GRAM

GUIDANCE FOR THE RATIONAL USE OF ANTIMICROBIALS

RECOMMENDATIONS FOR DOGS AND CATS

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In all cases, the reader should comply with the applicable laws and regulations, and consult the medication leaflet or the summary of product characteristics (SPC) before any antibiotic use.
The recommendations contained in this guide are based on the technical, scientific, clinical and practical information compiled by different experts.
The national legislation that regulates the purchase, prescription, dispensing and use of the antibiotics mentioned is not presented here. In particular, certain antibiotics mentioned in this book may be unavailable or even prohibited in certain countries.
The reader is warned that compliance with regulations outweighs the recommendations mentioned in this book. In this regard, the use of antibiotics shall be compliant with official and local applicable laws and regulations on antibiotic use.
Therefore, the recommendations listed in this guide and the reasoning behind them do not engage the responsibility of the authors, editors and publishers of this guide. Application of said recommendations and reasoning are the sole responsibility of the reader. Authors and publisher cannot be held responsible or co-responsible for any harmful consequences that may result from it.

FOREWORD

Antibiotics and resistance to them have become a major concern in recent years.

What is at stake here? Antibiotics were discovered in the 20th century and have made a greater contribution to extending life expectancy than any other medical treatment. They remain of vital importance today and are irreplaceable when it comes to treating infectious diseases in humans and animals alike. The emergence of resistance to antibiotics is a cause of concern, however, and discoveries of new molecules are becoming a rarity. Some physicians fear that there may no longer be any effective antibiotics left at all by the end of the 21st century.

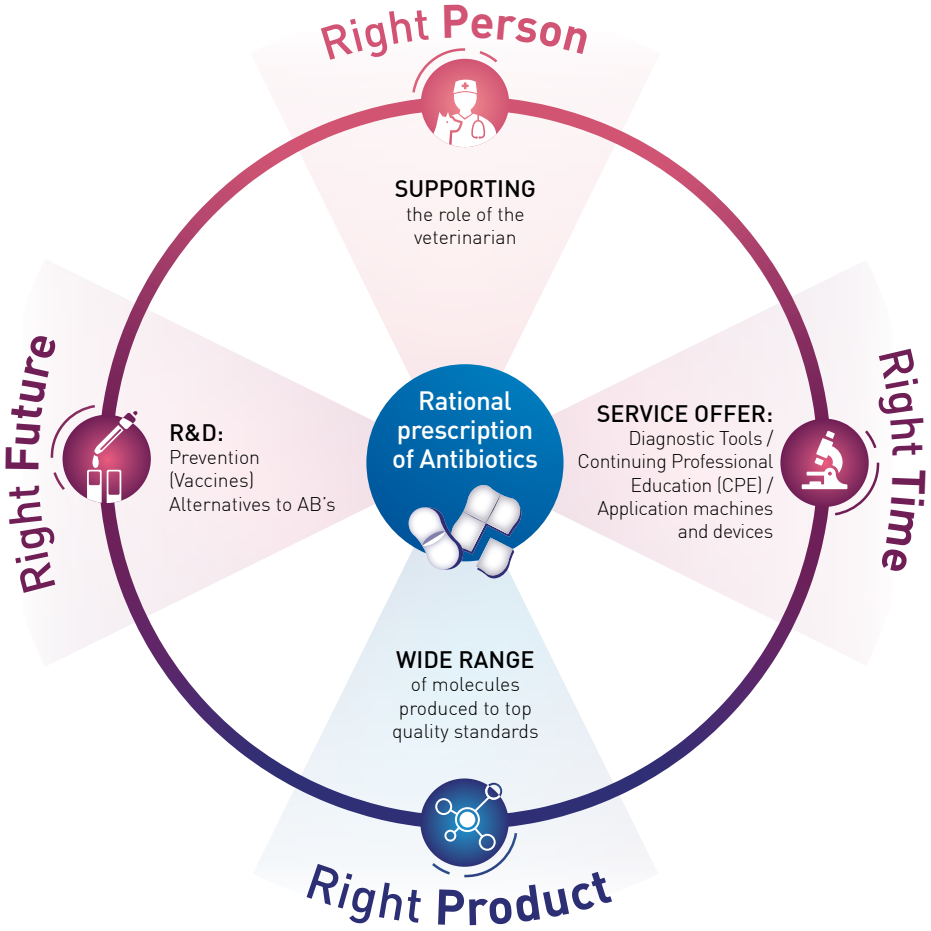
Humans and animals live in close contact, share the same germs and can transmit them to each other, including those that contain resistance genes.

It is therefore by ensuring best practices among physicians and vets and by uniting these two forms of medicine in the "One Health" concept that the development of resistance can be limited and the efficacy of antibiotics preserved.

The first step is to use antibiotics *as little as possible and only as much as necessary* to treat infected animals – and humans. Antibiotics should therefore be reserved only for treating infected animals further to a precise diagnosis by a veterinarian.

Prohibiting the use of antibiotics in veterinary medicine would be detrimental to both animal and human health, as 60% of infectious diseases in humans have an animal reservoir.

The veterinarian is therefore central to the decision-making process by making the right diagnosis, choosing the best antibiotic to prescribe to the right patient, at the right time and only for animals that are infected.



It is along this far-from-easy road towards rational prescription that Ceva wishes to accompany veterinarians through this GRAM (Guidance for Rational use of AntiMicrobials) guide for companion animals.

In 2015, Ceva brought together a multi-disciplinary group of ten experts from 7 European countries in order to reflect, in total independence, upon the most rational possible prescription of antibiotics in canine and feline medicine and surgery.

The discussions were often lively between microbiologists, pharmacologists, dermatologists, internal medicine specialists and surgeons.

In the end, the group of experts co-produced 37 clinical best practice guidance fact sheets proposing a rational therapeutic approach for each disease that is diagnosed, including the first and second-line antibiotics and avoiding the most critical molecules whenever possible.
These 37 sheets are accompanied by 29 precise, practical recommendations.
Finally, 6 synopsis articles review the fundamentals of microbiology, pharmacology and resistance phenomena.

This guide will provide practitioners with precise, well-supported answers to their questions. It provides a useful complement to the applicable regulations, although obviously without replacing them.

We would like to thank the ten experts who put all their professionalism and conviction into this work: Hervé Brissot, Salvador Cervantes, Luca Guardabassi, Angie Hibbert, Hervé Lefebvre, Ana Mateus, Chiara Noli, Tim Nuttall, Constança Pomba and Bianka Schulz. The keen interest and presence at meetings of the International Cat Care, the Federation of European Companion Animal Veterinary Associations (FECAVA) and the Bella Moss Foundation also provided precious support, as well as bearing testimony to the importance of this challenge. Finally, this book would not have been possible without Karin de Lange and Eric Vandaële who coordinated the work with the greatest efficiency.

Ceva is a responsible player in public health and if we have produced this guide, it is to ensure that antibiotics carry on saving lives in the future.

Dr. Mélanie Belliard
Global Marketing Manager
Ceva Santé Animale

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Global Technical Manager
Ceva Santé Animale

FOREWORD

EDITORIAL

Antibiotics: three key issues at stake

Karin de Lange, a qualified veterinarian (Ghent 1987).

After several years in mixed and companion animal practice in the UK, she moved to France where she worked as a European Editor for a veterinary publishing company. She has been self-employed in the field of written communication in animal health at European level since 1999. Her clients include European veterinary organisations and expert groups, publishers and members of the animal health industry.

Eric Vandaele, a veterinarian by training.

Eric started his career teaching veterinary pharmacy at the veterinary school in Nantes. As a scientific journalist and consultant, he closely follows all matters related to veterinary medicines and legislation. He has coordinated numerous round tables and consensus conferences.

For veterinarians, whether in large or small animal practice, there are three key issues at stake regarding antibiotic therapy and the management of resistance.

■ The first issue is **medical**. Our medical colleagues keep repeating it over and over again, in meetings and in the media: the development of resistance is reducing their arsenal which is required to save certain patients. It is too often forgotten: antibiotics save lives, both of humans and animals, and it is this essential advantage that justifies combating wasteful use whether caused by bad practice or unnecessary treatment.

■ The second issue, **public health**, is also at stake, because the microbial world in animals is not completely isolated from that in humans. It is futile and pointless for physicians to accuse veterinarians of being the cause of resistance in humans. It is just as futile and pointless for veterinarians to deny the transfer of resistant bacteria from humans to animals and *vice-versa*. We all live in the same microbial environment and we exchange our microbes, whether or not carriers of resistance, with each contact, each handshake, each pat or lick. The globalisation of exchanges, the multiplication of travel and contacts explain why emerging diseases, most of which are shared by animals and people, spread around the globe within a few weeks. Unless living in a bubble, this of course also applies to those sharing the same household, crèche, hospital, community, region or country... In other words, there is only "One World, One Health, One Medicine" for the medical and veterinary practitioners of the world. Scientists and, increasingly, political decision-makers, no longer separate both medical disciplines in terms of antibiotic resistance...

■ The third issue is an **ethical and legal** one. Physicians are asked to make efforts in order to decrease antibiotic consumption and veterinarians are asked to do likewise. They can no longer ignore that their prescription practices are, and will increasingly be, closely scrutinised by health agencies and surveillance authorities. Veterinary prescribing practices must therefore be entirely rational, evidence based and therefore irrefutable...

The ambitious aim of this project is to mobilise companion animal veterinarians with regards to these three key issues, by creating this GRAM book of good antibiotic practices in cats and dogs. This guide is the result of the **teamwork of a European expert panel of recognised practitioners and academics including pharmacologists, microbiologists, and several specialists of clinical medicine such as dermatologists, surgeons and internal medicine specialists.**

The recommendations proposed have been established collectively, following a preparatory work by the experts based both on scientific publications and their professional experience, as well as a two-day consensus meeting on the 3rd and 4th of December 2015.

This guide is not intended to be the only reference in the field of antibiotic therapy in cats and dogs, however a common voice always carries louder and further than someone singing alone.

GRAM EXPERT PANEL

Dr Hervé Brissot
Surgery
Derby

Dr Salvador Cervantes
Internal Medicine
Barcelona

Prof Luca Guardabassi
Microbiology
Copenhagen / St. Kitts

Dr Angie Hibbert
Feline Medicine
Bristol

Prof Hervé Lefebvre
Pharmacology
Toulouse

Dr Ana Mateus
Epidemiology & Public Health
Hatfield

Dr Chiara Noli
Dermatology
Turin

Dr Tim Nuttall
Dermatology
Edinburgh

Dr Constança Pomba
Internal Medicine
Lisbon

Dr Bianka Schulz
Internal Medicine
Munich

GRAM

Hervé Brissot, DEDV, Dip ECVS, MRCVS European Specialist in Small Animal Surgery

Hervé Brissot graduated from the Veterinary School of Toulouse in France in 1994. Since then he has pursued his interest and training in small animal surgery.

Hervé became a Diplomate from the European College of Veterinary Surgeons in 2005 and is a European Recognised Specialist in Small Animal Surgery. He has been working in the UK since 2006 in different referral settings.

Hervé is mainly interested in soft tissue surgery and especially oncosurgery, lung surgery and mini-invasive surgery. He has published original papers in peer reviewed international veterinary journals and textbooks, and has spoken and lectured at UK and European congresses.

Salvador Cervantes, DVM

Salvador Cervantes qualified as a veterinarian in 1998 from the Autonomous University of Barcelona (UAB), followed by an internship at the Companion Animal Hospital of the same institution.

He has a particular interest in therapeutics, anaesthesia, pain control and feline medicine, and he recently obtained Accreditation as Specialist in Feline Medicine in Spain (Acred Med Fel AVEPA).

He is a member of the American Association of Feline Practitioners, the Spanish Study Group of Feline Medicine (GEMFE) and Companion Animal Clinics committee member of the statutory body, the Colegio Oficial de Veterinarios de Barcelona.

In 2001, he founded a companion animal practice in central Barcelona, with a strong interest in internal medicine. He is the author of the 2012 textbook on small animal geriatrics (in Spanish), *Manual de Geriatria Canina y Felina*. In 2016, he co-founded the Clinica Felina Barcelona, a cats-only hospital in Barcelona, Spain.

GRAM EXPERTS

Luca Guardabassi DVM, PhD, Dip ECVPH

Luca Guardabassi is a microbiologist and Professor of Clinical Microbiology at the Ross University School of Veterinary Medicine in St Kitts, West Indies and Adjunct Professor at the University of Copenhagen.

He graduated in Veterinary Medicine at the University of Pisa in 1994, obtained his PhD in Microbiology at the University of Copenhagen in 2000 and became de-facto Diplomate of the European College of Veterinary Public Health (ECVPH) in 2005. He was associate professor, then professor in Antimicrobial Resistance and Antibiosis at the University of Copenhagen from 2005 to 2015.

His research interests focus on improving understanding of the evolution and epidemiology of multidrug-resistant bacteria of clinical or zoonotic interest and on development of new strategies for diagnosis, therapy and prevention of bacterial infections in animals. He has published 5 book chapters and over 110 peer-reviewed articles in scientific journals. He is also Editor of the book *Guide to Prudent Antimicrobial Use in Animals*, published by Wiley-Blackwell in 2008.

He is currently principal investigator of a One Health interdisciplinary research centre for control of antibiotic resistance (UC-Care) and coordinator of an EU Initial Training Network in the area of antimicrobial drug R&D (TRAIN-ASAP). He is also chairman of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Veterinary Microbiology (ESGVM), member of international veterinary committees for antimicrobial susceptibility testing (CLSI and VetCAST) and of national and international working groups for antimicrobial guidelines in veterinary medicine, and section editor for the Journal of Global Antimicrobial Resistance.

Angie Hibbert, BVSc(Bristol), CertSAM, Dip ECVIM-CA, RCVS Specialist in Feline Medicine

Angie Hibbert graduated from the University of Bristol in 2000 with distinction. After 5 years in general small animal practice, she returned to Langford (Bristol) to undertake an International Cat Care (formerly Feline Advisory Board) residency in feline medicine. She became a Diplomate of the European College of Veterinary Internal Medicine in 2008 and an RCVS Recognised Specialist in Feline Medicine in 2010. She currently is the clinical lead for the Feline Centre at the University of Bristol, receiving referrals, supervising residents and teaching veterinary undergraduates in clinical rotations.

Angie enjoys all aspects of feline internal medicine and small animal emergency care. She runs the radioiodine service and is passionate about feline geriatric care. Angie has published in this area and spoken extensively at British and European veterinary meetings, with particular focus on feline hyperthyroidism. She is a member of the Journal of Feline Medicine and Surgery's editorial board. Her research interests include feline hyperthyroidism, antibiotic use in practice and evaluating the welfare of cats in the hospital environment.

Hervé Lefebvre, DVM, PhD, HDR, Dip ECVPT

Hervé Lefebvre is Professor in physiology at the Department of Physiology and Therapeutics, National Veterinary School of Toulouse (ENVT), France. He is also head of the Clinical Research Unit at ENVT.

He obtained his DVM from the ENVT, France, in 1988. He received his PhD in 1994. He became Diplomate of the European College of Veterinary Pharmacology and Toxicology in 2000. He is Board member of the International Renal Interest Society (IRIS). His current research interests are drug pharmacokinetics, renal and cardiovascular pharmacology, kidney and cardiovascular functional testing, and early diagnosis of chronic kidney disease in at-risk populations, reflected in over 100 original peer-reviewed articles and book chapters.

Hervé received the ESVNU-Hill's Excellence in Veterinary Nephrology and Urology Award at the 2006 ECVIM-CA congress.

He was a member of the expert panel of the French GRAM book.

Ana Mateus, LMV, MVPH, PhD, Dip ECVPH

Ana Mateus is a lecturer in Veterinary Public Health and part of the Veterinary Epidemiology, Economics and Public Health group at the Royal Veterinary College in London. Her main interests are foodborne diseases, zoonoses and antimicrobial resistance.

Ana completed her Veterinary Medicine degree in 2001 in the Technical University of Lisbon, Portugal. She first worked for two years as a companion animal and exotic pets practitioner in Milan, Italy. In 2003, she moved to the UK and worked for over 2 years in food safety and meat hygiene. In 2005, she enrolled in a residency program in Veterinary Public Health by the University of Glasgow Faculty of Veterinary Medicine, where she was actively involved in public health teaching of undergraduate students.

In October 2011, Ana pursued a traineeship at the European Medicines Agency (EMA) with the veterinary unit where she was involved in projects monitoring antimicrobial use and antimicrobial resistance in food-producing and companion animals. Between 2012 and 2014, she worked in Public Health England as a Field Epidemiology Training Program (FETP) fellow. In 2012, Ana completed a PhD on the extent and patterns of antimicrobial usage in dogs and cats in the UK.

She is member of the FECAVA working group on hygiene and the use of antimicrobials in veterinary practice, which developed guidance posters for veterinary practitioners.

Chiara Noli, DVM, Dip ECVD

Chiara Noli graduated in veterinary medicine from the University of Milan, Italy, in 1990. After a residency at the University of Utrecht, the Netherlands, she obtained the European Diploma in Veterinary Dermatology in 1996. Since then, she has been working as a referral dermatologist and dermatopathologist in Northern Italy. Chiara was President and Founder Member of the Italian Society of Veterinary Dermatology, President of the European Society of Veterinary Dermatology and Board Member of the International Society of Veterinary Dermatopathology and of the World Association for Veterinary Dermatology. She is currently Board Member of the European College of Veterinary Dermatology.

Chiara is author of more than 100 articles in Italian and international journals, of nine book chapters and three veterinary dermatology textbooks, and co-editor of the book *Veterinary Allergy* published by Wiley (2014). She has given several hundred lectures in Italy and in other countries spanning three continents.

Tim Nuttall Bsc, BVSc, CertVD, PhD, Cbiol, MSB, MRCVS RCVS Specialist in Veterinary Dermatology

Tim Nuttall graduated from the University of Bristol in 1992 and originally joined the Dick Vet in 1995 to train in dermatology and study for a PhD on canine atopic dermatitis. He joined the University of Liverpool in 2001, developing a dermatology clinic that now sees over 1000 cases each year. In August 2013 he returned to the Dick Vet as Head of Dermatology.

Tim has written over 80 clinical and scientific publications, co-authored *A Colour Handbook of Skin Diseases of the Dog and Cat*, and presented over 100 lectures throughout the world. In addition, Tim has served on RCVS, BSAVA, ESVD and DEFRA scientific committees, the International Committee on Atopic Diseases in Animals. He is a scientific advisor to the Bella Moss Foundation and has been a co-editor of the journal Veterinary Dermatology.

He also has an active research programme, studying antimicrobial resistance, skin infections and the genetics of canine atopic dermatitis. In 2014 he received the BSAVA Woodrow Award for outstanding contributions to veterinary medicine.

Constança Pomba, DVM, PhD

Constança Pomba is Associate Professor of Internal Medicine, Department of Clinical and Hospital School of the Faculty of Veterinary Medicine, University of Lisbon (FMV-U Lisboa), Portugal. She graduated from the Faculty of Veterinary Medicine of the Technical University of Lisbon in 1991, obtaining a master's degree in 1994 and her PhD in 2002 at the same University.

She is currently Technical Director of the Veterinary Blood Bank and Head of the Laboratory of Antibiotic and Biocide Resistance of FMV-U Lisboa. She is also Member of the Scientific Advisory Group on Antimicrobials of the European Medicine Agency (EMA) and Vice-chair of the EMA Antimicrobial Working Party (AWP/CVMP), formerly known as SAGAM. She is a founding member of the Special Interest Group Medical Felina (GIEFEL) and Special Interest Group of Internal Medicine (GIEMINT) of the Portuguese Association of Veterinary Medical Specialists in Animal Company (APMVEAC). She is also a member of the European Society of Veterinary Internal Medicine (ESVIM) and the European Society of Veterinary Nephrology and Urology (ESVNU).

She is the author of several publications and national and international communications on these issues, and is editor of the *Journal of Antimicrobial Chemotherapy*. Her research interests include internal medicine, antimicrobial resistance and therapy and bacterial pathogenesis.

Bianka Schulz, DVM, Dr habil., Dip ECVIM-CA (Internal Medicine)

Bianka Schulz obtained her DVM from the Ludwig Maximilian University in Munich in 1997. Following an internship and residency in internal medicine at the LMU and at the Department of Small Animal Medicine at the University of Georgia in Athens (USA), she became lecturer in internal medicine at the LMU. In 2007 she became Diplomate of the European College of Veterinary Internal Medicine for Companion Animals (ECVIM-CA).

Her research interests include respiratory disease in dogs and cats, with a particular focus on infectious respiratory diseases, feline asthma and antimicrobial therapy.

GRAM EXPERTS

Federation of European Companion Animal Veterinary Associations

Simon Orr (UK)
FECAVA President 2011-2013

Monique Megens (NL)
FECAVA President 2013-2015

"Not all infections are caused by bacteria: some are viral and do not respond to antibiotics. Also, not all bacterial infections require antibiotic therapy." This is one of the warnings for pet owners on the waiting room poster, produced in 2011 by the FECAVA Working Group on Hygiene and the Use of Antimicrobials in Practice, in collaboration with the Bella Moss Foundation. The working group (which included Luca Guardabassi and Ana Mateus) produced four posters altogether:

- Recommendations for appropriate antimicrobial therapy,
- Decision tree on whether or not antibiotics should be used,
- Key recommendations on hygiene in practice,
- Advice to pet owners on responsible antibiotic use.

The four posters have been translated into several languages and have been distributed throughout Europe. They are freely available upon request.

In order to raise awareness on antimicrobial resistance among companion animal veterinarians, FECAVA organised a Hygiene Symposium at the WSAVA/FECAVA Congress in Geneva in 2010 and a Symposium on antimicrobial resistance at the FECAVA EuroCongress in Dublin in 2013.

FECAVA is also a long-standing associate partner of the European Platform for the Responsible Use of Medicines in Animals (EPRUMA).

In short, FECAVA has a solid track record in combating antimicrobial resistance, one of its top priorities.

It was therefore with great pleasure that we heard about the GRAM initiative and accepted an invitation to attend the meetings of the European GRAM expert panel. This has allowed us to witness first-hand the discussions and debates that were at its heart. What is ideal from a scientific viewpoint is not always practical and we were happy to see that feasibility was part of the consensual process.

The European GRAM book is a valuable, practical tool and we hope that it will contribute to the responsible use of antimicrobials, for the benefit of the health of people and their pets - and allow a continued, reliable use of our worthy allies in case of need: antibiotics.

The **Federation of European Companion Animal Veterinary Associations** (FECAVA) represents more than 25,000 companion animal veterinarians in 40 European countries. FECAVA is the platform for the promotion of professional development and the representation of companion animal veterinarians in Europe, and strives to improve the veterinary care of pets, to highlight the human-animal bond and the "One Health" concept. It does this through professional development, liaisons with relevant organisations and stakeholders and by facilitating the interaction between European companion animal veterinarians.

www.fecava.org **www.ejcap.org**

FECAVA
Federation of European Companion Animal Veterinary Associations

International Society of Feline Medicine

Andrew Sparkes

BVetMed, PhD, DipECVIM, MANZCVS, MRCVS

Veterinary Director, International Society of Feline Medicine and International Cat Care

Tisbury, UK.

The International Society of Feline Medicine is delighted to see the GRAM project initiated by CEVA come to fruition with the publication of this multi-author book, written by a number of leading European experts.

The growing threat of antibiotic resistance to both human and animal health is not something that can be ignored and continues to receive much media coverage. Just as in the medical profession, there is a need for veterinary practitioners to be critical about their use of antibiotics and ensure they are not used inappropriately.

This can be challenging, and **to have a comprehensive and reliable source of information (such as this book) will be an invaluable resource for busy practitioners... congratulations to all involved!**

Andy has worked as a feline-only vet since 1987 and trained as a specialist at the University of Bristol. He is a popular speaker and internationally recognised as a feline specialist. He has published widely, and in 2004 co-authored *Self-Assessment Colour Review of Feline Medicine* with Dr Sarah Caney. Andy is the co-editor-in-chief and founding editor of the Journal of Feline Medicine and Surgery, and in 2012 after being associated with International Cat Care for more than 25 years, he joined the charity as their full-time Veterinary Director.

The Bella Moss Foundation

Jill Moss

The Bella Moss Foundation is a charity that promotes prudent antimicrobial use and hygiene in human and veterinary medicine, with the aim to achieve a world where multi-drug resistant bacteria are a rarity.

The Foundation communicates with the general public, academic institutions, government departments and leading researchers around the world on a regular basis. It works in collaboration with these and other bodies to provide education, information and support for veterinary professionals and animal owners to improve infection control, knowledge and practice.

The Bella Moss Foundation does this to save lives and to prevent the spread of infections in humans and animals.

The guidance contained within GRAM, produced by a Pan-European expert panel, is consistent with these aims.

The Foundation shares Ceva's commitment to responsible and rational use of antimicrobials with the aim of using "as little as possible and only as much as necessary". The Bella Moss Foundation is pleased to support the GRAM initiative.

GRAM OBSERVERS

CONTENTS

PART 1
DISEASE FACT SHEETS

URINARY AND REPRODUCTIVE TRACT

DISEASE FACT SHEETS

CANINE CYSTITIS

- The majority of bladder infections in dogs are due to a **single bacterial species**.

Bacteria involved

Bacteria	Prevalence *
Escherichia coli	44-60%
Staphylococcus spp.	11-12%
Proteus mirabilis	9-12%

** large geographical variability*

Antibiotics that can be used

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	5	
Trimethoprim sulfonamides[a]	4	4	
Amoxicillin + clavulanate	4	5	
Cefalexin	3	5	
Marbofloxacin[b] / Enrofloxacin[b]	4	5	
Cefovecin[c]	4	5	
Nitrofurantoin[d]	5	4	
Pradofloxacin[b,e]	5	3	
Gentamicin[f]	4	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	5	
Trimethoprim sulfonamides[a]	4	4	
Amoxicillin + clavulanate	4	5	
Cefalexin	4	5	
Marbofloxacin[b] / Enrofloxacin[b]	4	5	
Cefovecin[c]	4	5	
Nitrofurantoin[d]	5	4	
Pradofloxacin[b,e]	4	3	
Gentamicin[f]	4	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[6].*

[b] *Avoid use in growing dogs of large breeds.*

[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[d] *Nitrofurantoin is a human preparation useful in multi-drug resistant UTIs; use should be guided by culture and sensitivity testing and by cascade guidelines.*

[e] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

[f] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

DISEASE FACT SHEETS

CANINE CYSTITIS

Therapeutic approach

Urinary cytology - Empirical treatment

- Bacilli (assume) *Escherichia coli* → **Amoxicillin+clavulanate, trimethoprim sulfonamides**
- Cocci (assume) *Staphylococcus* spp. → **Amoxicillin, trimethoprim sulfonamides**

Culture and sensitivity

- *Escherichia coli* → **Amoxicillin ± clavulanate, trimethoprim sulfonamides** → **Cefalexin, marbofloxacin, enrofloxacin, cefovecin, nitrofurantoin** → **Pradofloxacin, gentamicin**
- *Staphylococcus* spp. → **Amoxicillin ± clavulanate, trimethoprim sulfonamides** → **Cefalexin, marbofloxacin, enrofloxacin, cefovecin, nitrofurantoin** → **Pradofloxacin, gentamicin**

Urine samples for susceptibility testing should be refrigerated immediately after collection and submitted to the laboratory as quickly as possible.

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli	Amoxicillin + clavulanate	12.5-25 mg/kg/12h PO	7 days (uncomplicated cystitis) 28 days (complicated cystitis)
	Trimethoprim sulfonamides[a]	15 mg/kg/12h PO	
Staphylococcus spp.	Amoxicillin	15 mg/kg/8-12h PO	
	Trimethoprim sulfonamides[a]	15 mg/kg/12h PO	

Second choice antibiotic (with culture and sensitivity testing and only if first choice is not an option)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp.	Amoxicillin ± clavulanate	10-25 mg/kg/12h PO	7 days (uncomplicated cystitis) 28 days (complicated cystitis)
	Cefalexin	15-30 mg/kg/12h PO	
	Marbofloxacin[b]	2 mg/kg/24h PO	
	Enrofloxacin[b]	5 mg/kg/24h PO	
	Nitrofurantoin[d]	4.4-5 mg/kg/8h PO	
	Cefovecin[c]	8 mg/kg SC for 14d (for complicated UTIs repeat dose after 14d)	

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[6].*

[b] *Avoid use in growing dogs of large breeds.*

[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[d] *Nitrofurantoin is a human preparation useful in multi-drug resistant UTIs; use should be guided by culture and sensitivity testing and by cascade guidelines.*

DISEASE FACT SHEETS

CANINE CYSTITIS

Diagnostic approach

■ Bacterial cystitis follows the colonisation of the urinary bladder by (usually) aerobic bacteria ascending from the urogenital area. Bacteria persist in the urine or adhere to the urothelium, where they will start multiplying. A urinary infection implies a transitory failure of natural defence mechanisms (Table 1)[3,8].

■ Although all ages can be affected, prevalence increases with age due to the occurrence of other diseases (e.g. prostatic disease, kidney disease, endocrine disease, tumours...). Bitches are predisposed due to a wider and shorter urethra. The most common clinical signs are pollakuria (frequent urination in small amounts), stranguria and dysuria. Other less common signs are: urinary incontinence and haematuria[4] (Figure 1).

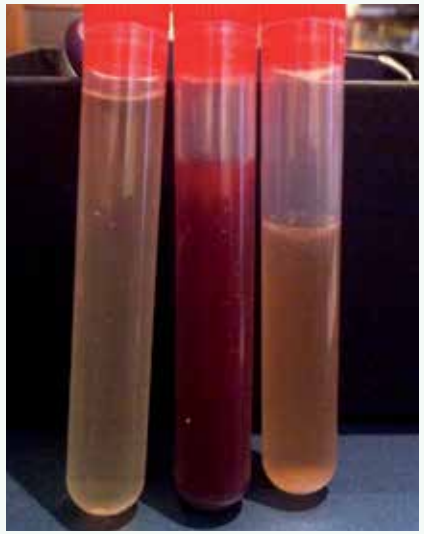

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Figure 1 *- Appearance of different urines. From left: normal urine; severe haematuria; haematuria and severe crystalluria in an infection due to Proteus mirabilis.*

■ Classification of UTIs

• **Simple uncomplicated UTI** - sporadic infection in an otherwise healthy dog with normal urinary tract anatomy and function; treatment 7 days.

• **Complicated UTI** - infection in dogs with structural or functional urogenital tract abnormalities, immunosuppression or comorbid disease that predisposes to UTI or recurrent episodes (> 3 in 12 month period); treatment 28 days.

• **Subclinical bacteriuria** - identification of bacteria on urine culture in the absence of clinical or cytological signs of infection[9]. The clinical significance is not fully understood and currently treatment is warranted only in very specific circumstances such as immunocompromised patients (e.g. patients with endocrinopathies) or those with underlying renal disease (N.B. this lacks an evidence base).

The cornerstone of diagnosis is a complete urinalysis (test strip, specific gravity and sediment) and urinary culture of a urine sample obtained by cystocentesis. Test strips usually reveal haematuria, proteinuria and give an indication of urinary pH.

In-house direct sediment examination should be performed *before* sample refrigeration.

Table 1 - Host urinary defence mechanisms.

Regular and complete micturition
- Correct laminar flux

Normal urinary tract anatomy

Intact mucosal defences
- Glycosaminoglycan layer
- Cell exfoliation
- Ig excreted with urine and urinary surface
- Normal genito-urinary tract flora

Antimicrobial properties of urine
- Osmolality
- pH
- Urea concentration (with exception of urease producing bacteria, e.g. *Proteus mirabilis*, *Staphylococcus* spp., *Corynebacterium urealyticum*, *Ureaplasma* spp.)
- Other factors, e.g. Tamm-Horsfall mucoprotein or uromoduline

Systemic immunocompetence
- This can be decreased in Cushing's disease, diabetes mellitus, hypothyroidism or by corticosteroid administration.

Reasoning

■ The main factor for choosing an antibiotic to treat cystitis is its ability to concentrate in the urine, reaching at least 4x times the MIC (in an active form!).

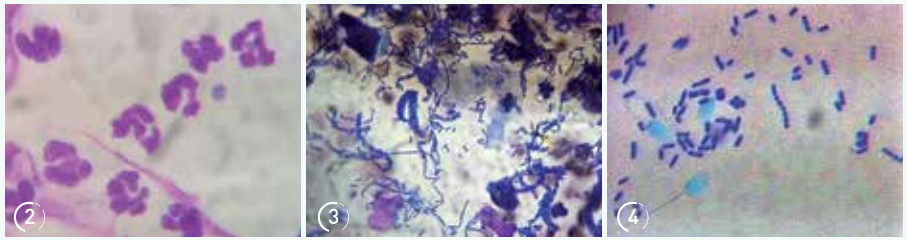
■ For uncomplicated and first-time cases, it is probably not necessary to perform culture and sensitivity testing: cytology (shape of microorganisms) and pH of urine may suffice. **However, urinary culture is the only reliable tool to confirm or rule out a urinary tract infection**. In other words, bacterial cystitis may be diagnosed on the basis of positive urinary cytology (e.g. microorganisms phagocytised by neutrophils) and test strips, but cannot be ruled out if these tests are negative (Figures 2, 3 and 4).

■ In the absence of sensitivity data, the use of amoxicillin or TMS as a first choice in both cases (infections by cocci or bacilli) is justified[9].

■ The use of fluoroquinolones and long-term cephalosporins (e.g. cefovecin) should be reserved for cases showing a resistance to the usual antibiotics or where a lack of compliance is highly probable. The use of fluoroquinolones

DISEASE FACT SHEETS

CANINE CYSTITIS



Figs. 2 & 4 © Salvador Cervantes

Figures 2,3 & 4 *- Cytology. Urinary sediment from dogs with cystitis.*

Fig 2. Note the phagocytosed coccoidal organisms inside neutrophils (culture result: Staphylococcus spp.).

Fig 3. Note the Bacilli (culture result: Klebsiella spp.) Image courtesy Dr. Eva Varela.

Fig 4. French bulldog receiving corticosteroid therapy for atopy. The patient did not show UTI signs (subclinical bacteriuria) but in culture, mixed populations of E. coli (bacilli) and Streptococcus spp. (cocci in chains) were detected. The dog was not castrated and 3 spermatozoids are seen. (Diff Quik® x1000).

as a first choice for bacterial cystitis in dogs is not recommended as this may lead to the selection of a multi-resistant strain of *E.coli*. Fluoroquinolones in these cases should be used with caution[1,2,7].

■ If a TMS combination is used, the clinician should be concerned regarding idiosyncratic and immune-mediated adverse effects in some patients, especially with prolonged therapy. If prolonged (>7 days) therapy is anticipated, baseline Schirmer's tear testing is recommended, with periodic re-evaluation and owner monitoring for ocular discharge. Avoid in dogs that may be sensitive to potential adverse effects such as KCS, hepatopathy, hypersensitivity and skin eruptions[9].

Difficulties and particularities

■ For **uncomplicated** cases, a 7-day course of treatment is usually enough (>80% of cases) but for **complicated** cases, a longer course of antibiotics is recommended (28 days). For complicated cases, culture and sensitivity are essential before starting treatment but also after discontinuation to make sure infection has fully cleared.

■ Treatment failure may occur in three situations[9]:

• **Relapse** is recurrence of a UTI within 6 months of cessation of previous, apparently successful treatment and isolation of an indistinguishable organism from the one that was present previously, which is presumably because of failure to completely eliminate the pathogen.

• **Reinfection** is recurrence of a UTI within 6 months of cessation of previous, apparently successful treatment and isolation of the same or a different microorganism. This suggests an underlying disease that predisposes the dog to repeated infections. It should prompt a careful search for any interference with the innate defence mechanisms or evidence of immunosuppression (e.g. hyperadrenocorticism, glucocorticoid use, diabetes).

• **Refractory infection** is similar to a relapse except that it is characterized by persistently positive results using culture during treatment.

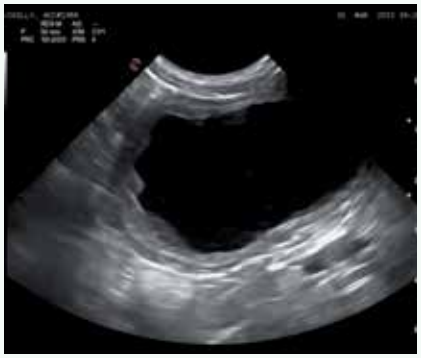


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Figure 5 *- Longitudinal sonogram of the urinary bladder in a dog showing moderate, diffuse, hypoechoic, thickening of the bladder wall. Urine culture was negative but Mycoplasma cynos DNA was detected by PCR.*

For uncomplicated and first-time cases, cytology and urinary pH may suffice. However, urinary culture is the only reliable tool to confirm or rule out a urinary tract infection.

FELINE (BACTERIAL) CYSTITIS

Bacterial cystitis is an uncommon cause of Feline Lower Urinary Tract Disease (FLUTD).

- The majority of bladder infections in cats are due to a **single bacterial species**.
- If the cat has chronic kidney disease, see Bacterial urinary tract infection in cats with CKD, p.44.

Bacteria involved[1, 3, 4, 9, 11, 12]

Bacteria	Prevalence
Escherichia coli	25-59%
Enterococcus spp. (*E. faecalis* most common)	10-43%
Staphylococcus spp.	8-20%

Antibiotics that can be used[6,8,11,12,18,19,20]

Only if the use of antibiotics is justified:

Pathogen 1: *Escherichia coli* (Gram-negative)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	5	
Trimethoprim sulfonamides[a]	4	4	
Amoxicillin+clavulanate	4	5	
Cefalexin	3	5	
Marbofloxacin / Enrofloxacin[b]	5	5	
Nitrofurantoin[c]	4	4	
Cefovecin[d]	4	5	
Pradofloxacin[e]	5	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: *Enterococcus* species (Gram-positive)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin[f]	4	5	
Amoxicillin+clavulanate[f]	4	5	
Marbofloxacin / Enrofloxacin[b]	3 - 4	5	
Nitrofurantoin[c]	5	4	
Pradofloxacin[e]	5	3	
Cefalexin[g]	2	5	
Cefovecin[d,g]	2	5	
Trimethoprim sulfonamides[a,g]	4 - 5	4	
Clindamycin[g]	2	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[14].*

[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[c] *Nitrofurantoin is a human preparation useful in multi-drug resistant UTIs; use should be guided by culture and sensitivity testing and by cascade guidelines.*

[d] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[e] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

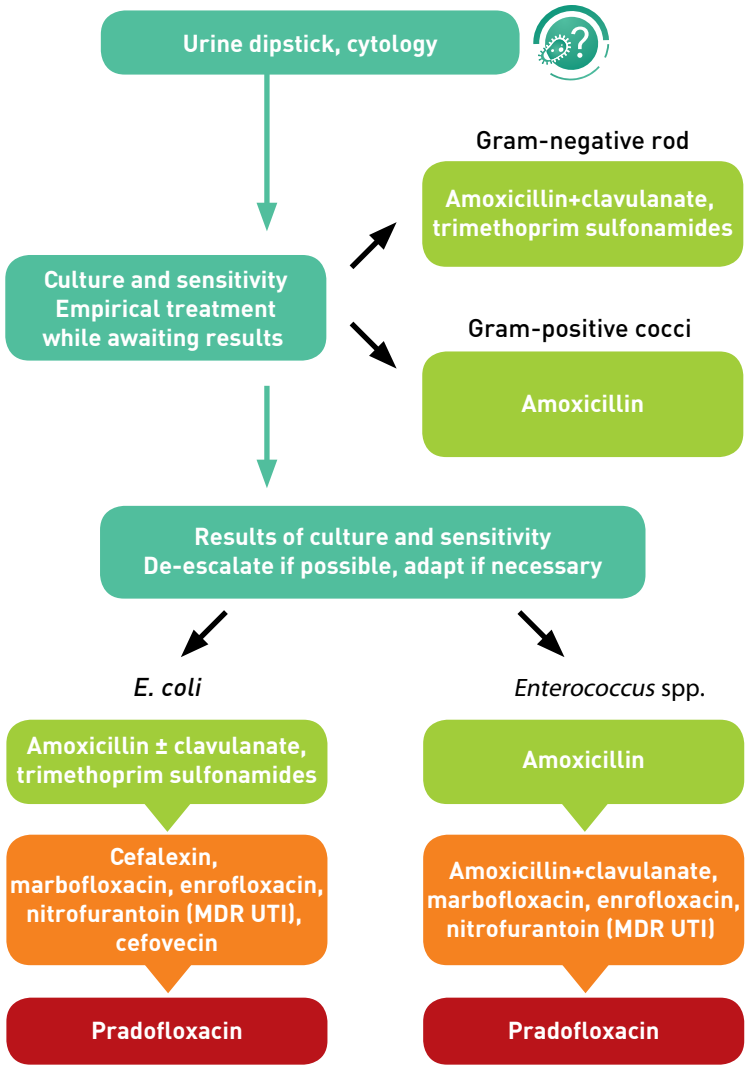
[f] *Use of a ß-lactamase inhibitor (clavulanate) is not usually required for treatment of Enterococcus spp. infections hence amoxicillin+clavulanate is designated as 2nd choice, however use may be a compromise to achieve patient/owner compliance.*

[g] *Enterococcus spp. do not typically respond in vivo to cephalosporins, TMS or clindamycin due to inherent resistance mechanisms; be aware when interpreting in vitro results that these antibiotics are not recommended for treatment[6].*

DISEASE FACT SHEETS

FELINE (BACTERIAL) CYSTITIS

Therapeutic approach



Treatment recommendations[15,20]

■ **Non-antibiotic treatment**: Analgesia should be provided (e.g. buprenorphine transmucosally; NSAID if normally hydrated and normal renal function) and treatment of comorbid disease where appropriate.

First choice antibiotic (empirical)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli	Amoxicillin+clavulanate	12.5-25 mg/kg/8-12h PO	7 days uncomplicated UTI 28 days complicated UTI
	Trimethoprim sulfonamides[a]	15 mg/kg/12h PO	
Enterococcus spp.	Amoxicillin[f]	11-15 mg/kg/8h PO	

Second choice antibiotic (following culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli	Amoxicillin	10-15 mg/kg/8h PO	7 days uncomplicated UTI 28 days complicated UTI
	Cefalexin	15-30 mg/kg/12h PO	
	Marbofloxacin	2 mg/kg/24h PO	
	Enrofloxacin[b]	5 mg/kg/24h PO	
	Nitrofurantoin[c]	4.4-5 mg/kg/8h PO	
	Cefovecin[d]	8 mg/kg SC for 14d (for complicated UTIs repeat dose after 14d)	
Enterococcus spp.	Amoxicillin+clavulanate[f]	12.5-25 mg/kg/8-12h PO	
	Marbofloxacin	2 mg/kg/24h PO	
	Enrofloxacin[b]	5 mg/kg/24h PO	
	Nitrofurantoin[c]	4.4-5 mg/kg/8h PO	

For footnotes, see p. 37.

DISEASE FACT SHEETS

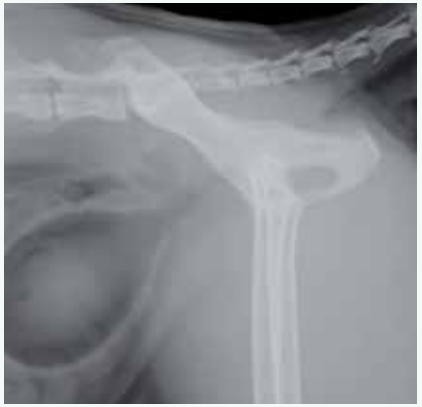
FELINE (BACTERIAL) CYSTITIS

Diagnostic approach

■ **Bacterial cystitis is an uncommon cause of feline lower urinary tract disease (FLUTD)**; sterile idiopathic cystitis is the cause of approximately 60% of cystitis cases and is a primary exclusion that does not warrant antibiotic treatment[5].

■ Predispositions: age, sex (more common in mature-geriatric female cats), comorbidity (e.g. diabetes mellitus, CKD, hyperthyroidism), use of an indwelling urethral catheter, perineal urethrostomy, immunocompromise and neurogenic bladder.

■ **The presenting signs are non-specific** and may be seen with other sterile causes of FLUTD e.g. idiopathic cystitis and urolithiasis.



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Double contrast cystogram revealing a diffusely thickened bladder wall in a male cat presenting with FLUTD. Final diagnosis: sterile idiopathic cystitis.

■ Diagnosis requires localisation of signs to the lower urinary tract, identification of bacteria on urine cytology, culture (quantitative) & sensitivity and exclusion of other causes of FLUTD.

■ Presenting signs: dysuria, stranguria, pollakuria, haematuria, periuria, vocalisation, increased perineal grooming, incontinence, agitation and inappetence. Collapse and shock may be associated with urethral obstruction (male cats).

■ Clinical examination: caudal abdominal discomfort, small or empty bladder, pyrexia and dehydration. Urethral obstruction may result in a distended painful bladder, collapse, pallor, tachycardia or bradycardia (secondary to hyperkalaemia), hypothermia and poor peripheral pulses.

■ Urinalysis

• Biochemistry (dipstick): proteinuria (mild); leukocyte readings are unreliable.

• Cytology: pyuria, haematuria, bacteriuria; Gram staining.

• Culture and sensitivity: on cystocentesis samples (or via aseptically placed urinary catheter); culture of free-catch samples is only useful if negative (to exclude urinary tract infection - UTI).

■ Classification of UTIs

• **Simple uncomplicated UTI**: sporadic infection in an otherwise healthy cat with normal urinary tract anatomy and function; treatment 7 days.

• **Complicated UTI**: infection in cats with structural or functional urogenital tract abnormalities, immunosuppression or comorbid disease that predisposes to UTI or recurrent episodes (> 3 in 12 month period); treatment 28 days.

• **Subclinical bacteriuria**: identification of bacteria on urine culture in the absence of clinical or cytological signs of infection[20]; significance not fully understood and currently treatment is warranted only in very specific circumstances e.g. concurrent kidney disease, where the risk of ascending infection could be increased (N.B. this lacks an evidence base).

Urine samples for bacterial culture and sensitivity testing should be refrigerated as soon as possible and processed at a microbiology lab within 24 h to prevent false positives and false negatives. In-house direct sediment examination should be performed before sample refrigeration.

© Salvador Cervantes

Cystocentesis is the preferred sampling technique for culture and sensitivity testing.

DISEASE FACT SHEETS

FELINE (BACTERIAL) CYSTITIS

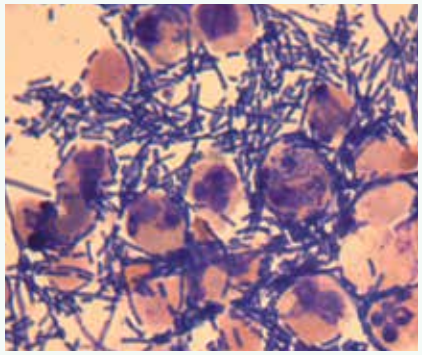
Reasoning

■ **Urine cytology and culture are strongly recommended for selection of effective first line antibiotics** due to inherent microbial resistance patterns and regional resistance profiles e.g. *Enterococci* spp. are typically resistant to cephalosporins (including cefovecin) and TMS in *vivo*[6].

■ Cytology can be used to guide an empirical treatment pending culture and sensitivity results:
- Gram-negative bacteria: amoxicillin ± clavulanate.
- Gram-positive bacteria: amoxicillin[10].

■ Choice of antibiotic may be a compromise between ideal drug *vs.* owner ability to medicate with a specific preparation, such as:
- Trimethoprim sulfonamide is often problematic to administer due to the bitter taste of the medication.
- Amoxicillin is ideally recommended 8 hourly (product instructions may indicate 12 hourly).
- Cefovecin has a duration of action that is longer than required for simple UTIs; reserve for when oral medication is impossible.
See also recommendation R.2.

■ When a simple uncomplicated UTI is considered likely and urine culture is not performed (e.g. impossible to obtain sample due to small bladder size, financial constraints), treatment with amoxicillin+clavulanate is a reasonable first choice[13] and resolution of clinical signs can be taken as evidence of a positive response. Remember that the use of a ß-lactamase inhibitor (clavulanate) is not usually required for treatment of *Enterococcus* spp. infections. Typically amoxicillin will suffice and is preferred due to a narrower spectrum of activity (if compliance can be achieved).



© Angie Hibbert

Urine cytology: neutrophils (degenerate) and bacilli (intracellular and extracellular) in a cat diagnosed with a bacterial urinary tract infection (x1000 magnification, modified Wright's stain).

■ For complicated UTIs urine culture should be performed:
- 5-7 days following the start of treatment to assess efficacy,
- 5-7 days after completion of treatment course (Note: with cefovecin, sampling should be delayed to 21 days after the last dose[20]).

■ Nitrofurantoin is a human preparation useful in multi-drug resistant UTIs. Its use should be guided by culture and sensitivity testing and by cascade guidelines.

Difficulties and particularities

■ Recurrence or failure to resolve clinical signs is justification for further investigation if the initial antibiotic choice was appropriate and was administered effectively. A search for underlying causes or predispositions should be performed (including full urinalysis, haematology, serum biochemistry, T4, FeLV/FIV serology, urinary tract imaging including contrast studies). Prevalence of UTI in association with CKD is 17-30%, diabetes mellitus 11-13%, hyperthyroidism 12%[1,2,22].

■ Bacterial cystitis associated with an indwelling urinary catheter may not resolve until the catheter is removed. Prophylactic antibiotic treatment whilst the catheter is *in-situ* is not recommended, due to the risk of development of resistant UTI[20]. Culture of urine by cystocentesis following removal of the catheter is indicated only when lower urinary tract signs persist and in male cats where the risk of urethral obstruction due to spasm is higher. Culture of the removed urinary catheter tip is not reliably predictive[7].

■ For polymicrobial infections, one or two antimicrobials may be required based on sensitivity profiles. Anecdotally, *Enterococcus faecalis* infection may resolve without specific antimicrobial therapy when other bacteria are treated effectively[20].

BACTERIAL URINARY TRACT INFECTION IN CATS WITH CKD

Bacteria involved[1, 6, 12]

Bacteria	Prevalence
Escherichia coli	59-71%
Enterococcus spp. *(E.faecalis)*	6-15%

Antibiotics that can be used[2, 3, 4, 5, 9, 10, 11, 13]

Antibiotics that can be used **based on culture and sensitivity results:**

Pathogen 1: *Escherichia coli* (Gram-negative)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	5	
Amoxicillin + clavulanate	4	5	
Trimethoprim sulfonamides[a]	4	4	
Cefalexin	3	5	
Marbofloxacin / Enrofloxacin[b]	5	5	
Cefovecin[c]	4	5	
Pradofloxacin[d]	5	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

For footnotes, see next page.

Pathogen 2: *Enterococcus* spp. (Gram-positive)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	4	5	
Amoxicillin + clavulanate[f]	4	5	
Marbofloxacin / Enrofloxacin[b]	3 - 4	5	
Pradofloxacin[d]	5	3	
Cefalexin[e]	2	5	
Cefovecin[c,e]	2	5	
Trimethoprim sulfonamides[a,e]	4 - 5	4	
Clindamycin[e]	2	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[7].*

[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[d] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

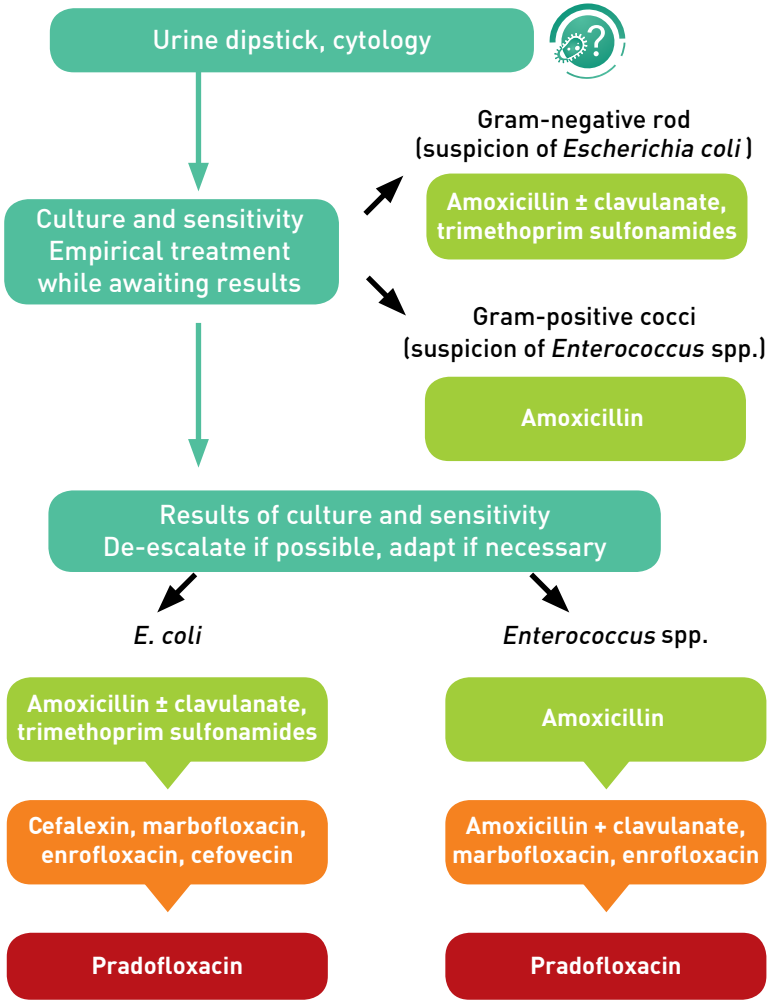
[e] *Enterococcus spp. do not typically respond in vivo to cephalosporins, TMS or clindamycin due to inherent resistance mechanisms; be aware when interpreting in vitro results that these antibiotics are not recommended for treatment[2].*

[f] *Use of a ß-lactamase inhibitor (clavulanate) is not usually required for treatment of Enterococcus spp. infections hence amoxicillin+clavulanate is designated as 2nd choice, however its use may be a compromise to achieve patient/owner compliance.*

DISEASE FACT SHEETS

BACTERIAL URINARY TRACT INFECTION IN CATS WITH CKD

Therapeutic approach



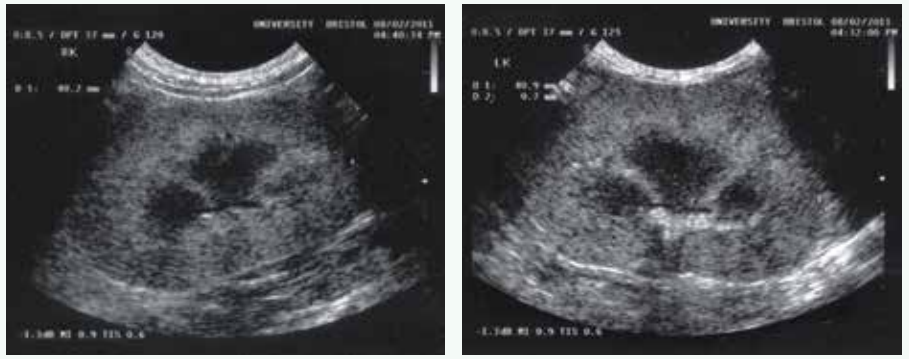


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Figure 1 *- Renal ultrasound demonstrating cortex hyperechogenicity and mild pelvic dilation in a cat with pyelonephritis, causing an exacerbation of pre-existing CKD.*

Treatment recommendations

■ In addition to on-going management for CKD, analgesia should be provided if lower or acute upper urinary tract signs (e.g. buprenorphine) and any fluid/electrolyte derangements should be addressed. Consider nutritional support e.g. anti-emetics, appetite stimulants or assisted feeding if inappetent. Initial treatment with intravenous antibiotic preparations is recommended in inappetent +/- dehydrated patients, with a transition to oral therapy once the cat is eating and fully hydrated.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli	Amoxicillin	10-25 mg/kg/8h IV 10-15 mg/kg/8h PO	28 days complicated UTI
	Amoxicillin + clavulanate	10 mg/kg/8h IV 12.5-25 mg/kg/8-12h PO	
	Trimethoprim sulfonamides[a]	15 mg/kg/12h PO	
Enterococcus spp.	Amoxicillin	10-25 mg/kg/8h IV 10-15 mg/kg/8h PO	

For footnotes, see p.45.

DISEASE FACT SHEETS

BACTERIAL URINARY TRACT INFECTION IN CATS WITH CKD

Second choice antibiotic (with culture and sensitivity testing)[8,11]

Pathogen involved	Antibiotics that can be used	Dosage Consider adjustment for Stage 3&4 IRIS	Duration of treatment
Escherichia coli	Cefalexin	15-30 mg/kg/12h PO	28 days complicated UTI
	Marbofloxacin	2 mg/kg/24h IV, SC, PO	
	Enrofloxacin[b]	5 mg/kg/24h SC, PO	
	Cefovecin[c]	8 mg/kg single dose SC (14d)	
Enterococcus spp.	Amoxicillin + clavulanate[f]	20 mg/kg/8h IV 12.5-25 mg/kg/8-12h PO	
	Marbofloxacin	2 mg/kg/24h IV, SC, PO	
	Enrofloxacin[b]	5 mg/kg/24h SC, PO	

For footnotes, see p.45.

Culture and sensitivity testing should be performed to select the most appropriate antibiotic and hence reduce the potential for further irreversible damage to the kidney.

Diagnostic approach

■ Bacterial UTI has been reported in 17-30% cats with CKD[1,6,12]. Commonly UTI is an incidental finding or there are vague signs of illness (e.g. weight loss, lethargy, reduced appetite); signs of cystitis (e.g. pollakuria, dysuria, stranguria) or pyelonephritis (acute, chronic; see Pyelonephritis, p.52) are infrequent.

