates are *S. aureus* and *S. epidermidis* (26%) and *Mycoplasma* spp. (5%). PCR tests for *C. 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 *C. felis* is suspected to be zoonotic, but reports of transmission from cats to humans are rare.

Treatment

Infection with *C. 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. If the patient lives with other cats, these should also be treated concurrently. 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.

Infection with *M. 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 *C. felis* infection. Use of doxycycline is recommended in younger patients to avoid damage to dental enamel. Cats vaccinated against *C. felis* experience less severe signs but are not completely protected against infection and are therefore a potential source of infection.

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 *Demodex*, *Sarcoptes* and *Leishmania*.

Diagnosis

The diagnosis is usually made from the clinical signs. Secretions from inflamed or infected meibomian glands or from pyogranulomata can be sent for culture and cytology.

Treatment

Eyedrops containing fusidic acid are the first-line treatment for confirmed bacterial infections of the eyelids. If the response to treatment is poor, side-effects occur or if sensitivity testing indicates resistance to fusidic acid then chloramphenicol is an excellent alternative. Eye flushing in combination with antibiosis is advisable. If the condition consists of more than just a few nodules then systemic therapy with amoxicillin, possibly potentiated with clavulanate, is recommended. Additional anti-inflammatory therapy to reduce irritation should be considered.

6.9.4. Non-ulcerative keratitis

Aetiology and prevalence

Keratitis is usually caused by mechanical or immunological factors rather than by bacterial infection. In cats, keratitis may be seen due to FHV-1 infection.

Diagnosis

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

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. Frequently these patients present with a mucopurulent conjunctival discharge which should be treated with topical antibiotics. Eyedrops containing fusidic acid are the first-line treatment for confirmed bacterial infections of the conjunctiva. If the response to treatment is poor, side-effects occur or if sensitivity testing indicates resistance to fusidic acid then chloramphenicol is an excellent alternative. Eye flushing in combination with antibiosis is advisable.

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, are seen more commonly in older patients. Corneal ulcers infected with *Pseudomonas* spp. or β-haemolytic streptococci can develop into 'melting' ulcers due to production of proteinases and collagenases by these bacteria.

Diagnosis

Corneal ulcers are classified by their depth. Relevant investigations include biomicroscopy (slit-lamp examination) and fluoroscein staining. Bacteriology and cytology should be undertaken for chronic ulcers, ulcers which increase in depth or ulcers which do not respond to treatment. Samples should be taken from the edge of suspected melting ulcers. Therapy should be initiated pending the culture and sensitivity results.

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. If the response to treatment is poor, if side-effects occur or if sensitivity testing indicates resistance to fusidic acid then chloramphenicol is an excellent alternative.

Chronic ulcers or poorly healing ulcers often require mechanical debridement of the loose epithelial edges. Keratotomy may be performed in these patients and antibiotic treatment supplemented with lubricating eye drops.

Topical ointments should not be used in deep stromal ulcers where there is a risk of perforation. Chloramphenicol eye drops are the treatment of choice in these cases. Amoxicillin/clavulanate should be given orally, and the ulcer managed surgically.

Melting ulcers must be treated topically with broad-spectrum antibiotics with ciprofloxacin as the first choice until culture and sensitivity test results are available. Oral antibiosis (amoxicillin/clavulanate) should be started as soon as possible along with frequent topical application of collagenase inhibitors. Antbiotic therapy should be adjusted based on sensitivity testing.

6.9.6. Uveitis

Aetiology and prevalence

Although uveitis has many potential causes, local bacterial infection is a rare cause unless there is perforation of the cornea or sclera. Although toxaemia, systemic disease, glaucoma, trauma, bleeding, neoplasia, lens protein and immunological conditions can all cause uveitis, idiopathic uveitis accounts for a large proportion of cases. Infection with *Borrelia*, *Anaplasma*, *Leptospira*, herpesvirus, canine distemper, *Toxocara*, *Toxoplasma*, *Leishmania* and septicaemia of any cause can result in uveitis in dogs. In cats uveitis may be seen due to FIP, FeLV and toxoplasmosis. An idiopathic lymphoplasmocytic uveitis is common.