■ Any deterioration in azotaemia, identification of an active urine sediment or pyrexia warrants investigation for bacterial UTI, as a potential exacerbating factor affecting renal function.

■ Evaluation

• **Urinalysis**

- biochemistry (dipstick): proteinuria (mild), +/- glycosuria, haemoglobinuria; leukocyte readings are unreliable

- cytology: pyuria, haematuria, bacteriuria; Gram staining

- culture and sensitivity (quantitative) on cystocentesis samples (or via aseptically placed urinary catheter); culture of free-catch samples is only useful to exclude UTI.

• Reassessment of **serum biochemistry** to assess for deterioration in azotaemia, hyperphosphataemia, inflammation (hyperglobulinaemia), electrolyte and acid base disturbances (especially if upper urinary tract involvement is suspected).

• **Haematology**: mild non-regenerative anaemia (CKD; acute inflammation), neutrophilia (+/-left shift) in cases with acute pyelonephritis.

• Abdominal **ultrasound** to assess for upper urinary tract involvement (see Pyelonephritis, p.52), evaluate bladder for neoplasia, cystoliths (uroliths less commonly associated with UTI compared to dogs).

Reasoning

■ Urine cytology and culture are strongly recommended for selection of effective first-line antibiotics due to inherent microbial resistance patterns and regional resistance profiles e.g. *Enterococci* spp. are typically resistant to cephalosporins (including cefovecin) and TMS *in vivo*.

■ Amoxicillin or amoxicillin+clavulanate are reasonable first-line empirical choices pending microbiological results; de-escalate to narrower spectrum where possible.

■ Treat as a complicated UTI for 28 days with culture 5-7 days after starting treatment to check chosen antibiotic is efficacious and 5-7 days after completion of course (for cefovecin, sample 21 days after the last dose was administered)[11].

■ Antibiotics excreted via the urinary tract will achieve high therapeutic concentrations at the site of infection; however, reduced GFR may result in drug accumulation.

■ Consider dose adjustment (i.e. increasing interval or reducing dose) in IRIS Stages 3 & 4.

■ Aminoglycosides, nitrofurantoin and tetracyclines (except doxycycline) are contraindicated.

Difficulties and particularities

■ Most of the cats reported with positive urine cultures and CKD have had occult infections[6,12]. The significance of positive culture in this scenario is unknown although the identification of pyuria suggests a local reactive immune response. One small study found no effect of occult UTI upon survival in cats with CKD, however cats received treatment[12]. Further investigation is needed to answer questions regarding monitoring and treatment, e.g. what is the real risk of exacerbation of renal function by an occult UTI or asymptomatic bacteriuria, how effective is antimicrobial treatment in fully resolving infections, how long should treatment courses be and should screening cultures ever be performed without cytological evidence of infection?

■ Increasing age and female gender are risk factors[12].

BACTERIAL URINARY TRACT INFECTION IN CATS WITH CKD

Short case study including table of biochemistry

A 14-year-old male neutered DSH was diagnosed with bacterial urinary tract infection following a one-year history of CKD. He presented with a single pyrexic episode and three-month history of lethargy, increased PU/PD and inappetence. Urinalysis revealed pyuria, haematuria and mild proteinuria. Treatment with amoxicillin+clavulanate was initiated. A negative bacterial culture was returned (likely due to prior antibiosis) however a marked clinical and biochemical response was seen to antibiotic therapy. Diagnosis: bacterial pyelonephritis secondary to chronic kidney disease.

Serum biochemistry results:

	Day 1	Day 4	Day 28	4 months	Ref range
		Receiving treatment with amoxicillin + clavulanate		Post treatment	
Urea (mmol/l)	60	35.3	32	32	6.5-10.5
Creatinine (µmol/l)	817	611	374	378	133-175
Phosphate (mmol/l)	4.06	2.5	1.89	3.4	0.95-1.55
Globulin (g/l)	64.6	-	48.2	49.0	21-51

Urine cytology and culture are strongly recommended for selection of effective first-line antibiotics due to inherent microbial resistance patterns and regional resistance profiles.

DISEASE FACT SHEETS

PYELONEPHRITIS

Bacteria involved

Bacteria	Prevalence
Escherichia coli	++++ (> 60 %)
Enterococcus spp. / *Streptococcus* spp.	++ (15 to 40 %)
Staphylococcus spp.	+ (< 10-20 %)
Proteus spp.	+ (< 10-20 %)

Note: In feline CKD, the prevalence of chronic pyelonephritis has been estimated at 9.5–42%[8]. In dogs, in a recent study[11], of the 1,028 incidents of UTI in dogs, 363 (35.3%) were classified as uncomplicated and 665/1028 (64.7%) as complicated. Of the complicated UTIs, 51/665 (7.7%) of dogs had pyelonephritis.

Antibiotics that can be used

Antibiotics that can be used **while awaiting C&AST results (if the use of antibiotics is justified):**

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	5	
Trimethoprim sulfonamides[a]	4	5	
Marbofloxacin[b] / Enrofloxacin[b,c]	4 - 5	5	

Pathogen 2: *Streptococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Penicillin G / Ampicillin	4 - 5	4	
Cefalexin	5	4	
Cefovecin[d]	5	4	

For footnotes, see at the end of the chapter.

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 3: *Enterococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Penicillin G / Ampicillin	4 - 5	4	
Penicillin G + Gentamicin[e,f]	4 - 5	4	

For footnotes, see at the end of the chapter.

Therapeutic approach

Culture and sensitivity

Empirical treatment while awaiting results or pending referral consultation → **Amoxicillin+clavulanate, trimethoprim sulfonamides**

Results of culture and sensitivity
De-escalate if possible, adapt if necessary

Ampicillin, penicilin, amoxicillin ± clavulanate, trimethoprim sulfonamides

Cefalexin, cefadroxil, marbofloxacin, enrofloxacin

Cefovecin, gentamicin

DISEASE FACT SHEETS

PYELONEPHRITIS

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli	Amoxicillin+clavulanate	12.5–25 mg/kg/8h PO	4-6 weeks
	Trimethoprim sulfonamides[a]	15 mg/kg/12h PO	
Enterococcus spp. *Streptococcus* spp.	Penicillin G	Penicillin G sodium 15-25 mg/kg/4-6h IV/IM Penicillin G procaine 30 mg/kg/24h SC	
	Ampicillin	20-50 mg/kg/6-8h IV/IM/SC	

Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli	Marbofloxacin[b]	2 mg/kg/24h PO (dogs and cats)	4-6 weeks
	Enrofloxacin[b,c]	5 mg/kg/24h PO (dogs)	
Enterococcus spp.	Ampicillin + Gentamicin[e,f]	Ampicillin 20-50 mg/kg/6-8h IV/IM/SC + Gentamicin 5-10 mg/kg/24h IM/SC	
Streptococcus spp.	Cefalexin	15-30 mg/kg/12h (PO) or 24h (IM/SC)	
	Cefovecin[d]	8 mg/kg single dose SC (can be repeated once after 7–14 d)	

For footnotes, see at the end of the chapter.

Diagnostic approach

- Dogs and cats with acute pyelonephritis of bacterial origin tend to present with a variable clinical picture: fever, depression, anorexia, gastrointestinal signs (e.g. vomiting, renal pain) and leucocytosis. Pyelonephritis may be complicated by bacteraemia and urosepsis or progress to chronicity.
It is essential to determine if a urinary obstruction is associated. If yes, it should be treated accordingly as it may be life-threatening. Consider referral if you have any doubt about the diagnosis.
- The clinical diagnosis of pyelonephritis is often presumptive based on results of complete blood cell counts, serum chemistry profile, urinalysis, quantitative urine culture and ultrasound (e.g. dilated renal pelvis). Always start with a urine sample by cystocentesis because ascending urinary tract infection (UTI) is one of the causes. **Definitive diagnosis requires urine obtained by percutaneous ultrasound-guided pyelocentesis**.
- Medical conditions that frequently predispose dogs to a UTI are diabetes mellitus, hyperadrenocorticism, exogenous steroid administration, renal failure, urethral catheterization, urinary retention, uroliths and urinary tract neoplasia. UTI including pyelonephritis is one of the common complications arising in cats associated with diseases such as hyperthyroidism, diabetes mellitus and chronic kidney disease. Affected cats may or may not demonstrate clinical signs associated with the infection.

Reasoning

- Initial treatment should be made with antimicrobial drugs known to have local or regional efficacy against Gram-negative Enterobacteriaceae[10].
- Always perform urine cytology and urine culture. When treating a UTI, the clinical efficacy of an antibiotic is expected if its urine concentration is maintained at 4 X above the MIC of the pathogen between doses[9]. However, in pyelonephritis, a deep tissue infection needs to be treated. The interpretation of susceptibility data should therefore be based on antimicrobial breakpoints for serum rather than urine concentrations[9].

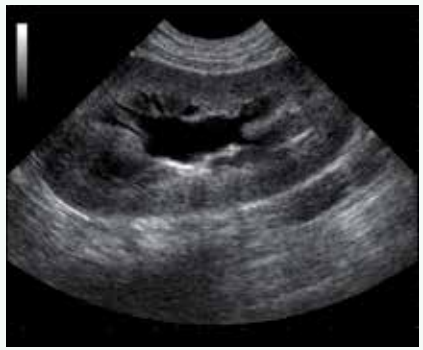

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Figure 1 *- Hydronephrosis in a dog with chronic pyelonephritis.*

DISEASE FACT SHEETS

PYELONEPHRITIS

■ Monitoring therapy is essential. The potential severity of the disease and the long treatment duration requires urinalysis (and/or cytology) and culture 1 week from the start and after cessation of treatment[10]. *In vitro* susceptibility results should guide antibiotic choice. Treatment of 4–6 weeks is often recommended, as is consultation and hospitalization with a specialist[10].

Difficulties and particularities

■ Recurrent pyelonephritis may be asymptomatic[9]. Unresolved chronic pyelonephritis may lead to chronic kidney disease. Therefore, diagnostic follow-up is important to document resolution of the pyelonephritis. Resolution is unlikely in dogs and cats with nephroliths, unless they are removed.

■ Antibiotics used should not be nephrotoxic. High serum and urinary antibiotic concentrations do not necessarily ensure high tissue concentrations in the renal medulla. Treatment of chronic pyelonephritis may be difficult to achieve. Aminoglycosides should be avoided. Trimethoprim sulfonamide combinations can cause significant adverse effects (keratoconjunctivitis sicca, blood dyscrasias and polyarthritis).

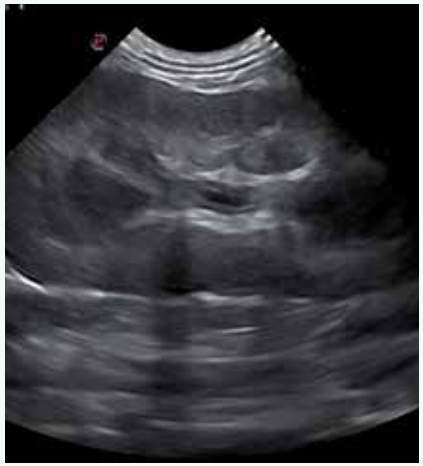


Figure 2 - Longitudinal image of a kidney in a dog with pyelonephritis due to Mycoplasma UTI.

Table 1 - Major clinical diagnostic features of upper urinary tract infection

Acute pyelonephritis	Chronic pyelonephritis
- Fever, renal pain	- Polydipsia/polyuria
- Leucocytosis (neutrophilia)	- Asymptomatic
- Leucocyturia (pyuria)	- Signs of chronic kidney disease
- Azotaemia, acidaemia	- Azotaemia
- Ultrasound imaging: dilated renal pelvis and retroperitoneal steatitis	- Ultrasound imaging: dilated renal pelvis (without cause of obstruction)
- May be associated with lower urinary tract infection signs	

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[6].*

[b] *Avoid use in growing dogs of large breeds.*

[c] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[d] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[e] *Only for high-level gentamicin susceptible strains of Enterococcus spp.[1,7]*

[f] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/ education/prevention.html).*

CANINE PROSTATITIS

Bacteria involved

Bacteria	Prevalence
Escherichia coli	++ (15 to 40%)
Staphylococcus spp.	++ (15 to 40%)
Streptococcus canis	+ (<10-20%)

Antibiotics that can be used

Only if the use of antibiotics is justified.
ß-lactams should never be used due to their inability to cross the blood/prostate barrier.

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Trimethoprim sulfonamides[a]	4	5	
Marbofloxacin[b] / Enrofloxacin[b]	4	5	
Pradofloxacin[b,c]	4	5	
Chloramphenicol	4	5	
Amoxicillin + clavulanate	3	1	
Cefalexin	3	1	

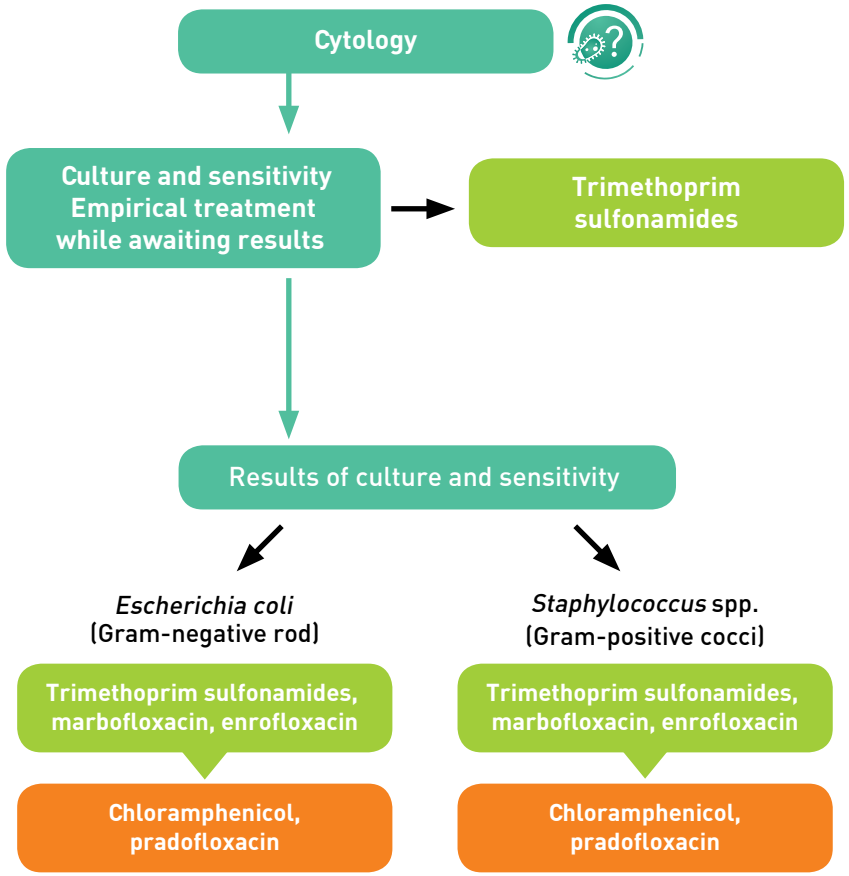
Pathogen 2: *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Trimethoprim sulfonamides[a]	4	5	
Marbofloxacin[b]/ Enrofloxacin[b]	4	5	
Pradofloxacin[b,c]	5	5	
Chloramphenicol	4	5	
Amoxicillin + clavulanate	5	1	
Cefalexin	5	1	

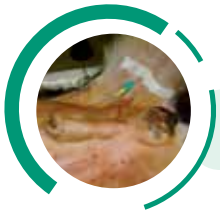
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Therapeutic approach



[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[9].*
[b] *Avoid use in growing dogs of large breeds.*
[c] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*



CANINE PROSTATITIS

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp.	Trimethoprim sulfonamides[a]	15 mg/kg/12h PO	3-4 weeks (acute prostatitis) 6 weeks (chronic prostatitis)

Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp.	Enrofloxacin[b]	5 mg/kg/24h PO	3-4 weeks (acute prostatitis) 6 weeks (chronic prostatitis)
	Marbofloxacin[b]	2 mg/kg/24h PO	

For footnotes, see on the previous page.

Diagnostic approach

- Prostatitis is an inflammation of the prostate gland, and may be acute or chronic. Although prostatic disorders are very common in dogs, **bacterial prostatitis represents 30% of all cases**, and is the second most common cause of prostatic disease.
- The signs associated with acute bacterial prostatitis include: lethargy, weakness, fever, abdominal pain and, in severe cases, sepsis and shock. In chronic cases there is a decline in fertility and recurring cystitis. Rectal palpation is very painful in acute prostatitis. Rectal massage may be used to obtain a sample (cytology, culture and sensitivity) (Figure 1).

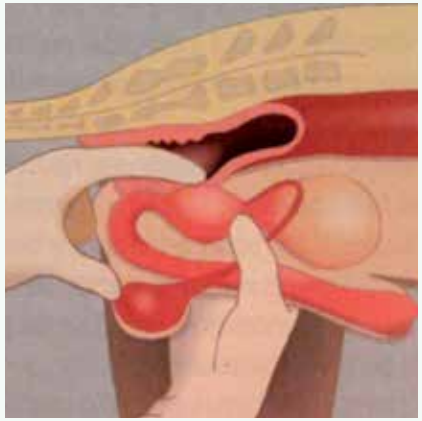


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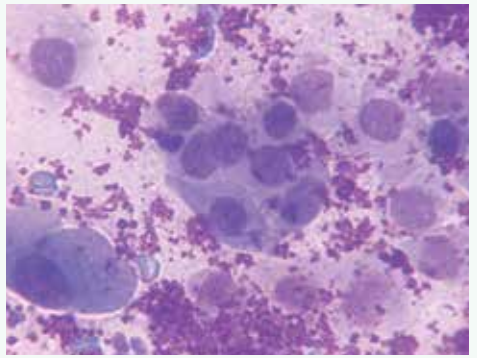
Figure 1 *- Prostatic massage[3].*



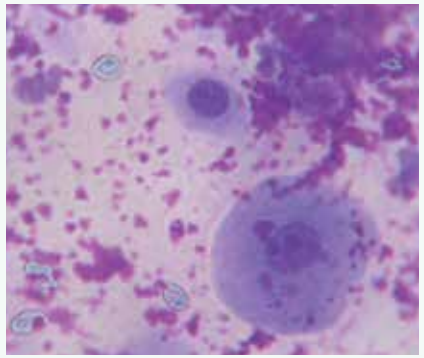


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Figure 2 *- Cytology. Prostatic massage sample from a dog with urothelial adenocarcinoma and secondary prostatitis. Epithelial cells (normal and abnormal) are observed. Abnormal cells are grouped as clusters and have a greater nucleus/cytoplasm ratio. Although infection or inflammation was not observed on cytology, C&AST detected an infection by E.coli (Diff Quik®, 1000x).*

- A negative culture result of prostatic fluid will nearly always (89%) rule out an infection while a positive culture will confirm bacterial infection in only half of cases. Contamination during the sampling procedure is the most common cause of false positive cultures[6,8]. Ultrasonography is the method of choice when investigating the prostate, imaging the size of the gland as well as the homogeneity of the parenchyma[4,7].
- If concurrent cystitis is present, urine culture has a good correlation with the prostatic bacteria (>90%). **Ultrasound examination of the prostatic gland is always recommended to confirm or rule out the presence of cysts or abscesses** that may change the therapeutic approach. If cavities are detected during the ultrasound exam a sample of liquid should always be taken to differentiate an abscess from a cyst.
- If urine and prostatic liquid culture are negative it may be useful to take a biopsy for culture and sensitivity testing.

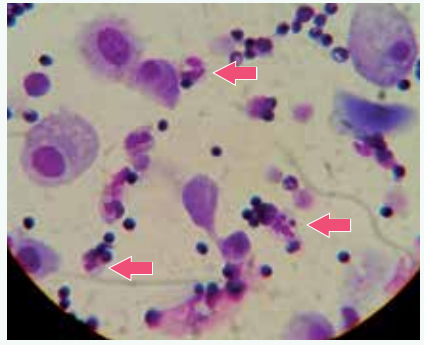

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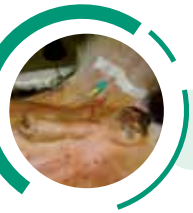
Figure 3 *- Cytology: Urine sediment from a dog with prostatitis and secondary cystitis, arrows show neutrophils. Transitional cells from bladder and numerous erythrocytes are also observed. Infection with Staphylococcus spp. was confirmed by urine and prostatic culture.*

DISEASE FACT SHEETS



CANINE PROSTATITIS

Reasoning

- In acute prostatitis, the blood–prostate barrier is broken[1], resulting in an easy penetration of antibiotics and other drugs into the gland. In chronic prostatitis, the blood–prostate barrier prevents the penetration of many drugs. Antibiotic choice is based on sensitivity testing and tissue distribution. Only weak alkaline antibiotics, with high pKa (acid dissociation constant) and high lipid solubility, are able to diffuse into the prostatic parenchyma. The effectiveness of trimethoprim sulfonamides or clindamycin has been proven, fluoroquinolones are also effective.
- **Culture and sensitivity testing of prostatic fluid (or urine if concurrent bacterial cystitis is suspected) is required** because of the special anatomical structure and chemical composition of the prostatic gland.
- Although inflammation increases the penetration capacity of some antibiotics such as **ß-lactams**, they **should not be used because therapeutic concentrations cannot be guaranteed** during the treatment course. Once the infection is under control, castration (chemical or surgical) is recommended to help control inflammation. If fertility is to be maintained, osaterone (0.25-0.5 mg/kg/24 h for 7 days every 6 months) may help control benign prostatic hyperplasia. Duration of treatment in acute cases is 3-4 weeks, in chronic cases at least 6 weeks.
- In acute cases, clinical re-examination after 3-5 days should confirm antibiotic efficacy. In chronic cases, a second culture should be performed 7-15 days after the start of treatment.
- In both cases, bacterial culture should be performed at the end of treatment to confirm full clearance of the infection.

Table 1 - Sepsis criteria in cats & dogs[2,5].

Criteria	Cats	Dogs
Temperature (ºC)	<37.7 or >39.4 ºC	<37.7 or >38.8 ºC
Respiratory rate (bpm)	>40	>20
Heart rate (bpm)	<140 or >225	>120
Leukocytosis or leukopenia (10^3/µL)	>19500 or <5000	>16000 or <6000

Difficulties and particularities

- Treatment of prostatitis is long, relapses are frequent (particularly in chronic cases) and known sequelae of bacterial prostatitis such as prostatic abscesses may be seen (Figure 4). Therefore, client compliance is vital.
- As treatment is long, side effects of antibiotics may appear more frequently.
- If trimethoprim sulfonamides are recommended, check tear production regularly to avoid keratoconjunctivitis sicca[9].
- In acute cases, depression may be followed by sepsis and shock. Hospitalization and aggressive therapy must be considered in all cases showing these signs (Table 1).

Figure 4 - Aspirates from a prostatic abscess (a) and a prostatic cyst (b). Note the enhanced sedimentation on the left.

DISEASE FACT SHEETS

EPIDIDYMITIS, ORCHITIS & BALANOPOSTHITIS

Bacteria involved

Bacteria	Prevalence
Escherichia coli	+++ (35 to 65 %)
Streptococcus spp.	++ (15 to 40 %)
Staphylococcus spp.	++ (15 to 40 %)

Antibiotics that can be used

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Trimethoprim sulfonamides[a]	4	4	
Amoxicillin	3	4	
Amoxicillin + clavulanate	3	4	
Cefalexin	4	4	
Marbofloxacin[b] / Enrofloxacin[b,c]	4	4	
Pradofloxacin[b,d]	5	4	

Pathogen 2: Gram-positive cocci (*Staphylococcus* spp./*Streptococcus* spp.)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Trimethoprim sulfonamides[a]	4	4	
Amoxicillin	4	4	
Amoxicillin + clavulanate	5	4	
Cefalexin	4	4	
Marbofloxacin[b] / Enrofloxacin[b,c]	4	4	
Pradofloxacin[b,d]	5	4	

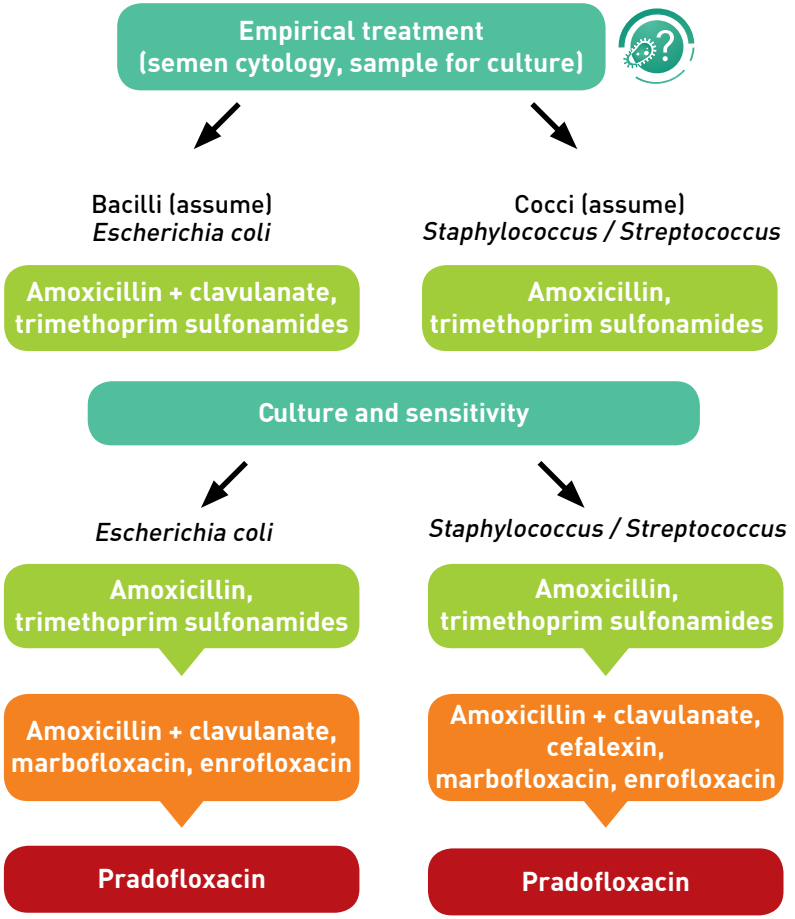
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

For footnotes, see at the end of the chapter.

Therapeutic approach (epididymitis, orchitis)

Balanoposthitis should be treated using **local antiseptics.**
When treating **orchitis (with or without epididymitis), the final step is surgical castration,** since antibiotics rarely fully cure these infections.



DISEASE FACT SHEETS

EPIDIDYMITIS, ORCHITIS & BALANOPOSTHITIS

Treatment recommendations

■ Non-antibiotic treatment: **For balanoposthitis, the administration of a local antiseptic suffices**. Solutions of chlorhexidine or stabilized hypochlorous acid are applied twice or three times on a daily basis until complete resolution (Table 1).

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Streptococcus* spp. *Staphylococcus* spp.	Amoxicillin	10-15 mg/kg/8h	14 days
	Trimethoprim sulfonamides[a]	15 mg/kg/12h	

Second choice antibiotic (with C&AST)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Streptococcus* spp. *Staphylococcus* spp.	Amoxicillin + clavulanate	12.5 -25 mg/kg/12h	14 days
	Marbofloxacin[b]	2 mg/kg/24h	
	Enrofloxacin[b,c]	5 mg/kg/24h	
Streptococcus spp. *Staphylococcus* spp.	Cefalexin	15-30 mg/kg/12 h	14 days

For footnotes, see at the end of the chapter.

■ Antibiotic therapy should be prolonged until castration can be performed and the clinician is totally sure the infection has been resolved.

Diagnostic approach

■ **Orchitis & Epididymitis**, inflammation of testis and epididymis respectively, are rare in dogs and extremely rare in cats. If orchitis is present, epididymitis is frequently associated due to the anatomic close relation. The three most common causes are ascending infection from the urinary system, traumatic (e.g. bites) and infection with *Brucella canis*. **Brucella infections are rare, but the zoonotic potential is very serious**. If orchitis is suspected, all precautions should be taken to prevent human infection (e.g. gloves when handling samples)[1]. Clinical signs are pain, oedema and increase in size of the structures affected (uni/bilateral depending on the case) as well as hyperthermia and hypo/anorexia. The diagnosis is based on clinical signs and testicular ultrasonography and fine-needle aspiration (FNA) of the testicle to rule out other conditions (e.g. testicular torsion, tumours)[2]. Sperm cytology and culture can confirm inflammation and infection, although contamination from the urethral flora is quite common. If cytology results show bacteria associated with an inflammatory component then bacterial orchitis is considered. However, if only bacteria are detected without inflammatory cells, contamination should be taken into consideration. Positive sperm cultures must show at least 10^5 bacteria/ml of sperm.

■ **Balanoposthitis**, inflammation of the foreskin and glans, is a very common condition in male dogs, usually caused by the commensal flora of the area. Clinical signs include inflammation of the foreskin, pruritus or pain of the preputial area and purulent discharge. Usually cytology allows differentiation between infection and normal preputial discharge.

Reasoning

■ For **balanoposthitis**, the selection of the local antiseptic depends on patient tolerance. Preferably use an antiseptic that is well tolerated and has a long-lasting effect (Table 1).

■ The treatment for **orchitis/epididymitis** consists of antibiotic treatment and castration. **The blood-testis barrier hinders good antibiotic tissue penetration**. It may therefore be difficult to fully remove an infection in these areas without castration. Cytology and culture of sperm is

In case of balanoposthitis, the administration of a local antiseptic suffices.

Table 1 - Disinfectants and their concentrations used as genital cleaners.

Disinfectant	Concentrations used
Chlorhexidine	0.05 - 0.5%
Povidone-Iodine	0.1 - 1
Stabilised hypochlorous acid	0.011%
Benzalkonium chloride	0.006 - 0.012%

DISEASE FACT SHEETS

EPIDIDYMITIS, ORCHITIS & BALANOPOSTHITIS

useful but samples are not always easy to obtain in patients experiencing pain. Testicular FNA can be tried in these cases although culture from these samples may be a challenge due to the low number of bacteria.
Once the patient has started antibiotic treatment and infection is under control, castration may be performed (usually not before 48h).

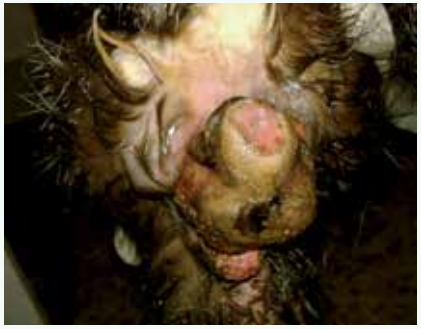


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Figure 1 *- Ulcerative balanoposthitis and orchitis in a cat due to pain (licking) caused by a chronic LUTD.*

Difficulties and particularities

- Orchitis and epididymitis are rare causes of testicular inflammation; testicular torsion and tumours must first be ruled out. In cases without a definitive diagnosis, a biopsy of the tissue or the entire testicles should be sent to a pathologist.
- It is very important to explain to the owner that **without castration, infection does not always clear up**. This is due to the blood-testis barrier preventing the antibiotics from reaching the infection focus.

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[3].*
[b] *Avoid use in growing dogs of large breeds.*
[c] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[d] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

METRITIS AND PYOMETRA

- **Ovariohysterectomy is the treatment of choice in any queen or bitch.**
- In young, clinically stable breeding animals with an open cervix, catheterization and lavage of the uterus and medical therapy with prostaglandins, dopamine agonists or progesterone receptor antagonists may be attempted.

Bacteria involved

Bacteria	Prevalence
Escherichia coli	++++ (> 60 %)
Staphylococcus spp.	+ (< 10-20 %)
Streptococcus spp.	+ (< 10-20 %)

Antibiotics that can be used

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	3	
Amoxicillin + clavulanate	3	3	
Trimethoprim sulfonamides[a]	3	3	
Cefalexin	3	3	
Marbofloxacin[b] / Enrofloxacin[b,c]	4	4	

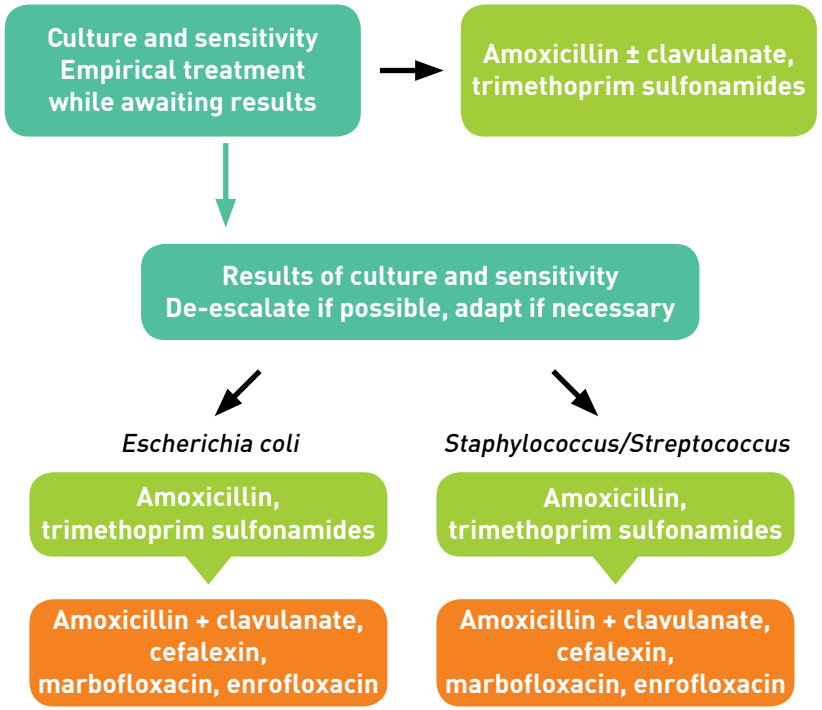
Pathogen 2: *Staphylococcus* spp. / *Streptococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Trimethoprim sulfonamides[a]	4	3	
Amoxicillin	5	3	
Amoxicillin + clavulanate	5	3	
Cefalexin	3	3	
Marbofloxacin[b] / Enrofloxacin[b,c]	4	4	

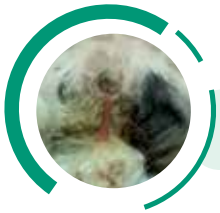
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Therapeutic approach



[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[3].*
[b] *Avoid use in growing dogs of large breeds.*
[c] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*



METRITIS AND PYOMETRA

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp. *Streptococcus* spp.	Amoxicillin ± clavulanate	10-25 mg/kg/12h PO, SC, IV	2-3 weeks
	Trimethoprim sulfonamides[a]	15 mg/kg/12h PO, IV	

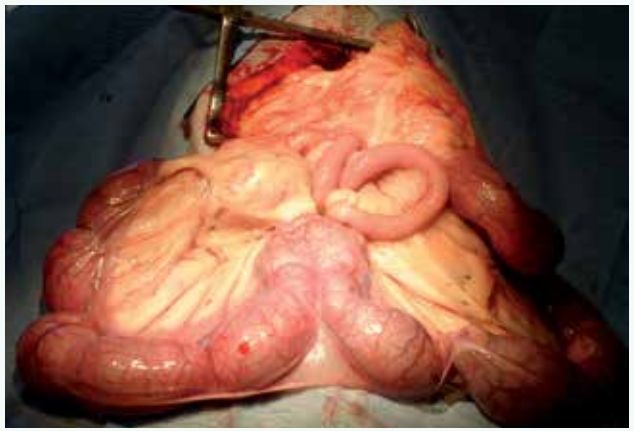
Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp. *Streptococcus* spp.	Cefalexin	15-30 mg/kg/12h PO	2-3 weeks
	Marbofloxacin[b]	2 mg/kg/24h PO, SC, IV	
	Enrofloxacin[b,c]	5 mg/kg/24h PO, SC	

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[3].*

[b] *Avoid use in growing dogs of large breeds.*

[c] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*



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Complete ovariohysterectomy is the preferred treatment.

Diagnostic approach

- Endometritis and pyometra are common diseases in the dog, but rare in the cat. Metritis can be caused by chronic subclinical inflammation and bacterial infection of the uterine wall leading to infertility in the bitch.
- In contrast, postpartum metritis refers to infection of the endometrium and myometrium that develops within 3-7 days after whelping.
- Pyometra is an acute or chronic suppurative inflammation of the uterine wall leading to accumulation of a neutrophil-rich exudate in the uterine lumen, which typically occurs 4-14 weeks after an oestrous cycle. Typical clinical signs of acute endometritis and pyometra are lethargy, anorexia, fever, polydipsia and polyuria. Vaginal discharge is present in about 65 % of cases with pyometra. Abdominal imaging can help identifying endometrial thickening and fluid-filled distended uterine horns (Figure 1).

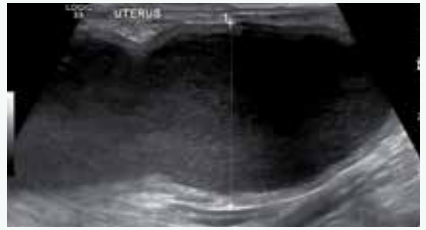

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***Figure 1** - Ultrasonographic image of pyometra in a dog: note the enlarged, fluid-filled uterus.*

Reasoning

- Initial treatment should include fluid therapy and analgesia in systemically ill patients.
- Bacterial culture and sensitivity testing should be performed in cases of acute and chronic endometrial disease. Ideally, fluid for bacterial culture and sensitivity testing is collected transcervically from the uterus. If this is not possible, a cranial vaginal sample can be obtained by using a speculum and a guarded swab. The most commonly isolated bacteria in dogs with endometritis and pyometra are uropathogenic *Escherichia coli*. In addition, vaginal commensals such as *Staphylococcus aureus*, *Streptococcus* spp., *Klebsiella* spp. and *Proteus* spp. have been recovered[2,4].
- Recommendations for antibiotic therapy are amoxicillin, amoxicillin+clavulanate, trimethoprim sulfonamides or fluoroquinolones. If sepsis is suspected, antibiotic choice and dose should be adapted to the situation (see Bacteraemia (sepsis), p.158). In sick and dehydrated animals antibiotics should be given intravenously initially, if possible. Many patients with acute uterine infection are septic and need aggressive fluid management and additional stabilizing measures. Complete ovariohysterectomy is the preferred treatment in any

METRITIS AND PYOMETRA

queen or bitch. In young, clinically stable breeding animals with an open cervix, catheterization and lavage of the uterus and medical therapy with prostaglandins, dopamine agonists or progesterone receptor antagonists can be attempted.

Difficulties and particularities

- Antibiotic therapy is considered supportive therapy in animals with endometritis and pyometra. It cannot substitute manual or medical drainage of pus and bacteria from the uterus or ovariohysterectomy. Severely sick animals can have decreased kidney and liver function due to sepsis and dehydration. Therefore, **antibiotics should not have a nephrotoxic or hepatotoxic potential**[1].
- In cases of acute post-partum metritis, the chosen antibiotics should not be toxic to the puppies (e.g. amoxicillin+clavulanate, cephalosporins), if they stay with the mother. With conservative treatment, antimicrobial therapy should be continued for at least 14 days after resolution of vulvar discharge and removal of all fluid from the uterine lumen as determined by ultrasonography. Especially in bitches and queens that are managed conservatively, close monitoring of vaginal discharge, CBC, and abdominal ultrasound is necessary to evaluate the success of treatment.
- For non-breeding animals, ovariohysterectomy is the treatment of choice. Because patients are often in poor condition for surgery, they should be stabilized first with intravenous fluids and antibiotics. Antibiotic treatment should be given for at least 10-14 days. In animals with sepsis and endotoxaemia, antibiotics should be given intravenously.

DISEASE FACT SHEETS

VAGINITIS

Juvenile vaginitis rarely requires antibiotic treatment and usually resolves spontaneously.

Bacteria involved

Bacteria	Prevalence
Escherichia coli	++ (15 to 40 %)
Staphylococcus spp.	++ (15 to 40 %)
Streptococcus spp.	++ (15 to 40 %)

Antibiotics that can be used

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	3	
Amoxicillin + clavulanate	3	3	
Cefalexin	3	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	4	

Pathogen 2: *Staphylococcus* spp. / *Streptococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	5	3	
Amoxicillin + clavulanate	5	3	
Clindamycin	4	4	
Cefalexin	3	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	4	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

Therapeutic approach

Culture and sensitivity

Escherichia coli	*Staphylococcus / Streptococcus*
Amoxicillin ± clavulanate	**Amoxicillin ± clavulanate, clindamycin**
Cefalexin, marbofloxacin, enrofloxacin	**Cefalexin, marbofloxacin, enrofloxacin**

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli	Amoxicillin	10-25 mg/kg/12h PO, SC, IV	2-3 weeks
	Amoxicillin + clavulanate	12.5-25 mg/kg/12h PO, SC, IV	
Staphylococcus spp. *Streptococcus* spp.	Clindamycin	5.5-11 mg/kg/12h PO, IV	

Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp. *Streptococcus* spp.	Cefalexin	15-30 mg/kg/12h PO	2-3 weeks
	Marbofloxacin[a]	2 mg/kg/24h PO, SC, IV	
	Enrofloxacin[a,b]	5 mg/kg/24h PO, SC	

VAGINITIS

Diagnostic approach

■ Vaginitis is more common in dogs than in cats. Canine vaginitis can be differentiated into juvenile vaginitis and vaginitis in the adult bitch. Juvenile or "puppy vaginitis" is a condition occurring in healthy puppies from 6 weeks up to puberty that is thought to be caused by an imbalance of the juvenile vaginal glandular epithelium. It is considered a sterile inflammation and rarely requires antibiotic treatment.

■ Adult onset vaginitis can be caused by various underlying problems, and is frequently accompanied by perivulvar and vulvar dermatitis. Chronic vaginitis in adult bitches can be caused by primary infectious organisms (canine herpesvirus, *Brucella canis*) or overgrowth of an atypical bacterial species if the normal vaginal flora is disturbed. Underlying causes include redundant dorsal and lateral vulvar folds, foreign bodies, urinary tract infections (urethritis), vestibulitis and vulvitis, conditions causing urinary incontinence, urogenital neo-plasms and vaginal strictures, but can often be idiopathic. Primary work-up should focus on the identification of possible underlying conditions and include blood work, urinalysis (sample obtained by cystocentesis) with culture and sensitivity, endoscopic vaginal examination, and vaginal cytology and culture. In addition, screening for canine herpesvirus and *Brucella canis* may be indicated.

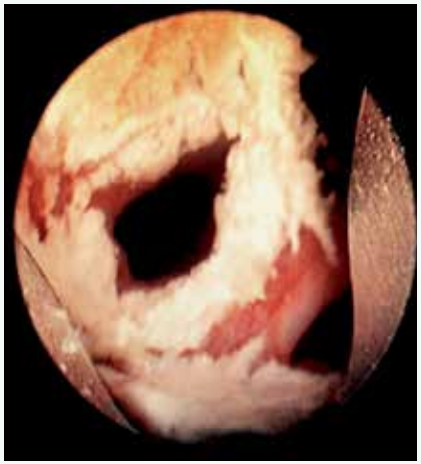

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Figure 1 *- Endoscopic image of vaginitis in a dog.*

Reasoning

■ **Juvenile sterile vaginitis normally does not require antibiotic treatment**; clinical signs usually improve with maturity.

■ In mature bitches, treatment should be aimed at the underlying condition. Dogs with severe clinical disease should receive antibiotic treatment depending on the results of culture and sensitivity testing. A vaginal sample can be obtained by using a speculum and a guarded swab. The most commonly isolated bacteria in dogs with vaginitis are uropathogenic *Escherichia coli*, *Streptococcus*, *Staphylococcus*, *Mycoplasma* spp., *Pasteurella* spp., and *Brucella canis*[1,2]. Results of bacterial culture need to be interpreted with care, because of the existing physiological urogenital microflora. While the massive growth of a single organism probably indicates bacterial infection, growth of several bacterial species most likely represents normal bacterial commensals that do not need antibiotic treatment. In cases of chronic bacterial infection, a course of treatment of two to three weeks has been suggested.

© Christelle Maurey

Figure 2 *- Juvenile sterile vaginitis normally does not require antibiotic treatment; clinical signs usually improve with maturity.*

Difficulties and particularities

■ In case of idiopathic adult-onset vaginitis, treatment can be frustrating, because animals often show a relapse of clinical signs following discontinuation of antibiotics. In these cases, oral oestrogen replacement therapy can be helpful in establishing normal vaginal mucosal integrity and to prevent chronic secondary bacterial infection.

■ For genital infections with *Brucella canis*, no treatment protocol has been shown to consistently achieve long-term cure. Due to the zoonotic potential of the disease, especially if owners are immunocompromised, euthanasia of the pet is suggested by some authors. If treatment is requested, a combination protocol of tetracyclines or fluoroquinolones and aminoglycosides has been recommended.

■ Although *Mycoplasma* spp. belong to the normal vaginal microflora, certain virulent strains of the organism are thought to be responsible for chronic vaginitis and infertility in the bitch. For detection of *Mycoplasma* spp., special culture media or PCR must be requested. Because the organism shows natural resistance to ß-lactam antibiotics, doxycycline or fluoroquinolones are recommended for treatment.

DISEASE FACT SHEETS

MASTITIS

Bacteria involved

Bacteria	Prevalence
Escherichia coli	++ (15 to 40 %)
Staphylococcus spp.	++ (15 to 40 %)
Streptococcus spp.	+ (< 10-20 %)

Antibiotics that can be used

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	3	
Amoxicillin + clavulanate	3	3	
Trimethoprim sulfonamides[a]	4	4	Not if nursing
Cefalexin	3	3	
Marbofloxacin[b] / Enrofloxacin[b,c]	4	4	Not if nursing

Pathogen 2: *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	5	3	
Amoxicillin + clavulanate	5	3	
Trimethoprim sulfonamides[a]	4	4	Not if nursing
Cefalexin	3	3	
Marbofloxacin[b] / Enrofloxacin[b,c]	4	4	Not if nursing

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[2].*
[b] *Avoid use in growing dogs of large breeds.*
[c] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

Therapeutic approach

Culture and sensitivity

Escherichia coli	*Staphylococcus*
Amoxicillin ± clavulanate, trimethoprim sulfonamides	Amoxicillin ± clavulanate, trimethoprim sulfonamides
Cefalexin, marbofloxacin, enrofloxacin	Cefalexin, marbofloxacin, enrofloxacin

Treatment recommendations

In nursing bitches and queens, only amoxicillin ± clavulanate and cefalexin should be used.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp. *Streptococcus* spp.	Amoxicillin ± clavulanate	10-25 mg/kg/12h PO, SC, IV	10-14 days
	Trimethoprim sulfonamides[a]	12.5-25 mg/kg/12h PO, SC, IV	

Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Staphylococcus* spp. *Streptococcus* spp.	Cefalexin	15-30 mg/kg/12h PO	10-14 days
	Marbofloxacin[b]	2 mg/kg/24h PO, SC, IV	
	Enrofloxacin[b,c]	5 mg/kg/24h PO, SC	

DISEASE FACT SHEETS

MASTITIS

Diagnostic approach

■ Mastitis occurs more commonly in dogs than in cats. Septic inflammation of the mammary gland can be caused by ascending infection due to injuries caused by the puppies or by haematogenous spread of bacteria and is commonly accompanied by systemic illness. This condition typically occurs post-partum; sometimes also in pseudopregnant animals. Non-septic mastitis is caused by milk stasis (e.g. sudden weaning) leading to swelling and inflammation. The affected glands become hot, swollen and painful and the milk can be discoloured. A milk sample can be obtained manually or by direct aspiration from the gland for cytology and culture and sensitivity testing. While cytology of the milk usually shows a high number of bacteria and degenerative neutrophils in animals with septic mastitis, cytology in animals with non-septic mastitis reveals few bacteria and a possible mild increase in neutrophils.

© Thomas Chapalain

Figure 1 *- Septic mastitis typically occurs post-partum.*

Reasoning

■ *Escherichia coli*, ß-haemolytic streptococci and staphylococci are the most commonly detected pathogens in cases of septic mastitis[1,3]. While non-septic mastitis is not an indication for antibiotic therapy, animals with septic mastitis require systemic antibiotic treatment. Furthermore, analgesia and fluid therapy might be indicated. **Puppies should be encouraged to continue nursing in order to support drainage of the glands** and promote adequate nutritional intake, as long as the glands are not abscessed or necrotic. However, care must be taken with the selection of antibiotics in these cases. While penicillins and cephalosporins are usually well tolerated by the puppies, fluoroquinolones, tetracyclines and aminoglycosides should be avoided. If the puppies stop feeding from the glands, manual stripping is recommended to ensure adequate drainage. In addition, warm compresses of the affected glands can be a supportive measure.

Figure 2 *- In case of acute mastitis, most antibiotics easily penetrate the blood-mammary barrier.*

Figure 3 *- If the bitch is nursing, some antibiotics should be avoided because of their undesirable effects on new-born animals.*

Difficulties and particularities

■ If the dam or puppies appear severely sick, puppies should be removed from the mother and hand-reared. In cases of abscessed and necrotic glands, surgical debridement and in severe cases mastectomy may be necessary and puppies must be separated.

■ Mastitis can be acute or chronic. **With severe inflammation in acute septic mastitis, most antibiotics easily penetrate the blood-mammary barrier** and reach high concentrations in the inflamed tissue. In more chronic cases, diffusion of antibiotics depends on the pH of the milk and lipid solubility of the antibiotics. While weak alkaline antibiotics such as clindamycin and erythromycin concentrate better in milk with an acid pH, amoxicillin + clavulanate and cephalosporins reach higher concentrations in milk with an alkaline pH.

■ **In non-septic mastitis, there is no need for antibiotic therapy**. This condition is best treated with continuous drainage of the gland (manual expression or continuous nursing).

DISEASE FACT SHEETS

RESPIRATORY TRACT

DISEASE FACT SHEETS

CANINE RHINITIS

Bacteria involved

Canine chronic rhinitis is not considered a primary bacterial disease, but a secondary bacterial infection following a primary nasal condition. There are no studies on prevalence rates of primary or secondary bacteria associated with canine nasal disease.

Therapeutic approach

Empirical treatment ONLY IF antibiotherapy is necessary

Amoxicillin+clavulanate, doxycycline

Marbofloxacin, enrofloxacin

If insufficient improvement, consider culture and AST of nasal biopsy or nasal flush

Treatment recommendations

Culture and sensitivity testing is **not justified** in most cases of canine nasal disease, but antibiotic treatment of secondary bacterial infections can be necessary.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Culture not recommended	Amoxicillin + clavulanate	12.5-25 mg/kg/12h PO, SC, IV	2-3 weeks
	Doxycycline	5 mg/kg/12h or 10 mg/kg/24h PO	

Second choice antibiotic (without culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Culture not recommended	Marbofloxacin[a]	2 mg/kg/24h PO, SC	2-3 weeks
	Enrofloxacin[a]	5 mg/kg/24h PO, SC	

[a] *Avoid use in growing dogs of large breeds.*

Diagnostic approach

- Canine rhinitis is not considered a primary bacterial disease but a secondary bacterial infection following a primary nasal condition. According to retrospective studies, the most common underlying problems are nasal neoplasia, lymphoplasmacytic rhinitis, nasal foreign body, sinonasal aspergillosis or dental problems (Figure 1)[1,2,3].
- Work-up of nasal disease commonly includes computed tomography, rhinoscopy (Figure 2) and histopathology of nasal biopsies. **Bacterial culture and sensitivity testing of nasal swabs or nasal discharge are not recommended** as

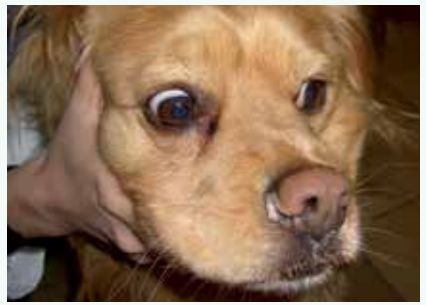

Figure 1 - Dog with chronic purulent nasal discharge. In this case, bacterial infection was secondary to chronic lymphoplasmacytic rhinitis.

DISEASE FACT SHEETS

CANINE RHINITIS

part of the work-up of canine nasal disease, because cultured bacteria most likely represent the physiological microflora of the upper respiratory tract and cannot be differentiated from bacteria that might be involved in infection. *Bartonella*, *Mycoplasma* and *Chlamydophila* species do not seem to play a role in dogs with chronic lymphoplasmacytic rhinitis or nasal neoplasia[4].

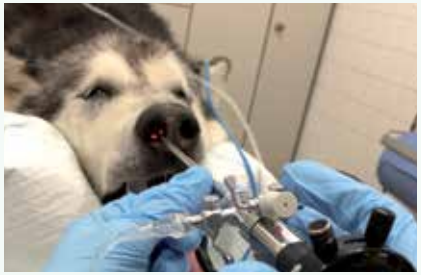

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Figure 2 *- Diagnostic work-up of chronic nasal disease includes rhinoscopic examination of the nasal cavity.*

Reasoning

■ Since canine chronic rhinitis is primarily a non-infectious problem that can be complicated by bacterial infection, treatment has to be directed primarily towards the underlying problem. However, in some case (e.g. chronic lymphoplasmacytic rhinitis, nasal neoplasia), aetiological treatment can be frustrating or even impossible and patients can benefit from treatment of the secondary bacterial infection. Dogs with purulent nasal discharge or neutrophilic inflammation on histopathology of nasal biopsies often respond rapidly to antibiotic treatment, although clinical signs often relapse after discontinuation of antibiotic treatment. Most dogs improve with antibiotic agents such as amoxicillin+clavulanate or doxycycline (first choice) over two to three weeks. Doxycycline might have an additional beneficial effect in dogs with chronic rhinitis due to its anti-inflammatory properties. There are no studies comparing the efficacy of different antibiotics and optimal duration of treatment in dogs with chronic rhinitis.

Difficulties and particularities

■ Many cases of chronic nasal disease improve initially on antibiotic therapy but relapse after discontinuation of antibiotics or even while still under therapy, because the underlying problem is not treated simultaneously. **In case of chronic rhinitis, work-up including imaging and rhinoscopy** is strongly recommended. If cultures are considered, they should be performed on nasal biopsies or nasal flush; however, there are no studies that prove the significance of this diagnostic method in identification of significant bacteria.

CANINE TRACHEOBRONCHITIS

Bacteria involved

Bacteria	Prevalence	Reported associations
Bordetella bronchiseptica	++ (15 to 40 %)	Frequently co-infections with respiratory viruses (canine distemper virus, canine adenovirus type 2, canine parainfluenza virus, canine herpesvirus-1, canine respiratory coronavirus, canine influenza).
Streptococcus spp.	+ (< 10-20 %)	
Mycoplasma cynos	+ (< 10-20 %)	

Antibiotics that can be used

Pathogen 1: *Bordetella bronchiseptica*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	3	
Doxycycline	4	4	
Trimethoprim sulfonamides[a]	3	4	
Marbofloxacin[b]	4	5	
Enrofloxacin[b]	4	5	

Pathogen 2: *Streptococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	5	3	
Cefalexin	4	4	
Doxycycline	3	4	
Marbofloxacin[b]	3	5	
Enrofloxacin[b]	3	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[3].*

[b] *Avoid use in growing dogs of large breeds.*

Therapeutic approach

Empirical treatment
ONLY IF antibiotherapy is necessary

↓

Amoxicillin+clavulanate, doxycycline

↓

Marbofloxacin, enrofloxacin

↓

If insufficient improvement, perform tracheal or bronchial lavage, cytology and C&AST

CANINE TRACHEOBRONCHITIS

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Bordetella bronchiseptica	Amoxicillin + clavulanate	12.5-25 mg/kg/12h PO, SC, IV	7-10 days, until clinical and radiographic cure
	Doxycycline	10 mg/kg/24h PO	
Streptococcus spp.	Amoxicillin	10-15 mg/kg/12h PO	

Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Bordetella bronchiseptica	Trimethoprim sulfonamides[a]	15-30 mg/kg/12h PO, IV	7-10 days, until clinical and radiographic cure
	Marbofloxacin[b]	2 mg/kg/24h PO, SC	
	Enrofloxacin[b]	5 mg/kg/24h PO, SC	
Streptococcus spp.	Cefalexin	15-30 mg/kg/12h PO	
	Doxycycline	10 mg/kg/24h PO	
	Marbofloxacin[b]	2 mg/kg/24h PO, SC	
	Enrofloxacin[b]	5 mg/kg/24h PO, SC	

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks*[3].

[b] *Avoid use in growing dogs of large breeds.*

Diagnostic approach

■ The so-called "Canine Infectious Respiratory Disease" (CIRD) is a **multi-factorial infection** of the upper respiratory tract caused by single or multiple viral and/or bacterial agents[1]. While traditionally canine distemper virus, canine adenovirus type 2, canine parainfluenza virus, canine herpesvirus-1, and *Bordetella bronchiseptica* were the common pathogens associated with this disease complex, recent studies showed involvement of new viral agents such as canine respiratory coronavirus and canine influenza virus as well as the bacterial agents *Streptococcus equi* subspecies zooepidemicus and *Mycoplasma cynos* [2,4]. Co-infections with multiple viral and bacterial pathogens are common in dogs with CIRD[6].

■ While most dogs suffering from viral infections are thought to exhibit rather mild and self-limiting clinical signs, dogs infected with primary or secondary bacterial pathogens frequently show more severe signs and antibiotic therapy is indicated in these cases. If dogs do not respond to empirical antibiotic therapy, tracheal or broncheo-alveolar lavage is indicated to perform cytology, culture, and sensitivity testing.

Reasoning

■ In cases of uncomplicated CIRD, **if dogs are not febrile and show only mild clinical signs, antibiotic therapy is not indicated** and clinical disease is usually self-limiting within seven to ten days. In these cases, disease is most likely caused by respiratory viruses. If clinical signs do not improve or dogs are febrile, anorexic and depressed, antibiotic therapy is indicated.

■ For empirical therapy, amoxicillin+ clavulanate or doxycycline can be used as first-line treatment. If *Mycoplasma* spp. are suspected or diagnosed, doxycycline can be given as first-line and fluoroquinolones as second-line treatment, since these organisms are naturally resistant to ß-lactam antibiotics. If dogs do not show significant improvement following empirical antibiotic therapy, cytology and culture and sensitivity testing of tracheal or broncheo-alveolar lavage fluid (BALF) samples is recommended. *Bordetella bronchiseptica* isolates have shown varying degrees of resistance to doxycycline and aminopenicillins[5].

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Figure 1 *- Nebulization of a pug with acute febrile tracheobronchitis to improve airway humidification.*

■ In addition, supporting therapy such as nebulization (Figure 1), fluid therapy and mucolytic drugs can help to improve mucociliary clearance in dogs with CIRD.

CANINE TRACHEOBRONCHITIS

Difficulties and particularities

- In cases of chronic coughing, uncomplicated viral tracheobronchitis is unlikely and the dog's case should be worked up for this clinical condition. Chronic coughing can have many different reasons, including underlying cardiac disease, chronic inflammatory airway disease, airway collapse or neoplasia.
- Some bacteria such as *Bordetella bronchiseptica* or *Mycoplasma* spp. also have the potential to cause chronic infection and should be identified by bacterial culture. Mycoplasmas require special culture media and might therefore be missed with conventional culture.
- Not all antibiotics penetrate well into the bronchial tree, which can also be a reason for treatment failure in bacterial bronchitis. Fluoroquinolones, trimethoprim sulfonamides and doxycycline can reach higher concentrations in the bronchi than most ß-lactam antibiotics. Although the optimal duration of antibiotic therapy is unknown, **treatment should be given at least until clinical signs disappear**, which is usually after seven to ten days.

If dogs do not show significant improvement following empirical antibiotic therapy, cytology and culture and sensitivity testing of tracheal or broncheo-alveolar lavage fluid (BALF) sample is recommended.

DISEASE FACT SHEETS

FELINE RHINITIS AND TRACHEOBRONCHITIS

Bacteria involved

Acute rhinitis and tracheobronchitis

Bacteria	Prevalence	Possible associations
Bordetella bronchiseptica *Chlamydia felis* (ocular and nasal disease) *Mycoplasma felis*	Prevalence is highly variable depending on background; highest prevalence is expected in group settings (e.g.in shelters and breeding catteries with large numbers of cats)	Viral co-infections (see following pages) Opportunistic secondary bacterial infection with commensal species.

Chronic rhinitis[6,7,11,16]

Bacteria	Prevalence	Possible associations
Pasteurella spp.	13-32%	Prior viral infection with feline herpes virus-1 (FHV) and/or feline calicivirus (FCV); FHV recrudescence possible.
Staphylococcus spp.	13-30%	
Mycoplasma spp.	20-34%	
Escherichia coli	5-40%	
Streptococcus spp.	6-20%	

Chronic bronchitis/asthma with complicating bacterial infection[14,16]

Bacteria	Prevalence
Mycoplasma spp.	++ (15%)
Pasteurella spp.	*3-21%*

Antibiotics that can be used

Doxycyline is the empirical antibiotic of choice for upper and lower bacterial respiratory infection.

Pathogen 1: *Bordetella bronchiseptica*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Doxycycline[c]	5	5	
Amoxicillin + clavulanate	3 - 4	4	
Marbofloxacin	5	5	
Enrofloxacin[a]	5	5	
Pradofloxacin[b]	5	5	

Pathogen 2: *Pasteurella* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Doxycycline[c]	5	5	
Amoxicillin	5	4	
Amoxicillin + clavulanate[e]	5	4	
Marbofloxacin	5	5	
Enrofloxacin[a]	5	5	
Pradofloxacin[b]	5	5	

Pathogen 3: *Mycoplasma* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Doxycycline[c]	Not routinely available	5	
Marbofloxacin		5	
Enrofloxacin[a]		5	
Clindamycin		5	
Pradofloxacin[b]		5	

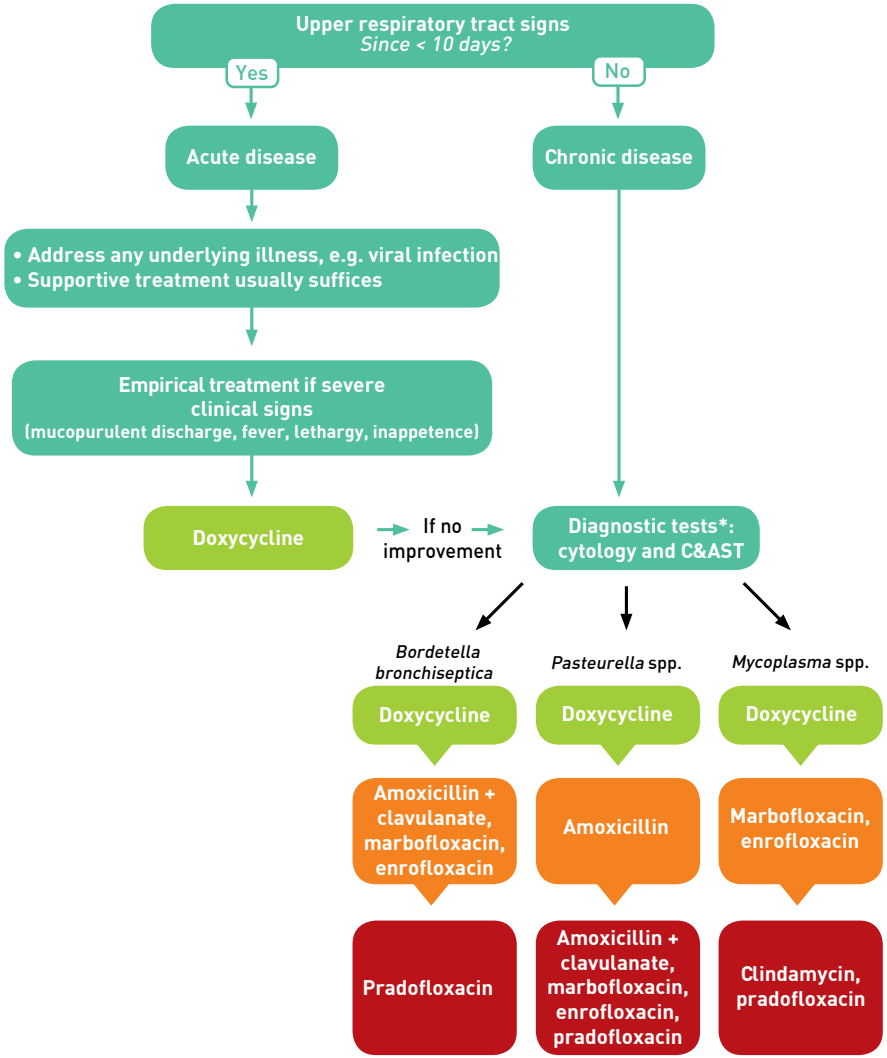
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

For footnotes, see at the end of the chapter.

FELINE RHINITIS AND TRACHEOBRONCHITIS

Therapeutic approach



** See tables for appropriate diagnostic test*

Treatment recommendations

Non-antibiotic treatment may include:

- **Acute rhinitis and tracheobronchitis:** removal of the underlying cause in acute rhinitis where possible (e.g. foreign body), fluid therapy to address dehydration/electrolyte derangements if present, saline nebulisation or steam therapy, frequent cleaning of nares, famcyclovir if acute FHV co-infection, oxygen therapy if dyspnoeic due to concurrent bronchopneumonia, NSAIDs (if hydrated and adequate renal function), nutritional support (e.g. small portions of warm strong smelling foods, mirtazapine, naso-oesophageal/oesophagostomy tube if severe signs).
- **Chronic rhinitis:** nasal flushing under anaesthesia, saline nebulisation or steam therapy, NSAIDs (if hydrated and adequate renal function), nutritional support (as above), famcyclovir if acute FHV recrudescence.
- **Chronic bronchitis/asthma:** anthelmintic treatment to exclude concurrent *Aleurostrongylus abstrusus* infestation in hunting cats (e.g. moxidectin/imidacloprid), bronchodilators (terbutaline in acute scenario), glucocorticoids at anti-inflammatory doses (e.g. inhaled fluticasone, oral prednisolone), avoidance of airway irritants (e.g. smoke, dust mites).

First choice antibiotic (empirical or with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Bordetella bronchiseptica, *Mycoplasma* spp., (*Chlamydia felis*) *Pasteurella* spp.	Doxycycline[c]	10 mg/kg/24h PO	**Acute rhinitis & tracheobronchitis** with *Bordetella bronchiseptica*, *Mycoplasma* spp. or secondary bacterial infection: 7-10 days; *Chlamydia felis*: 4 weeks
			Chronic rhinitis 6 weeks[d]
			Chronic bronchitis/asthma with *Mycoplasma* spp. infection: 6 weeks[d]
			Chronic bronchitis with *Pasteurella* spp. infection: 2-4 weeks

For footnotes, see at the end of the chapter.

DISEASE FACT SHEETS

FELINE RHINITIS AND TRACHEOBRONCHITIS

Second choice antibiotic (with culture and sensitivity testing)

If doxycycline cannot be given empirically

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Bordetella bronchiseptica, *Mycoplasma* spp.	Marbofloxacin	2 mg/kg/24h PO	**Acute rhinitis & tracheobronchitis** with *Bordetella bronchiseptica* or *Mycoplasma* spp. infection: 7-10 days **Chronic bronchitis/asthma** with *Mycoplasma* spp. infection: 6 weeks[d]
	Enrofloxacin[a]	5 mg/kg/24h PO	
Pasteurella spp.	Amoxicillin	10-25 mg/kg/8h IV, PO	**Acute rhinitis & tracheobronchitis** 7-10 days; **Chronic rhinitis** 6 weeks[d] **Chronic bronchitis** with *Pasteurella* spp. infection: 2-4 weeks
	Amoxicillin + clavulanate[e]	20 mg/kg/8h IV 12.5-25 mg/kg/8-12h PO	

For footnotes, see at the end of the chapter.

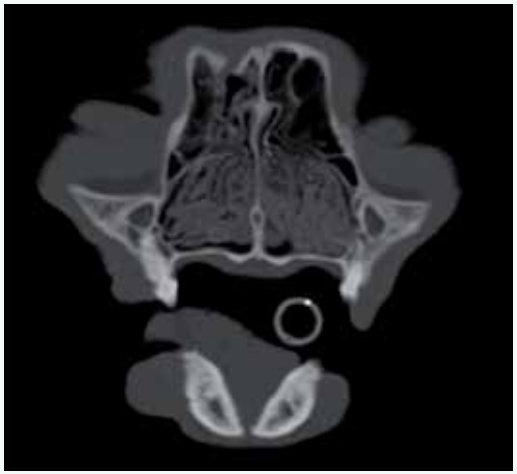


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Figure 1 *- Nasal CT (transverse section) of a cat diagnosed with acute neutrophilic rhinitis; Bordetella bronchiseptica was cultured from a nasal flush and nasal tissue biopsy. The scan image demonstrates a depressed right nasal bone fracture and soft tissue/fluid attenuating material within the nasal meati bilaterally. The fracture was secondary to a catfight.*

Diagnostic approach

Syndrome	Predispositions	Presenting signs may include	Clinical signs may include	Diagnostic tests
Acute rhinitis and tracheobronchitis with **primary** bacterial pathogens e.g. *Bordetella bronchiseptica*, *Mycoplasma felis* (& *Chlamydia felis* - ocular and nasal disease)	Young kittens & cats, multicat household (e.g. shelter, breeding colony), immunocompromised, exposure to recently kennelled dogs.	Sneezing, nasal & ocular discharge, chemosis (with *Chlamydia felis*), coughing, dysphonia, gagging, retching, ptyalism, lethargy, inappetence.	Nasal & ocular discharge, chemosis, blepharospasm (with *Chlamydia felis* especially), submandibular lymphadenopathy, tachypnoea, wheeze/crackles on pulmonary auscultation, increased inspiratory effort, stertor, dehydration, pyrexia.	Oropharyngeal swab for *B. bronchiseptica* PCR &/or culture & sensitivity. Conjunctival swab for *Chlamydia* PCR, *Mycoplasma* spp. PCR; consider FHV & FCV PCRs (common co-infections).
Acute rhinitis and tracheobronchitis with **secondary** bacterial infection	**Rhinitis & tracheobronchitis:** primary viral infection (FHV, FCV). **Rhinitis:** reflux of vomitus via nasal cavity, nasal trauma, neoplasia, fungal infection, oronasal fistula, dental.	As above; ocular involvement with FHV co-infection.	As above; ocular involvement with FHV, oral ulceration with FCV co-infection.	Evaluation for underlying disease e.g. FHV, FCV PCRs; aerobic and anaerobic bacterial culture & sensitivity, *B. bronchiseptica* and *Mycoplasma* spp. PCR on nasal flush/biopsy &/or bronchoalveolar lavage.

Doxycycline is a suitable empirical treatment choice for upper and lower respiratory tract infections however parenteral administration of an alternative antibiotic is required when bronchopneumonia has developed or if the cat resents oral pilling due to sinonasal congestion.

DISEASE FACT SHEETS

FELINE RHINITIS AND TRACHEOBRONCHITIS

Syndrome	Predispositions	Presenting signs may include	Clinical signs may include	Diagnostic tests
Chronic rhinitis	Prior FHV +/- FCV infection; prior fungal infection; idiopathic.	Sneezing (>1month), nasal discharge, +/- epistaxis, inappetence, lethargy, weight loss.	Nasal discharge, loss of air flow via nares, increased inspiratory effort, stertorous respiration, submandibular lymphadenopathy.	Evaluation for underlying disease e.g. FHV & FCV PCRs, imaging skull (x-ray/ CT), rhinoscopy, nasal biopsy (for histopathology); nasal flush/ biopsy for aerobic and anaerobic bacterial culture & sensitivity, *B. bronchiseptica* and *Mycoplasma* spp. PCRs.
Chronic bronchitis/asthma with complicating bacterial infection	Asthma-Siamese and Oriental breeds.	Cough (paroxysmal with terminal retch), acute episodes dyspnoea, exercise intolerance, lethargy, weight loss.	Tachypnoea, dyspnoea, increased expiratory effort, wheeze/crackles on pulmonary auscultation, hypersensitivity over larynx/ trachea.	Evaluation for underlying disease e.g. imaging thorax (x-ray/CT); bronchoalveolar lavage (scope/blind) for cytology, aerobic and anaerobic bacterial culture & sensitivity, *B. bronchiseptica* and *Mycoplasma* spp. PCRs; haematology and serum biochemistry, faecal analysis for lungworm.

Reasoning

Acute rhinitis and tracheobronchitis

■ Infection with feline herpesvirus (FHV) and/or feline calicivirus (FCV) is the most common cause of acute rhinotracheitis; development of secondary opportunistic infection with commensal bacteria is a complicating factor. FHV and/or FCV co-infection with *Bordetella bronchiseptica*, *Chlamydia felis* &/or Mycoplasma felis (*primary pathogens*) is common in the shelter setting[12]. Infection with *Streptococcus canis* and *Streptococcus equi* subsp *zooepidemicus* causing acute URT disease is an emerging problem in multicat settings[2].

■ Antibiotics may not be indicated in all cases; supportive treatment (as above) may be adequate in mild cases in adult cats. Antibiotics should be reserved for when there is a high clinical suspicion of bacterial involvement e.g. when ocular and nasal secretions become purulent and/or when there is a higher potential for the cat to have been infected with primary bacterial pathogens (e.g. from a multicat household, recent rehoming from a shelter or visit to a cattery).

■ **Doxycycline is a suitable empirical treatment for both primary pathogens and opportunistic bacterial infections provided the cat can tolerate oral administration of medication and there is no evidence of bronchopneumonia. In these circumstances parenteral treatment is required**.

■ Infectious rhinitis and tracheobronchitis ("cat flu") is typically diagnosed based on history and clinical signs however evaluation for viral agents, *Bordetella bronchiseptica*, *Chlamydophila felis* and *Mycoplasma felis* infection should be considered, especially in cats from multicat settings to guide duration of antibiotic therapy and household management e.g. *Chlamydophila felis* is treated for at least four weeks and in-contacts should be medicated where there is an endemic infection[4,5].

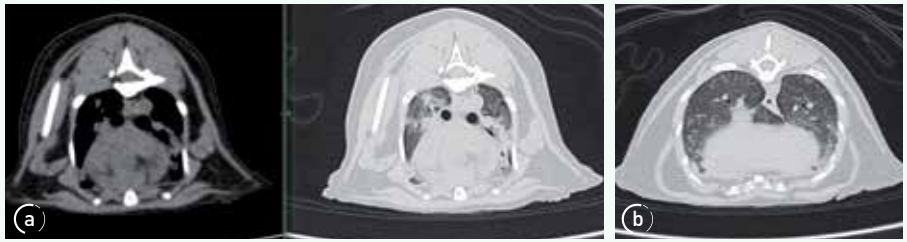

Figure 2 *- a) and b): Thoracic CT scans of a cat diagnosed with severely eosinophilic inflammatory airway disease with secondary Mycoplasma felis and Bordetella bronchiseptica infection. The images demonstrate areas of consolidation particularly in the left cranial lung lobe (caudal portion) and a patchy interstitial (granular-like) pattern in the left caudal lung lobe.*

DISEASE FACT SHEETS

FELINE RHINITIS AND TRACHEOBRONCHITIS

■ Identification of FHV may enable use of anti-viral therapy (e.g. famcyclovir).

Chronic rhinitis

■ The initiating factor is typically prior infection with FHV and/or FCV with subsequent secondary bacterial infection in 65-90% cases[14]. Opportunistic infection with commensal bacteria is associated with altered mucosal and turbinate structure and local immune defences.

■ Potential pathogens include *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus viridans*, *Staphylococcus pseudointermedius*, *Pasteurella multocida*, *Corynebacterium* spp., *Actinomyces* spp., *Bordetella bronchiseptica*, *Mycoplasma* spp., and all anaerobes[6]; similar agents may be involved in acute cases.

■ Empirical antibiotic choices should cover a broad spectrum (aerobic and anaerobic bacteria) with good penetration of bone and cartilage. Doxycycline is a good first choice, alternatives are amoxicillin, amoxicillin+clavulanate and clindamycin. Optimal duration of treatment is unknown.

■ At the time of investigation, a deep nasal flush +/- tissue biopsy should be obtained for culture and sensitivity testing, to guide antibiotic choices since an initial prolonged course of treatment is recommended (e.g. 6 weeks); growth of a single bacterial species is more likely to indicate a pathogen[7]. Nasal swabs are not recommended, due to the likelihood of sampling the commensal flora; it should be noted that published prevalence rates include data based upon nasal swab samples.

Chronic bronchitis/asthma with complicating bacterial infection

■ Altered airway structure and function in inflammatory bronchial disease may predispose to opportunistic bacterial infection and cause acute exacerbations of clinical signs.

■ The role of *Mycoplasma* spp. infection in chronic bronchitis/asthma is not fully understood[14]; *Mycoplasma* spp. may be part of the normal commensal flora of the upper respiratory tract, however identification in the lower airways in the presence of inflammation is considered significant and should be treated[13].

Difficulties and particularities

Acute rhinitis and tracheobronchitis

Co-infection with FHV +/- FCV is common and may be a reason for lack of resolution of signs following appropriate antibiotic treatment.

■ ***Bordetella bronchiseptica***

• Resistance to amoxicillin, trimethoprim sulfonamides and cephalosporins is common.

• Most infections are self-limiting; antibiotic treatment is recommended when there are persistent clinical signs >7-10 days, more severe signs or evidence of bronchopneumonia and is also recommended in young kittens (<6-8 weeks)[19].

■ ***Chlamydia felis***

Associated with primary ocular signs and only mild respiratory signs[4].

■ ***Mycoplasma* spp.**

Lack a peptidoglycan cell wall therefore ß-lactam antibiotics are ineffective; duration of treatment is controversial; sensitivity testing is not routinely available for *Mycoplasma* spp.

Chronic rhinitis

■ Multimodal treatment is required to manage the condition and it is rarely cured; there will be an on-going requirement for medications (intermittent prolonged antibiotic courses, anti-inflammatories, anti-virals if active FHV co-infection) and therapies that help manage nasal secretions (e.g. nebulisation, steam therapy, intermittent nasal flushing under anaesthesia).

■ Considering the recurrent nature of the disease, repeat culture and sensitivity is often declined by owners given the requirement for sedation or anaesthesia to obtain suitable samples. However, an inadequate clinical response to an antibiotic chosen empirically or based on prior sensitivity testing should prompt performing a nasal flush for culture and sensitivity testing, before switching to another antibiotic; development of *Pseudomonas* spp. resistance may occur following treatment with commonly used antibiotics due to elimination of other commensals[14]. Additionally nasal flushing can be therapeutic.

■ Pulse antibiotic therapy has previously been recommended, however it is more likely to lead to the development of antimicrobial resistant commensal bacteria and is not advocated.

Chronic bronchitis/asthma with complicating bacterial infection

■ Airway lavage and sampling for cytology, culture & sensitivity and PCRs should be performed 5-7 days after the antibiotic course has been completed (if signs have improved) to guide further treatment (usually corticosteroids +/- bronchodilators). If severe signs persist, anti-inflammatory steroids are commenced concurrently with antibiotics. It is important to remember that a clinical improvement may not be indicative of successful management of the underlying respiratory disease, due to the cat's ability to mask clinical signs well.

[a] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[b] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

[c] *Doxycycline hyclate/hydrochloride tablets must be followed with water or food to ensure passage into the stomach to prevent development of oesophagitis and/or strictures[3].*

[d] *Note: initial treatment course for chronic rhinitis is prolonged (e.g. 6 weeks), subsequent flare-ups may be managed with shorter courses e.g. 2-4 weeks.*

[e] *Use of a ß-lactamase inhibitor (clavulanate) is not usually required for treatment of Pasteurella spp. infections hence amoxicillin+clavulanate is designated as 3rd choice earlier, however use may be a compromise to achieve patient/owner compliance.*

DISEASE FACT SHEETS

BRONCHOPNEUMONIA AND PNEUMONIA

Bacteria involved

Dogs	Cats
Escherichia coli	*Pasteurella* spp.
Bordetella bronchiseptica	*Bordetella bronchiseptica*
Streptococcus spp.	*Mycoplasma* spp.

Results of bacterial cultures and sensitivity testing differ significantly in different studies and geographical regions.

Antibiotics that can be used

Dogs

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	3	3	
Amoxicillin + clavulanate	4	3	
Doxycycline	3	4	
Enrofloxacin[a]	4	5	
Pradofloxacin[a,b]	4	5	

Pathogen 2: *Bordetella bronchiseptica*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	4	3	
Amoxicillin + clavulanate	4	3	
Trimethoprim sulfonamides[c]	3	3	
Doxycycline	4	4	
Enrofloxacin[a]	4	5	
Pradofloxacin[a,b]	4	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Cats

Pathogen 1: *Pasteurella* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin	4	3	
Amoxicillin + clavulanate	4	3	
Doxycycline	5	4	
Marbofloxacin	5	5	
Pradofloxacin[b]	5	5	

Pathogen 2: *Bordetella bronchiseptica*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	3	
Trimethoprim sulfonamides[c]	3	3	
Doxycycline	3	4	
Marbofloxacin	4	5	
Pradofloxacin[b]	4	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*
[b] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*
[c] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[7].*

BRONCHOPNEUMONIA AND PNEUMONIA

Therapeutic approach

Mild pneumonia (stable patient)

Empirical treatment while awaiting results or if no workup

Doxycycline, amoxicillin ± clavulanate

Marbofloxacin, enrofloxacin

Results of culture and sensitivity
De-escalate if possible, adapt if necessary

Severe pneumonia (unstable patient)

Emergency empirical treatment (IV) while awaiting results

1st choice broad spectrum combination:
Amoxicillin, ampicillin, clindamycin IV
+
Marbofloxacin, enrofloxacin IV*

2nd choice broad spectrum combination:
Amoxicillin, ampicillin, clindamycin IV
+
Gentamicin IV*

Results of culture and sensitivity
De-escalate if possible, adapt if necessary

** Marbofloxacin, enrofloxacin and gentamicin are generally considered second-line antibiotics. However, in emergency situations like these, this is the recommended therapeutic approach.*

Treatment recommendations (mild pneumonia)

First choice antibiotic (with C&AST)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Bordetella bronchiseptica* *Pasteurella* spp.	Amoxicillin + clavulanate	12.5-25 mg/kg/8-12h PO, SC, IV	3-4 weeks, until clinical and radiographic cure
	Doxycycline	5 mg/kg/12h or 10 mg/kg/24h PO	

Second choice antibiotic (with C&AST)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Bordetella bronchiseptica* *Pasteurella* spp.	Marbofloxacin[a]	2 mg/kg/24h PO, SC, IV	3-4 weeks, until clinical and radiographic cure
	Enrofloxacin[a,d]	5 mg/kg/24h PO, SC	
Bordetella bronchiseptica	Trimethoprim sulfonamides[c]	15-30 mg/kg/12h PO, IV	

[a] *Avoid use in growing dogs of large breeds.*
[c] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks*[7].
[d] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

Diagnostic approach

■ Bacterial pneumonia seems more common in dogs than in cats. It can be caused by primary infectious pathogens, aspiration, foreign bodies and by acquired or congenital immune dysfunction. Patients with bacterial pneumonia can exhibit clinical signs such as coughing, dyspnoea, tachypnoea, abnormal lung sounds, lethargy and fever[5,8]. Thoracic radiographs typically display an alveolar lung pattern (Figure 1) and haematology might show leucocytosis with a left shift and toxic changes, although these abnormalities are not present in all cases. In dogs, C-reactive protein can be used to differentiate bacterial pneumonia from tracheobronchitis and inflammatory respiratory conditions[10].

BRONCHOPNEUMONIA AND PNEUMONIA

■ Bacterial pneumonia can be diagnosed by demonstrating suppurative inflammation with intracellular bacteria on bronchoalveolar-lavage-cytology, or if bacterial culture reveals significant bacterial growth (Figure 2, Figure 3). Sampling of the upper respiratory tract for culture and sensitivity testing is not helpful in case of pneumonia, since bacterial growth in the upper airways does not reflect the presence of bacterial pathogens in the lower airways[2]. The most commonly detected bacteria in dogs and cats with lower respiratory tract infections are *E. coli*, *Enterococcus* spp., *Streptococcus* spp., *Staphylococcus* spp., *B. bronchiseptica*, *Pasteurella* spp., and *Mycoplasma* spp. However, results of bacterial cultures and sensitivity testing can differ significantly in different studies and geographical regions[1,4,5,9].

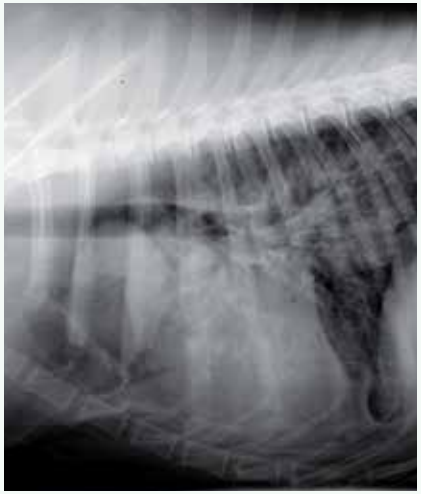

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Figure 1 *- Radiograph showing bronchoalveolar lung pattern in a dog with bacterial pneumonia.*

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Figure 2 *- Blind bronchoalveolar lavage procedure in a cat to obtain material for cytology, culture and sensitivity testing. Sterile sodium chloride solution (0.9%) is applied into the lower airways over a sterile catheter inserted into a sterile endotracheal tube and recovered via collection tube and mechanical suction.*

Reasoning

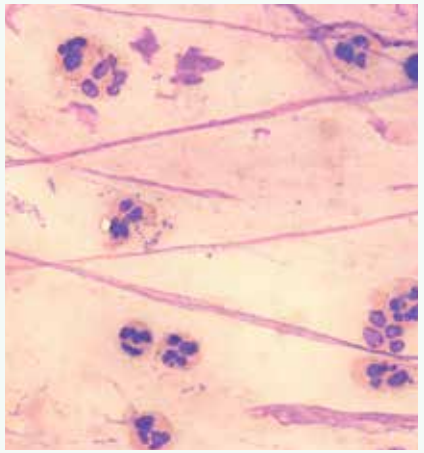

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Figure 3 *- Cytological picture of broncho-alveolar lavage fluid of a dog with pneumonia showing suppurative inflammation with degenerative neutrophils and intracellular bacteria.*

■ Many bacteria show varying degrees of resistance, especially Enterobacteriaceae and *Pseudomonas* spp. Therefore, the best way to choose the appropriate antibiotic therapy for an individual patient would be to obtain a broncho-alveolar lavage fluid sample and perform cytology, culture and sensitivity testing. However, in many patients antibiotic therapy must be initiated without that information due to instability of the patient or the owner declining further testing. In that case, amoxicillin+clavulanate or doxycycline can be a reasonable first-line choice. Doxycycline is especially indicated if *B. bronchiseptica* or *Mycoplasma* spp. infection is suspected, although its effectiveness against other bacteria can be very variable[9]. Many respiratory pathogens are susceptible to fluoroquinolones, which penetrate very well into the respiratory tract; however, they are considered second-line treatment in animals, because of their importance in human medicine.

■ In severely sick animals (severe respiratory compromise, signs of sepsis, see Bacteraemia (sepsis), p.158), a combination of IV ampicillin, amoxicillin+/-clavulanate, or clindamycin in combination with a fluoroquinolone or aminoglycoside can be indicated for empirical therapy, or while awaiting C&ST results. De-escalation should be carried out on the basis of culture and sensitivity testing, if available.

■ **If a patient does not improve three to four days after initiation of empirical antibiotic therapy, bronchoalveolar lavage and culture and sensitivity testing is strongly recommended**. In case of pneumonia following aspiration of foreign material or foreign bodies, good anaerobic coverage should be attempted. Ampicillin, amoxicillin or clindamycin are usually effective against most anaerobic organisms.

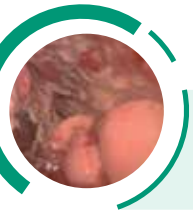
BRONCHOPNEUMONIA AND PNEUMONIA

Difficulties and particularities

- Treatment failure can be linked to several factors. If an underlying problem can be identified (e.g. recurrent aspiration, bronchial foreign body) this needs to be managed as well to prevent recurrence.
- Some pathogens might require specific antibiotics, such as *Mycoplasma* spp., that are resistant to ß-lactams. Furthermore, mycoplasmas require special culture media and might therefore be missed with conventional culture methods.
- Not all antibiotics penetrate equally well into the bronchial tree, which can also be a reason for treatment failure. Fluoroquinolones, trimethoprim-sulfonamide combinations and doxycycline can reach higher concentrations in the bronchi than most ß-lactam antibiotics[3].
- For animals with pneumonia, it has traditionally been recommended to give antibiotic treatment for at least 3-4 weeks, beyond the resolution of clinical signs, laboratory and radiographic abnormalities. However, this recommended time has never been evaluated in studies in dogs and cats, therefore the optimal duration of treatment is unknown and a shorter period of antibiotic treatment might be indicated based on resolution of all these abnormalities.
- Especially in cats, clinical signs of pneumonia such as fever, radiographic changes and left shift can be absent or subtle and patients presenting with cough can be falsely diagnosed with inflammatory bronchial disease[4,6]. Therefore, cats with respiratory signs that do not respond to anti-inflammatory therapy should be evaluated for bacterial pathogens by cytology, culture and sensitivity testing of bronchoalveolar lavage fluid.

Thoracic radiographs are essential for diagnosis, especially in feline patients.

DISEASE FACT SHEETS



PYOTHORAX IN DOGS

Bacteria involved

Bacteria	Prevalence	Reported associations
Pasteurella spp. *Escherichia coli*	++ (15 to 40 %)	Gram-negative aerobes and anaerobes 24%[1] to 31% of cases[8], *Peptostreptococcus* spp. being the most frequent anaerobe (27%) before *Bacterioides* (25%)
Staphylococcus *Corynebacterium*	++ (15 to 40 %)	*Peptostreptococcus*
Nocardia	++ (15 to 40 %)	*Clostridium*

Antibiotics that can be used

If the use of antibiotics is justified:

Pathogen 1: Gram-positive bacteria *(Staphylococcus, Corynebacterium, Nocardia)*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin or ampicillin	3	3	
Amoxicillin + clavulanate	4	3	
Clindamycin	3	5	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a]	4	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: Gram-negative bacteria *(Pasteurella, E. coli...)*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin or ampicillin	3	3	
Amoxicillin + clavulanate	4	3	
Marbofloxacin[a] / Enrofloxacin[a]	4	5	
Cefalexin / Cefadroxil	3	3	
Cefovecin[b]	5	3	
Aminoglycosides[c]	5	3	

Pathogen 3: Obligate anaerobes *(Peptostreptococcus, Bacteroides...)*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	3	
Metronidazole	4	3	
Clindamycin	4	5	
Pradofloxacin[a,d]	4	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*

[b] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[c] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html)*

[d] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

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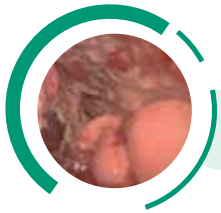
Figure 1 *- Conservative treatment of pyothorax. This dog (in sternal recumbency), has 2 chest drains placed, the pleural cavity is lavaged with saline. Note the appearance of the pleural effusion before initiating the lavage.*

DISEASE FACT SHEETS



PYOTHORAX IN DOGS

Therapeutic approach

Emergency empirical treatment (IV)
while awaiting results of culture and sensitivity

Broad spectrum combination therapy:
Amoxicillin, ampicillin, amoxicillin+clavulanate
+
Clindamycin

or

Alternative combination:
Clindamycin, metronidazole
+
Marbofloxacin, enrofloxacin

or

Alternative combination:
Amoxicillin, ampicillin, amoxicillin+clavulanate
+
Marbofloxacin, enrofloxacin
(+ metronidazole)

↓

Results of culture and sensitivity
De-escalate if possible, adapt if necessary
(avoid combinations)
Continue antibiotherapy for 4-6 weeks

Treatment recommendations

■ Non-antibiotic treatment: imaging, chest drainage with large-bore drains and pleural lavage, mediastinal surgical debridement.

■ **Sampling for culture and sensitivity testing is highly recommended before starting antibiotic therapy**. It should be done with the initial sample collected for the diagnostic thoracocentesis and from tissue collected during exploratory thoracotomy. Initial clinical management may indicate the use of IV antibiotics. The use of aminoglycosides should be carefully evaluated as the general condition of the patient might make these antibiotics unsuitable due to their inherent toxicity.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Gram-positive (Gram-negative) and anaerobes	Amoxicillin + clavulanate	12.5-25 mg/kg/12h	4 weeks minimum (2 weeks after imaging resolution)
Staphylococcus, Gram-negative bacteria	Marbofloxacin[a]	2 mg/kg/24h	
	Enrofloxacin[a]	5 mg/kg/24h	
Obligate anaerobes	Metronidazole	15 mg/kg/12h	
ß-haemolytic *Streptococcus*, *Pasteurella*	Potentiated sulfonamides[e]	15-30 mg/kg/12h	
Gram-positive and obligate anaerobes	Clindamycin	5.5-11 mg/kg/12h	

[a] *Avoid use in growing dogs of large breeds.*

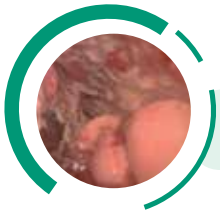
[e] *Trimethoprim sulfonamide: avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks*[5].

Diagnostic approach

■ Pyothorax is a septic pleural effusion. Common clinical signs associated with pyothorax are lethargy, dyspnoea and hyperthermia. The diagnosis is based on the findings of a purulent pleural effusion after thoracocentesis. Imaging (radiographs, CT, ultrasonography) is useful to support the diagnosis.

■ Pyothorax may be secondary to lung infection, perforation/damage to the thoracic wall, migration of foreign material, perforation/damage to the oesophagus, or could be a postoperative complication of thoracic surgery. In dogs, it is often

DISEASE FACT SHEETS



PYOTHORAX IN DOGS

suspected that pyothorax is secondary to the migration/inhalation of a grass awn although physical evidence of intrapleural vegetal material is rare.

- There are three stages: exudative (stage I), transitional to fibrinopurulent (stage II), organising or consolidative phase (stage III).
- Traditionally, pyothorax in dogs was treated conservatively using chest drainage and antibiotics. Clinical experience shows that dogs are frequently presented with advance stage II or stage III, making conservative treatment unsuccessful as **thorough evacuation of the pleural cavity is difficult due to fibrinous obstruction of the drains**. Therefore, surgical debridement needs to be considered in dogs. For some authors, surgery carries the best chance of recovery. However, there is still no consensus on whether surgery should be performed as a first-intention treatment or only after conservative management has failed.

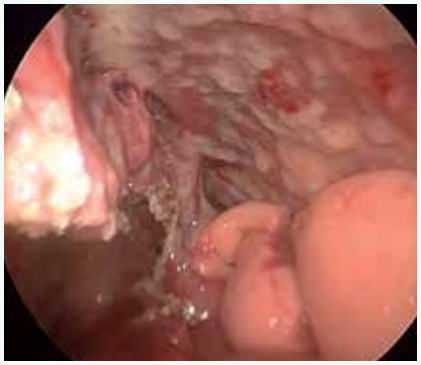


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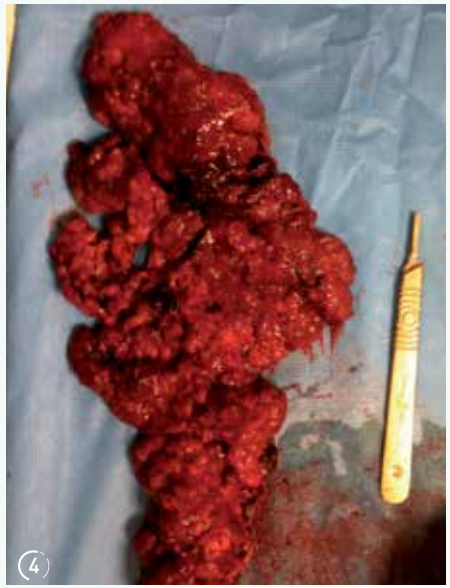
Figure 2 - Thoracoscopic observation of a pyothorax. Note the severity of the mediastinal inflammation and the fibrinous deposits.

- **In dogs, the therapeutic approach of this disease differs markedly from that in cats** (see Pyothorax in cats, p.122).

Reasoning

- Although one study reported good results with a single pleural evacuation by thoracocentesis followed by long-term antibiotics[3], the usual recommendation is to establish pleural drainage with a large-bore chest tube, usually bilaterally, in association with surgical debridement if needed. Fluid samples should be collected for cytology (Gram stain) and culture and sensitivity testing. Pleural lavage is also recommended. Although there is no definitive protocol for this, there is consensus to use plain saline rather than an antiseptic or antibiotic solution. In general, drainage is discontinued once daily effusion drops below 2 to 5 ml/kg/24 hours.
- Treatment of the underlying cause, if necessary by surgery (lung abscess, oesophageal damage) is an essential part of the treatment.
- Parenteral antibiotics (via the intravenous route) are recommended until the dog is stable, rehydrated and eating voluntarily.
- Bacteria involved in pyothorax are highly diverse. Therefore, broad-spectrum antibiotics are recommended until results of the culture and sensitivity tests are known (note that, in up to 40% of the cases, samples may yield no growth).
- In pyothorax, mixed populations of aerobes and anaerobes are commonly found (*Pasteurella* spp., *Nocardia* spp. and *E. coli* were the most frequently observed aerobes when multiple strict anaerobes were cultured). Monotherapy is therefore rarely considered sufficient to treat pyothorax. Recommended combination therapies include: aminopenicillins+clindamycin, fluoroquinolones+clindamycin, fluoroquinolones+aminopenicillins. Several retrospective studies in the UK and the US showed that treatment was successful in associating amoxicillin + clavulanate with enrofloxacin and metronidazole. See recommendation R.12.
- Although often efficient *in vitro*, **aminoglycosides are not suitable for the treatment of pyothorax due to their potential toxicity** in septic patients.
- Treatment is usually conducted for a minimum of 4 weeks; cessation of antibiotic treatment 2 weeks after full resolution as confirmed by imaging.



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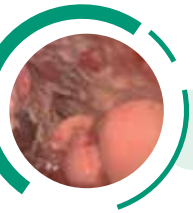
Figures 3 - 4 - This dog underwent open surgical debridement of a pyothorax. A sternotomy was necessary to access both sides of the chest. Two large drains have been placed. Note the appearance and the size of the inflamed/infected mediastinum.



PYOTHORAX IN DOGS

Difficulties and particularities

■ Pyothorax is usually diagnosed as an acute infection with systemically affected patients requiring long-term treatment. Usually, treatment is started by the IV route for several days until efficacy is confirmed. This is followed by oral medication for 4 to 6 weeks.

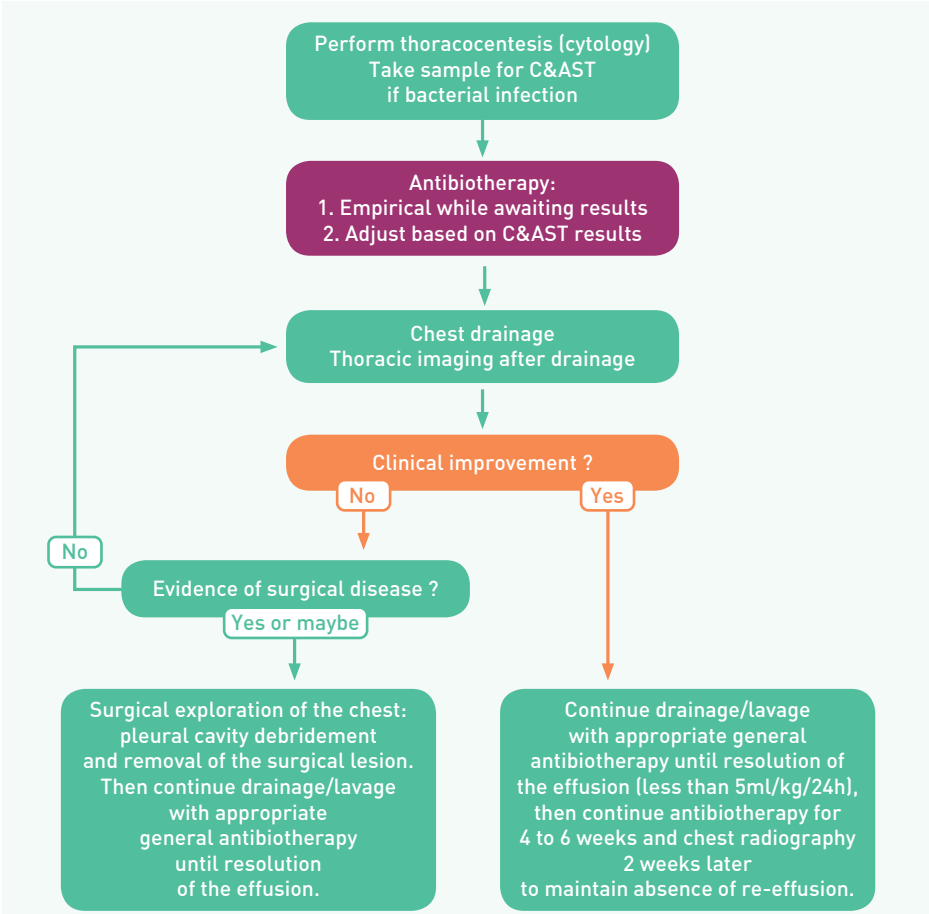
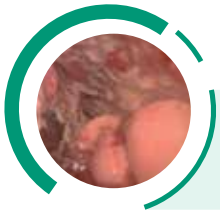


Figure 5 - *Clinical approach to pleural effusion.*

DISEASE FACT SHEETS



PYOTHORAX IN CATS

• Pyothorax is frequently due to a polymicrobial infection of obligate anaerobes +/- facultative anaerobes.

Bacteria involved[3, 5, 7, 10, 14, 15]

Bacteria	Prevalence	Reported associations
Pasteurella spp.	12-63%	Polymicrobial infections with obligate and facultative anaerobes are very common.
Bacteroides spp.	13-42%	
Fusobacterium spp.	13-23%	

Antibiotics that can be used[6, 11, 12, 15]

Empirical choice: amoxicillin+clavulanate or ampicillin/amoxicillin/clindamycin + fluoroquinolone (marbofloxacin preferred) pending culture and sensitivity results.

Pathogen 1: *Pasteurella* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Ampicillin / Amoxicillin	4	4	
Amoxicillin + clavulanate	5	4	
Marbofloxacin	5	5	
Enrofloxacin[a]	5	5	
Cefovecin[b]	4	4	
Pradofloxacin[c]	5	4	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[b] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[c] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

Pathogen 2: Obligate anaerobes (e.g. *Bacteroides* spp., *Fusobacterium* spp., *Clostridium* spp.)

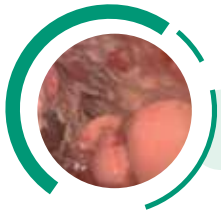
Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Ampicillin / Amoxicillin	4	4	
Clindamycin	4	4	
Metronidazole	5	4	
Amoxicillin + clavulanate	5	4	
Cefovecin[b]	3	4	
Pradofloxacin[c]	5	4	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[b] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[c] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

The primary cause of feline pyothorax is considered to be a parapneumonic infection secondary to inhalation of oropharyngeal bacteria and pneumonia e.g. following upper respiratory infection with FCV or FHV.



PYOTHORAX IN CATS

Therapeutic approach

Pleural fluid analysis suggestive of pyothorax
Empirical treatment while awaiting results of culture and sensitivity

Amoxicillin ± clavulanate

or

Ampicillin, amoxicillin, clindamycin
+
Marbofloxacin, enrofloxacin*

Results of culture and sensitivity
De-escalate if possible, adapt if necessary (avoid combinations)
Continue antibiotherapy for 4-6 weeks

Pasteurella spp.	Obligate anaerobes (false negatives possible)
Amoxicillin, ampicillin, amoxicillin+clavulanate	**Amoxicillin, ampicillin, clindamycin**
Marbofloxacin, enrofloxacin	**Amoxicillin + clavulanate, metronidazole**
Pradofloxacin, cefovecin	**Pradofloxacin, cefovecin**

** Ampicillin, amoxicillin and clindamycin are generally considered first-line antibiotics. However, this broad-spectrum combination includes fluoroquinolones, and is therefore less preferred.*

Treatment recommendations

- **Adjunctive (non-antibiotic) treatment**: oxygen therapy (if dyspnoeic), intravenous fluid therapy to address shock +/- dehydration, electrolyte and acid-base derangements if present, thoracocentesis to remove pleural exudate, placement of thoracostomy tubes for intermittent pleural drainage and lavage with sterile isotonic fluids, nutritional support (if inappetent), analgesia.
- **Empirical choice pending culture and sensitivity**: amoxicillin+clavulanate or a combination of ampicillin/amoxicillin/clindamycin + fluoroquinolone (marbofloxacin preferred).
These choices will be effective against obligate and facultative anaerobic organisms (including *Pasteurella* spp.) and should be administered parenterally (preferably intravenously if appropriate formulation available).
- **The antibiotic(s) will then need to be modified**:

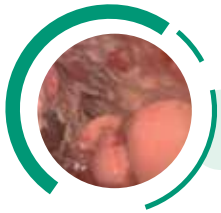
• according to culture and sensitivity results (include anaerobic cover; false negative anaerobic cultures possible).

• by formulation, moving to oral preparations once the cat is stable, hydrated and eating.

- Duration of treatment is typically extended (e.g. 4-6 weeks) and guided by repeat thoracic imaging to check for resolution of effusion. Current recommendations are for antibiotics to be continued for at least one week following resolution of thoracic effusion.

First choice antibiotic (empirical choice or after culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Pasteurella spp.	Ampicillin (sodium)	10-20 mg/kg/8h IV; not recommended for oral treatment	4-6 weeks
	Amoxicillin	10-25 mg/kg/8h IV, PO	
	Amoxicillin + clavulanate	20 mg/kg/8h IV 12.5-25 mg/kg/8-12h PO	
Obligate anaerobes	Ampicillin (sodium)	10-20 mg/kg/8h IV; not recommended for oral treatment	
	Amoxicillin	10-25 mg/kg/8h IV, PO	
	Clindamycin	5.5-11 mg/kg/12h IV, PO	



PYOTHORAX IN CATS

Second choice antibiotic (following culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Pasteurella spp.	Marbofloxacin	2 mg/kg/24h IV, SC, PO	4-6 weeks
	Enrofloxacin[a]	5 mg/kg/24h SC, PO	
Obligate anaerobes	Amoxicillin + clavulanate	20 mg/kg/8h IV 12.5-25 mg/kg/8-12h PO	
	Metronidazole	10-15 mg/kg/12h IV, PO	

[a] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

Diagnostic approach

■ Presenting signs may include dyspnoea, tachypnoea, cough, inappetence, lethargy, dehydration, ptyalism and weight loss[14].

■ Abnormalities on physical examination may include signs of shock (pallor, tachycardia or bradycardia, poor peripheral pulses, hypothermia) and dehydration, muffled heart sounds, loss of pulmonary sounds in the ventral thorax, pyrexia and reduced body condition[2,14].

■ The diagnosis is confirmed by:

• Identification of pleural effusion – using thoracic ultrasound, radiography/computed tomography (if patient is stable enough) or blind thoracocentesis.

• Pleural fluid analysis (cytology and biochemical) - septic exudate (predominantly neutrophils (degenerate) +/- intracellular and extracellular bacteria) with high protein levels (>30g/l).

• Pleural fluid bacterial culture - aerobic and anaerobic; pay particular attention to maximising potential for identification of anaerobes (see Recommendation R.4) and consider PCR for *Mycoplasma* spp.

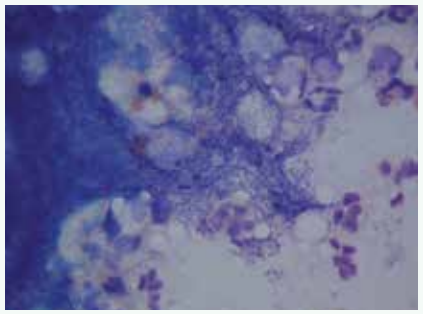


Figure 1 *- Cytology of thoracic effusion in a cat diagnosed with pyothorax. The image shows degenerate neutrophils and a branching fusiform bacillus confirmed as Actinomyces spp. on bacterial culture (modified Wright's stain, x 1000).*

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Reasoning

■ Successful management of pyothorax requires systemic antibiotic treatment and thoracic drainage (typically with indwelling thoracostomy tubes; small bore 14G tubes are well tolerated by cats) +/- lavage with isotonic fluids.

■ Parenteral antibiotics (via the intravenous route) are recommended until the cat is stable, rehydrated and eating voluntarily.

■ Empirical treatment can be chosen on the basis of cytological examination of the effusion, pending culture results; Gram-negative bacilli most often are *Pasteurella* spp., infection with *Enterobacteraciae* spp. are infrequent compared to canine pyothorax.

■ **The antibiotic should be effective against anaerobic bacteria since the majority of infections are due to obligate and/or facultative anaerobes**; amoxicillin+clavulanate or a combination of ampicillin/amoxicillin/clindamycin with a fluoroquinolone (marbofloxacin preferably) are reasonable empirical choices initially.

■ Culture and sensitivity testing should be performed upon samples of pleural effusions obtained before antibiotic treatment is administered and the antibiotic should be modified according to culture results.

■ *Nocardia* spp. infections may occur but may not be recovered on bacterial culture. Grossly there may be sulphur granules in the effusion and cytologically *Nocardia* spp. appear as Gram-positive acid-fast bacteria. Treatment of choice is trimethoprim sulfonamide.

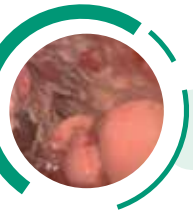
■ Adjunctive care is very important in addressing fluid, acid-base and electrolyte derangements, providing nutritional support (e.g. feeding via a naso-oesophageal tube) and analgesia (e.g. opioid analgesia buprenorphine 0.01-0.02mg/kg IV q6-8hrs) whilst thoracostomy tubes are *in situ*.

■ Surgical treatment is indicated in the following scenarios: identification of a foreign body, pulmonary or mediastinal abscess, failure of medical therapy (e.g. lack of cytological improvement, persistent infection or effusion after 5-7days).

Difficulties and particularities

■ The primary cause of feline pyothorax is considered to be a parapneumonic infection secondary to inhalation of oropharyngeal bacteria and pneumonia e.g. following upper respiratory infection with FCV or FHV. Other causes include bite wounds, migrating foreign bodies, haematogenous spread, oesophageal perforation and bacterial infection secondary to parasitic visceral migration[3].

■ A search for an underlying cause that may need specific treatment should be made, by repeating thoracic imaging following complete evacuation of the



PYOTHORAX IN CATS

pleural exudate.

- Pyothorax may be unilateral or bilateral depending upon whether the mediastinum is intact.
- Following placement of a single thoracostomy tube, imaging should be repeated to ensure that effective drainage has been achieved and if not, bilateral thoracostomy tubes should be placed. Failure of medical treatment thereafter may occur due to pocketing or inspissation (thickening) of exudate, pulmonary or mediastinal abscess, inadequate length of antibiotic treatment or lack of culture to guide appropriate antibiotic choice.
- The prognosis for pyothorax is generally good, however patients with indwelling thoracostomy tubes and those requiring surgical treatment typically need intensive care treatment and monitoring.

Adjunctive care is very important in addressing fluid, acid-base and electrolyte derangements, providing nutritional support (e.g. feeding via an naso-oesophageal tube) and analgesia (e.g. opioid analgesia buprenorphine 0.01- 0.02mg/kg IV q6-8hrs).

DISEASE FACT SHEETS

DERMATOLOGY

SURFACE AND SUPERFICIAL PYODERMA

- In **surface pyoderma** (e.g. skin fold pyoderma, "hot spots" and bacterial overgrowth), topical disinfectant treatment suffices. No systemic antibiotics should be used.
- In **superficial pyoderma** (e.g. impetigo, bacterial folliculitis, mucocutaneous pyoderma), topical disinfectants usually suffice. If this fails and systemic antibiotic treatment is required, see Deep pyoderma p.138.

Bacteria involved

Bacteria	Prevalence	Reported associations
Staphylococcus spp.	+++++ *(> 75 %)*	Bacterial overgrowth can be associated with *Malassezia pachydermatitis*
Escherichia coli	+ *(< 10-20 %)*	When present, *E. coli* and *Pseudomonas* are often in association with *Staphylococcus* spp.
Pseudomonas aeruginosa	+ *(< 10-20 %)*	

Antiseptics that can be used

Antibiotics should preferably **not be used** in cases of surface and superficial pyoderma. **Antiseptics should be used instead.**

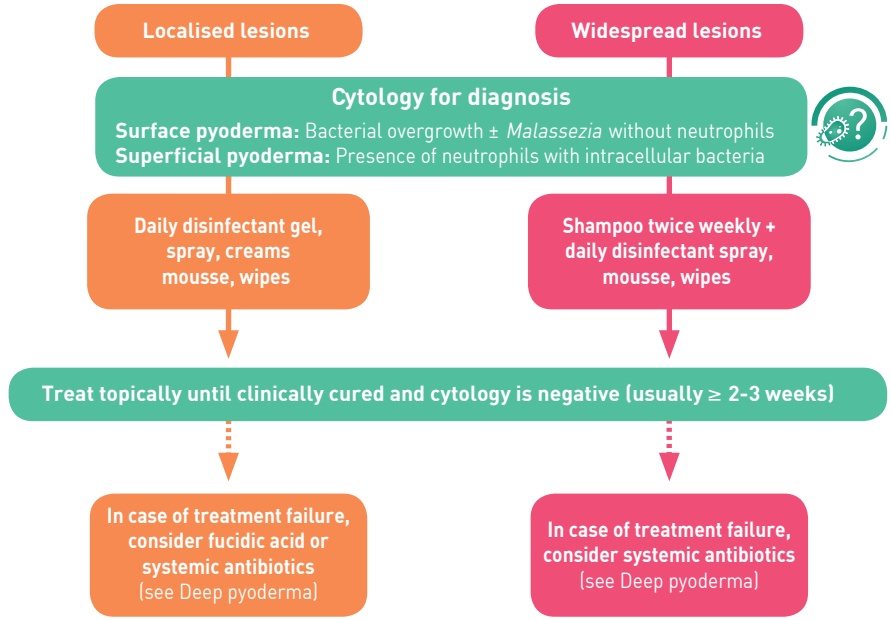
Antiseptic that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Chlorhexidine 2-4% shampoo	5	topical	
Chlorh.* wipes, mousse, spray	5	topical	
Benzoyl peroxide 2.5%	3	topical	
Ethyl lactate 10%	3	topical	Limited clinical evidence
Triclosan	5	topical	No clinical evidence
Hypochlorous acid	5	topical	No residual efficacy, use daily
Bleach 4%	5	topical	Daily soak
Benzalconium chloride	4	topical	No clinical evidence
Medical honey	5	topical	Do not mix with other topicals
Fusidic acid	5	topical	For localized lesions only
Mupirocin	5	topical	Not licensed for animal use

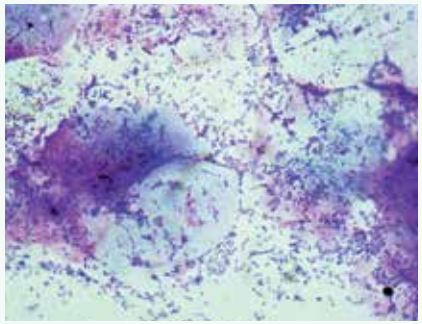
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

* Chlorhexidine

Therapeutic approach





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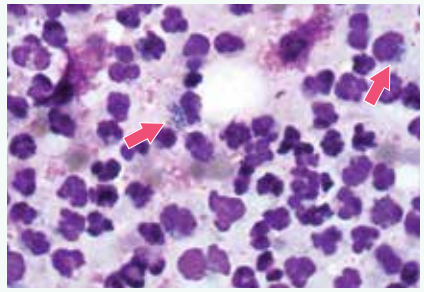
Cytological appearance of surface pyoderma: numerous bacteria are observed with the presence of mature corneocytes but with the absence of inflammatory cells.