Diagnosis

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

Treatment

Therapy should be directed at the primary cause, if identified. Topical and systemic analgesics should be administered, along with antibiotics if infection or perforation can be demonstrated. The choice of antibiotic depends on the diagnosis. Purulent conjunctivitis can be managed with chloramphenicol eye drops. Mydriatics (atropine) are indicated if miosis or photophobia are seen.

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 from the nasal cavity or dental roots are likely causes. The bacteria involved are commonly Gram-negative and include *Pasteurella* spp.

Diagnosis

The patient typically presents with unilateral exophthalmus, protrusion of the nictitating membrane, conjunctival hyperaemia and pain on opening the mouth. The abscess can be drained into the oral cavity caudal to the last molar and cytology and culture performed. Ultrasonography or CT scanning may be useful in some cases.

Treatment

Drainage should be established. Analgesics should be given along with antibiotics: clindamycin may be used until sensitivity results are available.

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.

Diagnosis

The diagnosis is based on clinical signs of mucoid or mucopurulent discharge from the medial canthus and swelling over the nasolacrimal sac. Passage of fluoroscein from the conjunctival sac to the nasal passages may 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 alongside systemic antibiotic therapy (amoxicillin/clavulanate or clindamycin) in most cases. The choice of preparation can be adjusted based on sensitivity results. Local and systemic anti-inflammatory treatment is recommended.

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7. Handling of antibiotics and other medicines

7.1. General

Handling of medications, including antibiotics, should be performed in a manner that avoids or minimises unnecessary contact with the active pharmaceutical agents. Various studies have shown that veterinarians have a higher risk than the general population of carrying MRSA.[1–4] This remains the case in countries with low prevalences of MRSA in companion animals, suggesting that other factors than animal contact - for example, handling of antibiotics - can be a risk factor for carrying MRSA. The normal human skin flora includes *S. aureus*, and repeated exposure to antibiotics could contribute to selection for MRSA. It should be noted that it appears to be normal practice amongst veterinarians in Denmark (and probably elsewhere) to handle antibiotics without gloves.

In general, the aim should be as far as possible to avoid both product contamination and unnecessary contact with the product in question. Gloves should be used when handling tablets, creams and ointments. Crushing of tablets should be performed in an enclosed container or fume cupboard. Dilution of injectables should be carried out in such a way to avoid aerosol formation (see Chapter 7.4 below). According to Danish Parliamentary Act number 785 (25th June 2010) regarding veterinary use, dispensing and prescription of medicines to animals, medicines must be stored solely at the practice address, in a clean and organised fashion, and be inaccessible to unauthorised persons. When a product is dispensed to animals other than production animals, the product must be accompanied by the following information:

- Owner's name
- Animal species
- Diagnosis
- Dosage, route of administration and duration of treatment
- Dispensing date
- Veterinarian's unique authorisation number

This information must be legible and placed on a sticker attached to the product package. If the package consists of multiple parts, the label should if possible be placed on the innermost part. The medicine must be stored according to the manufacturer's recommendations 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 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 conscientiously. Danish Parliamentary Act number 855 (4th August 2008) gives pharmacies a legal duty to collect leftover or expired medicines from patients and medical personnel for disposal, and such items should therefore be delivered to a pharmacy. Arrangements are in place in all regions of Denmark for disposal of clinical

waste. Veterinary hospitals and clinics must subscribe to these arrangements. 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 the treatment instructions. In some cases it can be beneficial to use alternative treatment options and possibly avoid the use of antibiotics, even though this could prolong recovery. 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 to be recommended, particularly when the owner is inexperienced or uncertain. 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.