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Cytological aspect of the content of a pustule in a case of superficial pyoderma: several neutrophils, including degenerate neutrophils, are visible, some of which contain coccal bacterial elements in the cytoplasm (arrows) (Diff Quik®, 1000x).

SURFACE AND SUPERFICIAL PYODERMA

Treatment recommendations

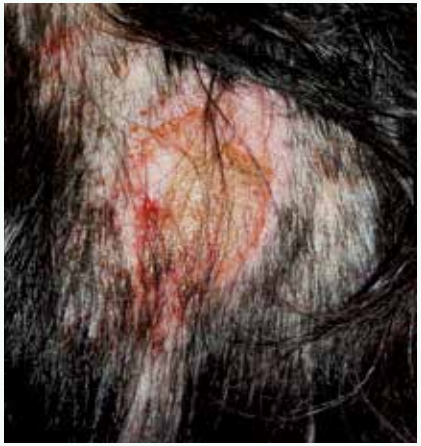
■ **Topical or systemic antibiotics should not be used as a first-line treatment** in cases of bacterial overgrowth, intertrigo (skin fold pyoderma) and hot spots (pyotraumatic pyoderma) or in cases of uncomplicated superficial pyoderma (superficial folliculitis, impetigo, mucocutaneous pyoderma). **Antiseptic products should be used instead.**

■ For widespread lesions, an antiseptic shampoo with a 10-minute contact time should be used at least twice weekly. A disinfectant spray, mousse or wipe should be applied daily on the lesions on the days that the animal is not shampooed.

■ In more localised lesions, antimicrobial sprays, gels, lotions, creams, mousses or wipes can be used daily.

■ Topical therapies should be applied until clinically and cytologically cured (usually 2-3 weeks).

■ **Topical or systemic antibiotics** should be used **only if topical antiseptic therapy is not successful or not possible**. Topical antibiotics are to be preferred to systemic ones. Please refer to Deep pyoderma, p.138, for the systemic antibiotic choice.



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Hot spot (pyotraumatic dermatitis) on the back of a dog with flea bite allergy.

■ The **identification and control of an underlying disease** (allergy, endocrine, anatomic defect, etc.) is mandatory for therapeutic success and in the prevention of relapse.

Diagnostic approach

■ Like any other dermatological condition, the approach to surface and superficial pyoderma should include a detailed history and a general examination. As most pyoderma is a complication of an underlying disease, this should be identified and controlled in order to obtain a long-lasting cure. A cytological examination of the skin surface or exudate will confirm the diagnosis by showing the presence of bacteria without neutrophils (in surface pyoderma) or bacteria within (phagocytosed by) neutrophils (in superficial pyoderma, such as impetigo, bacterial folliculitis and mucocutaneous pyoderma).

How to sample for cytological examination

In case of suspect bacterial overgrowth, cytological samples can be collected directly from plain skin by impression of a glass slide or (better) of a clear adhesive tape. Material can also be collected by superficial scraping smeared on a glass slide.

Skin folds can be sampled with a dry or moist cotton swab, which is then rolled (not smeared!) on the glass slide.

Cytology from **open exudative lesions**, collarettes or from under a crust is performed with an impression smear. **Pyotraumatic dermatitis** is sampled by an impression smear on the moist surface. **Pustules** are carefully opened with a small needle and their content is gently pressed on a glass slide without smearing, in order to avoid artefacts (nuclear stripes).

Glass slides and clear adhesive tape can be stained with rapid haematology kits and examined in the practice.

Reasoning

■ In all cases of surface and superficial pyoderma, whether localised or generalised, **topical treatment with disinfectants is preferred, in order to decrease antibiotic use and the development of bacterial resistance**. Chlorhexidine has demonstrated excellent *in vitro* and *in vivo* efficacy and has residual activity on the skin. Furthermore, it is **effective on both sensitive and multidrug-resistant staphylococci, with no need for bacterial culture and sensitivity testing prior to starting treatment**. Resistance to chlorhexidine is very rare in staphylococci, although it has been described in *Pseudomonas*. Other topical disinfectants are either more irritant, less effective or have insufficient published evidence of their efficacy.

■ Topical antibiotics should only be used in localized, deep lesions, where disinfectants would fail to penetrate.

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Skin fold pyoderma on the muzzle of a pug.

DISEASE FACT SHEETS

SURFACE AND SUPERFICIAL PYODERMA

Difficulties and particularities

- Shampoos should be applied at the right concentration, massaged in the hair and on the skin and left in place for 10 minutes. Animals should then be rinsed well. A cleansing shampoo can be used before the disinfectant product. Failure to use the right concentrations or to leave in place long enough can lead to insufficient efficacy.
- In case of treatment of localised lesions with creams or gels it is important to prevent the animal from licking them. An Elizabethan collar or distraction (e.g. playing, walking, feeding) for 10-15 minutes can be of help.
- Bacterial biofilm formation is a frequent cause of treatment failure, as it prevents antibiotics and antiseptics from reaching the causative agents. Also, antibiotics that act during bacterial replication will not be effective because in biofilms microorganisms are usually quiescent and do not multiply. Specific cleaning agents with biofilm disrupting properties, such as Tris-EDTA or detergent scrubs should be used in these cases.
- Underlying disease: superficial and surface pyoderma are generally complications of an underlying disease. If this is not identified and controlled, the skin infection will not cure or will relapse. Common underlying diseases are atopic dermatitis, food or fleabite allergy, parasites (*Demodex*), endocrine disease and keratinization disorders.

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Folliculitis of bacterial and parasitic origin (demodicosis).

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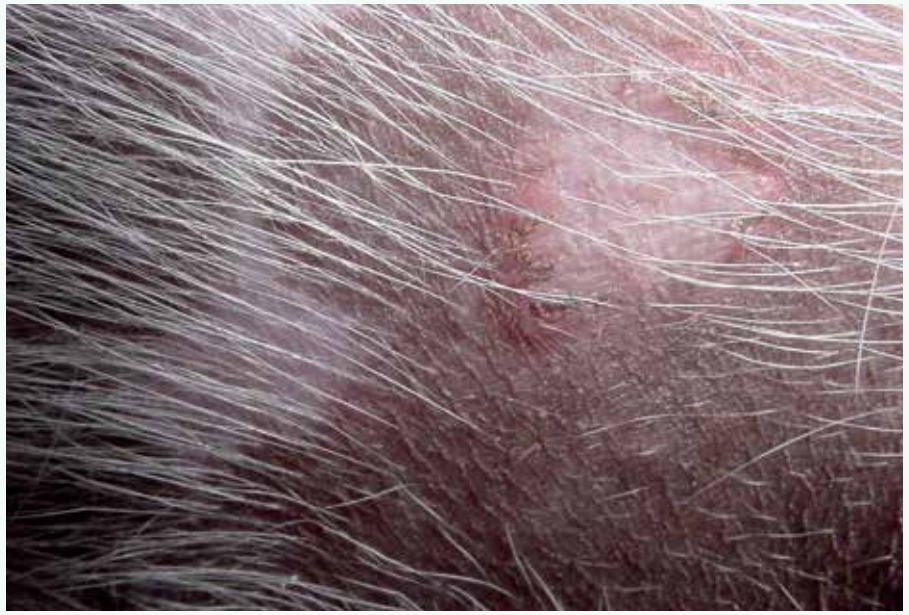
Bacterial overgrowth with hyperpigmentation, lichenification and a moist greasy exudate on the abdomen of an allergic German Shepherd dog.



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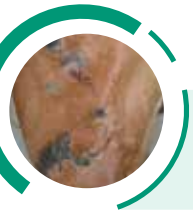
Collarette, a typical lesion of superficial pyoderma.

DISEASE FACT SHEETS



DEEP PYODERMA

- This chapter deals with the diagnosis and treatment of **deep pyoderma** (furunculosis, ulceration, draining tracts with a haemopurulent exudate...).
- For **superficial pyoderma** (e.g. impetigo, bacterial folliculitis, mucocutaneous pyoderma), topical treatment usually suffices (see previous chapter). However, in case systemic antibiotic treatment is required, the recommendations in this chapter can be followed.

Bacteria involved

Bacteria	Prevalence
Meticillin sensitive *Staphylococcus* spp.	++++ (>60%)
Meticillin resistant, multidrug-resistant *Staphylococcus* spp.	+ (<10-20%)
Pseudomonas	+ (< 10-20 %)
Escherichia coli	+ (< 10-20 %)

Antibiotics that can be used

Systemic antibiotics that can be used (for topical therapy, see Surface and superficial pyoderma, p.132).

Pathogen 1: Meticillin sensitive *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin +/- clavulanate	5	4	
Cefalexin / Cefadroxil	5	5	
Clindamycin	3	4	
Cefovecin[a]	5	5	

For footnotes, see at the end of the chapter.

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: Meticillin (multidrug) resistant *Staphylococcus* spp.

Antibiotics to be used only if sensitivity tests show resistance to the antibiotics mentioned for meticillin-sensitive antibiotics.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Trimethoprim sulfonamides[b]	3	4	
Doxycycline / Minocycline	4	5	
Marbofloxacin[c] / Enrofloxacin[c,d]	4	4	
Pradofloxacin[c,e]	4	4	
Rifampicin[f]	3	5	
Chloramphenicol / Florfenicol	3	4	
Gentamicin[g]	5	4	
Amikacin[g]	5	4	

Pathogen 3: *Pseudomonas aeruginosa*

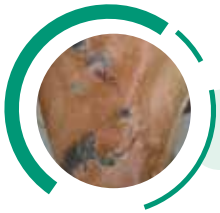
Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Marbofloxacin[c] / Enrofloxacin[c,d]	4	4	
Gentamicin[g]	5	4	
Amikacin[g]	5	4	
Ticarcillin + clavulanate	4	4	
Imipenem	5	5	

Pathogen 4: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	3	4	
Cefalexin / Cefadroxil	3	5	
Trimethoprim sulfonamides[b]	4	3	
Cefovecin[a]	5	5	
Marbofloxacin[c] / Enrofloxacin[c,d]	4	5	
Pradofloxacin[c,e]	4	5	
Rifampicin[f]	5	5	
Aminoglycosides[g]	5	4	

For footnotes, see at the end of the chapter.

DISEASE FACT SHEETS



DEEP PYODERMA

Therapeutic approach

Therapeutic approach for deep pyoderma and for superficial pyoderma that is unresponsive to topical treatment.

Cytology for diagnosis
- presence of intracellular bacteria (pyoderma)
- identification of cocci and/or rods

Empirical treatment only in case of:
- superficial pyoderma with failed topical treatment
- first occurence of superficial coccal infections

Amoxicillin + clavulanate, cefalexin, cefadroxil, clindamycin

In case of treatment failure, perform culture and AST

Culture & AST in case of:
- deep pyoderma
- presence of rods
- relapsing pyoderma (cocci and rods)
- failure of empirical treatment
- previous antibiotic treatment

Amoxicillin + clavulanate cefalexin, cefadroxil, clindamycin

Enrofloxacin, marbofloxacin, cefovecin

Pradofloxacin, rifampicin, chloramphenicol, fosfomycin, aminoglycosides

Treat until one week beyond clinical cure for superficial pyoderma and two weeks beyond clinical cure for deep pyoderma (usually at least 3-4 weeks)

Treatment recommendations

- Topical non-antibiotic treatment should be preferred in cases of superficial pyoderma (see previous chapter). **Systemic antibiotics should be reserved for cases of topical treatment failure or in the case of deep pyoderma**.
- The administration of empirical antibiotics (without culture and sensitivity testing) is acceptable only in first-occurrence superficial coccal pyoderma.
- In all other cases, bacterial culture and sensitivity testing should be performed first .
- Systemic antibiotics should be administered for a minimum of 3 weeks in the case of superficial pyoderma and 4 weeks in deep pyoderma.

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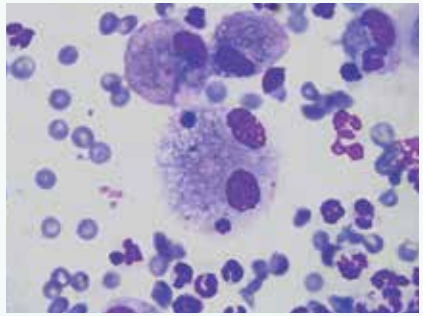
Pedal cellulitis.



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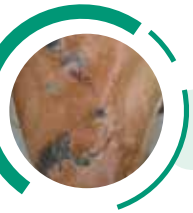
Cytological aspect of a lesion of deep pyoderma: both neutrophils and activated macrophages are visible (pyogranulomatous inflammation), but no bacteria, in spite of positive bacterial culture results (Diff Quik®, 1000x).

DISEASE FACT SHEETS



DEEP PYODERMA

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Meticillin sensitive *Staphylococcus* spp.	Amoxicillin+clavulanate	12.5-25 mg/kg/12h PO	1 week beyond cure for superficial pyoderma, 2 weeks beyond cure for deep pyoderma.
	Cefalexin	15-30 mg/kg/12h PO	
	Cefadroxil	15-30 mg/kg/12h PO or 30-40 mg/kg/24h PO	
	Clindamycin	5.5-11 mg/kg/12h PO	

Second choice antibiotic (following culture and sensitivity testing): only if bacteria are resistant to the first-choice antibiotics.

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Meticillin-resistant, multidrug-resistant *Staphylococcus* spp. *E. coli* *Ps. aeruginosa*	Trimethoprim sulfonamides[b]	15-30 mg/kg/12h PO	1 week beyond cure for superficial pyoderma, 2 weeks beyond cure for deep pyoderma.
	Marbofloxacin[c]	2 mg/kg/24h PO	
	Enrofloxacin[c,d]	5 mg/kg/24h PO	
	Doxycycline	10 mg/kg/24 h PO	
	Minocycline	20 mg/kg/12h PO	
	Rifampin[f]	5-10 mg/kg/12h PO	
	Chloramphenicol	50 mg/kg/8h PO	
	Fosfomycin	50 mg/kg/12h PO	
	Gentamicin[g]	10-15 mg/kg/24h SC in dogs 5-8 mg/kg/24h SC in cats	
	Amikacin[g]	15-30 mg/kg/24h SC in dogs 10-15 mg/kg/24h SC in cats	
	Cefovecin[a]	8 mg/kg single dose SC (14d)	Minimum 2 injections, suitable only in case of compliance problems

For footnotes, see at the end of the chapter.

Diagnostic approach

- Deep pyodermas are characterised clinically by furunculosis, ulceration or draining tracts with a haemopurulent exudate, as seen in cases of pyodemodicosis, callus infection and interdigital nodules.
- The approach to all types of pyoderma starts with a detailed history and a general examination. As most pyodermas are complications of an underlying disease (allergy, demodicosis, endocrinopathy, keratinization disorder) this should be identified and controlled in order to obtain a lasting cure. In superficial pyoderma, cytological examination of the exudate will confirm the diagnosis by the presence of microorganisms within neutrophils. In deep pyoderma, cytology will probably show pyogranulomatous inflammation but bacteria are not always seen. In these cases, bacterial culture will confirm the diagnosis. In any case, bacterial culture and sensitivity testing is mandatory for the correct antibiotic choice.

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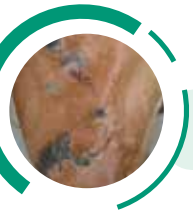
Deep callus infection on an elbow.

How to sample for cytology and bacterial culture

Cytology from open exudative lesions, from collarettes or from under a crust is performed on an impression smear. Pustules are carefully opened with a small needle and their content is gently pressed on a glass slide without smearing in order to avoid artefacts (nuclear stripes).

Sampling for bacterial culture from superficial lesions is ideally performed by opening an intact pustule and collecting the pus with a sterile cotton swab. In the absence of intact pustules, the sterile swab can be rubbed along the edges of a collarette, from under a crust or from open exudative lesions. Sampling for bacterial culture from deep lesions should best be performed by fine needle aspiration from the depth of a lesion or by skin biopsy, after surface disinfection. Collecting exudate expressed from the depth of a lesion by squeezing it is also acceptable.



DEEP PYODERMA

Reasoning

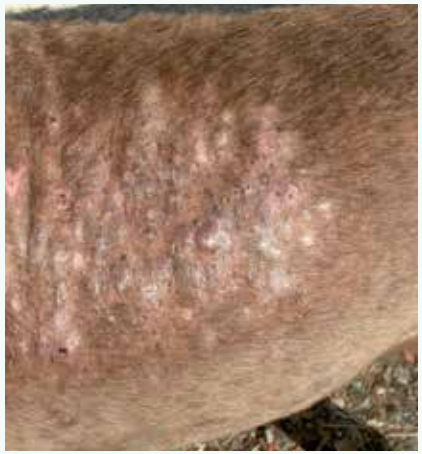
■ In the case of deep pyoderma or unsuccessful topical treatment of superficial pyoderma, systemic therapy is justified. The antibiotic of choice should be based on bacterial culture and sensitivity testing. The only exception would be first-occurrence superficial coccal pyoderma, in animals that were not treated with antibiotics before. In this case, empirical therapy with first-generation cephalosporins, amoxicillin+clavulanate or clindamycin can be tried. In case of failure of empirical antibiotic treatment, deep pyoderma, recurrent infections or the presence of rods in cytology, antibiotics should always be chosen following bacterial culture and sensitivity testing and following current guidelines. **Second-line antibiotics should be used only in case of resistance to first-line drugs**, while third-line antibiotics should only be used in case of resistance to first and second-line antibiotics.

Difficulties and particularities

■ Treatment failure in the case of superficial and deep pyoderma may be due to:

- wrong diagnosis (e.g. the pustular eruption is not due to impetigo but to pemphigus foliaceus),
- undetected or untreated underlying disease (e.g. atopic dermatitis, demodicosis),
- insufficient duration of antibiotic treatment (e.g. interrupted as soon an improvement is observed),
- incorrect administration (dosage, intervals, on an empty *vs.* full stomach, poor owner compliance),
- ineffective antibiotic (bacterial resistance).

■ In some cases of deep pyoderma, such as callus pyoderma or interdigital furuncolosis, it can be useful to decrease the inflammation with a short course of corticosteroids (1mg/kg/24h for 5 days) or long-term immunomodulatory drugs (e.g. ciclosporine 5mg/kg/24h).



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Furunculosis.

[a] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[b] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks [28].*

[c] *Avoid use in growing dogs of large breeds.*

[d] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[e] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

[f] *Hepatotoxic, refer to National regulations regarding use.*

[g] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

DISEASE FACT SHEETS

OTITIS EXTERNA AND MEDIA

Bacteria involved

Bacteria	Prevalence
Staphylococcus spp.	++++ (> 60 %)
Pseudomonas aeruginosa	++ (15 to 40 %)
Proteus mirabilis	+ (< 10-20 %)
Escherichia coli	+ (< 10-20 %)
ß-haemolytic streptococci	+ (< 10-20 %)
Klebsiella spp.	+ (< 10-20 %)

Reported associations
Bacterial otitis is often polybacterial
Otic bacterial overgrowth can be associated with *Malassezia* spp. yeasts

Antibiotics that can be used (topically)

Topical antibiotics are only to be used if there is no evidence of a ruptured tympanic membrane and/or otitis media.

Systemic antibiotics should be used **only following bacterial culture and susceptibility testing** in case of a ruptured tympanic membrane and/or otitis media. In this case refer to antibiotics described in Deep pyoderma, p.138.

Pathogen 1: *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Neomycin	5	topical; Inactivated in pus	1st line
Fusidic acid	5	topical	1st line
Framycetin	5	topical	1st line
Florfenicol	5	topical	1st line
Gentamicin[a]	5	topical	2nd line
Marbofloxacin / Enrofloxacin	5	topical	2nd line
Pradofloxacin	5	topical	Last resort
Amikacin[a]	5	topical	Last resort

[a] *Do not mix with acidic cleaners.*

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: *Pseudomonas aeruginosa*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Polymixin B	5	topical; Inactivated in pus	1st line
Silver sulfadiazine	5	topical	1st line
Gentamicin[a]	5	topical	2nd line
Marbofloxacin / Enrofloxacin	5	topical	2nd line
Pradofloxacin	5	topical	Last resort
Amikacin[a]	5	topical	Last resort
Ticarcillin	5	topical	Last resort
Ceftazidime	5	topical	Last resort

[a] *Do not mix with acidic cleaners.*

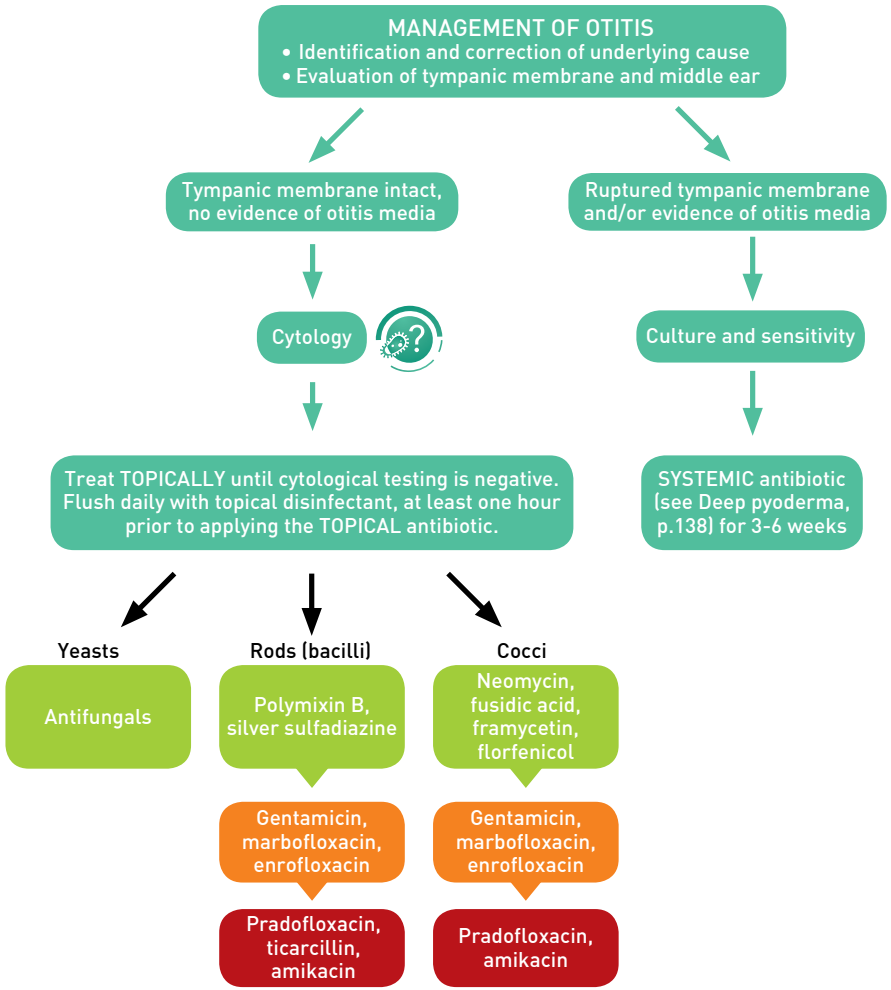
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

A cytological examination of the otic exudate will determine the presence and the nature of the microorganisms (yeasts or bacteria, cocci or rods, mixed infections) and of pus (presence of neutrophils).

OTITIS EXTERNA AND MEDIA

Therapeutic approach



Treatment recommendations

- **Otologic examination and cytological sampling should be performed in every otitis case:** the former to determine if the tympanic membrane is intact, the second to determine the micro-organism involved in the infection.
- If there is no evidence of a ruptured tympanic membrane or otitis media, a topical antibiotic will be sufficient, until cytology becomes negative.
- The ears should be flushed as necessary with a disinfectant solution prior to application of topical antimicrobial therapy, to be continued for one month beyond obtaining a negative cytology.
- Systemic and/or topical corticosteroids are needed in case of oedema, tissue proliferation and ear canal stenosis, for a minimum of 2 weeks.
- The identification and control of the predisposing, primary and perpetuating factors is mandatory for the successful treatment of otitis.
- In severe cases with unsuccessful treatment, consider referral to a specialist (who may consider surgery).

How to sample for cytological and bacterial culture

For cytological and culture samples from the vertical canal, a cotton swab is simply inserted in the ear (no sedation required). For samples from the horizontal ear canal or from the bulla, the animal has to be anaesthetised and samples should be taken under video-otoscopic guidance.

Diagnostic approach

- Like any other dermatological condition, the approach to otitis should include a detailed history and a general examination. As most otitis is a complication of an underlying disease, this should be identified and controlled in order to obtain a lasting cure. An otoscopic examination (preferably after a thorough ear flushing) will determine if the tympanic membrane is intact, and thus if systemic antibiotics will be needed or if topicals suffice.
- A cytological examination of the otic exudate will determine the presence and the nature of the microorganisms (yeasts or bacteria, cocci or rods, mixed infections) and of pus (presence of neutrophils). In case a systemic antibiotic is needed (ruptured tympanic membrane, otitis media), then sampling for bacterial culture and sensitivity testing is pivotal for the choice of the systemic antibiotic.

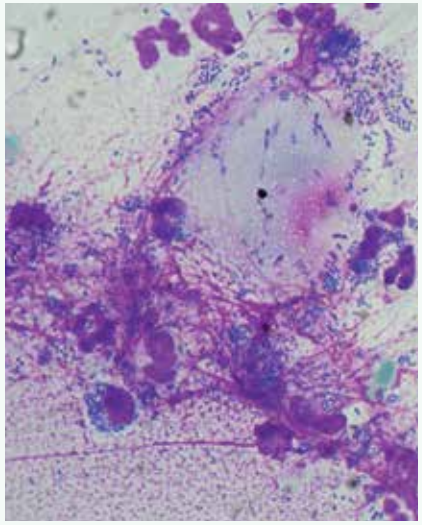
OTITIS EXTERNA AND MEDIA

Reasoning

■ If the infection is limited to the external ear (otitis externa), i.e. if the tympanic membrane is not ruptured and there is no evidence of otitis media, topical antibiotic treatment (chosen according to the guidelines) is usually sufficient. This is because, **after topical application, the antibiotic concentration present in the external ear canal is many times above the MIC of any bacteria**.

■ In any other case, a systemic antibiotic, chosen following sensitivity testing and guidelines for deep pyoderma (previous chapter) should be administered for 3-4 weeks, together with the topical therapy.

■ Other important aspects of otitis treatment include daily ear flushing with a disinfectant and astringent solution and the administration of potent topical or systemic corticosteroids, to decrease inflammatory changes that may hinder the healing of the ear canal.



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The cytological appearance of Pseudomonas otitis: numerous bacterial rods are visible inside neutrophils with degenerate nuclei, attached to a large corneocyte in the middle. (Diff Quik®, 1000x).

Difficulties and particularities

Frequent causes of treatment failure are:

■ **Incorrect ear cleaning and poor owner compliance:** deep ear cleaning is very important in otitis. It should be performed by the veterinarian, preferably under general anaesthesia and analgesia, at the start of treatment and then daily by the owners. Use a disinfectant, cleaning and drying solution containing chlorhexidine, tris-EDTA (particularly in the case of Gram-negative bacteria), acids and/or alcohols. Topical treatment containing an antibiotic and a corticosteroid should be applied after about one hour. In case of suspected low owner compliance or pain on application of topical medication, then a topical leave-on gel with one week's duration can be applied instead of eardrops and daily washing.

■ **The presence of otitis media**, even with an apparently intact tympanic membrane, will hinder the cure and predispose to frequent relapses. A (video) otoscopic examination will permit the identification of a ruptured or convex tympanic membrane, both indicative of otitis media. Diagnostic imaging such as open mouth RX, bullae ultrasound, CT scan or MRI allow identification of damage to the bulla and otitis media.

■ **Bacterial biofilm formation** is a frequent cause of treatment failure because it hinders antibiotics and antiseptics reaching the causative agents. Also, antibiotics that act during bacterial replication will not be effective, because in biofilms, microorganisms are usually quiescent and do not multiply. Specific cleaning agents with biofilm-disrupting properties, such as acetyl cysteine or tris-EDTA should be used in these cases.

■ **Underlying disease:** otitis is always a complication of an underlying disease and if this is not identified and controlled, the ear disease will not cure or will relapse frequently. Common underlying diseases are atopic dermatitis, food allergy, foreign bodies, ear canal masses (e.g. nasopharyngeal polyps in cats), parasites (*Otodectes* or *Demodex*), endocrine disease and keratinization disorders.

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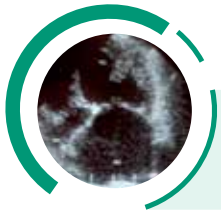
Suppurative otitis externa with erosive lesions of the ear canal following infection with Proteus mirabilis.

■ **Recalcitrant *Pseudomonas* otitis** can be a challenge, in that it almost always causes tympanic membrane perforation and otitis media and is caused by multidrug resistant bacteria. Dogs with *Pseudomonas* otitis suffer from a severely purulent, erosive-ulcerative, extremely painful ear disease with a very strong foul-smelling odour. Deep ear cleaning, analgesics, corticosteroids (prednisolone 1-2mg/kg for 2 weeks, then every 48h), topical and systemic antibiotics are needed for a minimum of 3-4 weeks. Consider referral to a specialist.

INTERNAL MEDICINE

DISEASE FACT SHEETS



PREVENTION OF INFECTIOUS ENDOCARDITIS

Luckily bacterial endocarditis is rare as it is potentially fatal.

• In animals which are at risk from endocarditis, pre-operative antibiotic **prophylaxis** is indicated.

• For **treatment** of infectious endocarditis, see Bacteraemia (sepsis), p.158. Antibiotherapy is indicated, based on a blood culture.

Bacteria involved

Bacteria	Prevalence
Streptococcus spp.	+++ (45-50 %)
Staphylococcus spp.	++ (20 %)
Escherichia coli	+ (10 %)

Treatment recommendations

Bacteria	Antibiotics that can be used	Dosage	Duration of treatment
Staphylococcus spp.	Amoxicillin ± gentamicin[a]	10 mg/kg/12h 8 mg/kg/8h	An injection before surgery or oral treatment
Streptococcus spp.	Amoxicillin ± clavulanate	10 mg/kg/12h 12.5 mg/kg/12h	

[a] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

Diagnostic approach

■ Bacterial endocarditis is a rare disease in dogs, but one which can be life-threatening. Transient or persistent bacteraemia may result in valvular lesions.

■ The bacterium in question can be one that is normally present in the mucous membranes of the ear, nose, throat (ENT) or digestive tract. Valvular damage and other congenital or acquired heart diseases (hypertrophic cardiomyopathy, valve dysfunction) are considered important risk factors.

■ In humans, oral streptococci are involved in 25% of cases, streptococci of a digestive origin in 20% of cases and staphylococci in 15 to 30 % of cases (*S. aureus* and *S. epidermidis* essentially). It should be noted that 10 to 20% of cases of infectious endocarditis have a negative blood culture.

■ In dogs, the same bacteria are often involved, as well as *Escherichia coli* or anaerobic bacteria[6]. *Bartonella* may also play a role in the development of infectious endocarditis in dogs[8].

■ Bacterial endocarditis is very difficult to diagnose. The diagnosis is based on a combination of major criteria (positive blood cultures, echocardiographic signs of infectious endocarditis) and minor criteria (predisposing cardiac factors, a heart murmur suddenly appearing or getting worse, fever, various immunological and microbiological phenomena).

■ All infectious sites where trauma of the oropharyngeal, gastrointestinal or urogenital mucous membranes occurs can lead to bacteraemia, which may lead to bacterial endocarditis. Oral infections in the context of severe periodontal illness are the most studied scenario in dogs. Periodontal disease, once established, provokes a discharge of endotoxins (LPS) and inflammatory cytokines which can initiate and exacerbate the outbreak of heart disease (atherogenesis, thromboembolism). Bacteria from dental plaque enter the blood stream and their platelet-aggregation properties contribute to the development of endocarditis, blood clots, coronary artery occlusion and heart attacks in humans[2].

■ In one study[2], 10% of the small dogs suffering from moderate to severe periodontal disease had echocardiographic and systemic signs compatible with bacterial endocarditis. Over 80% of dogs with a severe periodontal disease had at least one cardiac modification.

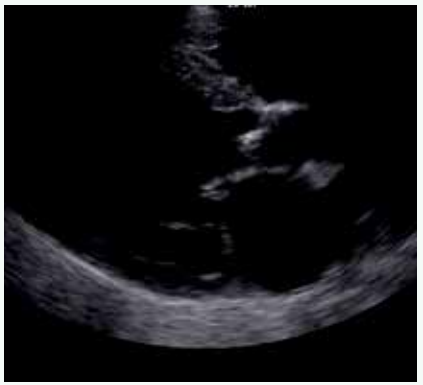


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Figure 1 *- Endocarditis. Right parasternal view (five chamber long-axis) with vegetation on the septal aortic valve in a (febrile) boxer with acute congestive heart failure associated with severe aortic regurgitation.*

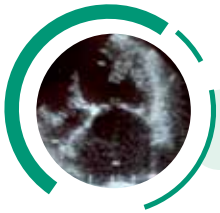
Therapeutic choices

■ Prevention of bacteraemia, which may lead to bacterial endocarditis, consists of eradicating all potential infectious entry sites, as previously noted.

■ In this scenario, antibiotic prophylaxis is recommended prior to any intervention that is likely to facilitate the passage of bacteria into the bloodstream.

■ According to the recommendations of AFSSAPS[1] published in 2001 for human

DISEASE FACT SHEETS



PREVENTION OF INFECTIOUS ENDOCARDITIS

medicine, standard prophylaxis of infectious endocarditis requires a single dose of antibiotic administered orally one hour before surgery, with a prescription of a 2 g dose of amoxicillin for an adult and 50 mg/kg for a child. In the case of an allergic reaction to ß-lactams, clindamycin can be used. If prophylaxis must be administered parenterally, it is recommended to administer amoxicillin during the hour prior to the operation (in a drip given for 30 minutes of 2 g IV for an adult and 50mg/kg IV for a child, then 1g orally for the adult and 25 mg/kg for a child, 6 hours later).

- In humans, in the face of strong evidence or the confirmed presence of bacterial endocarditis, anti-infectious treatment is implemented, consisting of high-dose, long-term antibiotherapy using amoxicillin combined with gentamicin or vancomycin, depending on the bacteria involved.

- **Animals suffering from advanced periodontal disease, with cardiac anomalies (heart murmur, cardiac valve and wall anomalies...) are at risk of bacterial endocarditis**. If such animals need to undergo a dental or oral intervention, antibiotic prophylaxis is indicated with amoxicillin administered intravenously. Anti-infectious treatment consists of high-dose, long-term antibiotherapy using notably amoxicillin combined with gentamicin, to be adapted depending on the blood culture results[7].

Difficulties and particularities

- In humans, the need for antibiotic prophylaxis in patients at risk of bacterial endocarditis is controversial. Two recent meta-analyses revisited this issue and confirmed certain contradictory aspects, but nevertheless proposed some recommendations. The effectiveness of antibiotic prophylaxis using penicillin has not been demonstrated in patients at risk from bacterial endocarditis[5]. However, such antibiotic prophylaxis is recommended in patients suffering from underlying cardiac conditions and in the case of oral surgery. It seems prudent to administer specific antibiotic prophylaxis in patients with a past history of bacterial endocarditis, with prosthetic heart valves, or patients that need to undergo periodontal (in particular periapical) or implant surgery[3,9]. On the other hand, antibiotic prophylaxis specific to bacterial endocarditis does not appear to be justified in patients undergoing surgery of the urogenital or digestive tracts[9].

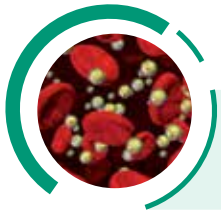
- Recent veterinary studies illustrate this contradictory situation. An epidemiological study of around 60 000 dogs confirmed that the presence of severe periodontal disease is significantly associated with increased risks of cardiovascular disease, such as bacterial endocarditis and cardiomyopathy. It showed that the risk of bacterial endocarditis is six times greater in dogs suffering from severe periodontal disease, compared to the rest of the population[4]. On the other hand, a retrospective study of 76 dogs suffering from bacterial endocarditis did not establish an association between bacterial endocarditis and a past history of infection or oral surgery[9]. As for humans, in the absence of a consensus, it would seem prudent to recommend antibiotic prophylaxis for bacterial endocarditis in patients suffering from cardiovascular disease when they need to undergo invasive oral surgery, in particular in cases of advanced periodontal disease.

Also, it seems prudent to consider that animals suffering from advanced periodontal illness, with cardiac anomalies (heart murmur, heart wall or valve anomalies...) are at-risk patients for bacterial endocarditis.

- In humans, infection prophylaxis in case of joint replacements is identical to that used for infectious endocarditis.

Animals suffering from advanced periodontal disease and cardiac anomalies (e.g. myxomatous mitral valve disease) are at risk of bacterial endocarditis.

DISEASE FACT SHEETS



BACTERAEMIA (SEPSIS)

Bacteria involved[2,3,4]

Bacteria	Prevalence	Reported associations
Gram-negative bacteria (*E.Coli most common*)	+++ canine (31-46%) +++ feline (43%)	Polymicrobial infections with Gram-negative and anaerobic bacteria are commonly associated with gastrointestinal tract perforation
Gram-positive bacteria (*Staphylococcus* spp. and *Streptococcus* spp. most common)	++++ canine (36-68%) +++ feline (45%)	Infections arising from the respiratory, genitourinary and gastrointestinal tract typically involve Gram-negative bacteria
Obligate anaerobes (e.g. *Clostridium* spp.)	+ canine (12-31%) + feline (12%)	Infections arising from the integument typically involve Gram-positive bacteria

Antibiotics that can be used

Pathogen 1: *Escherichia coli* (Gram-negative)

Antibiotics that can be used	*In vitro* sensitivity	Treatment choice
Amoxicillin	3	
Amoxicillin + clavulanate	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	
Cefalexin	2	
Gentamicin[c]	3 - 4	
Pradofloxacin[a,d]	4	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Note: In vitro sensitivities are estimates based on data[2,3,8,9]; sensitivities may vary locally.

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*
[d] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

Pathogen 2: *Staphylococcus* spp. (Gram-positive)

Antibiotics that can be used	*In vitro* sensitivity	Treatment choice
Amoxicillin + clavulanate	4	
Cefalexin / Cefazolin / Cefalothin / Cefadroxil	4	
Marbofloxacin[a] / Enrofloxacin[a,b]	5	
Pradofloxacin[a,d]	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

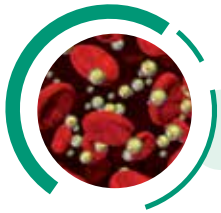
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 3: Obligate anaerobes

Antibiotics that can be used	*In vitro* sensitivity	Treatment choice
Amoxicillin	4	
Ampicillin	4	
Clindamycin	4	
Amoxicillin + clavulanate	4 - 5	
Metronidazole	5	
Pradofloxacin[a,d]	5	

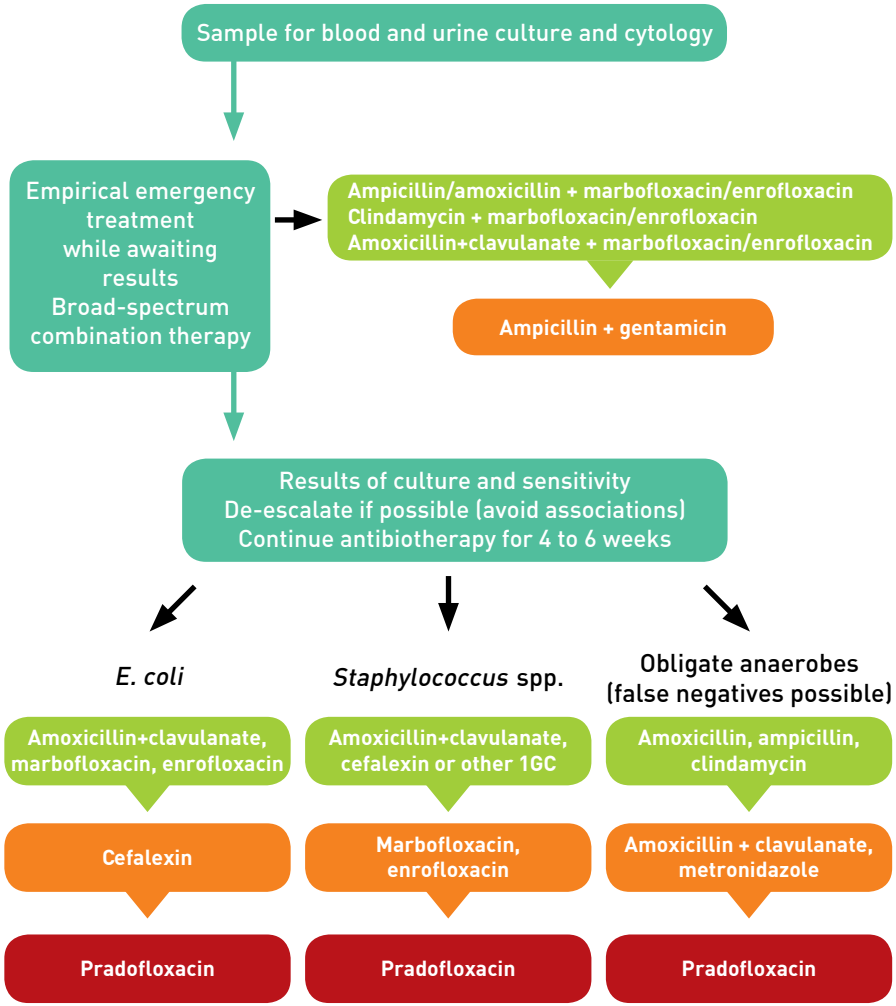
Note: In vitro sensitivities are estimates based on data[2,3,8,9]; sensitivities may vary locally.

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*
[d] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*



BACTERAEMIA (SEPSIS)

Therapeutic approach



Treatment recommendations

■ **Non-antibiotic treatment**:

• Identification of the source of bacterial infection and surgical debridement or resection (where possible) are the priorities of treatment, once the patient has been stabilised.

• Shock, acid-base and electrolyte derangements with appropriate fluid resuscitation and replacement must be addressed.

• Analgesia, oxygen therapy and vasopressors may be indicated.

First choice antibiotic combination (empirical/with C&AST)

Ampicillin/amoxicillin + fluoroquinolone, clindamycin + fluoroquinolone, or amoxicillin + clavulanate + fluoroquinolone, using the following doses:

Pathogen involved	Antibiotics that can be used in combination	Dosage	Duration of treatment
Gram-positive aerobic bacteria e.g. *Staphylococcus* spp. *Streptococcus* spp. Anaerobic bacteria e.g. *Clostridium* spp. Gram-negative aerobic bacteria e.g. *E. coli*	Ampicillin (sodium)	10-20 mg/kg/8h IV, not recommended for oral use	IV until patient is stable, hydrated and eating. Further treatment according to underlying disease.
	Amoxicillin	10-25 mg/kg/8h IV, PO	
	Clindamycin	5.5-11 mg/kg/12h IV, PO	
	Amoxicillin + clavulanate	12.5-25 mg/kg/8-12h IV, PO	
	Marbofloxacin[a]	2 mg/kg/24h IV, PO	
	Enrofloxacin[a,b]	5 mg/kg/24h IV, PO	

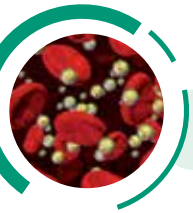
Second choice antibiotic combination (empirical/with C&AST)

Ampicillin + gentamicin, using the following doses:

Pathogen involved	Antibiotics that can be used in combination	Dosage	Duration of treatment
Gram-positive aerobic, Gram-negative aerobic and anaerobic bacteria	Ampicillin (sodium)	10-20 mg/kg/8h IV, not recommended for oral use	IV until patient is stable, hydrated and eating. Further treatment according to underlying disease.
	Gentamicin[c]	5-10 mg/kg/24h slow IV (over 30minutes), IM, SC	

For footnotes, see at beginning of the chapter.

DISEASE FACT SHEETS



BACTERAEMIA (SEPSIS)

Diagnostic approach

■ Bacteraemia is the presence of viable bacteria within the bloodstream. Bacteraemia may be associated with the development of a systemic inflammatory response leading to sepsis, severe sepsis or septic shock. Infections are more commonly due to a single bacterial species (70-88% of canine and feline infections)[2,4]. Presenting signs are variable depending upon the primary site of infection, involvement of other organ systems and development of shock.

■ The diagnosis is confirmed by

• **blood culture** for aerobic and anaerobic bacteria (see next page),

• **blood cytology** - Gram staining may aid empirical treatment choices,

• **culture and cytology** of samples of tissue/fluid from primary site of infection if accessible.

■ Adjunctive diagnostics to localise the primary site of infection and assess for systemic complications e.g. acid-base disturbances, disseminated intravascular coagulopathy (DIC):

• haematology: neutrophilia +/- left shift, neutropenia, monocytosis, mild non-regenerative anaemia, thrombocytopenia,

• serum biochemistry: hypoalbuminaemia, hyperbilirubinaemia, electrolyte disturbances, hypocalcaemia, raised ALKP, hypo/hyperglycaemia, azotaemia,

• blood gas analysis: metabolic acidaemia,

• urinalysis: include urine culture,

• coagulation tests: prolonged APTT and PT and raised D-Dimers in DIC; TEG (hypercoagulable> hypocoagulable in sepsis)[7],

• blood pressure measurement, pulse oximetry,

• imaging: abdominal ultrasound, echocardiography, thoracic radiography/CT.

Reasoning

■ **Antibiotic therapy cannot be delayed until culture and sensitivity test results are available** in patients suspected to be bacteraemic, due to the high risk of development of sepsis, severe sepsis and septic shock, each respectively associated with higher morbidity and mortality.

■ Initial empirical treatment should be bactericidal, administered intravenously (with a loading dose if appropriate) and cover a broad spectrum (i.e. aerobic, anaerobic, Gram-positive and negative). Consider the likely source of infection and expected bacteria, penetration of the antibiotics, typical susceptibility patterns and prior antibiosis.

■ Combination therapy is initially recommended to provide a broad spectrum and de-escalation to narrower spectrum drug(s) should be carried out on the basis of sensitivity results and clinical response.

• **Treatment with amoxicillin+/-clavulanate and enrofloxacin has been reported to be the most effective combination in cats and dogs with bacteraemia** but likely reflects commonly chosen antibiotics in practice[4]. The alternative combinations detailed in the tables provide a similar wide spectrum of activity as the use of enrofloxacin is generally avoided in cats where alternative fluoroquinolones exist (e.g. marbofloxacin).

• Pradofloxacin provides four-quadrant cover as monotherapy, however it is not available in a parenteral formula and there are regional variations in the product license for use in dogs.

Procedure for obtaining blood cultures

• Clip coat over venepuncture site e.g. over jugular and saphenous veins.

• Prepare skin for aseptic venepuncture (e.g. clean skin with 10% povidone iodine swabbing concentrically from the centre outwards, allow to dry).

• Clean stopper of culture tube/bottle with 70% alcohol; allow to dry.

• Perform venipuncture using sterile gloves to palpate the vein.

• Inoculate blood culture bottle without changing the needle.

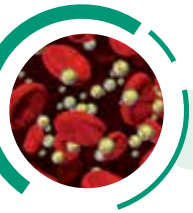
• Space cultures based on illness severity before starting antimicrobial therapy (acute febrile illness 2 sets from separate sites over 10 minutes to allow antimicrobials to be started quickly; acute endocarditis 3 sets from 3 separate sites collected within 1-2 hours). *Adapted from Sykes and Rankin, 2014.*

Difficulties and particularities

■ Bacteraemia may occur when a focal infection overwhelms local immune defences, the patient is immunocompromised or there is a virulent microorganism.

■ Diseases associated with acute bacteraemia include prostatitis, pyometra, gastrointestinal rupture and peritonitis, pancreatitis and pyelonephritis. Chronic bacteraemia may occur with infections

DISEASE FACT SHEETS



BACTERAEMIA (SEPSIS)

due to *Bartonella* spp. and Haemoplasmas, which may only be identifiable using PCR techniques.

- Identification and aggressive management of septic shock is critical in the successful management of bacteraemic patients; goal-directed fluid resuscitation[11], infection source identification and control are essential alongside early antibiosis.
- Prior treatment with antibiotics should be considered and alternative antibiotics used to reduce the chance of selecting inappropriate antimicrobials. The impact of inappropriate therapy before culture and sensitivity results are known is incompletely understood, due to the complexity of management of septic patients[1,6,10].
- Duration of treatment is determined by the underlying cause of bacteraemia and commonly prolonged where surgical resection of the infection source is impossible e.g. endocarditis ≥ 4-6 weeks, however currently recommendations are often based on best clinical judgement, lacking an evidence base or the ability to use biomarkers to guide withdrawal of antibiotics compared to human medicine[6].

Identification and aggressive management of septic shock is critical in the successful management of bacteraemic patients; goal-directed fluid resuscitation, infection source identification and control are essential alongside early antibiosis.

RARE MYCOBACTERIAL INFECTIONS

The relevant legislation in each country should be adhered to enabling appropriate zoonotic risk information to be given to owners, in particular regarding *M. tuberculosis*.
Following diagnosis the case should be managed in conjunction with an appropriate specialist and microbiologist.

Bacteria involved

Bacteria*	Host (pets)	Major reservoirs (Geographic distribution)	Human health Significance
Mycobacterium tuberculosis complex (MTBC)**			
M. tuberculosis	Dogs	Humans (USA, Africa, southern Europe)	Primary cause of tuberculosis in humans.
M. bovis	Cats, rarely dogs	South-western England and Wales	Rare cause of tuberculosis in humans.
M. microti	Cats, very rarely dogs	South-western Scotland, northern and southern England, western Europe	Very rare cause of tuberculosis in humans.
Mycobacterium avium-intracellulare complex (MAC)			
M. avium / M. intracellulare	Cats and dogs	Environmental saprophytes (worldwide, eastern England)	Humans acquire infection from environment. Direct transmission from animals has not been described.

** This table is not exhaustive; other types of mycobacterial infections exist.*
*** Transmission to humans may be possible.*

Diagnostic approach

■ The diagnosis of mycobacterial infections is based on the suggestive history, clinical signs and radiographic abnormalities, combined with the results of the histopathology, molecular tests and culture. *M. tuberculosis* infections cause pneumonia and tracheobronchial lymphadenopathy but rarely disseminate to the CNS, liver or kidney; while *M. bovis* and *M. microti* cause cutaneous lesions and peripheral lymphadenopathy. Occasionally, abdominal, bone and systemic dissemination occurs[4,9].

■ Several methods are available for the microbiological diagnosis of mycobacterial infections in dogs and cats. Acid-fast staining can be applied to tissue aspirates, buffy coat smears, body fluids, airway lavage specimens and biopsies.

The presence of acid-fast bacilli, often within macrophages, suggests mycobacterial infection, but it is not specific to *Mycobacterium tuberculosis* complex (MTBC) organisms. Some mycobacterial strains are unculturable. MTBC and *M. avium*-intracellulare complex (MAC) organisms are slow growing (several weeks) and culture is the gold-standard method because it allows mycobacteria typing and susceptibility testing. Once growth is evident, nucleic-acids based-methods or mycolic acid analysis with high-performance liquid chromatography or mass spectrometry (MALDI-TOF) may be used to determine if the organism belongs to MTBC. Real-time PCR is available for the rapid identification of mycobacterial infection and for the differentiation of MTBC organisms from other mycobacteria.

Reasoning

■ In many countries, euthanasia of infected animals is recommended taking into account the zoonotic risk and prognosis. Following diagnosis, the case should be managed in conjunction with an appropriate specialist and microbiologist.

VECTOR-BORNE BACTERIAL INFECTIONS

Bacteria involved

Bacteria	Vector	Hosts	Clinical signs	Geographic distribution in Europe*	Diagnostic method
Borrelia burgdoferi sensu lato	*Ixodes* spp.	Dogs (cats)	95% subclinical or transient fever, lameness, swollen joints, fatigue, anorexia. Rare chronic cases of joint disease or immune-mediated nephropathy.	Throughout Europe	Clinical signs and exclusion of other diagnoses, response to therapy. Serology and PCR from skin or synovia may be supportive.
Bartonella henselae *Bartonella clarridgeiae*	*Ctenocephalides felis felis*	Cats (dogs)	Usually asymptomatic. Possibly fever, gingivitis, lymphadenopathy, UTI, uveitis.	Throughout Europe	Histology, immuno-histochemistry, serology, PCR.
Bartonella vinsonii subsp. *berkhoggii*		Dogs (cats)	Asymptomatic, transient fever, endocarditis, granulomatous lesions		
Ehrlichia canis	*Rhipicephalus sanguineus*	Dogs	Monocytic ehrlichiosis. Lethargy, anorexia, weight loss, anaemia, petechiae, pancytopenia.	Mainly southern Europe	Clinical presentation, PCR, blood smear for *A. phagocytophylum* only, (serology).
Anaplasma phagocytophylum	*Ixodes* spp.	Dogs (cats)	Granulocytic ehrlichiosis. Acute fever, lethargy, anorexia.	Throughout Europe	
Anaplasma platys	*Rhipicephalus sanguineus*		Infectious cyclic thrombocytopenia and fever (every 1-2 weeks).	Mainly southern Europe	
Rickettsia conorii	Ticks	Dogs	Fever, lethargy, anorexia, stiff gait, myalgia, lymphadenopathy, dermal necrosis.	Mediterranean countries	PCR, (Serology).
Rickettsia felis	*Ctenocephalides felis felis*	Cats and dogs	Experimental: subclinical illness in cats with an incubation period of 2–4 months. Natural infection in cats and dogs: unknown.	Throughout Europe	

** according to ESCCAP (Control of vector-borne diseases in dogs and cats, 2012).*

Possible associations:

Ehrlichia, *Anaplasma*, *Borrelia*, *Bartonella* and *Rickettsia* may be associated with each other or with *Leishmania* and/or *Babesia*.

Treatment recommendations

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Borrelia burgdorferi s.l.	Doxycycline	10 mg/kg/12-24h PO	28 days
Bartonella spp.			28 days
Ehrlichia canis			28 days
Anaplasma			*A. phagocytophylum* 15-20 days *A. platys* 8-10 days
Rickettsia spp.			7 days

Clinically asymptomatic seropositive animals should not be treated with antibiotics, as very often seropositivity derives from contact or past infection (not necessarily current or active disease). Indeed the percentage of seropositive dogs can be very high in endemic areas for most of the bacterial vector-borne diseases.

Diagnostic approach

The diagnosis of vector-borne bacterial diseases is not always easy. There are only a few specific clinical signs and clinicopathological abnormalities, such as thrombocytopenia in ehrlichiosis and anaplasmosis. Co-infections are not infrequent and make the diagnosis even more challenging. Evidence of arthropod bites together with a combination of multiple tests for the same agent or for multiple agents is usually necessary. **A positive serology test is not diagnostic of the disease and is only indicative of contact**. In endemic areas there are many asymptomatic seropositive animals. Two or more quantitative serology

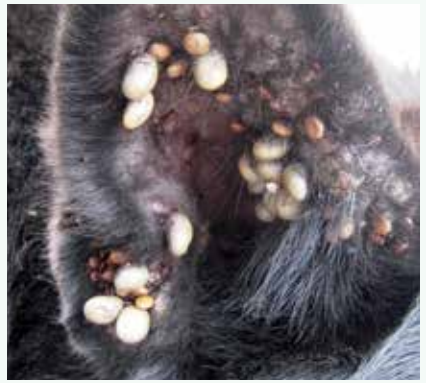


Figure 1 *- Numerous female ticks, engorged with blood, on the pinna of a dog.*

tests some weeks apart to evaluate IgG antibody kinetics may be necessary to assess the patient's infection status. On the other hand, recently infected animals may show clinical signs but may not yet have seroconverted. Blood smears can be useful in *A. phagocytophilum* infections, where morulae can be seen in platelets in about 60% of the cases, but not for *E. canis* and *A. platys*. PCR is useful to identify bacterial DNA in patients, but this does not mean that the microorganisms are viable and actively causing the disease. Whole blood in EDTA is the preferred sample material for *Ehrlichia*, *Anaplasma* and *Bartonella*, while synovial fluid or skin are preferable in borreliosis and skin alone for rickettsiosis. Response to treatment will confirm the diagnosis in many cases.