7.4. Extract from the working environment guidelines for veterinary hospitals and clinics

This information is taken from the Danish Workplace Safety Council's publication 'Guidance on the working environment at veterinary hospitals and clinics' (Branchevejledning om arbejdsmiljø på dyrehospitaler og dyreklinikker).[5]

Vials of powder for injection

When dissolving powders for injection and subsequently withdrawing doses for administration, the following procedure should be followed:

1. The needle and syringe containing the required amount of diluent is inserted into the vial and a small amount of air aspirated into the syringe. The diluent should be allowed to slowly run into the vial along the side to equalise the pressures. Repeat until all the diluent has been added to the vial.

2. Aspirate a small amount of air to generate a negative pressure in the vial before removing the needle and syringe. Swirl the vial gently to dissolve the powder.

3. Select a syringe of appropriate size for the dose being administered. Fill the syringe with air equivalent to about $^1/_3$–$^1/_2$ of the dose volume.

4. Insert the needle and syringe so that the needle tip is in the fluid. Withdraw the fluid against the resistance that will be present, and allow the pressures to equalise using the air already in the syringe. Repeat until the dose is drawn up.

5. Make sure the needle is in the airspace in the vial and withdraw additional air into the syringe before removing the needle and syringe from the vial.

6. Excess air should be expressed into a folded gauze swab.

Ampoules

When drawing up a preparation from an ampoule, the following procedure should be followed:

1. Remove fluid from the head of the ampoule by tapping gently.

2. Break the head off the ampoule, using an ampoule-opener or by breaking the neck of the ampoule while holding it wrapped in a gauze swab. Break the ampoule away from yourself.

3. Insert a needle and syringe into the ampoule and withdraw the required dose. Wipe the needle clean with a dry gauze swab.

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A. Abbreviations in the text

Abbreviation	Expansion
ACE	Angiotensin converting enzyme
AHDS	Acute haemorrhagic diarrhoea syndrome
ARD	Antibiotic responsive diarrhoea
ASA	American Society of Anesthesiologists
AUC	Area under the curve
BARF	Bones and raw food
BID	Twice daily (*bis in die*)
C_{max}	Maximal (peak) concentration
CNS	Central nervous system
CT	Computed tomography
EDTA	Ethylenediaminetetraacetic acid
ESBL	Extended spectrum beta-lactamase
FHV-1	Feline herpesvirus 1
FISH	Fluorescence *in situ* hybridisation
GI	Gastrointestinal
IM	Intramuscular
IV	Intravenous
KCS	Keratoconjunctivitis sicca
LPS	Lipopolysaccharide
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSP	Methicillin-resistant *Staphylococcus pseudintermedius*
NSAID	Non-steroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PO	Orally (*per os*)
SC	Subcutaneous
SIBO	Small intestinal bacterial overgrowth
SID	Once daily (*semel in die*)
SIRS	Systemic inflammatory response syndrome
SSI	Surgical site infection
T	Time
TID	Three times daily (*ter in die*)
Tris-EDTA	tris(hydroxymethyl)aminomethane-EDTA (buffered EDTA)
WHO	World Health Organisation

B. Bacterial names in the text

Binomial name	Shortened form
Anaplasma phagocytophilum	*A. phagocytophilum*
Bordetella bronchiseptica	*B. bronchiseptica*
Borrelia burgdorferi	*B. burgdorferi*
Brucella canis	*B. canis*
Campylobacter jejuni	*C. jejuni*
Campylobacter upsaliensis	*C. upsaliensis*
Chlamydophila felis	*C. felis*
Clostridium difficile	*C. difficile*
Ehrlichia canis	*E. canis*
Escherichia coli	*E. coli*
Helicobacter bizzozeronii	*H. bizzozeronii*
Helicobacter felis	*H. felis*
Helicobacter salomonis	*H. salomonis*
Mycoplasma felis	*M. felis*
Staphylococcus aureus	*S. aureus*
Staphylococcus epidermidis	*S. epidermidis*
Staphylococcus pseudintermedius	*S. pseudintermedius*

Bacteria which are only referred to in the text by their full binomial description are not included in the table.

93