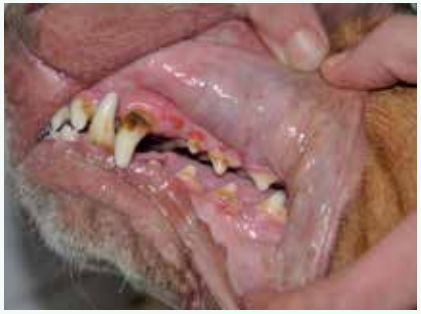


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Figure 2 *- Petechiae in a dog affected with Ehrlichia canis.*

Reasoning

- Even if other antibiotics are effective, doxycycline is recommended, because it is active in all bacterial vector-borne diseases and co-infections are very frequent. Treatment of bacterial vector-borne diseases may be a challenge, as it is not always possible to achieve a complete elimination of the pathogen even in the case of a clinical cure. Clinical improvement is expected within a few days but the antibody titre can remain high for a long period of time. For this reason, treatment should be aimed at negative PCR results.
- Depending on the pathogens concerned, secondary choices include amoxicillin +/- clavulanate, marbofloxacin, enrofloxacin and chloramphenicol.

Difficulties and particularities

- **Prevention of transmission of vector-borne disease is extremely important**. As some of the vector parasites, such as fleas and certain ticks, transmit the pathogens almost immediately when they bite, a repellent should be chosen to avoid a blood meal. These usually contain pyrethroids, such as permethrin, flumethrin or deltamethrin (collars or spot-ons). Spot-ons should be applied at regular interval and as per label instructions and frequent bathing should be avoided in these animals when appropriate evidence is not available. Collars should be applied on dogs several days prior to exposure to the parasites and their efficacy duration can be reduced as well by water immersion.
- **Vector control is also very important** as many of these micro-organisms can be transmitted to human beings and cause dangerous diseases.
- The geographical distribution of vectors is changing, it is therefore increasingly important to protect pets from an extended spectrum of parasites and for a longer period of time (ideally all year round). **Fleas in particular are underestimated as vectors, and repellent flea control products should be applied to every animal (whether indoors or outdoors) all year round**.
- If patients do not respond rapidly to treatment, then other co-infections or diseases with similar clinical signs should be investigated.
- *Borrelia* vaccination is controversial and experts generally do not advise it.

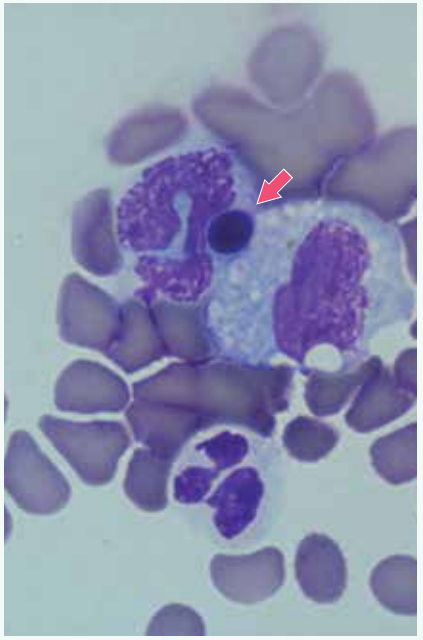

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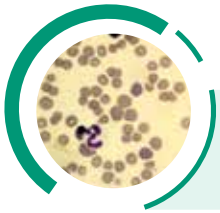
Figure 3 *- Ehrlichia morula in a blood smear from a dog.*

DISEASE FACT SHEETS



HAEMOTROPIC MYCOPLASMOSIS

Bacteria involved

Mycoplasma haemofelis.

Antibiotics that can be used

Pathogen 1: *Mycoplasma haemofelis*

Antibiotics that can be used	*In vitro* sensitivity	Intracellular distribution	Treatment choice
Doxycycline	5	5	
Clindamycin	*Not routinely available*	5	
Pradofloxacin[a]	5	5	
Amoxicillin + clavulanate	1	2	
Cefalexin	1	2	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Mycoplasma haemofelis	Doxycycline	10 mg/kg/24h	At least 21 days*

Second choice antibiotic (if first-choice antibiotic is ineffective)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Mycoplasma haemofelis	Clindamycin	5.5-11 mg/kg/12h PO	At least 21 days*
	Pradofloxacin[a]	5 mg/kg/24h PO	

* *PCR-guided treatment cessation at 3-4 weeks.*

[a] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

Diagnostic approach

- Feline haemoplasmas or haemotropic mycoplasmas are epicellular Gram-negative organisms. They produce different degrees of anaemia and illness in cats. Between 14-27% of cats with regenerative anaemia were found positive for haemoplasmosis[2,3]. Four distinct haemoplasmas have been detected in cats. *M. haemofelis* is the most pathogenic and usually causes haemolytic anaemia and can be fatal, while other mycoplasmas can induce anaemia in immunocompromised cats such as those infected by FIV or FeLV.
- Clinical signs depend on the level of anaemia (e.g. pale mucous membranes, tachypnoea, tachycardia...) and are commonly accompanied by fever. Diagnosis is based on identification of the haemoplasma in a blood smear and using PCR.

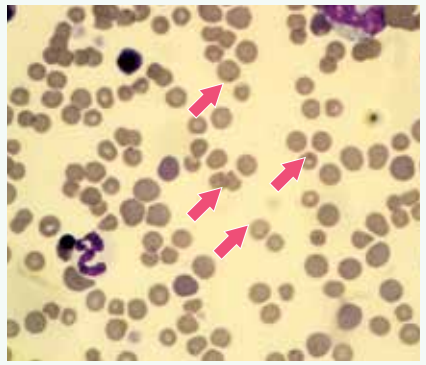


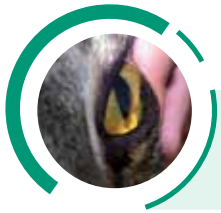
***Figure 1**- Cytology of Mycoplasmas (arrows) in a blood smear (Diff-Quik)®.*

Reasoning

- Infections with haemotropic mycoplasmas are not easily cleared, and long term treatments with appropriate antibiotics (doxycycline, fluoroquinolones) are needed. Parenteral treatment may be needed in severely ill cats. Fluoroquinolones are useful in solving clinical signs but with the exception of pradofloxacin, they cannot clear the infection[1].

Difficulties and particularities

- Sometimes a course of corticosteroids should be added to treatment with anti-mycoplasmal antibiotherapy, in order to reduce the immune-mediated haemolytic anaemia. Prednisolone (1mg/kg PO q 24h) or methylprednisolone are preferred. The owners should be informed about the risk and benefits of this strategy.



FELINE TOXOPLASMOSIS

Pathogen involved

Toxoplasma gondii.

Antibiotics that can be used

Pathogen 1: *Toxoplasma gondii*

Antibiotics that can be used	*In vitro* sensitivity	Intracellular distribution	Treatment choice
Clindamycin	4 - 5	4	
Trimethoprim sulfonamides[a]	4 - 5	5	
Doxycycline	Not routinely available	4	

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[4].*

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Toxoplasma	Clindamycin	11 mg/kg/12h	At least 21 days

Second choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Toxoplasma	Trimethoprim sulfonamides[a]	15 mg/kg/12h	At least 21 days

[a] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[4].*

Therapeutic approach

Clinical signs consistent with toxoplasmosis
→ Clindamycin
→ Trimethoprim sulfonamides
→ Doxycycline

Diagnostic approach

- **Toxoplasmosis** involves the central nervous system, the lungs, the liver, the pancreas and the striated muscle. It is more common in immunocompromised cats (e.g. FIV, immunomodulatory treatment such as ciclosporin).
- Typical clinical signs are: fever, pneumonia, icterus, abdominal discomfort, dyspnoea, ascites, pancreatitis and mesenteric lymphadenopathy[3,5]. Toxoplasma can cause diarrhoea but usually is self-limiting and resolves in more or less 2 weeks. In case of CNS involvement, multifocal neurological clinical signs may be present, including ataxia, blindness, seizures, depression, anisocoria, nystagmus, head tilt and abnormal behaviour[1,3].
- The diagnosis may be challenging. Serology (IFA or ELISA) to determine IgM or/and IgG titres against *Toxoplasma* are commonly used. Diagnosis is based on IgM titres above 1:64 or a fourfold increase in IgG titres over a 2-3 weeks' period, combined with clinical signs and ideally an appropriate response to anti-Toxoplasma treatment[2]. The identification of the parasite in cytology/biopsy or PCR techniques (e.g. muscle biopsy, CSF sample or fluid from bronchoalveolar lavage) can also be useful for the diagnosis of toxoplasmosis.

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Figure 1 *- Uveitis in a cat due to Toxoplasmosis.*

DISEASE FACT SHEETS

FELINE TOXOPLASMOSIS

Reasoning

■ It is impossible to completely eliminate *Toxoplasma* from an infected cat. **The aim of the treatment is therefore to resolve the clinical signs**. Clindamycin is the treatment of choice for toxoplasmosis but in neurological cases may not work well, and owners of cats diagnosed with neurological toxoplasma should be informed that treatment may not work or may require more time. Drugs such as trimethoprim sulfonamides have been used for this infection but it is important to find an oral formula adapted for cats as this combination is especially distasteful for cats.

Difficulties and particularities

■ Oral clindamycin can cause anorexia, vomiting, and diarrhoea in dogs and cats, especially at higher doses. These side effects appear to be related to local GI irritation, because parenteral therapy at similar doses does not cause them in the same animals. The side effects stop soon after the dose is reduced or therapy is discontinued. Some clinicians use probiotics with success during treatment when patients develop diarrhoea to avoid stopping antibiotic therapy.

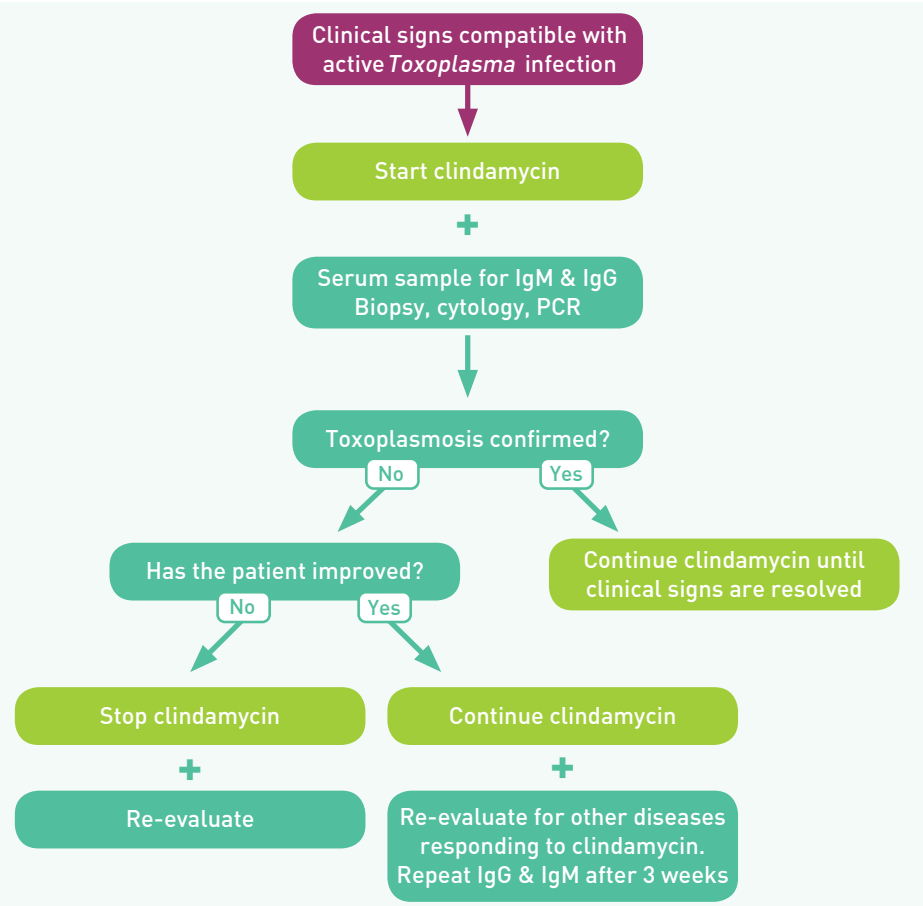

Figure 2 - Clinical approach to Feline Toxoplasmosis.

DISEASE FACT SHEETS

PYREXIA OF UNKNOWN ORIGIN

In case of pyrexia of unknown origin, **empirical antibiotic therapy is rarely indicated** and should not substitute a thorough work-up.

In dogs, in 80% of cases the cause is not bacterial.

Diagnostic approach

■ Pyrexia or fever of unknown origin (PUO) is defined as fever that does not resolve spontaneously, does not respond to antibiotic therapy and for which the diagnosis remains uncertain after an initial diagnostic workup[3].

■ **Empirical antibiotic therapy is not indicated in the majority of cases** of PUO without conducting a thorough diagnostic work-up first to screen the patients for inflammatory/immune-mediated diseases, neoplasia and infectious diseases.

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Figure 1 *- Chronic uveitis due to Toxoplasma.*

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Figure 2 *- FIP (wet form). Before a wet form is detected some cats may have fever for weeks. These cases can be very challenging.*

■ In three retrospective studies investigating unexplained fever in dogs, the most prevalent diseases were non-infectious inflammatory conditions. Infectious causes were only diagnosed in 16% to 18% of dogs[1,2,4].

■ While in cats, fevers are common, there are no retrospective studies. Most diseases associated with PUO in cats are infectious[8], but rarely bacterial. In cats, neoplasia is a less common cause of PUO, and PUO due to immune-mediated disease is rare[10].

■ PUO in cats is always a challenge. Usually body temperatures between 39.5 - 41.1°C (103-106°F) are considered true pyrexia.

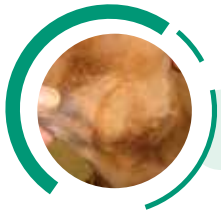
Table 1 *- Staged diagnostic approach to pyrexia of unknown origin in cats and dogs[5,6]*

Stage 1

- Take a thorough history (vaccination history, travel history, flea and tick control, indoor/outdoor status, contact with other animals. *Cats: hunting behaviour, cat fights*).
- Stop all medications to rule out drug-induced fever (72h is enough; penicillins, tetracyclines, sulfonamides & levamisole are more commonly related with drug-related fever).
- Perform a meticulous physical examination, including fundic and neurologic examination. Loss of rib spring may be a sign of a cranial mediastinal mass, lameness may indicate septic arthritis, enlarged lymph notes may indicate infection (Figure 4), while cats with FIP may have ophthalmic alterations.
- Obtain samples for CBC, blood smear and serum chemistry profile. Save serum for serology or other testing.
- Conduct a complete urinalysis, cytology and urine culture (even if urine cytology is negative). Submit a sample for UPC ratio if proteinuria and inactive sediment are present.
- Cats: test for FeLV and FIV. Dogs: test for vector-borne diseases (see Vector-borne bacterial infections, p.168).
- Conduct faecal centrifugation and faecal cytology (if neutrophils are detected then do a faecal culture to rule out *Campylobacter* and *Salmonella*. If clostridia are recognized in cytology, perform a entorotoxigenic PCR test).
- Consider thoracic radiographs (especially if abnormal auscultation sounds are detected or if rib spring is negative) and abdominal ultrasonography.
- Consider trial antibiotics if bacterial infection is suspected (e.g. doxycycline if mycoplasmosis or ehrlichiosis is suspected or amoxicillin+clavulanate if pyelonephritis is suspected).

If necessary, proceed to stage 2.

DISEASE FACT SHEETS



PYREXIA OF UNKNOWN ORIGIN

Table 1 (continued)

Stage 2

Repeat stage 1, tests as indicated.

- Obtain thoracic and abdominal radiographs if not obtained in stage 1.
- Conduct echocardiography if a heart murmur is present.
- Perform fine-needle aspiration with cytology of masses, lymph nodes, and fluids (cyst, pleural, peritoneal).
- Conduct blood culture.
- Perform arthrocentesis.
- Conduct bone marrow aspiration if warranted by CBC results (e.g. abnormal shape, size or numbers in blood cells).
- Conduct serology for infectious diseases (e.g. IgG & IgM *Toxoplasma* titres in cats).
- Obtain long bone and joint radiographs.
- Conduct an immune panel if indicated (e.g. species-specific Coomb's Test, antinuclear antibody determination).

If necessary, proceed to stage 3.

Stage 3

Repeat stage 1 and 2 tests as indicated.

- Conduct echocardiography even if no murmur is present.
- Perform bone marrow aspiration even if CBC results are normal.
- Perform biopsy as indicated.
- Perform bronchoscopy and bronchoalveolar lavage as indicated.
- Conduct cerebrospinal fluid analysis.
- Perform dental radiography.
- Consider advanced imaging.
- Perform laparoscopy or thoracoscopy as indicated.
- Consider exploratory laparotomy.

Administer trial antibiotic or antifungal (if indicated) therapy.

Reasoning

- In case of pyrexia of unknown origin, empirical antibiotic therapy is rarely indicated.
- However, if antibiotics are given to a patient with unexplained fever, care should be taken to obtain adequate samples (e.g. bacterial culture on blood/urine/tissue/fluid, samples for PCR testing for certain pathogens) prior to treatment.
- Infectious conditions that have been identified in dogs with fever include endocarditis, sepsis, pneumonia, abscess, discospondylitis, pyothorax, osteomyelitis and anaplasmosis[1,4]. It is therefore impossible to make general antibiotic recommendations for all febrile patients.
- Common non-infectious causes for PUO in dogs include immune-mediated diseases, primary bone-marrow-disorders and neoplasia[1,2,4].

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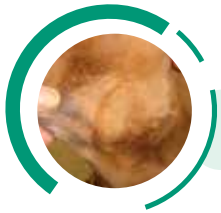
Figure 3 *- A cat with fever. Cold pads and IV fluids are applied.*

- Severe hyperthermia will require some kind of treatment, a fan directed to the cage or intravenous fluid administration could be enough to reduce the severity of the hyperthermia without using drugs. Empirical antibiotic therapy should be based on the organ system involved or the infectious agent suspected (Figure 3).



PYREXIA OF UNKNOWN ORIGIN

Table 2 - Causes of PUO in dogs and cats (in bold the most common causes)[5,6].

Origin of fever	Dogs	Cats
Bacterial infection (focal or systemic)	**Abscess, pyelonephritis, pyothorax**, bacteraemia, osteomyelitis, discospondylitis, infective endocarditis, septic arthritis, septic meningitis, prostatitis, stump pyometra, peritonitis	
Viral infection	**Canine distemper** **Canine parvovirus**	**FeLV, FIV, FIP, FCV, FHV,** FPV
Bacterial diseases	**Mycoplasmosis** (haemotrophic and non-haemotrophic), tuberculosis and other mycobacterial diseases, diseases caused by L-form bacteria (e.g. cellulitis or synovitis secondary to bite wounds or surgical incisions)	
	Bartonellosis, borreliosis, brucellosis	
Protozoal infection	**Toxoplasmosis**, neosporosis, leishmaniasis	
	Babesiosis, hepatozoonosis	Cytauxzoonosis
Non-infectious inflammatory diseases	**Pancreatitis, primary bone marrow disorders**, lymphadenitis, panniculitis, pansteatitis, granulomatosis	
Neoplasia	**Lymphoma**, leukaemia, multiple myeloma, necrotic solid tumours, malignant histiocytosis	
Rickettsial disease	Ehrlichiosis, anaplasmosis	
Fungal disease	**Cryptococcosis**, histoplasmosis, blastomycosis, coccidioidomycosis	
Immune-mediated diseases	Polyarthritis, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, meningitis, steroid-responsive neutropenia and fever	
	Immune-mediated haemolytic anaemia	
Miscellaneous	Portosystemic shunt, drug reaction, toxin, idiopathic causes	
	Shar-pei fever	**Hyperthyroidism**

Difficulties and particularities

- Treatment failure is mainly linked to the fact that the aetiology of fever is not a bacterial infection in most cases of PUO.
- **Antibiotic treatment is not only rarely indicated, but may also mask clinical signs**. In one study, pre-treatment of dogs with PUO prior to referral was even linked to a longer time until a diagnosis could be established in these patients (12 versus 9 days)[2].
- The most likely reason why some animals with PUO remain without a diagnosis is due to limitations in the diagnostic work-up. **If veterinarians prescribe antibiotics empirically, in dogs there is at least an 80 % chance of treatment failure because of the non-infectious aetiology of the potential underlying diseases**.
- Before starting treatment, the risk and benefits should be evaluated. Temperatures less than 41°C are unlikely to be harmful and may even be somewhat beneficial because they constitute a protective response.

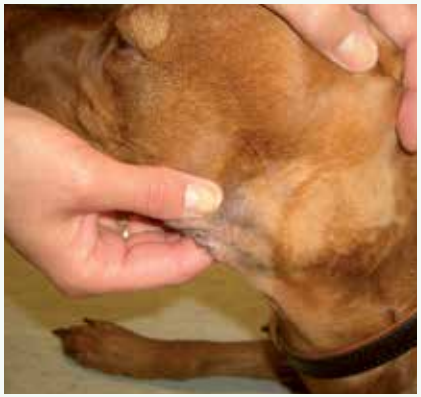


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Figure 4 - A Magyar Viszla dog with PUO and enlarged lymph nodes. Cytology and culture of the lymph node revealed systemic fungal infection.

- Although the use of NSAIDs may be indicated, it is important to remember that animals receiving NSAIDs should be normotensive and properly hydrated. NSAID treatments may also mask clinical signs that could help resolve the case[3].

OPHTHALMOLOGY

DISEASE FACT SHEETS

CONJUNCTIVITIS AND KERATITIS

Not all cases of conjunctivitis are infected with bacteria.

Bacteria involved

Dogs

Bacteria	Prevalence Conjunctivitis[3,8]	Prevalence Ulcerative conjunctivitis[8]
Staphylococcus spp.	40-47%	16%
Streptococcus spp.	23-26%	27%
Escherichia coli	4%	16%

Cats

Bacteria*	Prevalence[5]
Chlamydophila felis	66%
Mycoplasma spp.	49%
Aerobic bacteria (*Staphylococcus* spp., *Streptococcus* spp. & *Micrococcus* spp.)	39%

** association with FHV is common.*

Antibiotics that can be used

Dogs (and cats)

Pathogen 1: *Staphylococcus* spp.

Antibiotics that can be used as topicals	*In vitro* sensitivity	Local concentration	Treatment choice
Fusidic acid	5	5	
Neomycin-bacitracin-polymyxin B	4	5	
Chloramphenicol	5	5	

Pathogen 2: *Streptococcus* spp.

Antibiotics that can be used as topicals	*In vitro* sensitivity	Local concentration	Treatment choice
Fusidic acid	3	5	
Neomycin-bacitracin-polymyxin B	4	5	
Chloramphenicol	5	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Cats only

Pathogen 3: *Chlamydophila* spp.

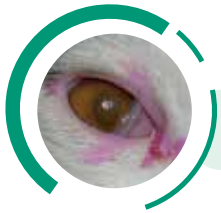
Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Doxycycline[a]	Not routinely available	5	
Amoxicillin + clavulanate[b]		4	

Pathogen 4: *Mycoplasma* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Doxycycline[a]	Not routinely available	5	
Amoxicillin + clavulanate[b]		4	
Marbofloxacin	4	5	
Pradofloxacin[c]	Not routinely available	5	

[a] *Oral doxycycline is the treatment of choice in adults cats.*
[b] *Oral amoxicillin + clavulanate is the treatment of choice in kittens and nursing queens.*
[c] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

DISEASE FACT SHEETS



CONJUNCTIVITIS AND KERATITIS

Therapeutic approach

Dogs

Corneal smear (cytology ± culture)

- *Escherichia coli* (Gram-negative rod)
  - Neomycin + bacitracin + polymyxin B
  - Chloramphenicol
- *Staphylococcus/ Streptococcus* spp. (Gram-positive cocci)
  - Neomycin + bacitracin + polymyxin B, Fucidic acid
  - Chloramphenicol

Cats

Corneal smear (cytology ± culture)*

- *Chlamydophila*
  - Doxycycline
  - Amoxicillin + clavulanate
- *Staphylococcus/ Streptococcus* spp. (Gram-positive cocci)
  - Neomycin + bacitracin + polymyxin B, Fucidic acid
  - Chloramphenicol

** Mycoplasma spp. cannot be diagnosed using a corneal smear or the usual culture techniques. For this pathogen, PCR is the gold standard diagnostic test.*

Treatment recommendations

First choice antibiotic (whilst waiting for culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Staphylococcus spp. *Streptococcus* spp.	Fusidic acid (eye drops/ointment)	1-2 times/day	8-10 days
	Neomycin - bacitracin polymyxin (eye drops)	5-6 times/day	
Chlamydophila spp.	Doxycycline (oral)	10 mg/kg/24h	30 days[4]
Mycoplasma spp.*	Doxycycline (oral)	10 mg/kg/24h	2-4 weeks

Second choice antibiotic (following culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Staphylococcus spp. *Streptococcus* spp.	Chloramphenicol (eye drops)	2-3 times/day	8-10 days
Mycoplasma spp.* *Chlamydophila* spp.	Amoxicillin + clavulanate (oral)	12.5-25 mg/kg/12h PO	30 days[9]

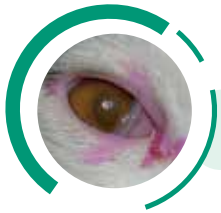
** Mycoplasma spp. cannot be diagnosed using a corneal smear or the usual culture techniques. For this pathogen, PCR is the gold standard diagnostic test.*

Diagnostic approach

- Conjunctivitis is the inflammation of the mucosal membrane that covers the cranial pole of the eye while keratitis is the inflammation of the cornea; the inflammation of both is called keratoconjunctivitis. **Not all conjunctivitis is infected with bacteria and the use of antibacterials in conjunctivitis cases should be reserved until infection has been confirmed (cytology)**. The aetiology of bacterial conjunctivitis is different in dogs and cats[2,3,5]. The clinical appearance of conjunctivitis includes hyperaemia, ocular discharge (mucoid to mucopurulent), chemosis and, in chronic cases, lymphoid follicles[11].

- It is important to perform a correct and systematic step-by-step ophthalmic examination in order to get the best samples and reach the correct diagnosis. Prior to applying fluorescein, or ophthalmic

DISEASE FACT SHEETS



CONJUNCTIVITIS AND KERATITIS

cleaners, a sample should be taken for cytology and culture.

- Cytology samples must be stained using a rapid differentiating staining system (e.g. Diff Quik®) and if inflammation is noticed then the second cytology sample should be stained using a Gram stain system.
- Microbiology samples should be kept just in case culture is needed. Probably **only the severe and/or repeated conjunctivitis/keratitis cases requires a culture and sensitivity test**. In cats, it is recommended to keep a third sample for viral and chlamydial/mycoplasmal DNA detection[1,5].
- In both species the inflammation may be due to a systemic infection (e.g. FHV-1, Canine distemper...) or secondary to a pre-existing cause (e.g. entropion, keratoconjunctivitis sicca...). After taking samples, perform a Schirmer's tear test and follow-up to complete the ophthalmic examination including the evaluation of the fundus (conjunctivitis may be just the tip of the iceberg of many other ophthalmic diseases).

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Figures 1 & 2 *- Cats with chlamydial conjunctivitis. The cat on the right has also FHV (in this case Rose Bengal staining has been applied in order to identify geographical ulcers commonly seen in FHV infections).*

Reasoning

- In **mild and superficial cases** the topical application of antibiotics allows a high local dose and a good penetration in affected tissues.
- In **mild and superficial cases**, carrying out a conjunctival+/-corneal smear and Gram staining is preferable to an empirical choice of a broad-spectrum antibiotic.
- In **canine bacterial conjunctivitis**, if Gram-positive cocci are detected, neomycin-bacitracin-polymyxin B (tri-antibiotic solution), chloramphenicol or fusidic acid eye drops may be recommended at least for 8-15 days. If Gram-negative bacteria are detected a tri-antibiotic solution or chloramphenicol eye drops are preferred.
- In **feline bacterial conjunctivitis**, chlamydial infections usually need oral doxycycline to clear the infection completely[6]. If patients live in a multi-cat household, all cats should be treated in order to avoid a carrier-state.
- In **recurrent or complicated cases** (melting ulcers), besides a corneal smear, a culture and sensitivity test should always be performed. Pending results, initial treatment with anticollagenases (e.g. EDTA, acetylcysteine, autogenous serum), cyclopegics (e.g. atropine in dogs and tropicamide in cats) and empirical antibiotics (e.g. Gram-positive: tri-antibiotic solution eye drops, Gram-negative: fluoroquinolone eye drops) should be started. In some of these cases, surgical repair of ulcers or perforations are needed without delay.

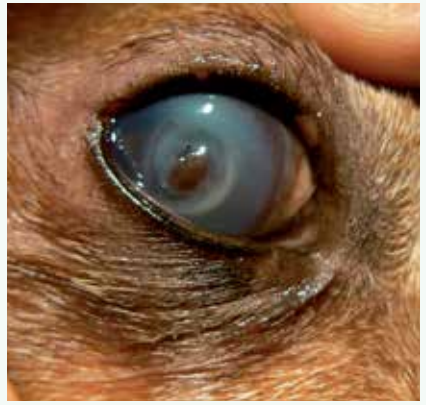

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Figure 3 *- Dog with a severe ulcerative keratitis.*

Difficulties and particularities

- In both conjunctivitis and keratitis, self-trauma should be prevented (e.g. Elizabethan collar). The cornea should also be lubricated properly, limiting eye dryness and eyelid self-trauma. To avoid eye dryness, mucinomimetic therapy with hyaluronic acid and/or carbomers is preferred[7].
- Antibiotic resistance is not a common feature in conjunctivitis or keratitis. If efficacy seems to be lacking, it is important to check owner compliance, as applying eye drops in a painful and non-cooperative patient may be a challenge.
- The most common cause of conjunctivitis, keratitis and keratoconjunctivitis in the cat is FHV-1. Sometimes, antiviral therapy may be required (e.g. famciclovir 40 mg/kg PO q 8h or ganciclovir topically).

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Figure 4 *- Severe herpetic keratitis in a cat with a secondary infection with Streptococcus spp.*

DISEASE FACT SHEETS

INFECTIOUS UVEITIS

• This chapter covers agents not treated in other parts of this book - not necessarily the most commonly diagnosed.

Infectious uveitis is rarely caused by bacteria; therefore, antibiotics are rarely indicated.

Pathogens involved

Dogs

Pathogens	Prevalence
All bacterial vector-borne pathogens*	++ (15 to 40 %)
Leishmania infantum	++ (15 to 40 %)
Leptospira spp.	+ (< 10-20 %)
Fungal pathogens (e.g. *Cryptococcus* spp., *Histoplasma* spp., *Coccidioides* spp.)	+ (< 10-20 %)
Brucella canis	+ (< 10-20 %)

Cats

Pathogens	Prevalence
FIP	+++ (35 to 65 %)
Toxoplasma spp.**	++ (15 to 40 %)
FIV	+ (< 10-20 %)
FeLV	+ (< 10-20 %)
Fungal pathogens	+ (< 10-20 %)

** see Vector-borne bacterial infections, p.168.*
*** see Feline toxoplasmosis, p.174.*

Antibiotics that can be used

Dogs

Pathogen 1: *Brucella canis*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Doxycycline	5	4	
Streptomycin	5	2	
Enrofloxacin[a]	5	4	
Rifampicin	5	4	
Trimethoprim sulfonamides[b]	2	5	

Pathogen 2: *Leptospira* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Penicillin G	4	2 - 3	
Amoxicillin / Ampicillin	4	2 - 3	
Doxycycline	5	4	
Gentamicin[c]	4	2 - 3	
Streptomycin[c]	4	2	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*
[b] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks[8].*
[c] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

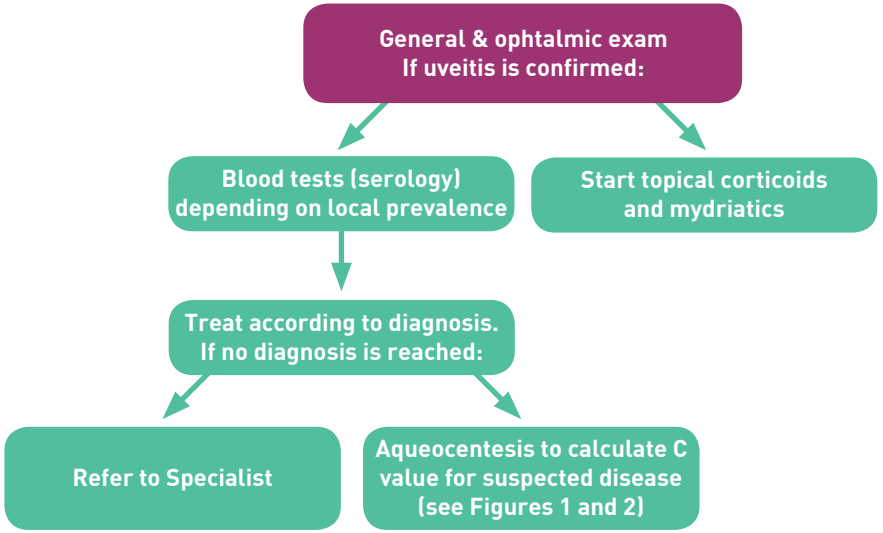
Cats

In cats, bacterial uveitis is extremely rare (see previous page).

DISEASE FACT SHEETS

INFECTIOUS UVEITIS

Therapeutic approach



Aqueous Antibody Coefficient (C-value):

$$\frac{\text{[Specific Ab concentration in aqueous humour]}}{\text{[Specific Ab concentration in serum]}} \times \frac{\text{[Other agent Ab concentration in serum]}}{\text{[Other agent Ab concentration in aqueous humour]}}$$

Specific Ab: e.g. against Toxoplasma
Other agent: e.g. feline panleukopenia virus

If the C-value is <1, there is no local production of specific antibodies (Ab)
If the C-value is between 1-8, the local production of specific antibodies (Ab) is probable.
If the C-value is >8, there is a local production of specific antibodies (Ab)
In this formula, specific Ab are the antibody titres against the disease which you are trying to rule out[1,6].

Figure 1 *- Aqueous Antibody Coefficient (C-value).*

Treatment recommendations

First choice antibiotic if presence of pathogen confirmed

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Brucella canis	Doxycycline + streptomycin	10 mg/kg/24h PO + 20 mg/kg/24h IM	8 weeks (with streptomycin inj. every other week)
Leptospira spp.	Penicillin G	25,000 – 40,000 units /kg/12h SC, IM, IV	3 weeks
	Ampicillin (for leptospiraemia)	22 mg/kg/8h SC, IM	

Second choice antibiotic if presence of pathogen confirmed

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Brucella canis	Rifampicin Enrofloxacin[a]	7.5 mg/kg/24h 10 mg/kg/24h	As needed 8 weeks
Leptospira spp.	Doxycycline (for kidney carrier state)	5 mg/kg/12h PO	3 weeks

[a] *Avoid use in growing dogs of large breeds.*

Diagnostic approach

Anterior uveitis is the inflammation of the anterior uvea, the vascular layer of the eye, composed of the iris and ciliary body. Posterior uveitis means both choroid and retina are affected, and when all areas are affected this is called panuveitis. **There are many possible causes of uveitis, but a bacterial infection is rare**. Depending on the geographical location of the patient, the list of possible diagnosis should be adapted (e.g. *Brucella canis* infections are more common in America than in Europe, Mediterranean areas are endemic for *Leishmania* spp.).

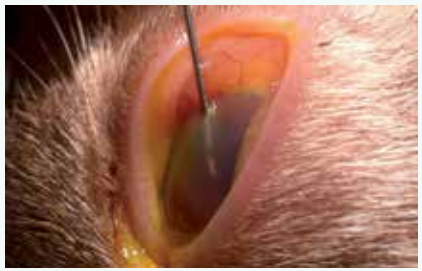


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Figure 2 *- Aqueocentesis is an easy technique allowing the comparison of titres between serum and aqueous humour. The needle should always be parallel to the iris.*

DISEASE FACT SHEETS

INFECTIOUS UVEITIS

- Some of the most common signs are: lacrimation, photophobia, ocular pain, blepharospasm, chemosis, conjunctival and/or scleral redness, hypopyon, hyphaema or fibrin flare at the anterior chamber, abnormal iris pigmentation, miosis and anisocoria.

- ***Brucella canis***: The clinical signs of *Brucella* infections are mostly related to reproductive abnormalities (abortions, stillborn and neonatal mortality) and testicular inflammation (epididymitis & orchitis)[7]. The non-reproductive signs include splenomegaly, generalized lymphadenopathy and there are some papers reporting discospondylitis, meningoencephalitis, osteomyelitis and polyarthritis. Ocular involvement is not rare in *Brucella* infections in dogs, with anterior uveitis, chorioretinitis and optic neuritis. Diagnosis of *Brucella* infections may be challenging. Haematological and biochemical values are either unaltered or nonspecific in canine brucellosis. Hyperglobulinaemia (ß and γ) with concomitant hypoalbuminaemia has been the most consistent finding in chronically infected dogs. Specific tests, such as cytoplasmic antigen agar gel immunodiffusion (CPAg-AGID) may be of help[2].

- **Leptospirosis**: Clinical signs may vary. In ***acute cases***, any of the following signs can be found: fever 39.5-40 °C, shivering, muscle tenderness, vomiting, prostration, dehydration, peripheral vascular collapse, tachypnoea, rapid irregular pulse, poor capillary perfusion, haematemesis, haematochezia, melena, epistaxis, widespread petechiae, icterus, intestinal intussusception, oliguria or anuria. In ***subacute cases***, these include fever, anorexia, vomiting, dehydration, polydipsia and polyuria, reluctance to move, paraspinal hyperesthesia caused by muscular, meningeal or renal inflammation, congested mucous membranes, petechial or ecchymotic haemorrhages, conjunctivitis, uveitis, rhinitis, tonsillitis, oliguria or anuria, coughing or dyspnoea and icterus. The most remarkable laboratory findings are leukocytosis and thrombocytopenia while elevated liver enzymes (ALT, AST, ALKP, LDH), azotaemia and creatinine are commonly detected. Urine specific gravity is usually below 1.029 and haematuria and pyuria are common features. Proteinuria and glycosuria (if present) are indicative of tubular damage.

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Figure 3 *- Cat with uveitis due to FeLV. Hyphaema and anisocoria are noted.*

- Sometimes after a complete ophthalmic exam and serum serology, diagnosis cannot be reached. One way to find out if a systemic disease is responsible for the ocular signs is by comparing the serum titres with aqueous titres for a specific pathogen (by aqueocentesis, see Figure 2). With these titres, the C-value can be calculated as shown in Figure 1.

Reasoning

- The treatment of *Brucella canis* infections rarely produces a total clearance of infection, despite high *in vitro* sensitivity. Long-term treatment is required. A combination of antibiotics is recommended, e.g. tetracyclines (doxycycline or minocycline) with streptomycin. Ocular infections require even a longer treatment with a combination of three or four antibiotics, the doses in these cases are higher and the course of treatment is longer.

- Treatment of *Leptospira* spp. infections is divided in two steps. The first step aims to eliminate bacteraemia, while the second step aims to clear the infection from the kidney and remove the carrier state. Treatment with penicillin or aminopenicillins is usually recommended to treat the leptospiraemia followed by doxycycline to solve the carrier state[5]. Aminoglycosides are no longer recommended due to their potential nephrotoxicity.

Difficulties and particularities

- If brucellosis is suspected, special measures should be taken to avoid human transmission. The use of gloves for sampling is highly recommended and owners should be informed about the zoonotic risk and the cost of long-term treatment with several annual checks to monitor if the disease is under control. Immunocompromised owners (HIV infection, chemotherapy...) must take extreme precautions to avoid infection.

- Leptospirosis is also a zoonotic disease. Immunocompromised owners are at particular risk for severe infection; therefore, if they live in an endemic area, their dogs should be screened serologically for exposure and possible infection, and their dogs should receive multivalent vaccination on a regular basis.

- In all cases of anterior uveitis, local anti-inflammatories are recommended even when a diagnosis has not yet been reached, because of the risk of blindness in cases of protracted inflammation. In the absence of corneal ulceration, topical 1% prednisolone or 0.1% dexamethasone ophthalmic solutions are indicated, used up to 4 times daily[3]. NSAID eye solutions may be used but they are more expensive and less potent than corticosteroids. NSAIDs should not be used parenterally or topically if hyphaema is present.

- The pain associated with anterior uveitis, resulting from a spasm of the ciliary muscle, can be treated with atropine 1% (initially 3 times daily)[4].

DISEASE FACT SHEETS

DIGESTIVE SYSTEM

DISEASE FACT SHEETS

COMMON DIARRHOEA IN DOGS AND CATS

Bacteria involved

Bacteria are rarely the cause of gastroenteritis in cats and dogs, and **antibiotic therapy is rarely justified.**

Antibiotics that can be used

- Most bacterial enteropathogens are associated with self-limiting diarrhoea, and injudicious administration of antimicrobials could be more harmful than beneficial.
- Correct diagnosis is crucial prior to initiating any antibiotic treatment as the incorrect use of antibiotics may trigger a bacterial overgrowth.
- Bacteriological stool analysis is not indicated as a first-line of action.
- *Salmonella* and *Campylobacter* are well-documented zoonoses, but antimicrobial administration is not routinely advocated in uncomplicated cases. For more information, see Gastroenteritis due to bacterial pathogens, p.204.

Diagnostic approach

- Gastroenteritis may be chronic or acute. Client history and clinical examination are generally sufficient to establish a diagnosis of common gastroenteritis. The causes of gastroenteritis are numerous and diverse. However, bacterial causes are rare and one of the least important causes of gastroenteritis in terms of prevalence.
- Therefore, **it is very important to follow a systematic step-by-step work-up prior to any antibiotic treatment**. Any viral, parasitic, drug-induced, toxin-induced and food-responsive causes should be ruled out.
- In cases of acute diarrhoea with systemic illness complete blood work, urinalysis and faecal (parasitological and viral) examination is indicated. This allows evaluation of patients for signs of sepsis (left shift, toxic changes in neutrophils) and to exclude metabolic diseases (e.g. renal or hepatic disease, pancreatitis, hypoadrenocorticism) and viral (Parvovirus, Coronavirus) or parasitic infections. Abdominal ultrasound can be helpful to rule out obstruction, masses, pancreatitis and involvement of other organs.
- Only if a definitive diagnosis of bacterial infection is reached, may antimicrobial treatment be justified in certain cases (see Gastroenteritis due to bacterial pathogens, p.204).
- **If the patient is in good general condition:**

1. Fast the patient for a short period (12-24h) and deworm. If there is vomiting or retching, provide anti-emetics.

2. Provide a bland, digestible diet. Probiotics can be tried for gastrointestinal support.

3. If there is no improvement, perform a complete work-up, including blood work, urinalysis and faecal examination. If this allows a diagnosis to be reached, then treat accordingly.

4. If food intolerance or allergy is suspected, consider an exclusion trial with a novel or hydrolyzed protein diet. This usually gives a response in less than 2-3 weeks, although several authors recommend 4-6 weeks before totally discarding food-related causes.

5. If there is no improvement, perform imaging (abdominal radiographies and/or ultrasound).

6. At this stage, an antibiotic therapeutic trial can be tried (using amoxicillin + clavulanate +/- metronidazole)

7. If diagnostic imaging provides a suspicion of intestinal disease or an intestinal tumour, then a laparotomy or endoscopy is recommended to get abdominal samples. If possible, samples should also be taken from the mesenteric lymph node, pancreas and liver.

- **If the patient is not well**, provide supportive treatment and take faecal samples for culture and/or PCR. Intravenous fluid therapy and antibiotics may be indicated if sepsis is present (see Bacteraemia (sepsis), p.158).

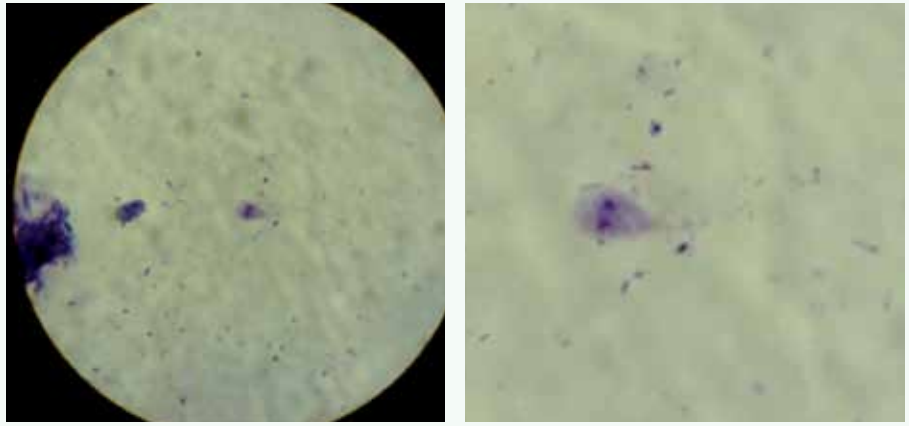

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Figure 1 - Giardia spp., a frequent non-bacterial cause of chronic gastroenteritis in dogs and cats.

COMMON DIARRHOEA IN DOGS AND CATS

Reasoning

- Most cases of uncomplicated acute diarrhoea resolve within several days. Supportive treatment should include fluid therapy to correct dehydration and electrolyte imbalances, anti-emetics, analgesia and gastroprotectants as needed.
- If dogs show fever and/or an inflammatory leukogram with toxic changes or if they do not improve with symptomatic therapy, further work-up including faecal analysis for enteric bacterial pathogens can be indicated.

Difficulties and particularities

- Faecal culture or PCR should be performed if there are systemic signs of illness (fever, anorexia, abdominal pain, haemorrhagic diarrhoea), if other causes have been ruled out (see Figure 2). The interpretation of these results is challenging, because the presence of these bacteria is not synonymous with infection.
- PCR does not help to determine antibiotic sensitivity. A positive result only means the presence of the pathogen in the sample. The presence of these pathogens in healthy and sick patients complicates the interpretation of the results. (For example, *Salmonella* spp. or *Clostridium* spp. may be present in a patient with chronic diarrhoea but, also, in healthy patients). Results should be interpreted with care.
- Treatment failure may reflect antimicrobial resistance or persistence of clinical signs due to another unidentified cause.
- Antibiotics may have a negative impact and may promote dysbacteriosis (e.g. *C. difficile* proliferation).
- In case of infection with *Campylobacter or Salmonella* injudicious antimicrobial administration may prolong the carrier state and contribute to antimicrobial resistance. This is particularly true for animals with uncomplicated diarrhoea living with immunocompromised individuals in the same household.

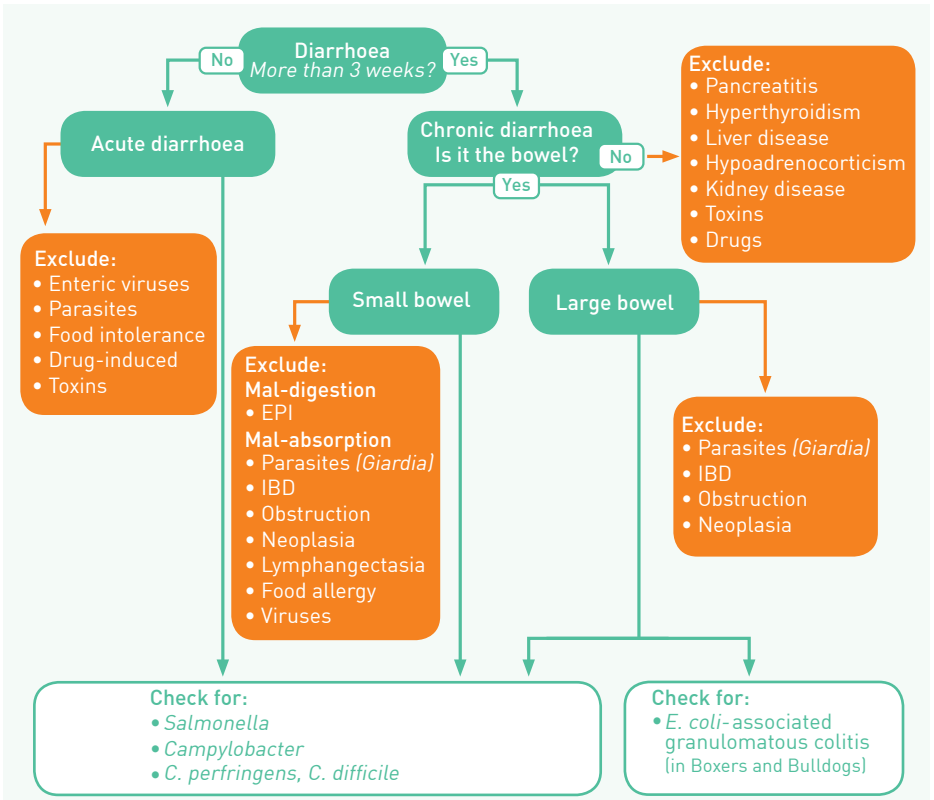

Figure 2 *- It is very important to follow a systematic* ***step-by-step work-up*** *prior to any antibiotic treatment.*

DISEASE FACT SHEETS

GASTROENTERITIS DUE TO BACTERIAL PATHOGENS

Campylobacter, Salmonella, Clostridium, E.coli

Bacteria involved

Bacteria	Prevalence
Campylobacter spp.	+ to ++++ (highly variable)
Salmonella spp.	+ to ++++ (highly variable)
Clostridium perfringens	+ to +++
Clostridium difficile	+ to ++
Escherichia coli (Boxer Granulomatous colitis)	Rare (in boxer-like breeds only)

Antibiotics that can be used

- **Antibiotic therapy is rarely justified in GI disease.**
- In general, bacterial gastroenteritis produces systemic signs (e.g. fever, lethargy, abdominal discomfort).
- Prior to antibiotic treatment, viral, parasitic, drug-induced, toxin-induced and food-responsive causes should be ruled out in acute diarrhoea, and systemic, small or large bowel causes in chronic diarrhoea (see Figure 2 of Common diarrhoea in dogs and cats, p.203).
- Only if a definitive diagnosis of bacterial infection is reached, may antimicrobial treatment be justified in animals manifesting systemic signs of illness (e.g. fever, lethargy, abdominal discomfort).

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Figure 1 *- Clostridial diarrhoea (faeces from the same cat as in Fig 2).*

- *Salmonella* and *Campylobacter* are well-documented zoonoses, but antimicrobial administration is not routinely advocated in uncomplicated cases.
- The relation between the presence of an enteric bacterial pathogen to clinical disease is not easy to establish, as most of these bacteria can also be detected in clinically healthy animals.

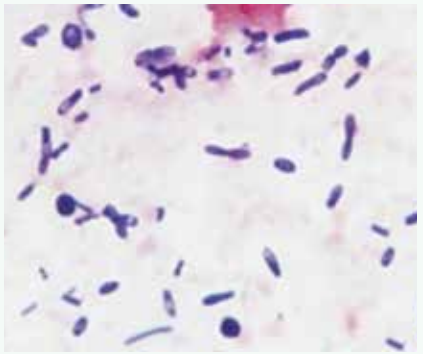

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Figure 2 *- Rectal cytology (Wright's stain) of the same cat as in Figure 1. Clostridiosis induced by treatment with clindamycin for dental disease.*

In general, bacterial gastroenteritis produces systemic signs (e.g. fever, lethargy, abdominal discomfort).

Diagnostic approach

- In cases of acute diarrhoea with systemic illness complete blood work, urinalysis, and faecal (parasitological and viral) examination is indicated. This allows evaluation of patients for signs of sepsis (left shift, toxic changes in neutrophils) and to exclude metabolic diseases (e.g. renal or hepatic disease, pancreatitis, hypoadrenocorticism) and viral (Parvovirus, Coronavirus) or parasitic infections. Abdominal ultrasound can be helpful to rule out obstruction, masses, pancreatitis, and involvement of other organs.
- The most commonly identified enteric bacterial pathogens in dogs include *Clostridium difficile*, *Clostridium perfringens*, *Campylobacter* spp., *Salmonella* spp., and *Escherichia coli* associated with granulomatous colitis in Boxers. However, **the causal relation between a positive result for one of these bacterial agents and clinical disease is not easy to establish in most cases, because these bacteria can also be detected in clinically healthy animals**.
- The methods for their identification are

DISEASE FACT SHEETS

GASTROENTERITIS DUE TO BACTERIAL PATHOGENS

Campylobacter, Salmonella, Clostridium, E.coli

often complex to carry out and interpret:

- *Clostridium difficile* can be identified by culture (specific media and anaerobic culture), antigenic ELISA or Polymerase Chain Reaction (PCR) assays, in combination with toxin analysis by ELISA or PCR;
- *Clostridium perfringens* presence can be demonstrated by culture (anaerobic) or PCR, in combination with toxin analysis by ELISA or conventional PCR or quantitative PCR toxin gene detection;
- *Salmonella* detection is done by specific selective culture or by PCR;
- *Campylobacter jejuni* can be detected by direct observation by cytological examination of stool samples, bacterial culture (special culture media and culture under microaerophilia for 72 to 96h) or molecular techniques (PCR).

Figure 3 *- Only systemically ill animals with confirmed bacterial gastroenteritis should be treated with antibiotics.*

Reasoning

Clostridium

In dogs with severe clinical signs, which tested positive for *C. difficile*, metronidazole can be tried, although there are not many data evaluating treatment in dogs[17]. *C. perfringens* infections should only be treated with antibiotics if animals are systemically ill. Ampicillin, erythromycin, metronidazole and tylosin are antimicrobials that were recommended for treatment[17].

Salmonella

Only systemically ill or immunocompromised dogs infected with *Salmonella* spp. should be treated with antibiotics. Treatment should be based on C&ST, if available, otherwise a combination of ampicillin and enrofloxacin has been advocated for empirical treatment.

Campylobacter

Similarly, dogs testing positive for *Campylobacter* spp. should only be treated if they are febrile and show systemic signs. In that case, erythromycin, azithromycin and fluoroquinolones have been proposed for treatment.

E. coli

For treatment of *E.coli*-induced granulomatous colitis, fluoroquinolones are the drug of choice. Although many strains show resistance to this antimicrobial class *in vitro*, most dogs respond *in vivo*. Note that treatment must be given for a full eight weeks, even if clinical response is much faster[17].

Difficulties and particularities

- Infection due to *Clostridium*, *Campylobacter* or *Salmonella* is often self-limiting and resolves with supportive treatment. **Injudicious antimicrobial administration may prolong the carrier state and contribute to antimicrobial resistance**. This is particularly true for animals with uncomplicated diarrhoea, creating an undue risk for any immunocompromised members of the household.
- Infection control measures and recommendations should be undertaken due to the zoonotic nature of both infections. Antibiotic treatment is an option for severely ill dogs and cats.
- Treatment failures may reflect antimicrobial resistance, infection with a non-pathogenic *Campylobacter* species or persistence of clinical signs due to another unidentified cause.
- Many veterinarians prescribe antibiotics if dogs show acute haemorrhagic diarrhoea and are systemically ill[12]. However, a recent study has provided evidence that in canine acute haemorrhagic diarrhoea syndrome (AHDS), antibiotics are rarely indicated[30].
- *C. difficile* was not found to be an important pathogen in dogs with acute haemorrhagic diarrhoea syndrome[1]. However, patients with AHDS should be monitored closely for fever or inflammatory changes on their leukogram, because these might be indicators for bacterial translocation and sepsis requiring antibiotic treatment (see Bacteraemia (sepsis), p.158).
- Basic practices of isolation, with proper cleaning and disinfection are the mainstays of infection control. Spores of *C. difficile* and *C. perfringens* are alcohol-resistant, but susceptible to bleach (1:10 to 1:20 dilution of regular household bleach) and accelerated hydrogen peroxide. Washing hands with soap and water should therefore be preferred over the use of alcohol-based hand sanitizers.

GASTROENTERITIS DUE TO BACTERIAL PATHOGENS

Campylobacter, Salmonella, Clostridium, E.coli

Treatment recommendations

Antibiotics that can be used if bacteria have been confirmed as the cause of diarrhoea in systemically ill animals:

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Campylobacter spp.	Erythromycin	20 mg/kg/12h PO	5-21 days
	Enrofloxacin[a,b]	5 mg/kg/24h PO, SC	5-7 days
Salmonella spp.	Amoxicillin, ampicillin	10-20 mg/kg/8h PO, IV	7-10 days
	Trimethoprim sulfonamides[c]	15-30 mg/kg/12-24h PO, IV	7-10 days
	Enrofloxacin[a,b]	5 mg/kg/24h PO, SC	5-7 days
Clostridium perfringens	Metronidazole	10-15 mg/kg/12h PO	5-10 days
Clostridium difficile	Metronidazole	10-15 mg/kg/12h PO	5-10 days
Escherichia coli in granulomatous colitis	Enrofloxacin[a,b]	5 mg/kg/24h PO, SC	8 weeks

[a] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[b] *Avoid use in growing dogs of large breeds.*

[c] *Avoid use longer than 3 weeks as risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks*[20].

DISEASE FACT SHEETS

HEPATOBILIARY INFECTIONS

Bacteria involved

Bacteria	Prevalence	Reported associations
Escherichia coli *	++ (15 to 40 %)	Aerobes + Anaerobes
Enterococcus spp.**	++ (15 to 40 %)	
Anaerobes (*Bacteroides* spp., *Clostridium* spp. and others)	++ (15 to 40 %)	

* *Most common Gram-negative aerobe*
** *Most common Gram-positive aerobe*

Antibiotics that can be used

Antibiotics that can be used while awaiting C&AST results (if the use of antibiotics is justified):

Pathogen 1: *Escherichia coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Ampicillin / Amoxicillin	3	4	
Amoxicillin + clavulanate	3	4	
Cefalexin / Cefadroxil	3	4	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Pradofloxacin[a,c]	4	5	

Pathogen 2: *Streptococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Ampicillin / Amoxicillin	4 - 5	4	
Amoxicillin + clavulanate	4 - 5	4	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

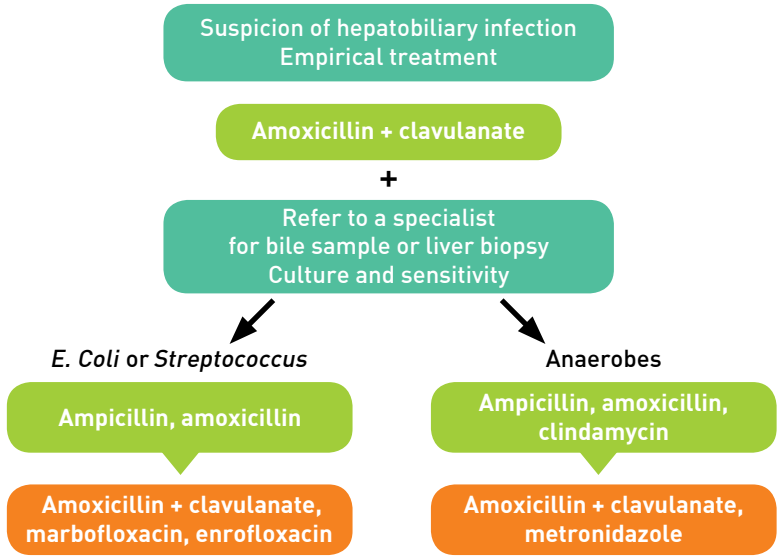
Pathogen 3: Anaerobes

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Ampicillin / Amoxicillin	4	4	
Clindamycin	5	5	
Metronidazole	5	5	
Amoxicillin + clavulanate	4	4	
Pradofloxacin[a,c]	3	5	

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Therapeutic approach



DISEASE FACT SHEETS

HEPATOBILIARY INFECTIONS

Treatment recommendations

First choice antibiotic

Some of them need culture and sensitivity before use (e.g. amoxicillin or ampicillin), as resistances are frequent (especially for *E. Coli*). While awaiting referral for sampling and culture and sensitivity, amoxicillin + clavulanate (second choice antibiotic) can be used empirically.

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Enterococcus* spp.	Amoxicillin	11-22 mg/kg/12h	Until clinical improvement, on average 6-8 weeks
	Ampicillin	10 mg/kg/12h	
Anaerobes	Amoxicillin	11-22 mg/kg/12h	
	Ampicillin	10 mg/kg/12h	
	Clindamycin	5.5-11 mg/kg/12h	

Second choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Escherichia coli *Enterococcus* spp.	Amoxicillin + clavulanate	12.5-25 mg/kg/8-12h PO	Until clinical improvement, on average 6-8 weeks
	Marbofloxacin[a]	2 mg/kg/24h PO (dogs and cats)	
	Enrofloxacin[a,b]	5 mg/kg/24h PO (dogs)	
Anaerobes	Metronidazole	Dogs: 10-15 mg/kg/12h PO, SC, slow IV infusion Cats: 8-10 mg/kg/12h IV, PO	
	Amoxicillin + clavulanate	12.5-25 mg/kg /8-12h PO	

[a] *Avoid use in growing dogs of large breeds.*

[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

Diagnostic approach

■ Several situations may be associated with bacterial hepatobiliary infections: septicaemia, hepatic abscesses (rare), granulomatous hepatitis (rare), cholangitis and cholangio-hepatitis (in cats), cholecystitis, emphysematous cholecystitis, (rare but associated with *Clostridium* spp.) and biliary peritonitis.

■ **Bile should be collected by ultrasound-guided or intraoperative cholecystocentesis or liver biopsies should be taken; aerobic and anaerobic bacterial**

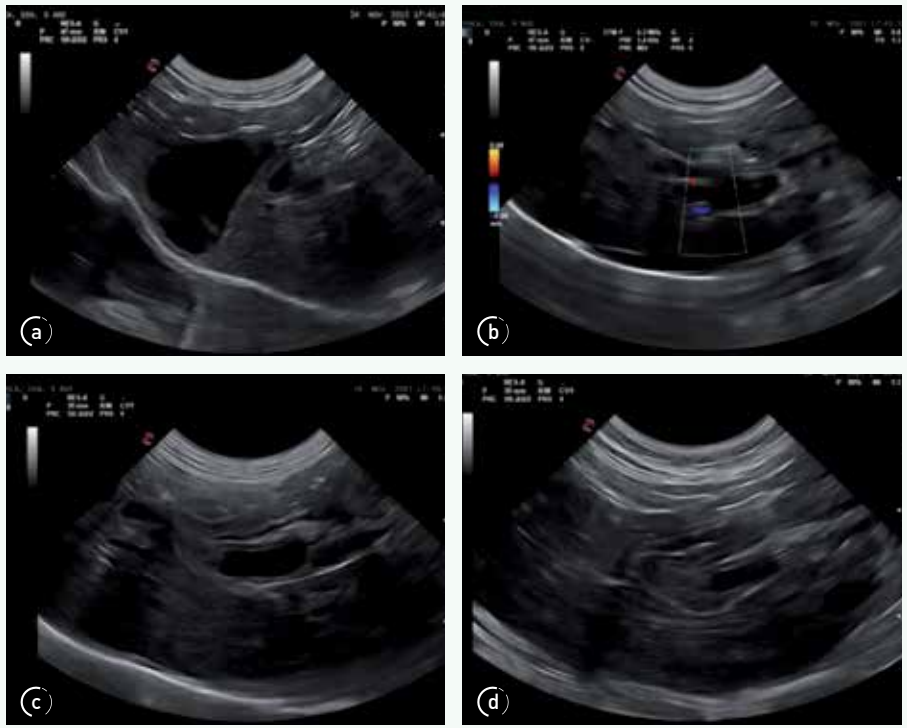


Figure 1 *- Suppurative cholangitis in a cat. Biliary obstruction in a cat with suppurative cholangitis/cholecystitis. Longitudinal image of the gallbladder (a) and common bile duct (b), which are both dilated and have a thickened wall. A small, moderately echogenic lesion is present in the distal common bile duct, just proximal to the duodenal papilla (c, d). This lesion was confirmed to be a pyogranulomatous inflammation. Ultrasound-guided cholecystocentesis was performed to obtain a sample of bile for culture (positive for Streptococcus).*

DISEASE FACT SHEETS

HEPATOBILIARY INFECTIONS

culture should be performed. Results of bile culture should be interpreted together with cytology results and clinical signs. In animals with hepatobiliary infection, the cytological examination of bile may show increased numbers of degenerated neutrophils, mononuclear cells and in some cases a mixed or monomorphic bacterial population[1].

- Biliary cultures are more likely to have positive results overall than hepatic cultures[8]. Cultures from cats tend to yield single bacterial growth (83%) compared to cultures from dogs, which tend to equally yield either multiple bacterial species or a single isolate[8]. If there is a risk of gallbladder leakage or rupture, cholecystocentesis should be avoided. Blood cultures may be useful. In human patients with acute cholecystitis, 30% to 40% of blood cultures are positive, and 50% to 95% of bile cultures are positive[7].

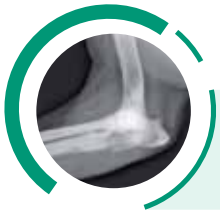
Reasoning

- Empirical treatment with amoxicillin + clavulanate can be done while waiting for the AST results. If the collection of bile is not possible by the veterinarian, this empirical treatment can be started while referring.
- For *E. coli*, amoxicillin and ampicillin would need culture before use as resistances are frequent. If sensitive, they should be the first-line treatment.
- The duration of antibiotherapy should be adjusted according to clinical signs, with treatments lasting several weeks often necessary.

Difficulties and particularities

- **In animals with jaundice or important hepatic damage** (revealed by hypoalbuminaemia, hypocholesterolaemia, hypoglycaemia, hypo-uraemia or an increase in plasma bile acids), **the antibiotic dose or administration interval should be adjusted**. Antibiotics associated with adverse liver effects or with extensive hepatobiliary activation, biotransformation or excretion should be avoided (e.g. doxycycline, lincomycin, erythromycin, sulfonamides, trimethoprim sulfonamides and chloramphenicol)[7]. The metronidazole dose is generally halved (maximum 7.5 mg/kg/12 h).

SURGERY



OSTEOMYELITIS

Bacteria involved

Bacteria	Prevalence
Staphylococcus spp.	+++ (35 to 65 %)
Streptococcus spp.	++ (15 to 40 %)
Escherichia coli	++ (15 to 40 %)

Reported associations
Mixed infection* in 30-60%
Anaerobes in up to 60%

** 30 % of mixed infections associate anaerobes (Bacteroides, Fusobacterium) and aerobes (Pasteurella, Klebsiella) when osteomyelitis was secondary to bites [3].*
Staphylococcus is more frequently isolated as the unique germ when only one germ is responsible for the infection[3].

Antibiotics that can be used

Antibiotics that can be used if the use of antibiotics is justified:

Pathogen 1: *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	2	
Clindamycin	4	4	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin[c]	5	3	
Gentamicin[d]	4	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: *Streptococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	2	
Clindamycin	4	4	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin	5	3	
Gentamicin[d]	4	3	

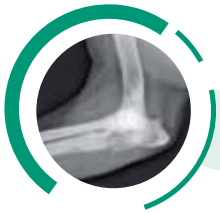
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 3: *E.coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	2	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin[c]	5	3	
Gentamicin[d]	3 - 4	3	

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*
[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

DISEASE FACT SHEETS



OSTEOMYELITIS

Therapeutic approach

Culture and sensitivity

↓

Empirical treatment while awaiting results + Implant removal if possible

Amoxicillin+clavulanate, cefalexin, cefadroxil, clindamycin

↓

Results of culture and sensitivity
De-escalate if possible, adapt if necessary + Implant removal if possible
Placement of antibiotic-impregnated implants if needed

Amoxicillin ± clavulanate, cefalexin, cefadroxil, clindamycin

Enrofloxacin, marbofloxacin

Gentamicin, cefovecin

Treatment recommendations

- Non-antibiotic treatment: remove infected implants, review unstable fixation, curettage of sequestra/abscesses.
- Local antibiotic treatment: placement of antibiotic-impregnated implants.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Staphylococcus spp. *Streptococcus* spp. *E.coli*	Cefalexin	15-30 mg/kg/12h PO	Up to 2 weeks beyond clinical and radiographic resolution of the infection.
	Cefadroxil	10-20 mg/kg/12h PO	
	Amoxicillin + clavulanate	12.5 -25 mg/kg/8-12h PO	
	Clindamycin	11 mg/kg/12h PO	

Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Staphylococcus spp. *Streptococcus* spp. *E.coli*	Marbofloxacin[a]	2 mg/kg/24h PO	Up to 2 weeks beyond clinical and radiographic resolution of the infection.
	Enrofloxacin[a,b]	5 mg/kg/24h PO	
	Gentamicin[d]	7 mg/kg/24h-IV Local beads[e]	
	Cefovecin[c]	8 mg/kg single dose SC (14 days)	Up to 2 weeks beyond clinical and radiographic resolution of the infection. (1 injection per 14 days)

[a] *Avoid use in growing dogs of large breeds.*

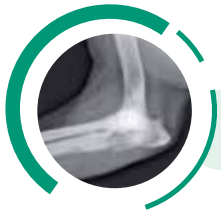
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

[e] *Unsuitable for long-term treatment (potentially nephrotoxic, systemic diffusion possible) – see www.iris-kidney.com/guidelines/index.html*

DISEASE FACT SHEETS



OSTEOMYELITIS

Diagnostic approach

- Osteomyelitis can be haematogenous, traumatic or post-surgical, and can be acute or chronic. The origin of infection must be determined to eliminate the cause, e.g. distant infection or a foreign body (gunshot, sutures, implants).
- Surgical treatment is usually mandatory to eliminate ischemic and necrotic tissue that harbour bacteria and protect them from antibiotics; to eliminate foreign bodies that form a biofilm, protecting germs from the immune system and from antibiotics; and to take samples for culture and sensitivity testing.
- **Bones can heal even in the presence of infection if the biological criteria for bone healing are present: stability, vascularisation of the bone and surrounding soft tissue.** When revising an infected fracture site, fracture stability needs to be assessed after debridement.
- Half of infections due to implants are secondary to colonisation of the surgical site by bacteria of the skin or the direct environment during surgery: *Staphylococcus aureus* or *S. pseudintermedius*.
- Bacteriology should include screening for anaerobes that may be present in case of telluric infections (e.g. soiled open fractures).

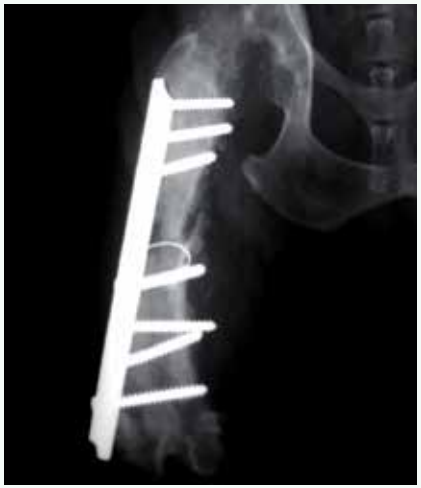


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***Figure 1** - Chronic osteomyelitis over a previous surgical repair of a femoral fracture. Despite the chronic infection and inadequate fixation, the fracture has healed but there is still bone resorption around the infected wire.*

Reasoning

- After surgery, effective broad-spectrum antibiotic treatment (e.g. cefalexin, cefadroxil, amoxicillin+clavulanate) should be provided until the result of the culture and sensitivity tests are known. Duration of treatment should be at least 4-6 weeks, and its clinical efficacy should be monitored (degree of lameness, pain upon deep palpation, radiographic evidence of bone healing).
- Most antibiotics have good bone penetration. Tetracyclines are not appropriate in the case of osteomyelitis as they are inactivated by calcium. Aminoglycosides are not a realistic option as the treatment will take weeks to months, but if they are used, the renal function should be regularly monitored (see IRIS guidelines for more information: www.iris-kidney.com/guidelines/index.html).

Difficulties and particularities

- Post-surgical chronic osteomyelitis is often diagnosed several weeks, months or even years after the operation. It is associated with the appearance of a fistula, local sensitivity at the level of the implants or lameness. It may be suspected during radiographic monitoring of fracture healing, in the case of delayed healing or implant migration.
- If the infection occurs after bone healing, simple removal of the implant and a short course of antibiotics are usually sufficient to resolve the infection.
- An acute postoperative infection, before healing is complete, can be a surgical challenge: an unstable fracture needs to be stabilised, which can be even more difficult after debridement of necrotic tissue in an infected context. Rigid osteosynthesis is essential and although external fixation is the method of choice in such cases, internal fixation is possible as long as implants are removed after healing.
- The use of antibiotic implants (beads or pellets) allows a high local antibiotic concentration for several days to weeks. They should not be considered as an alternative to debridement but as a complementary measure. Antibiotic implants are either absorbable (plaster of Paris, collagen matrix) or, more frequently, non absorbable (bone cement). Antibiotic implants can have a systemic diffusion. For implants, a follow-up of renal function is recommended.
- Blood-borne (haematogenous) osteomyelitis is rare. Radiographically, it is characterised by osteolytic and osteoproductive lesions and needs to be differentiated from bone tumours.
- Young, growing animals have a specific epiphyseal vascularisation that is potentially favourable for the sequestration of bacteria in the capillaries under the growth plate cartilage.

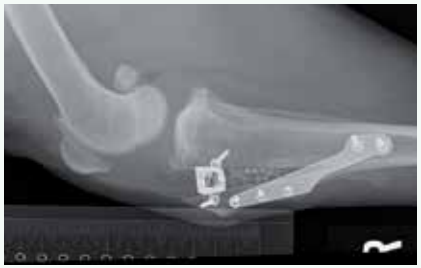

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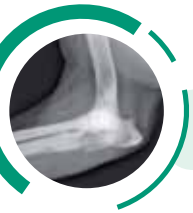
***Figure 2** - Implant of plaster of Paris impregnated with an antibiotic (tobramycin) in a revised TTA surgery. This pellet will induce bone formation in the osteotomy gap and will allow local high concentration of antibiotics.*

DISEASE FACT SHEETS



OSTEOMYELITIS

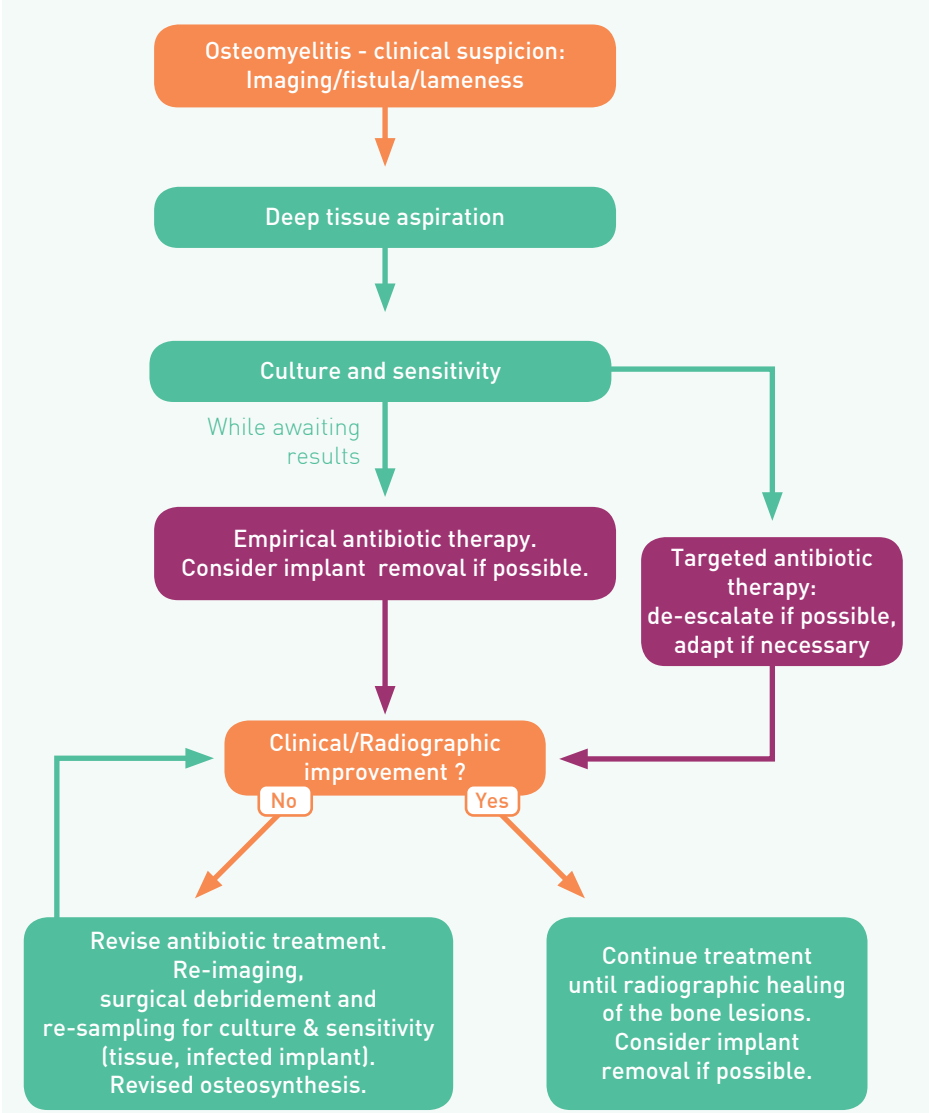
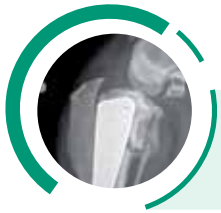


Figure 3 *- Diagnosis, treatment and follow-up for osteomyelitis.*

DISEASE FACT SHEETS



SEPTIC ARTHRITIS

Bacteria involved

Bacteria	Prevalence
Staphylococcus spp.	+++ (35 to 65 %)
Streptococcus spp.	++ (15 to 40 %)
Escherichia coli	+ (< 10-20 %)

Antibiotics that can be used

Antibiotics that can be used **if the use of antibiotics is justified:**

Pathogen 1: *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	2	
Clindamycin	4	4	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin[c]	5	3	
Gentamicin[d]	4	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: *Streptococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	2	
Clindamycin	4	4	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin[c]	5	3	
Gentamicin[d]	4	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 3: *E.coli*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	2	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin[c]	5	3	

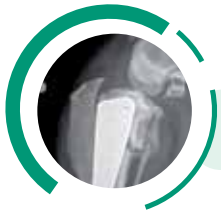
[a] *Avoid use in growing dogs of large breeds.*

[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

DISEASE FACT SHEETS



SEPTIC ARTHRITIS

Therapeutic approach

Cytology
Culture and sensitivity

↓

Empirical treatment while awaiting results

Amoxicillin+clavulanate, cefalexin, cefadroxil, clindamycin

↓

Results of culture and sensitivity
De-escalate if possible, adapt if necessary

Amoxicillin ± clavulanate, cefalexin, cefadroxil, clindamycin

Enrofloxacin, marbofloxacin

Gentamicin, cefovecin

Treatment recommendations

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Staphylococcus spp. *Streptococcus* spp. *E.coli*	Amoxicillin + clavulanate	12.5-25 mg/kg/12h PO	4 weeks minimum (2 weeks after clinical resolution)
Staphylococcus spp. *Streptococcus* spp.	Cefalexin	15-30 mg/kg/12h PO	
	Cefadroxil	10-20 mg/kg/12h PO	
	Clindamycin	11 mg/kg/12h PO	

Second choice antibiotic (with culture and sensitivity testing)

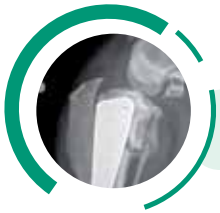
Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Staphylococcus spp. *Streptococcus* spp. *E.coli*	Marbofloxacin[a]	2 mg/kg/24h PO	4 weeks minimum (2 weeks after clinical resolution)
	Enrofloxacin[a,b]	5 mg/kg/24h PO	
	Gentamicin	7 mg/kg/24h IV Local beads[d]	
	Cefovecin[c]	8 mg/kg single dose SC (14 days)	

[a] *Avoid use in growing dogs of large breeds.*

[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

[d] *Unsuitable for long-term treatment (potentially nephrotoxic, systemic diffusion possible) – see www.iris-kidney.com/guidelines/index.html*



SEPTIC ARTHRITIS

Diagnostic approach

- Arthritis can be blood-borne (haematogenous), traumatic or postsurgical, and can be acute or chronic. The origin of infection must be determined to eliminate the cause, e.g. distant infection or a foreign body (gunshot, sutures, implants).
- Surgical treatment is mandatory to eliminate foreign bodies that form a biofilm, protecting germs from the immune system and antibiotics. It also allows taking samples for culture and sensitivity testing.
- Blood-borne septic arthritis is characterised by the infection of a single joint (as opposed to polyarthritis) in association with a major local inflammatory reaction (swelling, pain...).

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Figure 1 *- Severe septic arthritis of the carpus with marked oedema.*

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Figure 2 *- Arthrocentesis of the patient in Figure 1 allowed removal of frank pus.*

- The final diagnosis is made using arthrocentesis, yielding abundant, turbid synovial fluid. Cytology confirms a severe inflammation with polynuclear neutrophils, sometimes with bacteria (phagocytised).
- Culture and sensitivity testing of synovial samples can be a challenge as frequent false negatives occur. **Culture should include blood-based media incubated for at least 24 hours**.
- In the absence of foreign bodies, arthrotomy (debridement, biopsy of the synovial capsule) is only required in case of treatment failure. Irrigation and drainage of the joint will help counter the inflammation.
- In case of a traumatic lesion **penetrating** the joint, open flushing is required to ensure the removal of any foreign body and necrotic tissue.

Reasoning

- First-intention antimicrobial treatment (amoxicillin+clavulanate, cefalexin or clindamycin) should be prescribed for four weeks and should be continued for at least two weeks after resolution of the clinical signs. The treatment should be re-evaluated with the sensitivity results.
- In case of septic haematogenous arthritis, broad-spectrum antibiotics are recommended.
- Young growing animals are predisposed to septic arthritis. The use of fluoroquinolones should be limited as they can have a negative impact on the growth plate cartilage.

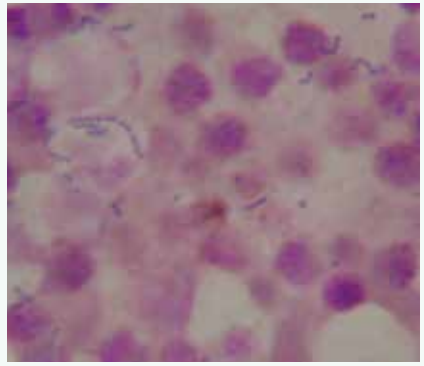

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Figure 3 *- Cytology of the arthrocentesis sample (Figure 2) showed degenerative neutrophils and cocci.*

Difficulties and particularities

- In the absence of clinical improvement after 2 weeks, treatment should be re-evaluated by joint lavage and re-sampling for new culture and sensitivity testing, followed by adjustment of the treatment. Sampling of synovial villi via small arthrotomy or arthroscopy is indicated. If re-sampling is considered, antibiotics should be discontinued for 24-48 hours to increase the odds of collecting a relevant sample.

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Figure 4 *- Articular lavage of a hock in a 7-month-old Gordon Setter with arthritis.*

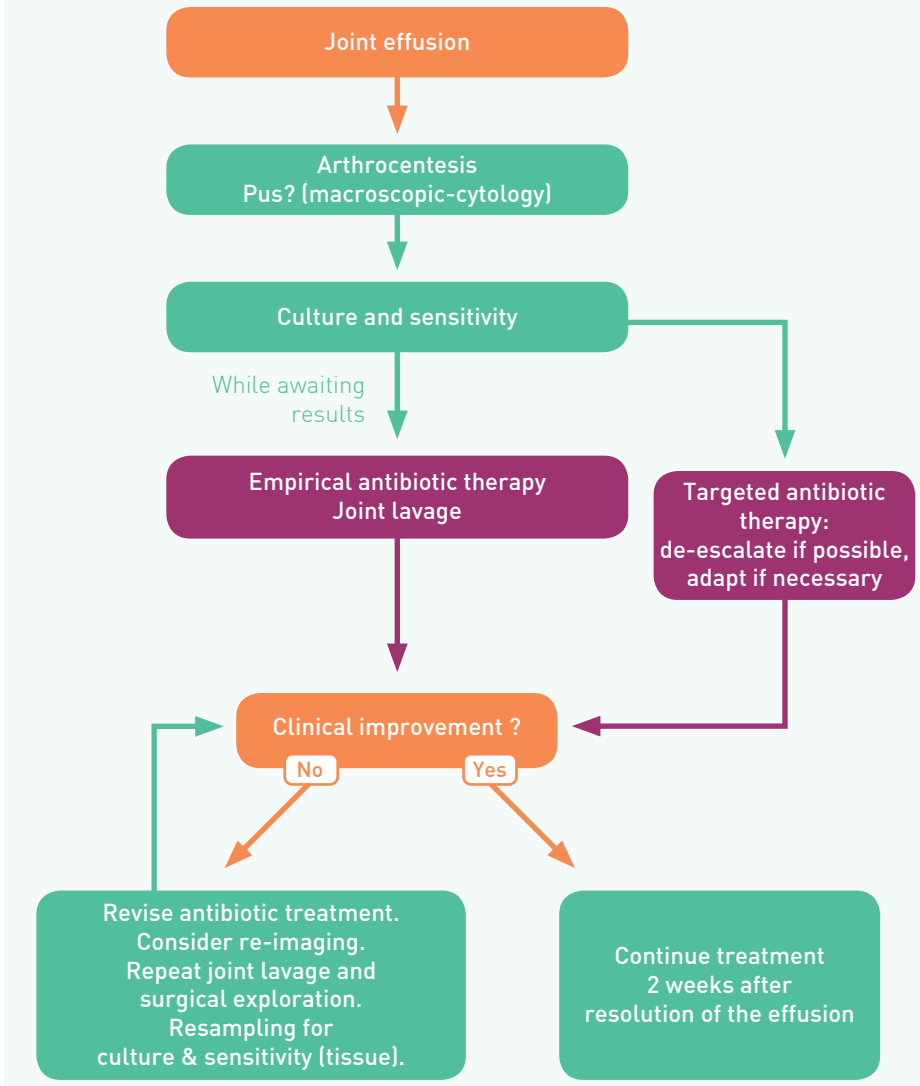


Figure 5 *- Diagnosis, treatment and follow-up for septic arthritis.*

Figures 6-7 *- Border collie showing severe pain and local oedema and sensitivity of the stifle, 4 weeks after extra-articular stabilization of a cranial cruciate ligament rupture. Perioperative view: lavage and debridement of a severe joint infection. The infected prothesis was removed and kept for culture and sensitivity.*

WOUND INFECTIONS AND ABSCESSES

Surgical debridement, abscess drainage and lavage are the first lines of treatment.
Antibiotics are reserved for contaminated/dirty wounds, deep lacerations or systemically impaired patients (fever or severe systemic infection).
Only a short course of antibiotics (4-5 days) is indicated after closure of open contaminated wounds.

Bacteria involved

Bacteria	Prevalence	Reported associations
Pasteurella multocida (cats)	+++ (35 to 65 %)	Aerobes + anaerobes (e.g. *Fusobacterium* in cats, *Bacillus* or *Clostridium* in dogs).
Staphylococcus spp. (dogs)	++ (15 to 40 %)	
Enterococcus / Escherichia coli (dogs)	++ (15 to 40 %)	

Antibiotics that can be used

Antibiotics that can be used: **only in presence of fever or systemic impairment**

Pathogen 1: *Pasteurella*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution		Treatment choice
		Wound	Abscess	
Amoxicillin	5	4	2	
Amoxicillin + clavulanate	5	4	2	
Cefalexin / Cefadroxil	5	5	2	
Marbofloxacin[a] / Enrofloxacin[a,b]	5	5	2	
Cefovecin[c]	2	5	2	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: *Staphylococcus* spp.

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution		Treatment choice
		Wound	Abscess	
Amoxicillin + clavulanate	5	4	2	
Cefalexin / Cefadroxil	5	5	2	
Marbofloxacin[a] / Enrofloxacin[a,b]	5	5	2	
Cefovecin[c]	2	5	2	
Gentamicin[d]	4	4	2	

Pathogen 3: Anaerobes

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution		Treatment choice
		Wound	Abscess	
Amoxicillin + clavulanate	5	4	2	
Cefalexin / Cefadroxil	5	5	2	
Clindamycin	5	4	2	
Metronidazole	5	5	2	
Cefovecin[c]	5	5	2	
Pradofloxacin[a,e]	5	5	2	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*
[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*
[e] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

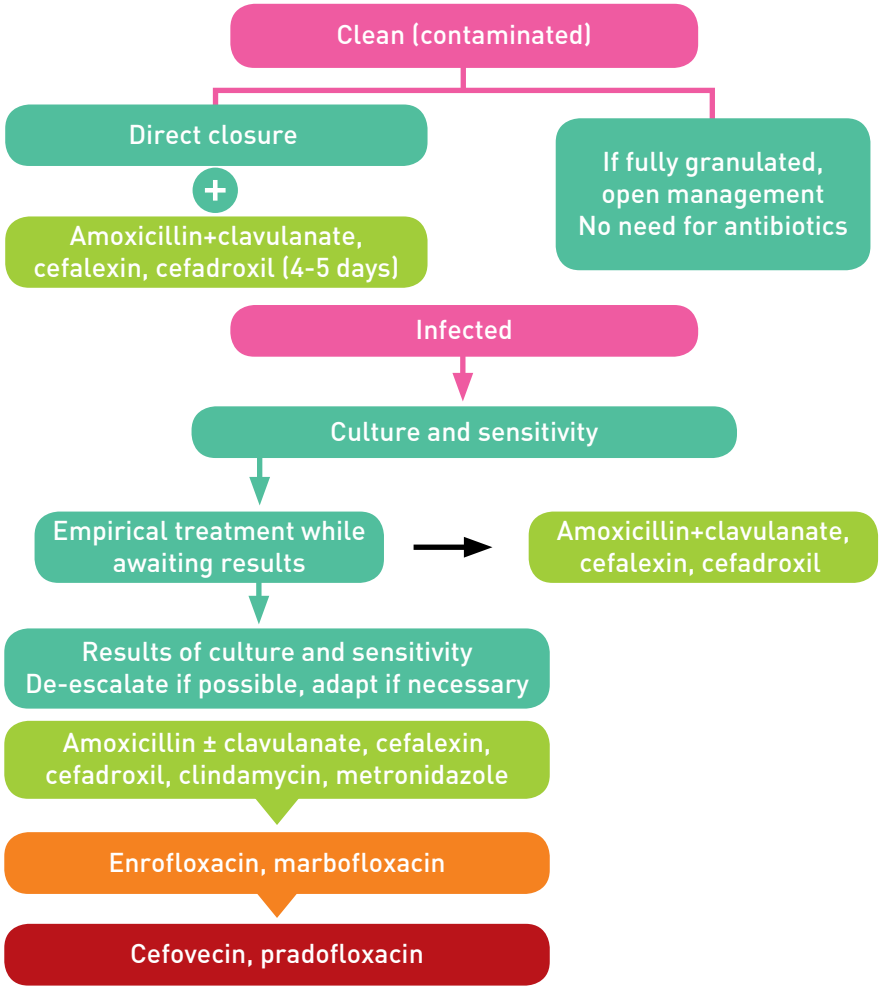
DISEASE FACT SHEETS

WOUND INFECTIONS AND ABSCESSES

Therapeutic approach

Abscesses: No antibiotic unless fever or severe systemic infection. Surgical debridement, abscess drainage and lavage usually suffice.

- **Open wounds** (by definition, any open wound is contaminated):



Treatment recommendations

- Non-antibiotic treatment: **surgical debridement, abscess drainage and lavage are the first lines of treatment**. Antibiotics are reserved for contaminated/dirty wounds, deep lacerations or systemically impaired patients.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Pasteurella multocida (cats)	Amoxicillin	11-22 mg/kg/12h	Clean: 4-5 days if closure. Dirty or deep: until establishment of healthy granulated tissue, usually 7-10 days.
Staphylococcus *Escherichia coli* *Pasteurella* Anaerobes	Amoxicillin + clavulanate	12.5-25 mg/kg/12h	
	Cefalexin	15-30 mg/kg/12h	
Anaerobes	Clindamycin	5.5-11 mg/kg/12h	

Second choice antibiotic (with culture and sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Pasteurella *Staphylococcus* *Pseudomonas*	Marbofloxacin[a]	2 mg/kg/24h	Clean: 4-5 days if closure. Dirty or deep: until establishment of healthy granulated tissue, usually 7-10 days.
	Enrofloxacin[a,b]	5 mg/kg/24h (Up to 11-20 mg/kg/12 h for resistant *Pseudomonas*)	

For footnotes, see p.235.

Diagnostic approach

- Open wounds can be classified as clean (surgically created in sterile setting), clean contaminated (clean wound with surgical opening of an internal tract or older than 6 hours), contaminated (as above with tract spillage or clean older than 12 hours) and dirty (pus, necrotic tissue).

- **In general, the flora within the wound is likely to be restricted to opportunistic environmental germs without extreme pathogenicity**. Infection is the result of the interaction between tissue, patient and germs (pathogenicity and quantity). Healthy tissues in a healthy patient

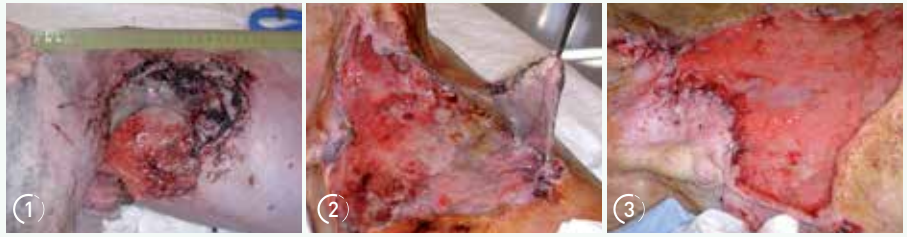
DISEASE FACT SHEETS

WOUND INFECTIONS AND ABSCESSES

will not develop infection and will therefore not need extensive antibiosis. Sick or weak patients will be more prone to develop infection even with non-aggressive bacteria.

■ Antibiotics are not an alternative to physical cleaning and debridement. Debridement of healthy granulation tissue around a wound is not always indicated as it helps seal the wound content away from the rest of the body.

■ Bacterial contamination can also be managed with the use of antiseptic solutions or specific dressings. **Topical antibiotic therapy is not routinely recommended**. Local exudation at the level of the wound is likely to dilute the antibiotics locally. This will lead to a concentration lower than the MIC, creating favourable conditions for the selection of resistant bacteria.



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Figures 1, 2, 3 *- Treatment of an open wound. This dog developed a deep abscess and skin necrosis in the flank following bite wounds.*
Figure 1 *- Aspect of the wound upon admission, with pus and clear necrotic tissue.*
Figure 2 *- Initial treatment involving surgical debridement and instauration of first-intention antibiotic therapy (amoxicillin+clavulanate). The wound was dressed and superficially debrided on a daily basis.*
Figure 3 *- Aspect of the wound after 7 days. Necrotic tissue or evidence of infection are no longer visible, the wound is almost completely covered by healthy (pink) granulation tissue, making surgical reconstruction possible.*

Reasoning

■ Abscesses should be treated by lancing, flushing and draining. Antibiotics may be considered in patients with systemic signs. Sampling for culture and sensitivity testing should be reconsidered if the treatment fails or if another abscess appears close to the first one or soon afterwards.

The systematic use of antibiotics in patients with a cutaneous/subcutaneous abscess without systemic signs is questionable. Surgical debridement, abscess drainage and lavage usually suffice. This does not apply for cases with extensive septic cellulitis.

■ Antibiotics are not indicated unless the wound is infected, contains devitalised tissues and/or the patient is in poor condition. Ideally, culture and sensitivity testing is performed prior to initiating antibiotic therapy. The bacteria most likely to be found in open wounds are *Staphylococcus* spp., *Streptococcus* spp. and *E.coli* (from the patient's skin/hair-coat), *Pasteurella* spp. and anaerobes in case of bite wounds.

■ ß-lactams (amoxicillin±clavulanate, cefalexin or cefadroxil) can be used empirically. If anaerobes are a concern (e.g. deep wounds with soil contamination or secondary to bites) trimethoprim sulfonamides, possibly associated with metronidazole or clindamycin, are indicated.

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Figure 4 *- Partial closure of the wound with an axial pattern flap. A small area has been left open to allow drainage and prevent tension. Antibiotics can be discontinued after 3 days as only healthy tissue remains.*

■ **Fluoroquinolones are not indicated for first-intention use unless sensitivity testing shows this is the only effective antibiotic**.

Difficulties and particularities

■ Regardless of size, open wounds should be treated with antibiotics until healthy granulation tissue is observed to adequately control bacterial growth.

- Chronic open wounds may harbour low-grade multiresistant bacteria that may prevent successful healing after closure/reconstructive surgery. In these cases, tissue samples should be taken of the granulation tissue in order to have a sensitivity test result at the time of the surgery.

- However, long-term use of antibiotics for the treatment of open wounds can lead to the selection of multiresistant *Staphylococcus* or *Pseudomonas* or even to yeast colonisation. If this happens, antibiotic treatment should be discontinued and be replaced by specific antibacterial dressings (honey or silver based) or even biological debridement (maggots) to achieve healing.

WOUND INFECTIONS AND ABSCESSES

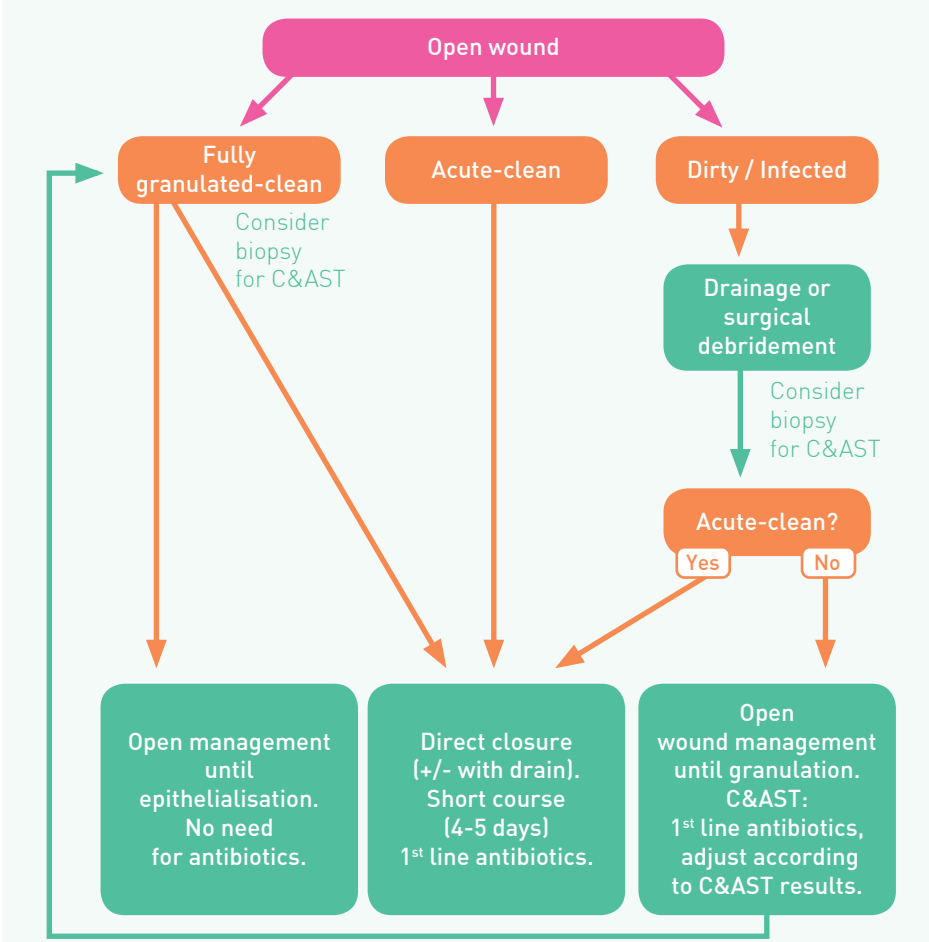
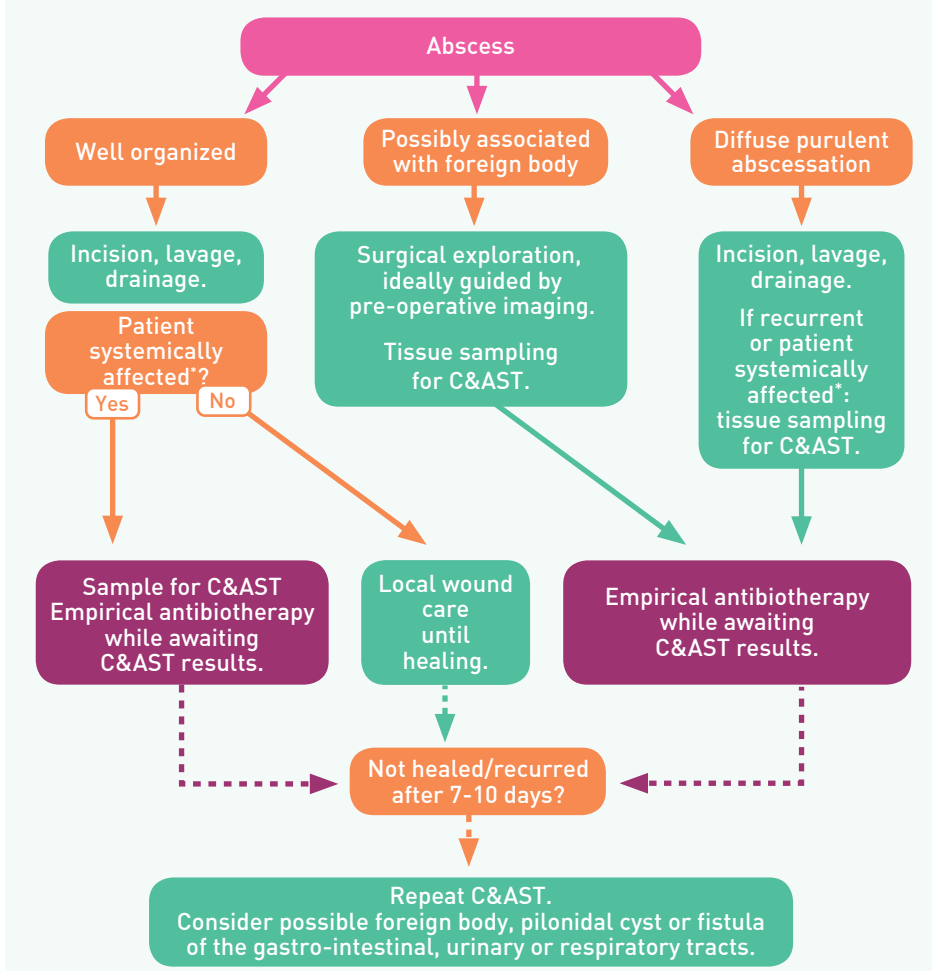


Figure 5 - Diagnosis, treatment and follow-up for an open wound.



* *Signs of sepsis: marked hyperthermia, lethargy, leucocytosis (with/without left shift), possible alteration of glucose levels*

Figure 6 - Diagnosis, treatment and follow-up for abscesses.

SEPTIC PERITONITIS

Bacteria involved

Bacteria	Prevalence
Escherichia coli	+++ (35 to 65 %)
Enterococcus spp.	++ (15 to 40 %)
Pasteurella spp.	+ (< 10-20 %)
Staphylococcus	+ (< 10-20 %)

Antibiotics that can be used

The first route for patients with septic peritonitis is IV, which may guide the choice of antibiotic.

Pathogen 1: Gram-negative (*E. coli*, *Pasteurella*, *Klebsiella*)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	3 - 4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefalexin / Cefadroxil / Cefazolin / Cefalothin	3	3	
Cefovecin[c]	5	3	
Aminoglycosides[d]	5	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 2: Gram-positive (*Enterococcus*, *Staphylococcus*)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin / Ampicillin	4	3	
Clindamycin	4	5	
Amoxicillin + clavulanate	4	3	
Cefalexin / Cefadroxil / Cefazolin / Cefalothin	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin[c]	4	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

Pathogen 3: Obligate anaerobes (e.g. *Clostridium*, *Bacteroides*, *Fusobacterium*)

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin / Ampicillin	4	3	
Clindamycin	4 - 5	5	
Metronidazole	5	3	
Amoxicillin + clavulanate	4	3	
Pradofloxacin[a,e]	4 - 5	5	

[a] *Avoid use in growing dogs of large breeds.*

[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*

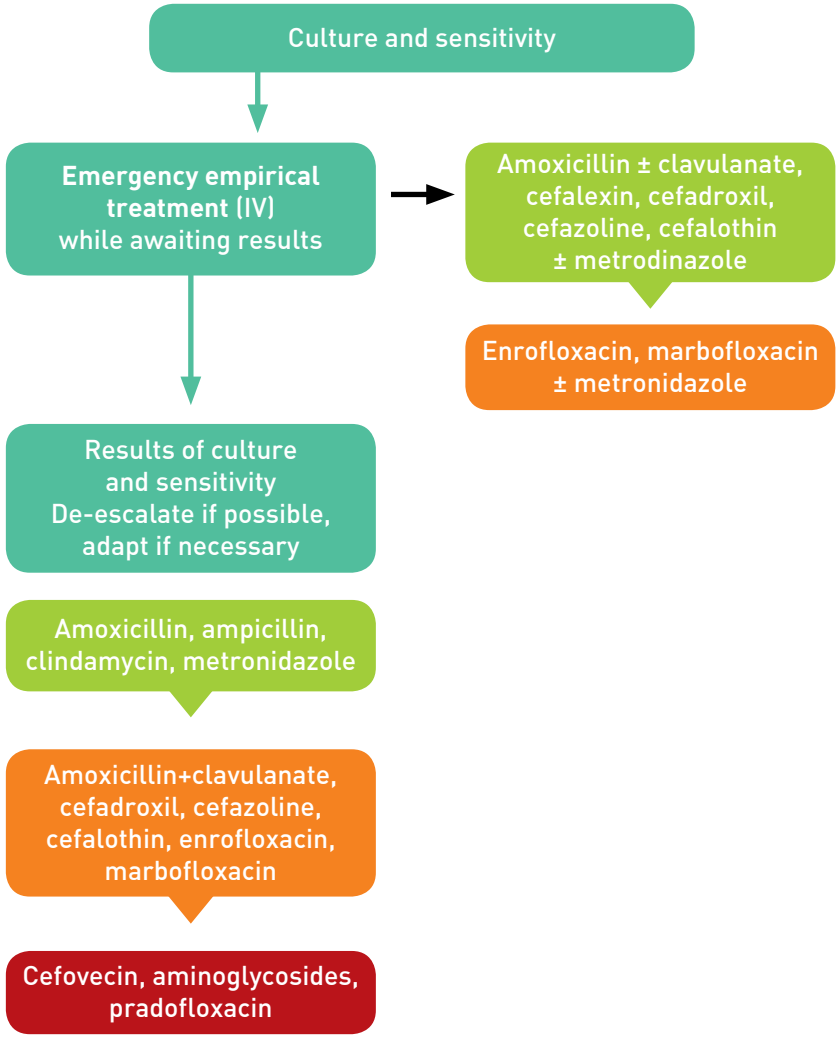
[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

[e] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

DISEASE FACT SHEETS

SEPTIC PERITONITIS

Therapeutic approach



Treatment recommendations

- Abdominal exploration, debridement, control and resolution of the source of contamination, abdominal drainage, feeding strategy to control and reverse hypoproteinaemia.
- **Sampling for culture and sensitivity testing is highly recommended before starting antibiotic therapy. It should be done with the initial sample collected for the diagnostic paracentesis or from tissue collected during exploratory laparotomy**. Initial clinical management will implicate the use of IV antibiotics. The use of aminoglycosides should be carefully evaluated as the general condition of the patient might make these antibiotics unsuitable due to their inherent toxicity.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Obligate anaerobes	Metronidazole	10-15 mg/kg/12h	2 weeks
Obligate anaerobes Gram-positive	Amoxicillin	20-25 mg/kg/8h	
	Clindamycin	5.5-11 mg/kg/12h	
Gram-negative	Amoxicillin + clavulanate	12.5-25 mg/kg/8 to 12h	

Second choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Mixed population of Gram-negative and Gram-positive aerobes and facultative anaerobes	Amoxicillin + clavulanate	12.5-25 mg/kg/8 to 12h	4 weeks minimum (2 weeks after clinical resolution)
	Amoxicillin	20-25 mg/kg/12h	
	Cefalexin	15-30 mg/kg/12h	
	Marbofloxacin[a]	2 mg/kg/24h	
	Enrofloxacin[a,b]	5 mg/kg/24h	

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*

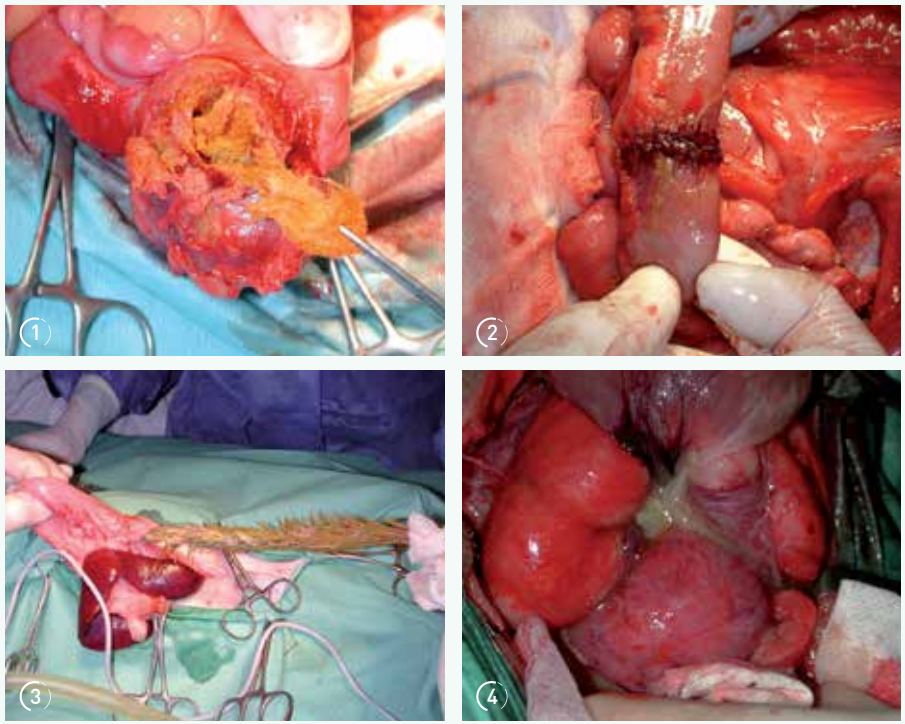
DISEASE FACT SHEETS

SEPTIC PERITONITIS

Diagnostic approach

■ Septic peritonitis is defined by an infection of the peritoneal cavity. Primary peritonitis due to haematogenous embolisation of bacteria is a rare condition that is poorly documented in veterinary medicine.

■ Secondary peritonitis is a much more frequent condition. **80% of cases are related to rupture of the gastro-intestinal tract**. This may be due to a trauma (e.g. road traffic accident, bite or gunshot wound, foreign body), failure of a surgical procedure or to tumour erosion. Septic peritonitis can also be related to the rupture of hepatic or pancreatic abscesses, or of the urogenital tract (e.g. pyometra or prostatic abscess).



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Figures 1, 2, 3, 4 *- Frequent causes of peritonitis including forgotten foreign bodies during abdominal procedures like a surgical sponge (Fig. 1), defective/leaking intestinal anastomosis (Fig. 2), intestinal perforation by foreign material (Fig. 3) or ruptured prostatic abscess (Fig. 4).*

■ Septic peritonitis requires surgical intervention to debride necrotic tissue, evacuate infected fluid and treat the origin of the infection. Septic peritonitis is also a medical challenge as inflammation and infection can lead to hypoproteinaemia, sepsis and ultimately multi-organ failure.

■ The prognosis is guarded with an overall survival rate of 50%.

Reasoning

■ Broad-spectrum antibiotics are recommended until results of the culture and sensitivity testing are available. IV bactericidal antibiotics are necessary for the management of this severe infection, preferably using an association of ß-lactam penicillins or first-generation cephalosporins, aminoglycosides and possibly metronidazole. Due to the poor state of animals presented with abdominal sepsis, aminoglycosides are often judged unsafe due to their nephrotoxicity. In these cases, fluoroquinolones are preferred until the results of sensitivity testing are known. Peritonitis is usually diagnosed as an acute infection in systemically unstable patients that will often require hospitalisation for 1 to 2 weeks. Usually, treatment is started by the IV route for several days until there is evidence of efficacy, then followed by oral treatment.

■ Multiple bacteria are frequently involved with abdominal sepsis, especially in dogs. Typically, intestinal rupture will be associated with Gram-negative strains (*E. coli*, *Klebsiella* and *Bacteroides*), but Gram-positive strains such as *Staphylococcus* or *Streptococcus* can also be observed. *E. coli* should be suspected in case of urogenital or biliary rupture. In cats, *Enterococcus* is frequently observed in urinary tract rupture.

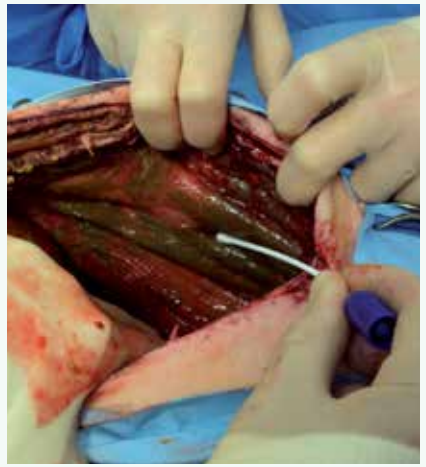

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Figure 5 *- Swabbing is part of the treatment for especially severe peritonitis requiring long term medication e.g. in this biliary peritonitis.*

DISEASE FACT SHEETS

SEPTIC PERITONITIS

Difficulties and particularities

- Hypoproteinaemia, presence of infected foreign material or necrotic tissue and effusion all need to be corrected to allow the antibiotics to be effective. Bacteria inside necrotic tissue or the effusion are protected from the immune system and out of reach of the antibiotics. Aggressive surgical debridement and effective drainage is paramount for the management of peritonitis.
- **Antibiosis is no substitute for surgery but should be used in combination with this treatment**.

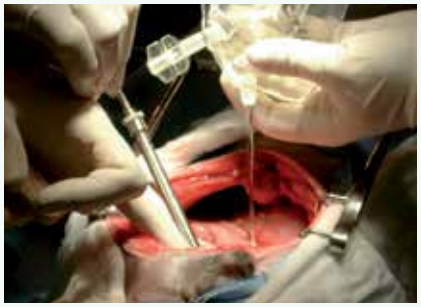

Figure 6 - Abundant irrigation and thorough aspiration are the main component of peritonitis treatment and should be started as soon as the peritoneal cavity is open.

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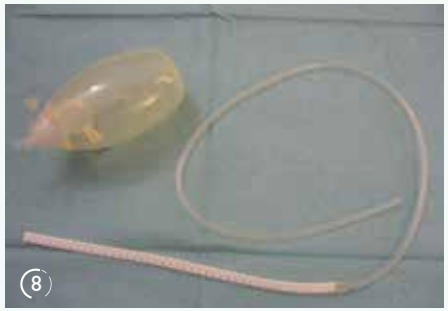

Figures 7, 8, 9 - Abdominal drainage achieved via an open abdominal wound which required frequent dressing changes under aseptic conditions and eventually surgical closure (2 to 4 days after the initial surgery) or the use of closed drainage system with Jackson-Pratt's drains and suction grenades. For these, daily cytology of the effusion collected from the drain (not from the grenade) is recommended. Daily volume of fluid effusion and cytology allow assessment of the progression of the inflammatory process.

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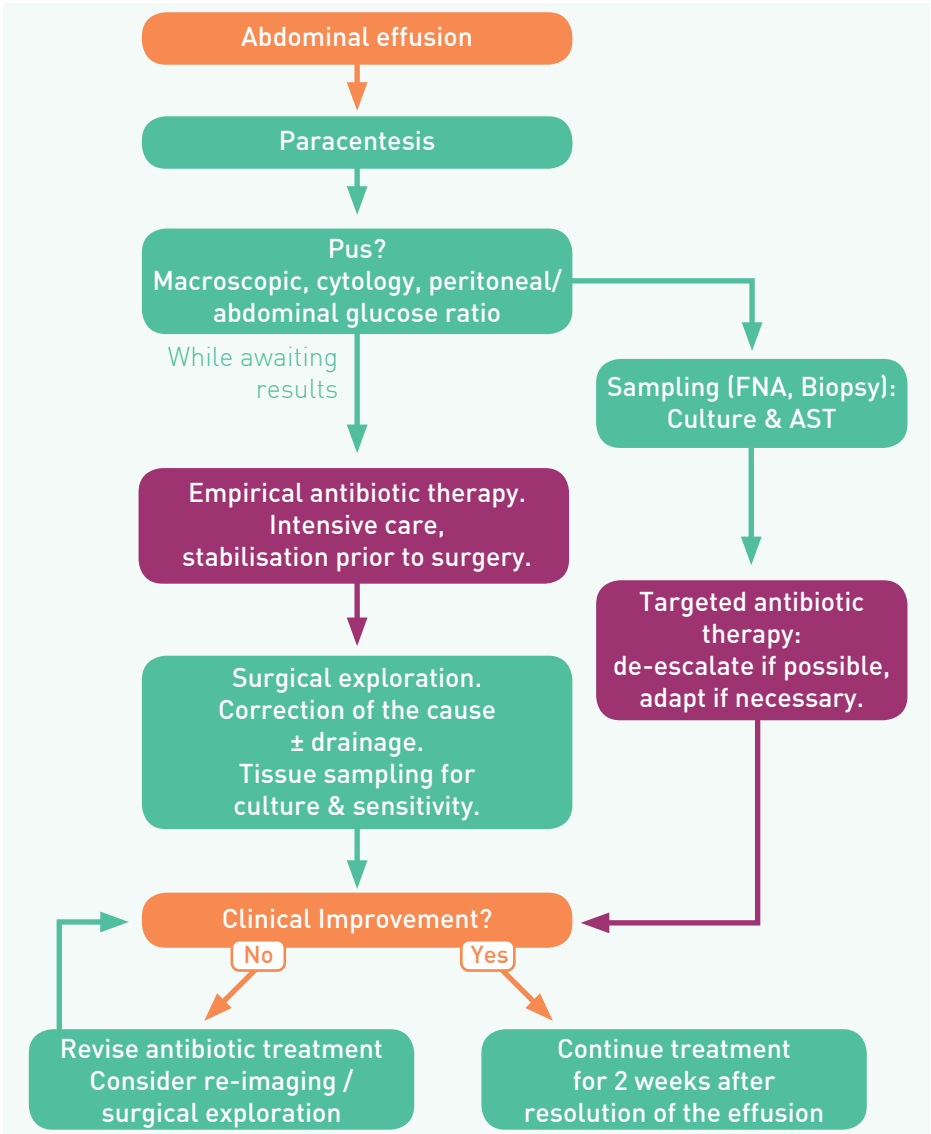

Figure 10 - Diagnosis, treatment and follow-up for septic peritonitis.

POST-OPERATIVE INFECTIONS

Bacteria involved

Bacteria	Prevalence	Reported associations
Staphylococcus pseudintermedius	+++++ (> 75 %)	Orthopaedic surgery, wound infections
Meticillin-resistant *S. pseudintermedius* (MRSP)	++ (15 to 40 %)	
Meticillin-resistant *S. aureus (MRSA)*	+ (< 10-20 %)	
Escherichia coli	++ (15 to 40 %)	Wound infections, gastro-intestinal tract, abdominal surgery, perineal surgery
Extended spectrum ß-lactamase (ESBL) and/or AmpC producing *E. coli*	+ (< 10-20 %)	
Enterococcus	+ (< 10-20 %)	
Anaerobes	+ (< 10-20 %)	Oral cavity, gastrointestinal tract, anal sacs
Pseudomonas aeruginosa	+ (< 10-20 %)	Wound infections, ear surgery

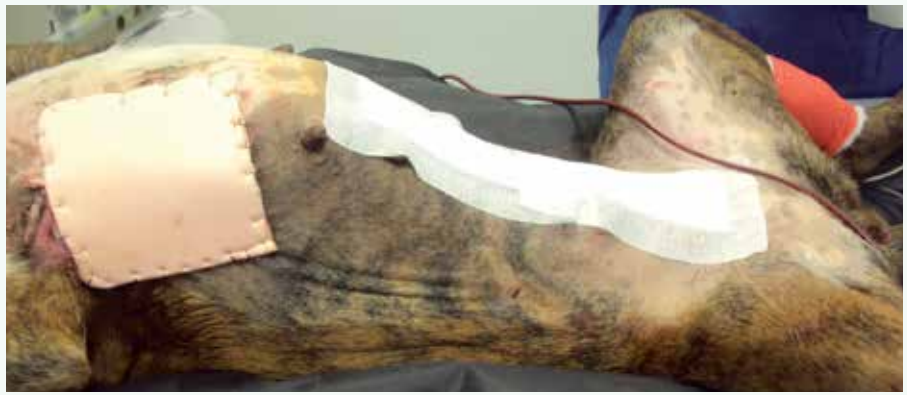

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Figure 1 *- Post-operative view. This boxer underwent an exploratory laparotomy. After the procedure, the wound was cleaned and a non-stick adhesive dressing has been placed immediately. On the side of the thorax, a mass has been removed where it may be challenging to keep the dressing in place. A non-adhesive foam dressing was sutured in place to protect the wound and if necessary absorb any secretion.*

Antibiotics that can be used

■ A sample should be taken for culture and sensitivity testing before initiating treatment. Response to treatment should be monitored and if no improvement is observed after 24-48h (in case of acute and potentially life-threatening infection) to 5 days (chronic infection), treatment should be revised and surgical re-sampling is required.

Pathogen 1: *Staphylococcus pseudintermedius*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	3	
Clindamycin	4	5	
Cefalexin / Cefadroxil	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefovecin[c]	4	3	
Aminoglycosides[d]	5	3	

Pathogen 2: Gram-negative

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	
Cefalexin / Cefadroxil	3	3	
Cefovecin[c]	5	3	
Aminoglycosides[d]	5	3	

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

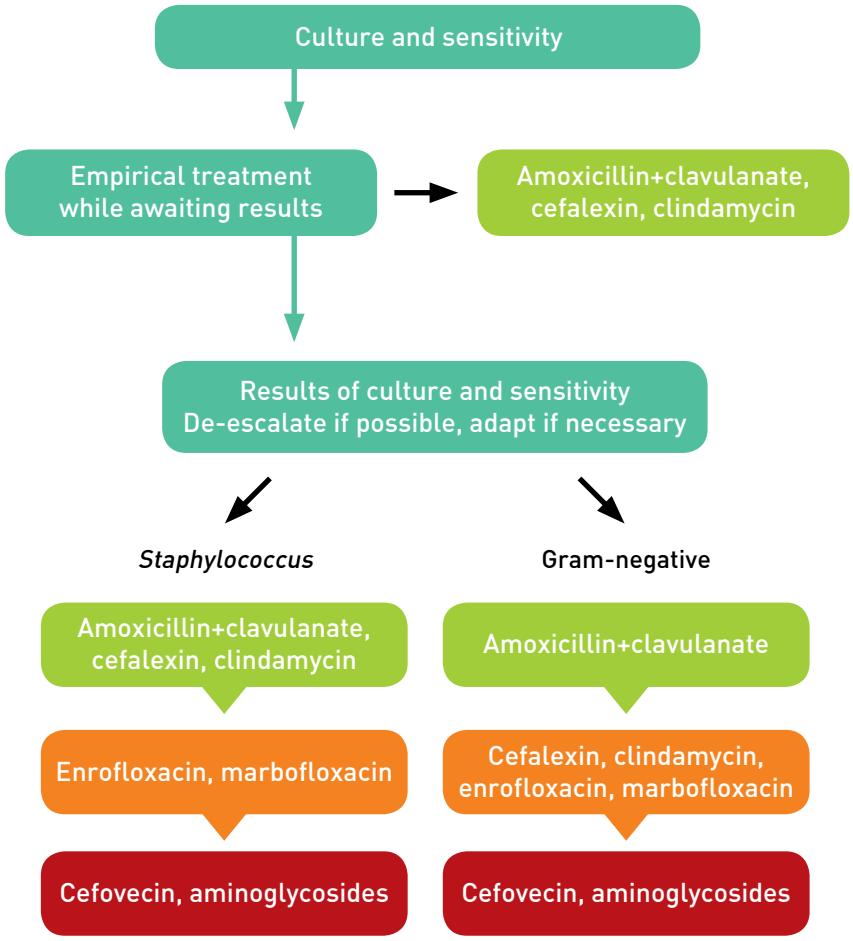
Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*
[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.htlm).*

DISEASE FACT SHEETS

POST-OPERATIVE INFECTIONS

Therapeutic approach



Treatment recommendations

■ The antibiotic should be available in an IV formulation for acute and potentially life-threatening infection (see below). Amoxicillin+clavulanate and pradofloxacin have better anti-anaerobic activity than other ß-lactams and fluoroquinolones, but metronidazole can be considered where there is specific concern over anaerobic contamination.

First choice antibiotic

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Gram-positive *(Staphylococcus)*	Amoxicillin + clavulanate	12.5-25 mg/kg/12h	Until evidence of healing
	Cefalexin	15-30 mg/kg/12h	
	Clindamycin	5.5-11 mg/kg/12h	
Gram-negative	Amoxicillin + clavulanate	12.5-25 mg/kg/12h	

Second choice antibiotic (after culture & sensitivity testing)

Pathogen involved	Antibiotics that can be used	Dosage	Duration of treatment
Gram-positive *(Staphylococcus)* or Gram-negative	Marbofloxacin[a]	2 mg/kg/24h	Until evidence of healing
	Enrofloxacin[a,b]	5 mg/kg/24h	
	Cefovecin[c]	8 mg/kg/14j-SC	
	Gentamicin[d]	8 mg/kg/24h	
	Amikacin[d]	10-15 mg/kg/24h	

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*
[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

DISEASE FACT SHEETS

POST-OPERATIVE INFECTIONS

Diagnostic approach

■ Infection of the surgical site may jeopardize the final results and be associated with minor (superficial wound breakdown) to potentially fatal complications (bacteraemia, sepsis).

■ Diagnosis of a postoperative infection is based on type of surgery and its risk of infection (clean/clean-contaminated/contaminated/infected) as well as on clinical and laboratory findings.

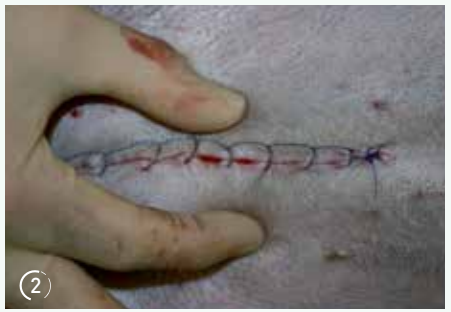
■ Postoperative inflammation (fever, local redness and sensitivity) is a normal response of the organism to surgical insult. However, if prolonged (more than 48 hours or starting 48 hours after surgery) or associated with local discharge, then infection is suspected.

■ Evidence of neutrophilia with left shift is another element arousing suspicion of active infection.

■ Prevention of post-operative sepsis is paramount. This is achieved by:

- strict control of the surgical environment;
- surgical technique: atraumatic, precise dissection, precise haemostasis;
- strict post-operative hygiene;
- antibiotic prophylaxis if indicated (see recommendation R.26 p.408).

■ In uncomplicated healing, the surgical wound is sealed by fibrin and oedema within 24-48 hours. During this period, the wound should be dressed for protection from colonisation by commensal flora (patient, environment). Special attention should be given to prevent contact with hospital surfaces (e.g. X-Ray or examination tables, kennels). The seal should also be protected from the patient – use an Elizabethan collar or additional dressing if necessary.



Figures 2, 3 *- Close-up view of a surgical wound closed with a continuous suture.*
Figure 2 - The wound at the end of the procedure. Despite good apposition, there is a slight tension, allowing some gaps to be seen.
Figure 3 - However, 24 hours later, the wound is fully sealed by the fibrin adhesion and local normal postoperative oedema.

Reasoning

■ A classic mnemonic to remember the usual causes of postoperative fever are the 5 W's: Wind (e.g. pneumonia, atelectasis, pleural space), Water (urinary tract), Wound, Walkings (or "Weins " for postoperative thrombosis – rare in veterinary medicine) and Weird drugs or "What did we do" for reactions to medications or line access.

■ If infection is suspected, samples should be collected in a sterile manner prior to treatment, either by reopening the surgical site or by percutaneous fine needle aspiration and submitted for culture and sensitivity.

■ **Samples of pus or a draining tract of open wounds are unreliable as they are likely to show no growth at all or growth of an opportunist contaminant rather than of the germs responsible**.

■ Initial empirical antibiosis is based on the surgical site and its likely contamination: *Staphylococcus* spp. in case of clean surgery (ß-lactams: amoxicillin, amoxicillin+clavulanate or first-generation cephalosporins) or based on the most likely contaminant for contaminated surgery (e.g. Gram-negative *Enterobacteriaceae* in case of GI tract surgery).

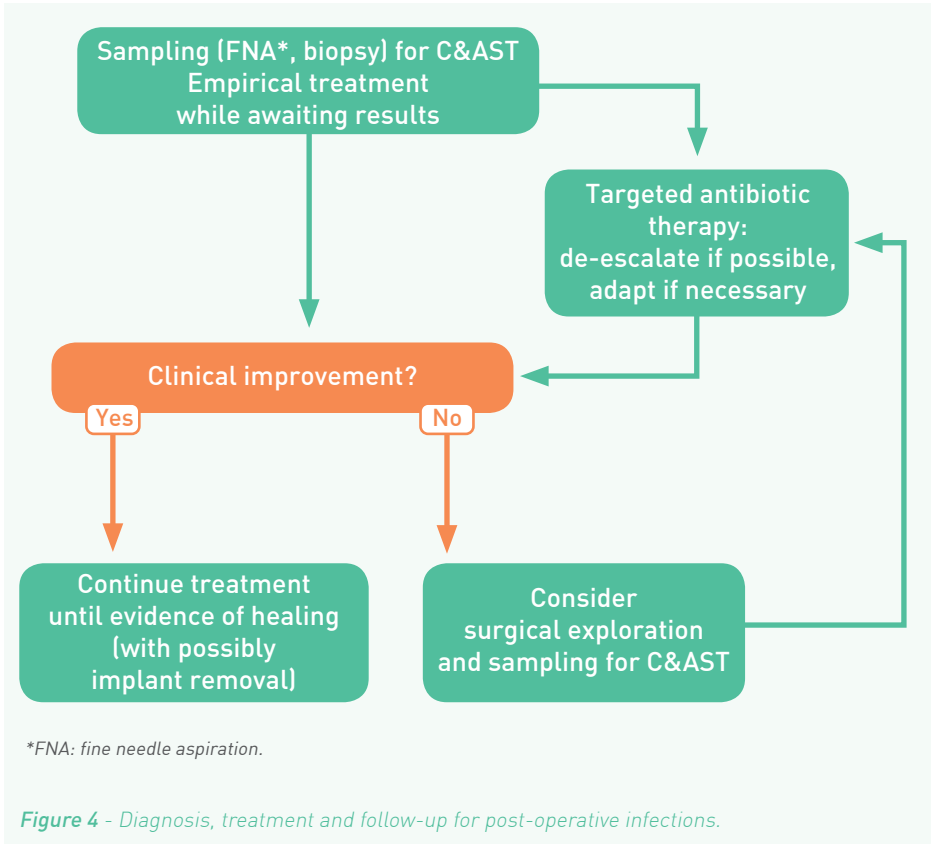
■ Postoperative infection can be classified as acute, sub-acute and chronic.

■ Chronic infections are usually associated with implants (usually orthopaedic implants but also prosthetic sutures, meshes). Common clinical signs include a discharging fistula with or without associated clinical signs (pain, lameness).

Difficulties and particularities

■ Antibiotics only have a very limited role in the management, as **infected implants will be covered by a biofilm protecting the bacteria from the immune system and from antibiotics**. Although they may limit bacterial growth, long-term use of antibiotics will favour the selection of resistant strains. Treatment requires removal of the implant, which is cultured to identify the germs involved, possibly followed by a short course of targeted antibiotics.

POST-OPERATIVE INFECTIONS



*FNA: fine needle aspiration.

Figure 4 *- Diagnosis, treatment and follow-up for post-operative infections.*

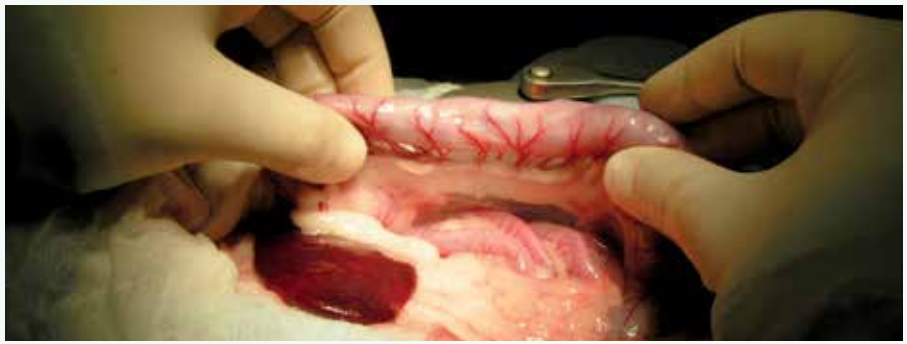
DISEASE FACT SHEETS

PREVENTION OF SURGICAL COMPLICATIONS (INCLUDING PERITONITIS AND ABSCESSES)

- Perioperative or postoperative antibiotic therapy is not justified.
- Exceptions: surgery > 90 minutes, orthopaedic procedures involving implants and/or contaminated sites.

Bacteria involved

Bacteria	Prevalence	Reported associations
Staphylococcus pseudintermedius	+++++ (> 75 %)	Orthopaedic surgery, wound infections
Meticillin-resistant *S. pseudintermedius* (MRSP)	++ (15 to 40 %)	
Meticillin-resistant *S. aureus (MRSA)*	+ (< 10-20 %)	
Escherichia coli	++ (15 to 40 %)	Wound infections, gastro-intestinal tract, abdominal surgery, perineal surgery
Extended spectrum ß-lactamase (ESBL) and/or AmpC producing *E. coli*	+ (< 10-20 %)	
Enterococcus	+ (< 10-20 %)	
Anaerobes	+ (< 10-20 %)	Oral cavity, gastrointestinal tract, anal sacs
Pseudomonas aeruginosa	+ (< 10-20 %)	Wound infections, ear surgery



Keep surgery time to a minimum – the risk of infection doubles every hour.

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Antibiotics that can be used

Antibiotics that can be used if the use of antibiotics is justified:

Pathogen 1: *Staphylococcus pseudintermedius*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin + clavulanate	4	3	1st line
Clindamycin	4	5	1st line
Cefalexin / Cefadroxil	4	3	1st line
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	2nd line
Cefovecin[c]	4	3	Last resort
Aminoglycosides[d]	5	3	Last resort

Pathogen 2: *E. coli* and *Klebsiella*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin / Ampicillin	4	4	1st line
Amoxicillin + clavulanate	4	4	1st line
Cefalexin / Cefadroxil	3	3	2nd line
Marbofloxacin[a] / Enrofloxacin[a,b]	4	4	2nd line
Cefovecin[c]	5	5	Last resort
Aminoglycosides[d]	5	5	Last resort

Pathogen 3: *Pseudomonas*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	1st line
Aminoglycosides[d]	4	3	2nd line
Ceftazidime	4	3	Last resort

Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Cefovecin is a third generation cephalosporin and therefore a last resort antibiotic. It should only be used if sensitivity testing indicates that other antibiotics would be ineffective or if oral administration of medication is not possible.*
[d] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

PREVENTION OF SURGICAL COMPLICATIONS (INCLUDING PERITONITIS AND ABSCESSES)

Pathogen 4: *Enterococcus*

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin / Ampicillin	4	3	
Amoxicillin + clavulanate	4	3	
Marbofloxacin[a] / Enrofloxacin[a,b]	4	5	

Pathogen 5: Anaerobes

Antibiotics that can be used	*In vitro* sensitivity	Tissue distribution	Treatment choice
Amoxicillin / Ampicillin	4	3	
Amoxicillin + clavulanate	4	3	
Metronidazole	4	3	
Pradofloxacin[a,e]	4	5	

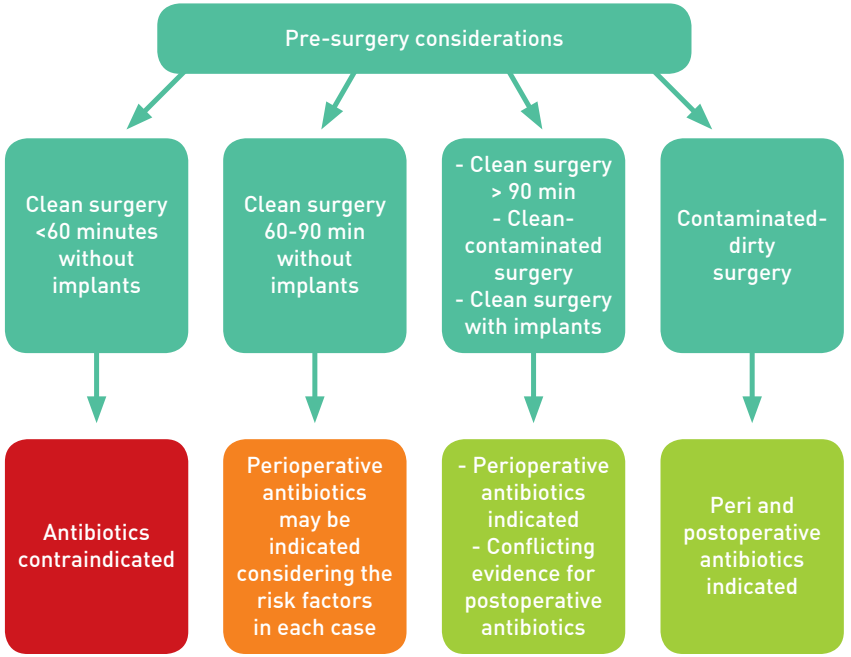
Sensitivity and distribution
1 = nil
2 = weak
3 = average
4 = good
5 = excellent

Treatment choice
1st line
2nd line
Last resort
Excluded for this indication

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[e] *Pradofloxacin is a last resort choice due to its very extended spectrum of activity and should only be used if a narrower spectrum antibiotic cannot be used (based on sensitivity testing results).*

Antibiotic treatment is contraindicated in clean surgery of less than 60 minutes without implants.

Therapeutic approach



Other recommendations

- Non-antibiotic treatment: high standards of patient preparation, tissue handling and surgical technique.
- Perioperative antibiotic treatment:
  - Antibiotic treatment is not a substitute for good surgical technique and patient care.
  - Antibiotic treatment is definitely contraindicated in clean surgery of <60 minutes without implants.
  - Perioperative antibiotics may be indicated in:
    - Clean 60-90min surgery involving implants or risk of contamination,
    - Clean surgery >90min,
    - Contaminated surgery.
  - Perioperative antibiotics reduce bacterial contamination and the risk of postoperative infection (see flow diagram).

PREVENTION OF SURGICAL COMPLICATIONS (INCLUDING PERITONITIS AND ABSCESSES)

- Initiate IV treatment 30-60 minutes before surgery starts.
- Repeat every 60-90 minutes during surgery according to drug pharmacokinetics (concentration-dependent antibiotics only need to be administered once).

• Post-operative antibiotics are indicated where there is pre-existing contamination and/or infection. There is conflicting evidence whether post-operative antibiotic treatment reduces surgical site infections in clean orthopaedic surgery.

• Antibiotic impregnated solutions, beads, gels and foams may be indicated if there is a high risk of contamination with antibiotic-resistant bacteria in appropriate sites – the choice should be based on prior culture and antibiotic susceptibility tests.

• Clinicians should adapt their approach if the factors affecting the patient change during the surgical procedure (e.g. prolonged anaesthesia, hypoxia, contamination etc.).

General approach

- High standards of patient and surgical site preparation (see box 1).
- Good tissue handling and surgical technique (see box 2).
- Sterile theatre environment (see box 3).
- High standards of post-operative patient care (see box 4).
- Perioperative antibiotic treatment if justified (see flow diagram on previous page).
- If possible, delay surgery until concurrent problems have been managed (skin infections, skin inflammation, hypothyroidism, hyperadrenocorticism, diabetes mellitus, obesity etc.).
- If possible, avoid concurrent use of potentially immunosuppressive treatment (e.g. glucocorticoids, ciclosporin, oclacitinib and cytotoxic drugs).

Reasoning

- Surgical interventions involve incisions through the skin or other barriers, tissue disruption, hypoxia and/or the use of implants that all predispose to contamination and infection.

Concurrent medical conditions may lower immunity and delay wound healing.

- Post-operative inflammation and pain may further compromise immunity and wound healing through loss of appetite and self-trauma.
- Most infections involve commensal bacteria - most commonly *S. pseudintermedius* from the skin and mucosal surfaces but also organisms from the oral cavity, gastro-intestinal tract or urogenital tract. Environmental bacteria are less common but can be acquired from contaminated environments or equipment. Animals colonised with MRSP or other antibiotic-resistant bacteria are at greater risk of post-operative infection with these bacteria.
- Veterinary premises and personal are risk factors for colonisation and infection with MRSP and MRSA.
- Routine use of antibiotics eliminates susceptible commensal bacteria, facilitating colonisation with antibiotic resistant bacteria.

Difficulties and particularities

- Staphylococci, *Pseudomonas* and other bacteria can form biofilms within 1-2 hours of surgery.
- **Biofilms facilitate adherence to implants, sutures, wound surfaces and the skin, and protect bacteria against antibiotics and phagocytic cells**.
- Use appropriate sutures, and consider absorbable and non-braided products wherever possible.
- Use smooth titanium implants where possible, and avoid damage during the procedure.
- Antimicrobial-impregnated implants may reduce contamination and biofilm formation, but controlled studies are required.

Box 1. Patient and surgical site preparation

- Clean gross soiling if necessary, but otherwise avoid pre-operative bathing (this can increase bacterial contamination).
- Protect open wounds with water-soluble jelly during clipping.
- Clip an appropriate area immediately prior to surgery – avoid traumatising the skin as this increases the risk of contamination and infection.
- Gently vacuum up clipped hair.
- Use drapes, gloves or bandages to protect contaminated areas (e.g. feet).
- Prepare the surgical site in two stages, working from the incision site to the periphery:
  - Outside theatre - clean the surgical site with 50:50 warm water/4% chlorhexidine.
  - In theatre - as above followed by an alcoholic solution with chlorhexidine or iodine using sterile gloves and swabs.
  - Avoid over-vigorous rubbing and skin trauma.
  - Lavage contaminated sites and open wounds.
- Apply sterile drapes - consider waterproof adhesive drapes in high-risk procedures.

DISEASE FACT SHEETS

PREVENTION OF SURGICAL COMPLICATIONS (INCLUDING PERITONITIS AND ABSCESSES)

Box 2. Good tissue handling and surgical technique

- Keep surgery time to a minimum – the risk of infection doubles every hour.
- Avoid tissue damage and necrosis.
- Effective haemostasis avoids excessive clots and preserves the blood supply.
- Good tissue apposition to eliminate dead space and avoid tension.
- Lavage clots, debris and contamination.
- Only use drains if necessary - consider closed sterile drains, use for the minimum time needed and prevent self-trauma.

Box 3. Sterile theatre environment

- Hand hygiene – chlorhexidine (preferred due to persistent activity on the skin) or iodine detergent washes followed by alcohol gels. Avoid over-vigorous scrubbing, as this results in increased colonisation and shedding of bacteria. Alcohol and disinfectant gels may be sufficient for subsequent hand disinfection if they are visibly clean.
- Closed gloving.
- Change gloves if punctured.
- Clean theatre-specific scrubs, footwear, hat and gloves.
- Single-use, water-resistant sterile surgical gowns.
- Sterile equipment for each patient.
- Effective cleaning and disinfection protocols for the theatre suites and non-sterile equipment.

Box 4. High standards of post-operative patient care

- Maintain oxygenation, blood pressure and tissue perfusion to avoid hypoxia - this increases the risk of infection.
- Maintain core and peripheral body temperature - hypothermia increases the risk of infection.
- Use analgesia and supportive care to avoid pain, and maintain nutrition and hydration.
- Follow high standards of hygiene when handling patients and wounds.
- Prevent self-trauma but make sure that collars do not interfere with feeding or become contaminated.
- Minimise hospitalisation and discharge patients as soon as they are clinically fit.

Routine use of antibiotics eliminates susceptible commensal bacteria, facilitating colonisation with antibiotic resistant bacteria.

DISEASE FACT SHEETS

PREVENTION OF SURGICAL COMPLICATIONS (INCLUDING PERITONITIS AND ABSCESSES)

Recommendations of use

- Ideally, the antibiotic should be available in an IV formulation for perioperative use (see below). Amoxicillin+clavulanate and pradofloxacin have better anti-anaerobic activity than other ß-lactams and fluoroquinolones but metronidazole can be considered where there is specific concern over anaerobic contamination.
- Please see recommendation R.19 p.366 for more information about MRSA/MRSP, ESBL/AmpC producing *E. coli* and *Klebsiella*, and multi-drug resistant *Pseudomonas*.

Pathogen involved	Antibiotics that can be used	Dosage
Staphylococcus spp.	Amoxicillin+clavulanate	12.5-25 mg/kg
	Clindamycin	5.5-11 mg/kg
	Cefalexin	15-30 mg/kg
	Marbofloxacin[a]	2 mg/kg
	Enrofloxacin[a,b]	5 mg/kg
Escherichia coli *Klebsiella* spp.	Amoxicillin / Ampicillin	10-15 mg/kg
	Amoxicillin+clavulanate	12.5-25 mg/kg
	Cefalexin	15-30 mg/kg
	Marbofloxacin[a]	2 mg/kg
	Enrofloxacin[a,b]	5 mg/kg
Pseudomonas	Marbofloxacin[a]	2-5 mg/kg
	Enrofloxacin[b]	5 mg/kg
	Gentamicin[c]	5-10 mg/kg
Enterococcus	Amoxicillin / Ampicillin	10-15 mg/kg
	Amoxicillin+clavulanate	12.5-25 mg/kg
Anaerobes	Amoxicillin / Ampicillin	11-15 mg/kg
	Amoxicillin+clavulanate	12.5-25 mg/kg
	Metronidazole	10-15 mg/kg

[a] *Avoid use in growing dogs of large breeds.*
[b] *In cats, use of enrofloxacin has been associated with a risk of retinal toxicity. Do not exceed 5 mg/kg.*
[c] *Aminoglycosides are potentially ototoxic and nephrotoxic; do not use in patients with renal dysfunction (see www.iris-kidney.com/education/prevention.html).*

DENTISTRY

PERIODONTAL DISEASE

Bacteria involved

Bacteria	Prevalence	Reported associations
Actinomyces spp.	++ (15 to 40 %)	Diseased periodontium will harbour Gram-positive and obligate anaerobes
Peptostreptococcus spp.	++ (15 to 40 %)	Multiple strain of anaerobes
Porphyromonas spp.	++ (15 to 40 %)	Normal flora is a mix of Gram-negative and anaerobic germs

Antibiotics that can be used

Antibiotic therapy is not indicated in periodontal disease. Antibiotics are only indicated where there is a risk of bacteraemia associated with periodontal bleeding.

Treatment recommendations

- Non-antibiotic treatment: the basis of treatment is the mechanical removal of the periodontal plaque and ultrasound descaling, flushing of gingival recesses and possibly dental extraction.
- Control of dental plaque is achieved by oral hygiene and tooth brushing.
- **Antibiotics are not an alternative to plaque removal and descaling**.
- Antibiotics may be considered to prevent disorders secondary to bacteraemia possibly favoured by periodontal treatment (see Prevention of infectious endocarditis, p.154).
- Antibiotic therapy may need to be considered after dental extraction and bone curettage in case of alveolar osteomyelitis due to severe periodontal disease.

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Figure 1 *- Descaling and mouth hygiene are the only way to prevent development of periodontal disease.*

Diagnostic approach

- The periodontium consists of the gingiva, periodontal ligament, cement and alveolar bone. First signs of periodontal disease include gingivitis which may lead to periodontitis and ultimately to tooth loss.
- The oral cavity is a naturally contaminated area with mainly anaerobic and Gram-negative bacteria. The periodontium is always covered with dental plaque, which is a biofilm harbouring and protecting commensals. *Actinomyces*, *Streptococcus* and *Pasteurella* are frequently isolated strains.
- The ratio between Gram-positive and Gram-negative bacteria varies with the state of inflammation of the gingiva. In healthy patients, Gram-negatives dominate. With increasing inflammation and periodontal disease, the ratio is inversed[1].
- The oral cavity is a highly vascularised area, making it very resistant to infection with excellent healing properties despite its high bacterial content.
- **Treatment of periodontal disease consists of hygiene with frequent tooth brushing and occasional descaling with assessment of the gingival recess. Antibiotics are rarely needed.**
- However, any periodontal procedure (descaling, extraction) is likely to be associated with bacteraemia. A short course of antibiotics may therefore be indicated in patients that:
  - are immunocompromised,
  - are elderly or systemically ill,
  - have large or critical implants (e.g. hip prosthesis, pacemaker, large non-resorbable mesh).
- Patients with severe oral infection or needing multiple extraction with obvious concomitant osteomyelitis, patients undergoing extensive oral surgery (e.g. mandibulectomy/maxillectomy) are also good candidates for antibiotherapy.

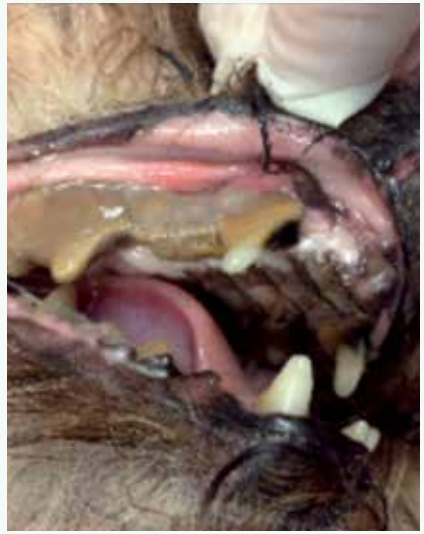

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Figure 2 *- Severe dental plaque (calculus). The plaque is a solid biofilm which is not affected by any kind of antibiotic.*

DISEASE FACT SHEETS

PERIODONTAL DISEASE

Reasoning

- Antibiotics effective against Gram-positive and anaerobic bacteria are used as an antibiotic prophylaxis when performing periodontal procedure. Intravenous medications are preferred and are injected 30 to 60 minutes prior to the procedure (cf. protocol for antibiotic prophylaxis). Antibiotic therapy should be discontinued 24 hours after the procedure as there is no indication for longer treatment unless specific conditions (immunodepressed or elderly patient) are involved.
- Culture and sensitivity testing is not routinely performed.

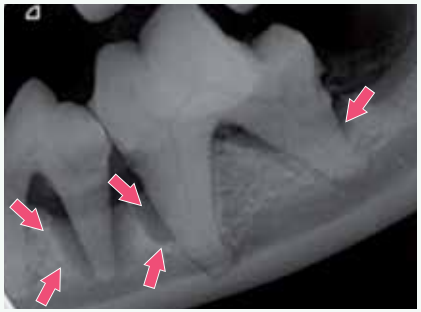

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Figure 3 *- Chronic gingivitis and periodontitis will lead to bone inflammation and infection. Note the bone lysis around the teeth root (pink arrows).*

Difficulties and particularities

- Long-term antibiotic treatment will affect the normal balance of the oral flora and is not recommended.
- Antibiotics should be given at the time of an oral intervention to control the potential risks associated with transient bacteraemia or post-operatively to ensure healing of the surgical site.
- Antibiotics should be broad-spectrum with a specific efficacy against Gram-negative and anaerobic bacteria. Usually amoxicillin+clavulanate or first generation cephalosporin can be used, possibly in association with metronidazole or clindamycin.
- If indicated, post-operative antibiotic treatment should be given for 1 to 2 weeks to allow mucosal healing.
- See Bacteraemia (sepsis), p.158, if antibiotic treatment is needed (risk of sepsis).

DISEASE FACT SHEETS

PART 2
RECOMMENDATIONS

APPROACH TO A SUSPECTED BACTERIAL INFECTION

RECOMMENDATIONS

R.1 How do I sample for cytology in cases of suspected bacterial infections?

- A sample should be collected from tissues and organs whenever there is suspicion of a bacterial infection. The material collected should be as representative as possible of the lesion.
- Preference should be given to the quality and not to the quantity of the cells collected, so that a thin, single cell layer should be obtained with smears. Large amounts of clustered cells are impossible to evaluate. Streaking of purulent material should be avoided, as it leads to nuclear stripes (artefacts) and renders the sample unassessable.
- The most suitable sampling procedure should be chosen depending on the organ or tissue sampled.
- Stains should be fresh and free from debris, as insufficient staining or foreign material can negatively influence the evaluation of the cytological sample.

Equipment

Required:

- slides with frosted ends (in order to write on it the name of the patient and the origin of sample),
- 5-10 ml syringes, 21 and 24 gauge needles,
- cotton swabs, transparent acetate tape,
- staining liquids,
- a good binocular microscope with 4, 10, 40 and oil immersion (preferably planar or semi-planar) 100x objectives, an adjustable light source and condenser.

Specimen collection

There are different cytological collection techniques, depending on the tissue, organ and type of lesion.

Fine needle aspiration biopsy

The fine needle aspiration (FNA) technique is useful for nodules, plaques, tumours, lymph nodes, solid organs (e.g. spleen, liver) and cystic organs (e.g. joints, bladder).

For **solid organ** tissues, a 21-gauge needle, connected to a 5 or 10 ml-syringe, is inserted into the centre of the lesion and a negative pressure of circa 2 ml is applied.

For **cutaneous and subcutaneous nodules**, the needle can also be moved back and forth into the lesion in different directions three or four times – without releasing the negative pressure. Before the needle is withdrawn from the lesion, the negative pressure is released in order to avoid the collected material entering into the syringe barrel. The syringe and the needle (containing the sample) are then separated, 5 ml of air is aspirated into the syringe, before needle and syringe are connected again. Finally the material is blown onto a glass slide by rapidly pressing on the syringe plunger. In case liquid or abundant material is deposited on the slide it can then gently be spread with another glass slide, with the exception of pus, which should never be streaked.

Fine needle insertion

This technique is very useful for very small solid lesions, if excessive bleeding is obtained by fine needle aspiration, and in the case of very delicate tissues and cells, such as lymph nodes. A 21-22-gauge needle alone (i.e. not connected to a syringe) is repeatedly inserted in the tissue, and connected afterwards to a syringe full of air, in order to blow on a glass slide the few cells collected by capillarity into the needle.

Impression smears

Impression smears are useful in open exudative lesions, greasy seborrhoeic skin and from freshly cut surfaces of extirpated tissues (e.g. skin nodules, liver biopsies). With this technique the glass slide is simply pressed repeatedly (not streaked) on the lesion. In a similar manner, pus from pustules and under crusts can be collected after gently opening the pustules or lifting the crusts with a small 25-gauge needle (Figure 1).

If extirpated nodules or pieces of tissue are cut for an impression smear, it is advisable to dry the sectioned surface on paper before pressing it on the slide, in order to avoid excessive blood contamination of the cytological preparation. The fresh section of the mass is then firmly applied to the glass slide in several successive imprints.

Figure 1 *- For impression smears, the glass slide is pressed repeatedly, and not streaked, on the lesion.*

R.1 How do I sample for cytology in cases of suspected bacterial infections?

Scrapings

Superficial scrapings performed with a number 10 or 20 blade on greasy seborrhoeic skin may be smeared on a glass slide, like "butter on bread", in order to look for bacteria or *Malassezia* yeasts.

Swabs

Material for cytology can be collected with a swab from fistulas, holes obtained after punch biopsies, ear canals or a greasy skin surface, particularly in areas where a direct impression smear with a glass slide would be difficult to perform, e.g. skin folds or interdigital spaces (Figure 2). The swab is then gently rolled (not streaked!) across the slide.

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Figure 2 *- A cotton swab is a useful tool for collection of material for cytological examination of exudates from fistulas or skin areas difficult to reach with a glass slide impression smear, such as interdigital spaces.*

Adhesive tape

Repeatedly pressing a strip of clear adhesive (acetate) tape on the skin, particularly on greasy areas, is a suitable technique for the collection of seborrhoeic material searching for surface bacteria and *Malassezia* on the keratin scales. Adhesive tapes can be stained in the same way as glass slides (see p.282).

Lavage

This technique is useful for cavities and tubular organs, such as the middle ear and bulla, the respiratory and reproductive tract. Generally, a few ml of sterile saline solution are injected into the cavity to be sampled and re-aspirated immediately thereafter. Readers are referred to textbooks for the particular methodology for each particular organ.

Centrifugation of liquids

Concentration by centrifugation should be considered for fluid samples with low cellularity. Centrifugation (speed as for separation of serum) of specimens is used to concentrate cells in a pellet at the bottom of a conical tube (e.g. Eppendorf). The supernatant is eliminated and cells are then resuspended in a small amount of the fluid remaining in the tube, which is then put on a slide and smeared.

Suggested technique by lesion and organ

Skin

Greasy skin: clear acetate tape, saline moistened cotton swab rubbing and rolling on a slide, superficial skin scraping and smearing on a slide.

Pustules, collarettes, crusts: gentle impression sampling on material obtained by opening a pustule or lifting a crust with a small needle. Do not streak pus!

Erosions, ulcerations, draining tracts: impression smear.

Papules and small nodules: fine needle insertion.

Plaques and larger nodules: fine needle aspiration, cotton swab sampling from holes obtained by punch biopsies (e.g. for bacterial culture or histopathology).

Ears

Cotton swab sampling and rolling on a glass slide. Centrifugation of lavage liquid from middle ear.

Sinus, bronchi and lungs

Centrifugation of lavage liquid from sinuses, nasal conchae, trachea, bronchi and alveoli. For highly cellular bronchi and alveoli samples, direct smears can be an alternative to centrifuged samples.

Eyes

Cotton swab sampling of the conjunctiva and cornea.

Urine

Take a urine sample by cystocentesis preferably, or if not possible, from spontaneous micturition.

Bones and joints

Cotton swabs of a fistulous tract or from where a pin emerges or directly from the orthopaedic implant (screw) after removal. Fine needle aspiration from joints, liquid from articular lavage if performed during treatment.

Large cavities

The sample can be taken by aspiration using a syringe.

Solid organs

Fine needle aspiration.

R.1 How do I sample for cytology in cases of suspected bacterial infections?

Fixation and staining

All cytological samples have to dry on the slide. Slides with greasy or waxy material or specimens collected with a moistened swab may be lightly heated on a match or lighter flame before staining.

Common rapid stains used in cytology include Romanowsky stains e.g. Diff Quik®, Hemacolor® (Figure 3). Samples are immersed 5-10 seconds each in ethanol (fixation), in the red stain and in the blue stain.

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Figure 3 *- Romanowsky-type staining (e.g. Diff Quik®), easy to carry out in practice for rapid cytology results. (a) From left, fixation liquid, red (eosinophilic) stain, blue (basophilic) stain. (b) Samples are immersed 5-10 seconds each in ethanol (fixation), in the red stain and in the blue stain. After staining, the slides are briefly rinsed under tap water (c) and air-dried (d). Adhesive tape preparations can also be stained (sticky side on the glass slide).*

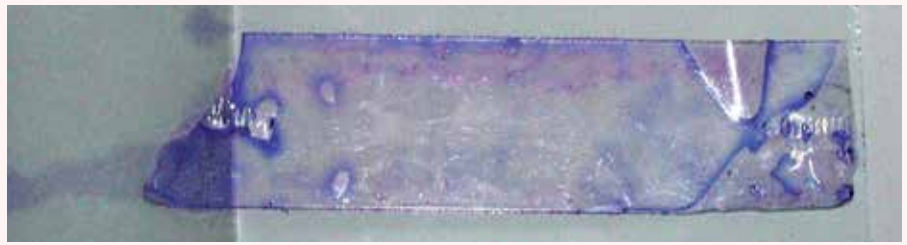

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Figure 4 *- A clear adhesive tape is pressed onto greasy skin, stained as other cytological samples, pressed on the glass slide and then excessive liquid is eliminated with a paper cloth.*

After staining the slides are quickly rinsed under tap water and air-dried. Adhesive (acetate) tape preparations can also be stained, rinsed and pressed to a microscope slide with the sticky face on the glass slide (Figure 4).

Rapid stain fluids should be changed frequently, in order to avoid artefact precipitates on the slides and to preserve their staining capacity. It is important to filter the liquids (a coffee filter will do) and to clean the containers periodically, as well as to replace liquids when expired or not performing as they should. It is advised to reserve a staining set for otitis samples, as it often gets contaminated by cerumen and debris.

Rapid stains are widely used by veterinarians in practice, however, they preclude fine cytological analyses. Other stains may need laboratory equipment, such as Gram, PAS (Periodic Acid Schiff), May-Gruenwald-Giemsa (MGM) and Ziehl-Neelsen (for acid-fast bacteria). ■

R.2 How do I interpret cytology results and how should I act upon them?

- Use only samples that are representative of the disease or lesion and of good quality.
- Scan the cytology slide in a systematic manner to identify the most representative and suitable fields to be evaluated.
- Decrease the chances of false negative or false positive findings by:
  - asking an expert cytologist to interpret the samples,
  - use clean containers and fresh staining liquids,
  - immediate processing of the sample.
- Note that:
  - negative samples do not exclude infection,
  - false positive samples are possible (contamination, artefacts),
  - the presence of intracellular bacteria, in neutrophils or macrophages, is diagnostic of infection,
  - the presence of bacteria outside or in the absence of inflammatory cells can also be diagnostic of infection, however contamination or artefacts should also be considered in these cases.

Significance of negative and positive cytological bacterial findings

Finding infectious agents in cytological samples depends on the disease, lesion, organ, sampling and processing procedures and experience of the person evaluating the slide.

Generally, the presence of bacteria inside inflammatory cells (Figure 1), such as neutrophils or macrophages, is diagnostic of an infection. However, a negative sample cannot exclude it. The probability of finding infectious agents is obviously greater if the samples are evaluated by an expert cytologist. If infectious agents are suspected in some types of preparations (e.g. wet-mounts or unstained urine sediment), then evaluation of a stained sediment smear may be helpful to confirm this suspicion.

Finding bacteria outside inflammatory cells can be diagnostic of infection, but it can also be the consequence of contamination or artefacts. Melanosomes, granular precipitate, mast cell granules, gel (ultrasound, topical therapies) and debris can all resemble bacteria to the inexperienced eye. Bacterial contamination of samples can occur if the staining liquids are not filtered and changed often.

Pseudomonas aeruginosa is able to grow and multiply in eosin for up to two weeks if the liquid is contaminated with organic debris. Liquid samples that are not smeared immediately, and are kept overnight at room temperature before examination, can serve as a perfect culture medium for contaminants or bacteria present in the sample. This can lead to their presence or number being greatly overestimated. It is thus very important to make one or more smears of the liquid for cytological examination immediately after sampling. All laboratory material, such as glassware and pipettes, should be clean, and disposable pipette tips should be used to prevent contamination. Staining solutions should be filtered frequently or as soon as foreign material is detected.

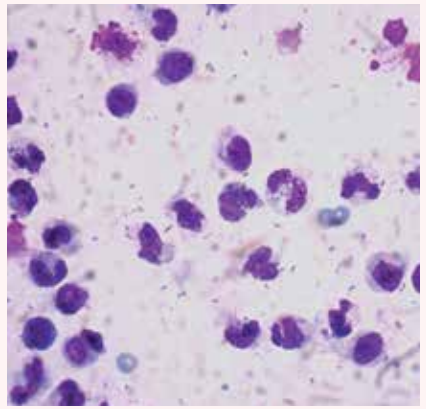

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Figure 1 *- Cytological appearance of a bacterial infection: bacteria are visible inside the cytoplasm of neutrophils. Note the swollen degenerate nuclei of the neutrophils. (Diff Quik® 100x).*

Methodology of the cytological examination

Slides should be evaluated in a systematic way under the microscope at increasing resolutions (4x, 10x, 40x and 100x with oil immersion). Initially the cellularity and representativeness of the sample, the quality of the smear and of the staining should be evaluated first at low power (4x). Groups of cells are then identified at 10x, these cells are later better observed at 40x and 100x. Special attention should be given to the feathered edge (if present), to the edges of the smear and within the smear to detect unusual features that may need subsequent examination at a higher magnification. The preparation should not be too thick and the cells should not be broken or streaked. Only intact cells should be examined and evaluated. The colour balance should be assessed: with modified Wright stains, nuclei should be clearly blue and eosinophils should have red-orange granules. If either colour is too weak, the sample should be re-stained in fresh dyes. There should be no artefacts or dirt, such as in old badly filtered and/or contaminated stains.

Interpretation of cytological samples

Once the quality and representativeness of the specimen have been evaluated, its nature should be determined.

In the case of inflammation, different immune cells such as neutrophils, eosinophils, macrophages, lymphocytes and plasma cells are observed, while in neoplastic samples, cellularity is usually more phenotypically homogenous.

Where inflammation is due to bacterial infection, neutrophils and/or macrophages are the main inflammatory cells to be expected and microorganisms may be observed in intra or extracellular positions. Signs of cell degeneration can be observed, such as nuclear swelling, karyorrhexis and karyolysis. Some microorganisms (such as pyogenic bacteria) elicit a neutrophilic infiltrate, others (such as some mycobacteria), a mainly macrophagic (granulomatous) or pyogranulomatous (a mixture of neutrophils and macrophages) infiltrate. Knowing the inflammatory pattern typical for each organ and disease is of great diagnostic help.

Finding bacteria inside neutrophils is diagnostic of pyogenic infections, such as those caused by *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *E.coli*, *Klebsiella*, *Proteus*, *Pasteurella* or *Corynebacterium*. In these cases, neutrophils are usually young (e.g. with 2-3 nuclear lobes) and show obvious signs of degeneration, such as nuclear swelling. Staphylococci can be differentiated from streptococci in that the former form

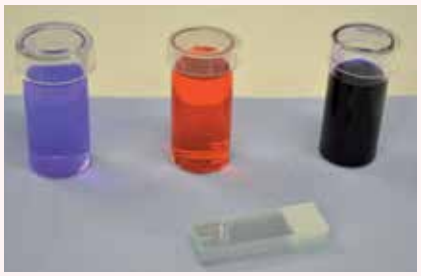

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Figure 2 *- Staining liquids must be filtered and changed often to avoid any bacterial contamination of samples.*

aggregates and the latter align in a linear pattern.

In cases where intracellular staphylococci are seen, and the animal presents with a first occurrence, previously untreated and uncomplicated infection, the choice of an empirical antibiotic (such as amoxicillin±clavulanic acid or cefalexin) is acceptable, as susceptibility patterns of staphylococci are well known.

However, as cytological identification of the bacterial species in case of rods is not possible, a bacterial culture and susceptibility test will be needed for the choice of an effective antibiotic.

Bacteria contained in macrophages usually belong to the genus *Mycobacteria, Nocardia, Actinomyces* and *Actinobacillus. Actinomyces* and *Nocardia* can also be seen as clumps of basophilic filamentous rods. As mycobacteria are acid-fast and do not take up rapid Romanowsky type stains, they are observed as "empty" spaces in the macrophage's cytoplasm. Depending on the mycobacterial species the number of microorganism present can be very variable. Ziehl-Neelsen stain can be useful to identify them as acid-fast bacteria, although a bacterial culture and/or a PCR will be needed for the precise definition of the mycobacterial species.

In cutaneous and otic samples large numbers of cocci or rods, in the absence of inflammatory cells, can be observed and are diagnostic of bacterial overgrowth (Figure 3). These conditions should be treated topically with antiseptics rather than systemically with antibiotics (e.g. if large numbers of bacteria without inflammatory cells are observed in specimens of organic fluids, then contamination and post-sampling bacterial growth should be considered). ■

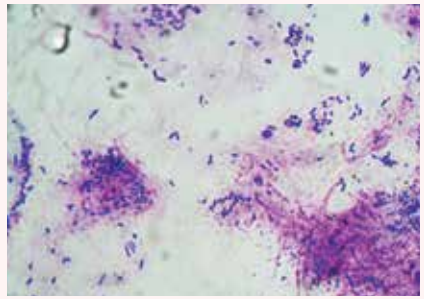

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Figure 3 *- Cytological appearance of bacterial overgrowth: numerous rods in the absence of inflammatory cells (Diff Quik®, 100x).*

Figure 4 *- Cutaneous and otic bacterial overgrowth should be treated topically with antiseptics rather than with antibiotics.*

RECOMMENDATIONS

BACTERIOLOGY

R.3 When is culture and sensitivity testing of little use, recommended, indispensable?

■ Culture and sensitivity testing is **contraindicated** for:

• Infections that require minimally invasive sampling procedures if:

- collection of the sample may complicate an acute infection (e.g. thoracoscopy in case of pneumonia),
- the patient suffers from abnormal clotting, or
- anaesthesia poses a high risk to the patient, especially when the risk of contamination with commensal bacteria is high (e.g. bronchoalveolar lavage).

• Infections for which correct interpretation of the culture results is hampered by the normal presence of commensal flora in the sample (e.g. faeces and nasal or vaginal swabs) unless the suspected pathogen may be cultured by selective media or detected by specific molecular tests.

■ Culture and sensitivity testing is **of little use** for those infections that are managed topically such as otitis externa and wound infections.

■ Culture and sensitivity testing is **recommended** in the following situations:

• if there is suspicion of a complicated infection (e.g. associated with underlying disease),
• if there are rods in cytology,
• if the patient has not responded to therapy,
• if the patient has a history of relapse or re-infection,
• if there is any reason to suspect infection with MDR bacteria.

■ Culture and sensitivity testing is **indispensable** in the following situations:

• if the patient is immunocompromised,
• if the infection is life-threatening.

■ Empirical therapy while awaiting the results from the laboratory is highly recommended for life-threatening infections, immunocompromised patients as well as for any infections causing pain or discomfort that cannot be easily relieved by non-antibiotic medication. Where possible, cytology can be used to try and guide empirical treatment choices.

In some patients the negative effects caused by the minimally invasive procedures required for sampling may exceed the positive effects derived from culture. Contraindications and disadvantages of minimally invasive abdominal and thoracic surgical procedures have been reviewed by Lansdowne et al.[2].

If no laboratory methods exist for detection of the suspected pathogen (e.g. use of selective media or molecular diagnostic methods), culture of biological specimens containing commensal bacteria is contraindicated because the results may be clinically irrelevant and lead to inappropriate or unnecessary antimicrobial therapy based on the resistance profiles of commensal strains[1]. The clinical significance of sensitivity testing is questionable for infections that require topical antimicrobial therapy because clinical breakpoints do not have any clinical predictive value when antimicrobial drugs are applied locally. This is because the drug concentrations achieved at the infection site by topical therapy are much higher than those obtained in serum after systemic administration.

Appearance of a primary culture contaminated with commensal bacteria. The presence of commensal bacteria is a major contraindication for culture of non-sterile biological specimens such as faeces and nasal or vaginal samples. Diagnostic processing of non-sterile biological specimens is only indicated if culture is aimed at detecting specific organisms for which selective media or molecular diagnostic methods are available.

R.3 When is culture and sensitivity testing of little use, recommended, indispensable?

Culture and sensitivity testing is recommended when:

- there is a high risk that empirical antimicrobial therapy may fail due to antimicrobial resistance,
- failure of therapy may lead to possible complication, or
- in case of life-threatening infections or immunocompromised patients where culture and sensitivity is regarded as indispensable because there is a high risk that therapy failure may result in serious health consequences for the patient.

Judicious antimicrobial use should not impact best practices in patient care.

This is why culture and sensitivity testing should be accompanied by empirical therapy in all situations where a delay in the start of the therapy may have a deleterious impact on animal health and welfare. In these situations the results of sensitivity testing can be usefully employed to correct the therapy if the cultured strain is reported as resistant to the antimicrobial used for empirical treatment. **It is the responsibility of the clinician to decide whether empirical therapy can be avoided based on the clinical conditions of the individual patient.** ■

TAKING AND SENDING SAMPLES

R.4 How should samples for bacterial culture and antibiotic sensitivity testing be taken (correctly)?

- As a matter of principle samples should be taken from a location where the infection is active.
- Particular precautions should be taken when collecting sterile specimens (urine, blood, etc.) to avoid contamination from the commensal bacteria inhabiting skin and mucosae.
- Sample types and techniques depend on the infection site.

Skin

Superficial or surface pyoderma

Sampling for bacterial culture from superficial lesions is ideally performed by opening an intact pustule and collecting the pus with a sterile cotton swab. In the absence of intact pustules, the sterile swab can be rubbed along the edges of a collarette, from under a crust or from open exudative lesions. Samples from seborrhoeic skin can be collected by vigorous rubbing with a swab.

Deep pyoderma

Sampling for bacterial culture from deep lesions should ideally be performed by fine needle aspiration from the depth of a lesion or by skin biopsy, after surface disinfection. Collecting exudate expressed from the depth of a lesion by squeezing it is also acceptable. The surface of deep lesions should always be disinfected prior to sampling. It is important not to use a persistent disinfectant (such as chlorhexidine) and to allow the alcohol to evaporate before collecting the sample.

Infected wounds and abscesses

Do not sample a discharging tract (pus is often sterile or contaminated by skin flora). Tissue biopsy is preferred with a biopsy punch or cold blade. For abscesses, sample the abscess capsule.

Otitis

For culture samples from the vertical canal, a sterile cotton swab is simply inserted in the ear. This can be performed without sedation in most animals. For samples from the horizontal ear canal or from the bulla, the animal has to be anaesthetised and sampling should be performed under video-otoscopic guidance. Care must be taken that the swab does not come in contact with the skin of the vertical ear canal. A myringotomy is necessary in case of middle ear infection with an intact tympanic membrane. This procedure should be performed by an expert dermatologist or otologist.

Good quality sampling is the condition for a good bacteriological analysis.

Osteo-articular system

Osteomyelitis and post-surgical infection

Do not sample a discharging tract (pus is often sterile and contaminated by skin flora). Ultrasound-guided fine needle aspiration of the surgical site may be useful. The best sample is a surgical biopsy of the necrotic bone and/or culture from the infected implant (screw/suture).

Septic arthritis

Do not sample a discharging tract (pus is often sterile and contaminated by skin flora). Sterile aspiration of the synovial fluid directly (immediately) placed in a blood culture vial. Consider surgical biopsy of the synovial capsule.

Periodontal disease

Sampling is rarely performed. In case of severe osteomyelitis, a surgical biopsy of the infected bone might be indicated. Consider conditions for possible anaerobic culture.

R.4 How should samples for bacterial culture and antibiotic sensitivity testing be taken (correctly)?

Urogenital system

Urine

Samples are taken preferably by cystocentesis or via sterile catheter, or if not possible, from spontaneous micturition.

Mastitis

A milk sample can be obtained manually or by direct aspiration from the gland for cytology and culture & AST.

Cystocentesis in a cat.

Endometritis/pyometra

Fluid for bacterial culture and sensitivity testing is collected transcervically from the uterus. If this is not possible, a cranial vaginal sample can be obtained by using a speculum and a guarded swab.

Vaginitis

A urine sample should be obtained by cystocentesis for urinalysis, culture and sensitivity testing, Furthermore, vaginal cytology and culture should be performed using a speculum and a swab.

Prostatitis

Sampling for prostatitis is made by passing a urinary catheter (aseptically placed) to the level of the prostate and massaging the gland to obtain fluid. If cysts are detected during ultrasonography then a FNA is a good option for sampling. In some cases, culture of a biopsy sample is required.

Epididymitis/Orchitis

Culture of semen is the preferred technique. However, it may be a challenge to obtain a good sample. FNA from the testicles can be performed but false negative results are quite common.

Digestive system

Stools

Intestinal bacterial infections are quite rare. Take a stool sample using a faecal loop or from the litter box (without litter contamination) and store as quickly as possible at 4ºC. Samples should be cultured in less than 24 h. A stained faecal smear has little to no diagnostic value for the diagnosis of bacterial associated diarrhoea.

Eyes

Conjunctivitis & Keratitis

Samples for cytology/AST should be taken before applying any stain (e.g. fluorescein or Bengal rose). Conjunctival/corneal cotton swabs are commonly used. Although, ideally, samples should be taken before applying local anaesthetics, their use probably does not modify cell morphology or culture results. In cats, a sample should be set aside for viral/chlamydial/*Mycoplasma* DNA detection.

Uveitis

Samples for sensitivity testing are not very useful. A complete blood work is recommended instead.

Eye sampling in a cat using a cotton swab.

Respiratory system

Rhinitis

Bacterial culture and sensitivity testing of nasal swabs or nasal discharge are not recommended. Fungal cultures of nasal biopsy samples can be indicated if primary fungal infection is suspected. If culture and sensitivity tests are required, nasal biopsies or a (deep) nasal flush should be performed. If *Mycoplasma* infection is suspected, special culture media or PCR testing are necessary.

Tracheobronchitis (dogs)

If dogs do not respond to empirical antibiotic therapy, tracheal or bronchoalveolar lavage (blind or endoscopic sample) or transtracheal wash is indicated to obtain material for cytology, quantitative culture, and sensitivity testing. If *Mycoplasma* or *Bordetella* infection is suspected, special culture media or PCR testing are necessary.

R.4 How should samples for bacterial culture and antibiotic sensitivity testing be taken (correctly)?

Pneumonia

Bronchoalveolar lavage (blind or endoscopic sample) or transtracheal wash is indicated to obtain material for cytology, quantitative culture, and sensitivity testing. If *Mycoplasma* or *Bordetella* infection is suspected, special culture media or PCR testing is necessary.

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Blind bronchoalveolar lavage procedure in a cat to obtain material for cytology, culture and sensitivity testing. Sterile sodium chloride solution (0.9%) is applied into the lower airways over a sterile catheter inserted into a sterile endotracheal tube and recovered via collection tube and mechanical suction.

Pyothorax

Sterile pre-surgical samples of pleural fluid obtained by thoracocentesis or in-surgery samples of necrotic tissue should be (immediately) placed in a blood culture vial. Observe the conditions required for both aerobic and anaerobic culture.

Other

Whole blood

In case of bacterial endocarditis or bacteraemia, take 2-3 blood samples at two separate sites.

Septic peritonitis

Sterile pre-surgical samples of abdominal fluid obtained by paracentesis or in-surgery samples of necrotic tissue should be (immediately) placed in a blood culture vial. Consider the conditions required for both aerobic and anaerobic culture. ■

Cat blood sampling.

R.5 Is it useful to take a sample in animals undergoing antibiotic treatment?

■ It may be useful to take a sample during or immediately after the end of antibiotic treatment in those situations where:

• culture and sensitivity testing are recommended or indispensable (see recommendation R.3) but a sample was not collected prior to the start of antibiotic treatment (e.g. some referral cases),

• there is clinical or paraclinical evidence of infection/inflammation indicating that the patient is not responding to empirical treatment,

• the clinician wants to evaluate the efficacy of therapy during a long course of treatment or before cessation of therapy.

■ Whenever possible, culture should be combined with cytology or other means of determining inflammation/infection when evaluating patients undergoing antibiotic therapy.

■ It is not useful to take another sample if the patient is responding to therapy, in those situations where a sample was collected prior to the start of treatment or culture is of little use (see recommendation R.3).

Ideally, samples for culture should be taken before antibiotic treatment to avoid results that are affected by the presence of antibiotic residues in the sample. However, culture of samples collected during therapy does not impact patient care. In fact, if a pathogen is inhibited by the presence of antibiotic residues in the specimen, it means that the organism is susceptible and therapy is likely effective.

Sampling during therapy

It is advised to take a sample during therapy in those cases where sensitivity testing is recommended or indispensable (see recommendation R.3) or if a sample was not taken prior to the start of therapy and no clinical improvements are observed 3-5 days after the start of therapy. In these cases, the culture results provide useful information on whether therapy should be discontinued (positive culture) or not (negative culture) based on bacteriological cure, thereby limiting the negative consequences on animal health associated with treatment failure.

Monitoring of outcome

Monitoring of the bacteriological outcome during therapy is also recommended for specific infections requiring long courses of antibiotic treatment, such as upper urinary tract infections and pyoderma[2,3]. In these patients, the purpose of this recommendation is to minimise the risk of relapse and the negative consequences of treatment failure.

Culture of samples taken during antibiotic treatment is unlikely to provide new information compared to samples collected before treatment. A study in human medicine showed that blood cultures taken from human patients during the initial 72 h of antibiotic treatment could be predicted on the basis of pre-antibiotic blood cultures[1].

In any case the microbiology laboratory should be informed if a sample has been collected during or shortly after antimicrobial therapy, so that this factor is taken into account in the report.

To confirm a bacteriological cure, samples are occasionally taken during antibiotic treatment. In a non-sterile environment, the culture may still be positive due to contamination by commensal bacteria. In that case, the decision to stop treatment should be guided by cytology results and clinical signs. ■

Swab and agar bottle.

R.6 What information should be supplied with the sample? Where should the sample be examined?

■ Information that should be supplied with the sample:

- patient name or identification number,
- patient species, age and sex,
- name and full address of the clinic submitting the sample,
- name and phone/e-mail contact of the veterinarian in charge,
- sample type,
- body site from which the sample was collected,
- date of sample collection,
- clinical diagnosis and any relevant history (e.g. suspected relapse, reinfection or concurrent conditions),
- cytological findings (if relevant),
- information on antimicrobial therapy (with dose, duration and drug),
- type of culture and tests requested.

■ Where should samples be sent for examination:

- samples should be analysed by an appropriate human or veterinary diagnostic laboratory,
- human laboratories can be used if they are qualified in processing animal samples,
- rapid in-house bacteriological diagnostic tests exist, but little information is available regarding their validity.

Veterinary diagnostic laboratories usually provide request forms to collect this information.

If the request form does not contain sections where this information can be included, the veterinarian should not hesitate to contact the diagnostic laboratory to propose possible changes in the content of the form. **Even if the methods used for culture and sensitivity testing of human and veterinary pathogens are the same, veterinary diagnostic laboratories should be preferred because some pathogens, antibiotics and clinical breakpoints are veterinary specific**.

Laboratory examination factors to consider

The most important factor in deciding where the sample should be sent is the proficiency and expertise of the recipient microbiology laboratory. Diagnostic licensing for sensitivity testing is generally not regulated and sensitivity tests could be performed by non-specialized laboratories that are not adequately equipped and trained to perform and interpret such tests. The use of human laboratories may result in reports indicating the use of human drugs.

It remains the veterinarian's responsibility to check on the summary of product characteristics (SPC) regarding the licence and species indications for the drug used.

Impoving standards and reporting

This situation shall be improved by setting clear rules and minimum quality standards for diagnostic licensing as well as by establishing continuing education to train laboratory personnel. Some veterinary clinics may use rapid **in-house bacteriological diagnostic tests for which limited information is available regarding their validity. Analysis by a qualified laboratory should be preferred**.

The sample ID number is particularly important when multiple specimens are submitted from the same patient. The diagnostic laboratory cannot report culture and sensitivity results for each individual sample if this information is not provided by the veterinarian.

Antibiotic efficacy is influenced by the infection site. Thus, information about the sample type and the body site from which the sample originates facilitates guidance on rational antibiotic choice by the diagnostic laboratory. For example, first-generation cephalosporins are not recommended for central nervous system infections due to the poor penetration of the blood-brain barrier, whereas clindamycin has good penetration into bone and fluoroquinolones achieve high concentrations in the prostate[2]. Ampicillin and amoxicillin/clavulanate concentrate in urine and the results of sensitivity testing should be interpreted by the laboratory using urine-specific breakpoints if the strain is cultured from the lower urinary tract (e.g. cystitis)[1].

Information on the time of sampling is particularly important for urine samples, which should be processed within 24 hours unless transported under specific conditions (see recommendation R.7).

It is useful to include as much history of the case as possible, so that the laboratory can suggest the most appropriate culture (e.g. anaerobic culture, culture on selective media or ELISA tests for detection of clostridial toxins or PCR tests for identification of specific organisms), in pursuit of a particular diagnosis. ■

Complete patient information should come with the sample.

R.7 How should samples be transported?

- The specimen should always be placed in a container designed to prevent leakage and potential safety hazards.
- The packaging and method of carriage should conform to any existing relevant national or international regulations.
- The container should be labelled to indicate the sample ID.
- The use of tubes containing transport medium is recommended for swabs sent via regular mail or otherwise not processed within 24 hours after collection.
- Samples for anaerobic culture should be transported in specific transport tubes (ask laboratory).
- Urine samples should be refrigerated immediately after collection and delivered to the laboratory as quickly as possible and within 24 hours. Alternatively, samples can be transported under refrigerated conditions (ask laboratory), using urine preservatives or processed in the clinic using point-of-care tests.

Common bacterial pathogens in companion animals are non-fastidious organisms, generally not sensitive to the conditions of sample transport. Various brands of tubes or vials for collection and transportation of anaerobic specimens are commercially available. They are designed to protect anaerobic bacteria from exposure to toxic amounts of oxygen until the specimen is processed in the laboratory (Figure 1). Specific products exist for transport of specimens to be tested for culture of other fastidious organisms such as *Mycoplasma*.

Transport of urine requires particular attention because urine is analysed by quantitative microbiology for the detection of clinically significant bacteriuria. It is therefore essential that the bacterial concentrations in the sample are not influenced by transport conditions such as time and temperature.

Certain international guidelines recommend caution in the interpretation of results and retesting if transportation of refrigerated urine samples exceeds 24 hours without urine preservatives[3].

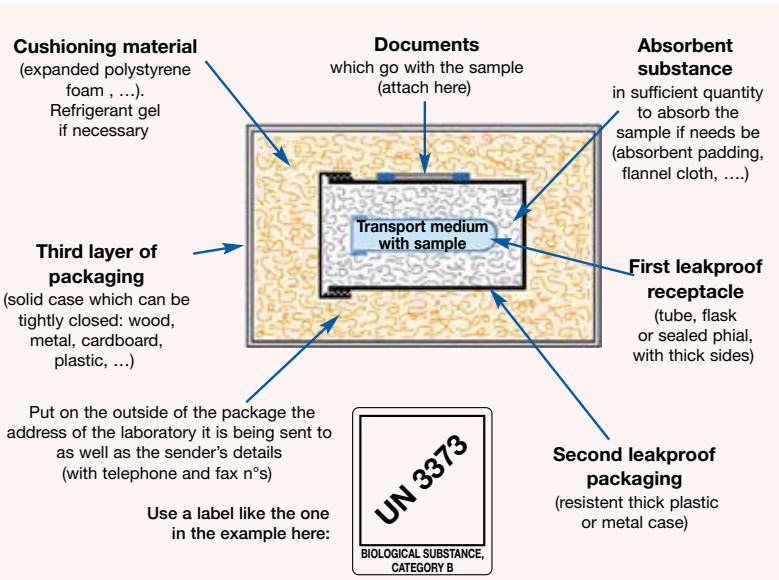

Figure 1 *- Simplified diagram of a triple package (according to standards of class 6.2 of the UN).*

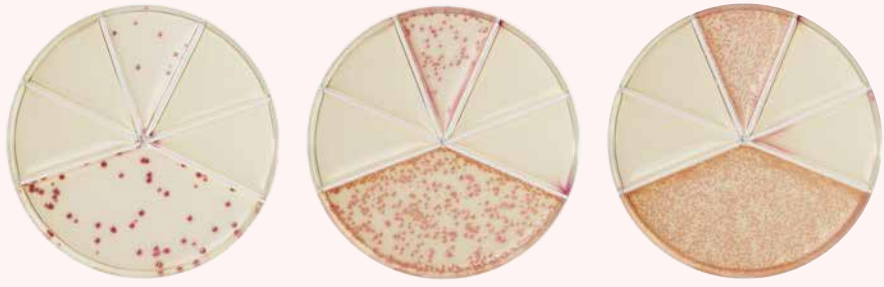

Figure 2 *- Growth on Flexicult® Vet of Escherichia coli at different concentrations: 10^3 CFU/ml (A), 10^4 CFU/ml (B) and 10^5 CFU/ml (C). The agar medium of Flexicult® Vet contains chromogenic medium for bacterial identification and is divided into five compartments for antimicrobial susceptibility testing and one compartment for semi-quantitative bacterial enumeration.*

RECOMMENDATIONS

R.7 How should samples be transported?

To avoid the cost of transportation under refrigerated conditions, urine can be inoculated onto commercial "urinary paddles" for *in situ* culture and submitted to the laboratory if growth is displayed after incubation (Figure 3). This approach has been suggested to save the costs for laboratory analysis of sterile samples[2].

Recently another point-of-care test has been developed and validated for detection, identification and antimicrobial susceptibility testing of bacterial uropathogens in small animal veterinary practice[1]. Use of this test (Flexicult® Vet, Figure 2) avoids problems related to transportation of urine samples, provided that clinical staff are adequately trained to interpret the results and that clinics meet minimum standards to operate in-house culture. ■

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Figure 3 *- Urine can be inoculated onto commercial "urinary paddles" for in situ culture and submitted to the laboratory if growth is displayed after incubation.*

INTERPRETATION OF RESULTS

R.8 How should results be interpreted? Is the classification "sensitive, intermediary, resistant" predictive of the clinical efficacy?

- If the strain is reported as **susceptible (S)**, the antibiotic is an appropriate choice for treatment because the strain is inhibited by drug concentrations achieved in plasma following standard dosage.
- If the strain is reported as **intermediate (I)**, the antibiotic may be effective if administered at a higher dosage for concentration-dependent antibiotics (e.g. fluoroquinolones), or if it is used to treat infections at specific body sites where antibiotics concentrate (e.g. urine, topical application).
- If the strain is reported as **resistant (R)**, the antibiotic is not recommended for treatment because the strain is not inhibited by drug concentrations achieved in plasma after standard dosage.
- *In vitro* sensitivity tests are not infallible and may have little clinical predictive value under specific circumstances (see recommendation R.9).
- A correct interpretation of the results requires specific knowledge on the susceptibility to specific antimicrobial classes/drugs used in clinical practice (or the presence of resistance).
- Based on the susceptibility results, clinicians should prefer first-line antibiotics and de-escalate whenever possible (see recommendation R.11).

Goals of sensitivity testing

The goal of sensitivity testing is to predict the clinical success or failure of the antibiotic being tested against a particular bacterial strain. Strains tested are classified by the laboratory as S, I or R based on clinical breakpoints, which are defined by modelling of pharmacodynamic and pharmacokinetic data. Only very few veterinary breakpoints are confirmed by clinical outcome studies.

Although this classification is predictive of clinically efficacy, ***in vitro* sensitivity tests are not infallible and may have little clinical predictive value under specific circumstances** (see recommendation R.9).

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Figure 1 - Culture and sensitivity testing using the disk method.

The intermediate category is also used as a buffer to reduce the risk of false positive or false negative results. The latter type of error (i.e. reporting a resistant strain as susceptible) may have a great impact on patient care, since the veterinarian can be induced to choose a drug that is not effective against the strain causing infection. False positive results (i.e. reporting susceptible strains as resistant) induce the veterinarians to unnecessary use of second-line antibiotics.

Figure 2 - Bacteria colonies on petri dish.

Sensitivity reports, difficulties

Interpretation of sensitivity reports from diagnostic laboratories is complicated by the inclusion of antibiotics that are not used in clinical practice, namely **surrogate drugs** that are **used to predict the efficacy of other antibiotics belonging to the same class** (e.g. sulfamethoxazole predicts susceptibility to sulfadiazine) and drugs used for detection of specific resistance phenotypes of clinical relevance. Among the latter drugs, oxacillin and cefoxitin are used for detection of meticillin resistance in staphylococci due to their ability to induce the meticillin resistance gene mecA under laboratory conditions. Strains resistant to oxacillin/cefoxitin should be regarded as resistant to all ß-lactams used in veterinary medicine. Table 1 provides practical information on how to interpret results for common antibiotics used for sensitivity testing.

Correct interpretation of the results requires specific knowledge on the susceptibility to specific antimicrobial classes/drugs used in clinical practice.

R.8 How should results be interpreted? Is the classification "sensitive, intermediary, resistant" predictive of the clinical efficacy?

Table 1 - Drug-specific interpretations of antibiotic sensitivity results. Modified from Jessen et al. 2012.

Antibiotic	Interpretation of sensitivity results
Ampicillin	It predicts susceptibility to amoxicillin in all bacterial species and to penicillin in Gram-positive cocci.
Amoxicillin clavulanate	It may be used for detection of extended-spectrum ß-lactamase (ESBL) in Gram-negative bacteria due to its capacity to inhibit the activity of these enzymes, i.e. ESBL-producing strains are sensitive if they do not carry other types of ß-lactamases.
Cefazolin or cefalotin	It may be used to predict susceptibility to first generation cephalosporins (e.g. cefalexin and cefadroxil). Cefalexin-specific breakpoints are now available for testing staphylococcal susceptibility to this drug, widely used for treatment of canine pyoderma.
Cefoxitin	It is used for detection of meticillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP). Meticillin resistance indicates that the strain is resistant to all ß-lactam antibiotics (penicillins and cephalosporins). It can also be used for detection of ESBL-producing strains, which are sensitive unless they contain another type of ß-lactamase.
Cefotaxime or cefpodoxime	It may be used to predict resistance to other third generation cephalosporins, which is the main phenotypic trait of ESBL-producing strains.
Cefovecin	Sensitivity results cannot be used to predict clinical outcome because there are no approved clinical breakpoints.
Clindamycin	It predicts susceptibility to lincomycin in Gram-positive bacteria (not active against Gram-negative bacteria).
Chloramphenicol	Second-line drug for treatment of infections caused by multidrug-resistant strains such as MRSA/MRSP and ESBL-producing strains.
Ciprofloxacin	It may be used to predict susceptibility to veterinary fluoroquinolones even though drug-specific breakpoints are available for enrofloxacin, marbofloxacin and difloxacin.

Table 1 (continued)

Antibiotic	Interpretation of sensitivity results
Enrofloxacin	It may be used to predict susceptibility to other veterinary fluoroquinolones even though drug-specific breakpoints are available for marbofloxacin and difloxacin.
Erythromycin	It predicts inducible resistance to lincosamides in staphylococci. Lincosamides (lincomycin and clindamycin) should not be used if the strain is resistant.
Fusidic acid	Sensitivity results cannot be used to predict the clinical outcome of topical therapy. Interpretation using the human breakpoint is not recommended since the drug is used systemically in human medicine and topically in veterinary medicine.
Gentamicin	Sensitivity results cannot be used to predict susceptibility to other aminoglycosides (e.g. amikacin). Interpretation using the human breakpoint is not recommended when the drug is used topically.
Lincomycin	It predicts susceptibility to clindamycin in Gram-positive bacteria (not active against Gram-negative bacteria).
Nitrofurantoin	Second-line drug for treatment of urinary tract infections (UTIs) caused by multidrug-resistant strains. It can only be used for management of UTIs because it is rapidly excreted and concentrates in urine.
Oxacillin	It is used for detection of MRSA and MRSP. Meticillin resistance indicates that the strain is resistant to all ß-lactam antibiotics (penicillins and cephalosporins).
Rifampicin	Second-line drug for treatment of infections caused by multi-drug-resistant strains. It should only be used in combination with another drug because resistance can easily develop during therapy by mutations.
Tetracycline	It predicts susceptibility to doxycycline in staphylococci.
Sulfamethoxazole	It predicts susceptibility to all sulphonamides in all bacterial species.

Back to basics

Interpreting microbiological results starts by identifying the isolated bacteria, followed by a bacterial count (to distinguish colonization from infection) and lastly by culture and sensitivity testing (C&ST).

C&ST assesses the *in vitro* activity of antibiotics against a bacterial strain responsible for an infection and helps to guide the clinician's therapeutic approach.

Culture and sensitivity results can be reported quantitatively, using minimum inhibitory concentrations (MIC) (µg/mL or mg/L) or indirectly, through the measurement (in mm) of inhibition diameters (diffusion test). MIC is the best measure of *in vitro* antibacterial effect.

Inhibition zones can be interpreted on the basis of critical diameters if these are known. If not, the indirect estimation of the MIC must be done with care because of the lack of available data in veterinary medicine.

Results can also be reported qualitatively. Three clinical categories are used[5] to interpret *in vitro* sensitivity tests: Sensitive (S), Resistant (R) and Intermediate (I):

- **S strains** are those for which the probability of treatment success is high, in case of systemic treatment at the recommended dosage,
- **R strains** are those for which there is a high probability of treatment failure, whatever the type of treatment and the antibiotic dose,
- **I strains** are those for which the effect of treatment is unpredictable. These strains may have a resistance mechanism whose *in vitro* expression is low. However, resistance to treatment can appear *in vivo*.

Conversely, these intermediate strains may also show resistance *in vitro* that is insufficient to be classified as resistant but low enough to expect treatment success under certain conditions (high local concentrations or increased doses).

Category Intermediate (I) is also a "buffer" zone, to avoid interpretation bias related to technical or biological uncontrolled uncertainties.

Table 2 *- Critical values: criteria of categorisation (according to the Antibiogram Committee of the French Microbiology Society, 2010).*

Category	MIC category (mg/L)	Diameter (ø) (mm)
Sensitive	MIC ≤ c	ø ≥ D
Intermediate	c < MIC ≤ C	d ≤ ø < D
Resistant	MIC > C	ø < d

c: lower critical concentration; C: upper critical concentration;
d: upper critical diameter; D: lower critical diameter.

Clinical category limitations

The limits of clinical categories are defined by critical values or breakpoints. Two critical concentrations can be defined: the lower critical concentration c and the upper critical concentration C (the corresponding critical diameters are d and D) (Table 2).

The terminology used to describe critical values is complex and ambiguous, because it corresponds to several different approaches[2] (Table 3). Critical values differ from one country to another. The Clinical and Laboratory Standards Institute has defined a large number of critical values for species of veterinary interest[1].

In 2009, in the United States, specific critical concentrations only existed for dogs, for[3]:

- enrofloxacin,
- difloxacin,
- marbofloxacin,

Table 3 *- Critical values: terminology [2].*

Epidemiological cut-off values	This approach is based on the distribution, for the same bacterial species and outside the clinical context, of MICs of wild strains and of resistant strains. Ideally the two populations are clearly distinct and the concentration dividing these two populations is defined as the epidemiological cut-off value. Epidemiological cut-off values are used as the most sensitive method of measuring the development of resistance. They alert microbiologists on sensitivity variations or pathogens. They are totally independent of antibiotic dosages. A bacterium is considered resistant if it tolerates *in vitro* concentrations higher than those tolerated by the majority of strains of the same species.
Clinical breakpoints	A bacterium is considered sensitive if the antibiotic concentration in serum is higher than the MIC. In these cases, antibiotic treatment is considered clinically effective. This is no longer about differentiating sensitive from resistant bacteria from a microbiological viewpoint, but to differentiate treatable and non-treatable infections using antibiotics.
PK/PD breakpoints	This approach takes into account pharmacokinetics (PK) and pharmacodynamics (PD) in order to estimate the clinical response to treatment.

- gentamicin,
- cefpodoxime proxetil,
- ampicillin (only for urinary infections),
- clindamycin.

In France, a specific veterinary culture and sensitivity working group within the Antibiogram Committee of the French Microbiology Society (SFM) establishes critical values (MIC and inhibition diameters) on the basis of epidemiological thresholds.

However, the results of clinical studies, dosing regimen and the pharmacokinetic (circulating and tissue concentrations) and pharmacodynamic characteristics of the antibiotic in the target species are not taken into consideration[4].

An alternative to MICs consists of measuring inhibition diameters. However, a regression line based on inhibition diameters is not a satisfactory method for determining the MIC. Several methods of analysis can be used to identify values from inhibition diameters, defining the limit between sensitivity and resistance with a predefined error margin[5]. In veterinary medicine, the estimation of an MIC from an inhibition diameter is difficult because of the lack of data.

In the field of companion animal infectious diseases, no studies have been carried out to establish a relationship between the efficacy of an antibiotic treatment and the result of culture and sensitivity testing.

The predictive value of culture and sensitivity testing in terms of clinical efficacy is only relative, for a number of reasons:

- Continued *in vitro* exposure of a limited number of bacteria to a constant antibiotic concentration is not representative of a clinical context in which larger populations of microorganisms are subject to fluctuating antibiotic concentrations.

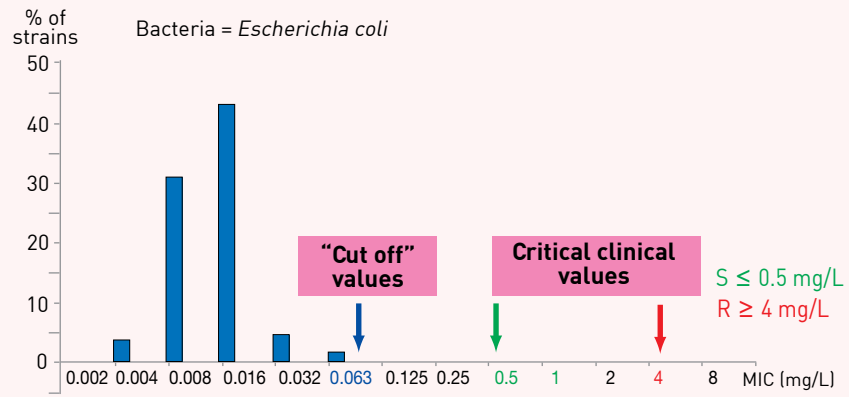

Figure 3 *- Critical values: the example of ciprofloxacin in humans.*

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Figure 4 *- Classification of a bacterium as sensitive, intermediate or resistant is defined by in vitro criteria.*

- The site of infection can play a role. For example, an S result obtained *in vitro* overestimates antimicrobial activity in the central nervous system, the prostate or mammary tissue. Conversely, an R result underestimates the activity of local treatments (very high antibiotic concentration) or activity in urine for an antibiotic eliminated via the kidneys.
- The possibilities of synergy between two antibiotics are not identified by culture and sensitivity testing.
- Local factors (e.g. pus, low partial oxygen pressure, necrotic tissue, low tissue perfusion) are not taken into consideration. For example, an aminoglycoside can be effective *in vitro* on a certain strain (therefore declared sensitive), but ineffective in necrotic tissue or an abscess[4].
- The patient's clinical state: the risk of treatment failure is higher in immunocompromised patients or those suffering from severe chronic illness.

Culture and sensitivity testing can also be used for epidemiological surveillance of bacterial resistance and the fight against nosocomial infections. ■

R.9 Why is the result of sensitivity testing not always reflected by clinical efficacy?

■ Antibiotic sensitivity testing represents a single time point *in vitro* measurement (snapshot) that does not take into account patient and infection-specific factors, nor technical errors affecting the clinical predictive value.

■ Main factors that can be responsible for the lack of correlation between AST results and clinical efficacy are:

- factors influencing drug PK (e.g. individual factors, poor tissue diffusion, drug interactions),
- mixed infections,
- underdosing (failure to optimize medication dosing regimens based on indication and patient-specific characteristics) by the clinician,
- underprescribing (omission of other potentially useful drugs) by the clinician,
- lack of compliance by the owner,
- unreliable clinical breakpoints (see recommendation R.8),
- errors or inaccuracies by the microbiology laboratory.

In vitro sensitivity testing is a useful diagnostic tool for predicting the activity of antimicrobial drugs *in vivo*. Various human studies have shown that there is a clear negative correlation between MICs and clinical outcomes of antibiotic treatment, i.e. the higher the MIC value of a drug, the lower the response rate to therapy[1]. The importance of sensitivity testing for rational antibiotic therapy is exemplified by an old human study showing that the clinical conditions improved in 3% and did not improve in 82% of the patients treated with antibiotics to which the cultured strains were classified as resistant[3].

However, *in vitro* sensitivity tests are not infallible and have shown **little clinical predictive value** under specific situations such as **urinary tract infections, polymicrobial infections, outpatient infections treated with oral antibiotics, or infections treated with multiple antibiotics**[2].

Variable correlation with clinical outcome

Several factors may be responsible for the lack of correlation with clinical outcome including individual factors influencing drug pharmacokinetics or response to therapy, strain virulence, underdosing or underprescribing by the clinician, lack of compliance by the owner, unreliable clinical breakpoints, errors or inaccuracies by the laboratory, drug inability to reach and be effective at the infection site, and drug interactions. Moreover, sensitivity tests represent a single time point measurement. As such, their predictive value may be influenced by other factors occurring in the patient after a specimen is taken and submitted to the laboratory.

Fungus infection combined with Staphylococcus on dog skin.

Microscopic view of Escherichia coli.

Clinical predictive value

The clinical predictive value of the results of *in vitro* antimicrobial susceptibility testing was assessed by a prospective study for a cephalosporin widely used in human hospitals (cefotaxime). Infections associated with fully susceptible strains were not eradicated in 9% of the patients. Even more surprisingly, infections associated with fully resistant strains were eradicated in 50% of the patients[2]. Although similar studies have not been performed in veterinary medicine, it is reasonable to expect that similar problems exist in veterinary sensitivity testing.

The clinical predictive value of veterinary sensitivity testing may be further affected by several sector-specific factors such as lack of:

- harmonized laboratory procedures,
- approved animal-specific and pathogen-specific breakpoints for several veterinary drugs,
- universal diagnostic licensing standards for sensitivity testing, and
- targeted training programs for veterinary laboratory and clinical personnel. ■

R.10

What should be done if results of sensitivity testing diverge from clinical outcome?

- The veterinarian should carefully consider any possible factors responsible for the lack of response to therapy in patients infected with a strain that has been reported by the microbiology laboratory as susceptible (S) (see recommendation R.9).
- Check first if the lack of clinical outcome may be due to failure of the prescribed drug to reach and be active at the infection site or for underdosing or lack of compliance by the owner (see recommendation R.9).
- Targeted action should be taken if an infection-specific factor affecting the clinical outcome is identified (e.g. presence of biofilms, implants and foreign material).
- Alternatively, therapy should be discontinued and another antibiotic should be chosen based on new sensitivity test results.
- On the contrary therapy should be continued if clinical improvement is observed in patients infected with a strain that has been reported as resistant (R). Clinical outcomes should always be prioritized over sensitivity results.

A number of factors may be responsible for the divergence between sensitivity results and clinical outcome (see recommendation R.9). The main factors to be considered for a negative response to therapy are:

- underdosing due to inaccurate weighing of the patient or inadequate tablets for correct dosing (large/small dogs),
- limited drug tissue penetration or reduced efficacy at the infection site,
- specific underlying conditions in the patient,
- pitfalls in the laboratory diagnostic procedure (from sampling to interpretation),
- non-compliance by the owner.

Figure 1 - Inadequacy of the prescribed drug to reach the target organ, underdosing or lack of compliance are major causes of poor clinical outcome.

Underdosing

Underdosing should be avoided because it is a **key cause of antibiotic treatment failure by reducing clinical efficacy** (especially of dose-dependent drugs such as fluoroquinolones) as well as **by favouring development of resistance** during treatment (see recommendation R.20).

Limited drug tissue penetration or reduced efficacy at the infection site

Limited drug penetration at the infection site should be considered for specific infections such as **prostatitis or CNS infections**. For these infections it is **recommended to use a drug able to penetrate the organ-specific blood barrier**, such as a fluoroquinolone.

For other infections, especially post-surgical and device-associated infections, the lack of clinical efficacy may be due to biofilms and/or implants and foreign material (presence of pus), inadequate drainage or debridement and any other factors affecting antibiotic activity at the infection site (e.g. anaerobic conditions interfere with the antimicrobial activity of aminoglycosides).

Underlying conditions

Specific underlying conditions in the patient may include any disorders that compromise the immune system of the patient. Indeed, the immune system plays a major role in curing the infection, especially when a bacteriostatic antibiotic is used. In such cases a new therapy with a bactericidal antibiotic should be started and the underlying condition should be identified and managed, if possible.

Pitfalls in the laboratory diagnostic procedure

They may include collection of an inappropriate sample type, contamination of the sample at the time of collection, and errors in the performance or interpretation of the sensitivity test by the microbiology laboratory. If one of these situations is suspected, a new sample should be collected and submitted to the laboratory with a detailed description of the case.

Non-compliance

Compliance by the owner is particularly important for time-dependent antibiotics such as the ß-lactams. Administering ß-lactams at regular intervals is essential to ensure drug levels above the MIC of the strain and ultimately to ensure clinical efficacy.

What should be done in practice?

It may well happen that a patient responds to therapy even if the infection has been attributed by the laboratory to a resistant strain[1]. This apparently illogical outcome may be observed when samples are submitted for culture at the time of initiating empirical therapy, and can be consequent to:

- self-limiting infections that would resolve without antibiotic therapy,
- polymicrobial infections in which the strain reported as resistant is not the primary cause of infection, or
- errors in the laboratory (e.g. reporting of sensitivity results for bacterial contaminants, mistakes in the performance of the test or application of inadequate breakpoints).

In all these cases, therapy should not be discontinued regardless of the sensitivity results. ■

BROAD-SPECTRUM ANTIMICROBIALS, COMBINATIONS, DE-ESCALATION

R.11 Does the use of a broad-spectrum antimicrobial (or combination of antimicrobials) assist in doing without bacterial sensitivity testing?

- The use of a broad-spectrum antibiotic (or combination of antimicrobials) as a first-line treatment does not excuse the practitioner from looking for the causal agent and site of infection.
- When choosing between antibiotics of comparable efficacy, it is recommended to choose the one with the narrowest spectrum whenever possible.
- In severe infections, septic shock and nosocomial infections, bacteriological analysis with culture and sensitivity testing is essential when prescribing a broad-spectrum antibiotic as a first-line treatment. A sample for bacteriological analysis should be taken before starting treatment.
- Initial treatment with broad-spectrum antibiotics should be short and reassessed on the basis of the bacteriological results (scaled down to a narrower spectrum). Broad-spectrum antibiotics are more likely to promote the selection and propagation of resistance in the host's normal (commensal) flora.
- For mild infections that do not require admission to hospital, empirical treatment can be carried out without bacteriological examination. However, in the event of failure or relapse, bacteriological examination is needed.
- For infections occurring in a group of animals, early bacteriological examination is recommended (see recommendation R.29).

Narrow-spectrum antibiotics (penicillin G, metronidazole, colistin) and intermediate antibiotics (aminoglycosides, macrolides, lincosamides) mainly act on one category of bacteria (Gram-positive or negative, anaerobic or aerobic) (see Table 1 of recommendation R.13). **It is recommended to choose the antibiotic with the narrowest spectrum whenever possible**.

Broad-spectrum antibiotics (ampicillin, amoxicillin ± clavulanate, 1st generation cephalosporins, trimethoprim-sulfonamides) and very broad-spectrum antibiotics (tetracyclines, chloramphenicol, 3rd generation cephalosporins, fluoroquinolones) act on both Gram-positive and Gram-negative bacteria, aerobic and sometimes even anaerobic bacteria (see Table 1 of recommendation R.13). These agents are widely used as first-line treatment in both dogs and cats (Figure 1), with differences according to the country[3,4]. Perceived higher efficacy and uncertainty of diagnosis are the most frequent reasons mentioned by veterinarians for the selection of broad-spectrum antimicrobials[8].

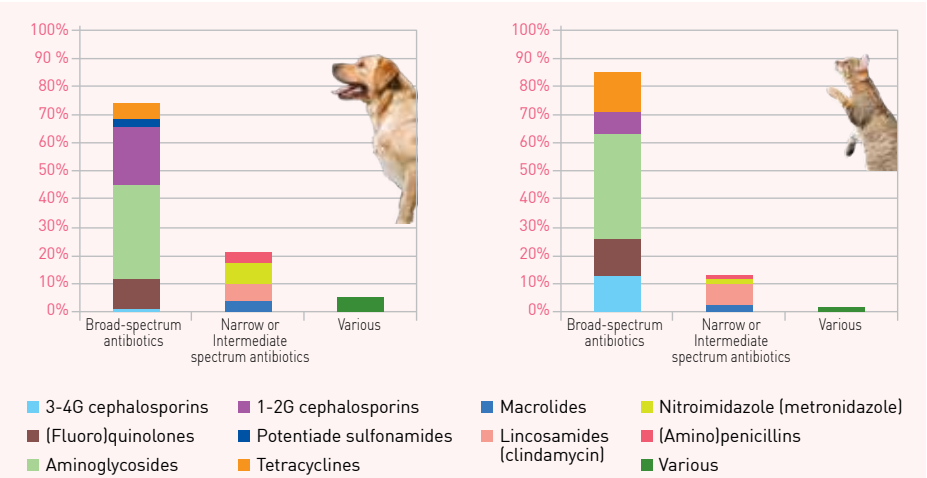


Figure 1 *- Most antibiotics prescribed by veterinarians are broad spectrum: >70% in dogs and >80% in cats. Data from an internet-based survey carried out in 2013 among 3,004 European veterinarians[4].*

However, there are several drawbacks associated with their use:

- There is no single broad-spectrum antibiotic (or combination) that is effective against all bacteria[2].
- Their broad spectrum is reassuring and encourages a blind, "just in case" treatment without actually confirming the presence of an infection (non-reasoned prescription), instead of rational prescription considering likely bacteria and whether a narrow spectrum drug could be efficacious (empirical or probabilistic treatment). For example, only 5% of urine cultures are positive in cats with urological signs[1]. In the majority of cases, no clinical hypotheses are made as to whether there actually is an infection present or the nature of the causal agent (or even the site of the infection).

Clinical and microbiological diagnosis also becomes of secondary importance for the practitioner, as the treatment is supposed to act on all the pathogenic bacteria potentially involved. Thomson[9], 2009 and Escher[5], 2011 report that the choice of the antimicrobial treatment is supported by culture and sensitivity testing in less than 5% in dogs and cats. **In Europe, sensitivity testing is always performed (when feasible) by only 3.4% of companion animal practitioners**[3].

Broad-spectrum antibiotics exert a **selective pressure on a greater number of microorganisms than narrow spectrum antibiotics,** and are consequently **more susceptible to promote the selection and propagation of resistance in the host's normal (commensal) flora**. Moreover,

a massive alteration of digestive flora will have a negative impact on its barrier function, which will promote the colonization of the digestive tract by pathogenic bacteria.

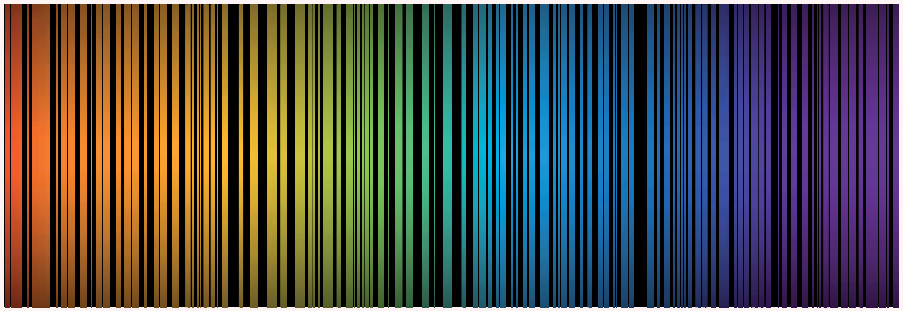
The need to carry out bacteriological analysis with culture and sensitivity depends on the clinical condition of the animal. The approach can be summarized as follows[10]:

• For serious infections (e.g. pyothorax, osteomyelitis, pyelonephritis, septic shock and nosocomial infections), the sample for bacteriological examination must be taken before starting treatment. In such conditions, the antimicrobial treatment should be initiated as soon as possible after the onset of sepsis, i.e. generally before the causative pathogen is known. As therapy is to be initiated empirically the antimicrobial spectrum of the agent should be broad enough to cover the potential causative microorganisms.

Antimicrobial management therefore incorporates early implementation of broad-spectrum empirical coverage with possible de-escalation of therapy after 48-72 hours based on culture and sensitivity (Figure 2). This strategy, while ensuring a high likelihood of adequate initial coverage, avoids the long-term use of unnecessary antibiotics, thereby minimizing resistance concerns[6]. The use of narrower spectrum antibiotics limits the impact of antibiotic therapy on non-targeted bacteria in normal flora. De-escalation may also include discontinuation of empirical antimicrobial therapy based on clinical criteria and negative culture results.

• For mild infections that do not require admission to hospital, empirical (probabilistic) treatment can be carried out without culture. In the event of failure or a relapse, bacterial sensitivity testing is requested.

• For every infection occurring in a group of animals, a bacteriological examination is recommended, regardless of the seriousness of the clinical signs and the spectrum of action of the antibiotic used in the first-line treatment (see recommendation R.29). ■



Broad spectrum antibiotics act on both pathogenic bacteria and digestive flora indiscriminately.

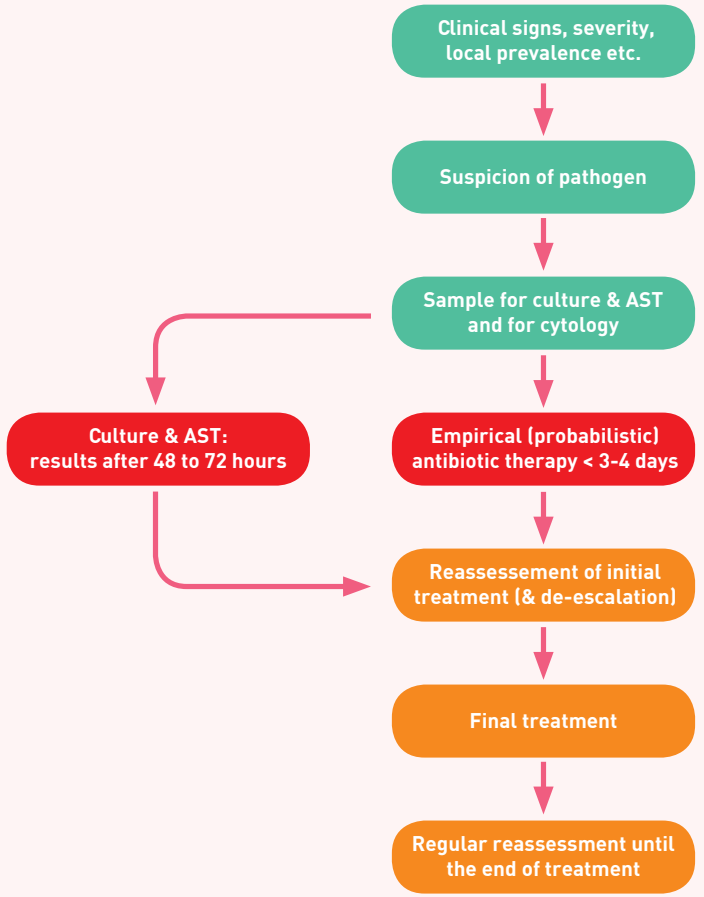


Figure 2 *- Strategy for prescribing antibiotics to an animal with a serious infection.*

What are the rules of antibiotic combinations?*

- **Antibiotic combinations are usually pointless and should be avoided.**
- Monotherapy should be the first choice in the majority of infections. It must be used when:
  - the bacterial agent is identified and sensitive to the antibiotic,
  - the antibiotic prescribed as a probabilistic treatment is generally recognized as being effective for the infection involved,
  - the infection is not very serious.
- In spite of the absence of data, using a combination is possible in specific clinical circumstances, namely first-line emergency treatment of infections that are:
  - polymicrobial,
  - caused by a large quantity of bacterial inoculum,
  - serious or potentially lethal,
  - in immunodepressed dogs and cats.
- A probabilistic treatment is not a blind treatment. A combination cannot be justified on the basis of broadening the antimicrobial spectrum.
- In theory, the main objectives of prescribing an antibiotic combination are the following:
  - to broaden the therapeutic spectrum,
  - to obtain a synergy,
  - to decrease the appearance of resistance.

Broadening the spectrum

Broadening the spectrum is certainly the easiest objective to achieve through a combination, in particularly in cases of polymicrobial infections with mixed aero-anaerobic flora.

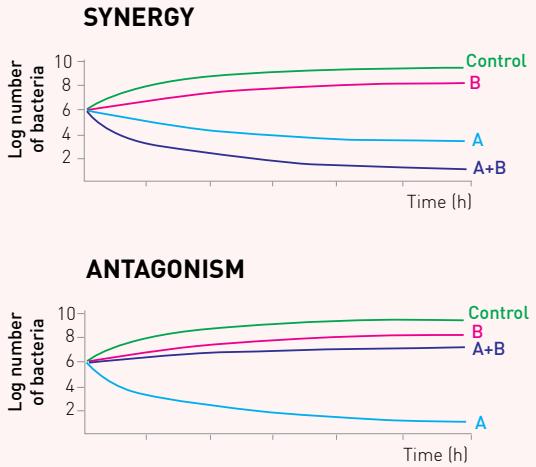
During probabilistic treatment, however, the prescription of an antibiotic combination is very frequently not justified. So-called probabilistic antibiotherapy must correspond to a treatment that is recognized as being regularly effective in the given situation.

On the contrary, it is a prescription that has to be well-thought, considering all available information to make the best possible choice.

Prescribing a combination with the sole aim of broadening the antibiotherapy spectrum without any other reason generally indicates a lack of ability in diagnosing and a lack of knowledge in the field of infectiology. For example, in a study carried out on 74 dogs hospitalized in an intensive care unit, the percentage of sensitive bacteria isolated was significantly identical for gentamicin (74%) and for an enrofloxacin-ampicillin combination (71%). The probabilistic treatment chosen by the emergency physician was efficacious in 75% of cases[2]. A consensus of the American College of Veterinary Internal Medicine recommends using narrow spectrum antibiotherapy in the majority of infections[8]. In cases of polymicrobial infections, multiple sites, large quantities of bacterial inoculum, potentially lethal infections or infections in immunodepressed subjects whose aetiology is uncertain, there is a consensus in veterinary literature on the subject which allows the possible use of an antibiotic combination.

However, broadening of the spectrum is no longer legitimate once the bacteriological diagnosis has been carried out and a targeted treatment can be started.

* *Not including trimethoprim sulfonamide and amoxicillin+clavulanate combinations.*



a. An antibiotic combination (A+B) is said synergetic when its effect is greater than the sum of the effects of two antibiotics (A,B) taken separetely compared to control.

b. When the effect of a combination is lower than the sum of the effects of each antibiotic taken separately, this is called antagonism.

Figure 1 *- Synergetic or antagonistic effect of an antibiotic combination.*

Combination synergy

Synergy (or antagonism) is defined as being a positive (or negative) interaction between two antibiotics, leading to a joint antibacterial action which is greater (or lower) than the sum of the actions of each antibiotic prescribed separately (Figure 1)[6]. The aim is also to have a bactericidal action, which is faster if possible.

R.12 What are the rules of antibiotic combinations?*

Traditional rules of combination (Jawetz laws), for example the antagonism between bacteriostatic and bactericidal drugs, are old concepts with many exceptions.

The most common strategy is to combine two agents (e.g. penicillins, cephalosporins, aminoglycosides, fluoroquinolones). The synergy mechanisms are:

- easier penetration of an antibiotic (e.g. aminoglycoside) into the bacteria due to another antibiotic (ß-lactams),
- sequential inhibition of the same metabolic pathway (e.g. trimethoprim and sulfonamides),
- inhibition of bacterial cell wall synthesis (vancomycin and ß-lactams),
- inhibition of ß-lactamases (amoxicillin and clavulanate).

Bacteriological tests to determine the effects of a combination are often laborious and not available. The synergy (or antagonism) observed *in vitro* cannot necessarily be extrapolated to *in vivo* conditions.

In fact, each antibiotic's mode of action is influenced by pharmacokinetic and pharmacodynamic parameters. These two factors can be modified by *in vivo* interactions when the two agents are administered together.

A combination cannot be justified on the basis of broadening the antimicrobial spectrum.

Decrease in the appearance of resistance

The effect of combinations on the appearance of resistance is debatable. In fact, combinations accentuate selective pressure and therefore the risk of multi-drug-resistant strains appearing. When antibiotics are combined to this end, the antibiotics chosen should have different modes of action.

Clinical interest

The clinical advantage of an antibiotic combination over a monotherapy remains to be demonstrated when treating dogs and cats.

In human medicine, it has certainly been shown by several meta-analyses that the ß-lactam/aminoglycoside combination is superior to a monotherapy with ß-lactams in cases of infectious endocarditis in young neutropenic patients.

Apart from these examples, no difference in terms of superinfection and resistance development has been observed between the bi- and monotherapy. The risk of adverse effects, in particular nephrotoxicity, is on the other hand greater when using a bi-therapy[1,3,5,7,9,10,11]. ■

** Not including trimethoprim sulfonamide and amoxicillin+clavulanate combinations.*

R.13 Which antimicrobials have a narrow spectrum?

- The "broad *vs.* narrow spectrum" classification can be misleading for the practitioner as its definition is not clear.
- Generally, drugs with narrow-spectrum activity are considered effective against a limited variety of pathogens while drugs with broad-spectrum activity are effective against a wide variety of pathogens.
- Narrow-spectrum antibacterial agents include penicillin G, nitroimidazoles (metronidazole) and colistin.
- Appropriate use of narrow-spectrum antibiotics implies a targeted antimicrobial therapy, ensuring a high likelihood of cure while minimizing resistance concerns and is based on identification of the causal pathogen, bacterial sensitivity testing and knowledge of the PK/PD characteristics of the agent.
- Whenever possible, a narrow-spectrum antibiotic should always be preferred over a broad-spectrum antibiotic.

The use of the "broad *vs.* narrow spectrum" classification is increasingly uncommon in most textbooks in human and veterinary medicine, as its interpretation may be misleading for the practitioner.

The expression "broad-spectrum antibiotic" was first mentioned in the literature in the 1950s for comparison of the spectrum of chloramphenicol and tetracyclines to the narrow spectrum of penicillin G and streptomycin[1]. Parent molecules were also chemically modified to extend the range of antimicrobial activity (e.g. amoxicillin is an extended-spectrum antibiotic compared to its parent molecule penicillin G, which has a narrow spectrum). Therefore, the terms broad or narrow spectrum were initially given to an antibiotic by comparison to other antimicrobial agents.

Later, broad and narrow spectrum became independent characteristics of the antimicrobial agent, mainly based on its specific activity against a spectrum of microorganisms, according to their Gram-stain. **Narrow-spectrum antibiotics are defined as agents only active against Gram-positive or Gram-negative bacteria**, whilst broad-spectrum antibiotics are active against both Gram-positive and Gram-negative bacteria. However, this classification is not always straightforward, as some agents may be primarily active against Gram-positive bacteria but will also inhibit the growth of certain Gram-negative agents[2] (Table 1). Among the narrow spectrum agents some antimicrobials are "broader" than others (e.g. macrolides *vs.* metronidazole), while in the broad-spectrum category some antibiotics are "narrower" than the very broad ones (e.g. tetracyclines *vs.* 3rd generation fluoroquinolones).

More generally, drugs with narrow-spectrum activity are considered as agents effective against a limited variety of pathogens, while drugs with broad-spectrum activity are effective against a wide variety of pathogens. In a given class of antibacterial drugs, such a classification still remains confusing. For example, amoxicillin is considered a broad-spectrum penicillin, suggesting that it is effective against a wide variety of pathogens. Although amoxicillin has indeed a wider activity against

Table 1 *- Antibacterial activity of selected antibiotics.*

	Aerobic bacteria		Anaerobic bacteria		
Spectrum	Gram +	Gram -	Gram +	Gram -	Examples
Very broad					Chloramphenicol
Very broad					3rd generation fluoroquinolones
Very broad					3rd and 4th generation cephalosporins
Very broad					Tetracyclines
Broad					Ampicillin, amoxicillin (± clavulanate)
Broad					1st generation cephalosporins
Broad					Trimethoprim - sulfonamides
Intermediate					Aminoglycosides
Intermediate					Macrolides, lincosamides
Narrow					Penicillins G (or M)
Narrow					Nitroimidazoles (metronidazole)
Narrow					Colistin

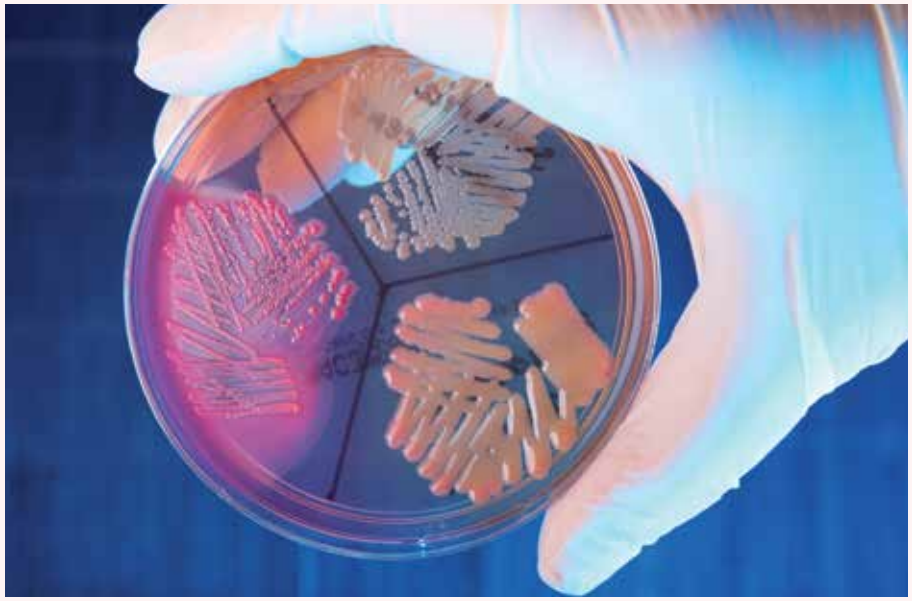
Excellent activity
Moderate activity
Limited activity
No or negligible activity

RECOMMENDATIONS

R.13 Which antimicrobials have a narrow spectrum?

Gram-negative bacteria, it is slightly less active against Gram-positive and anaerobic bacteria than penicillin G. The emergence of many resistant strains of Gram-negative bacteria reduces the spectrum of clinical use for amoxicillin.

Today, narrow-spectrum agents require targeted antimicrobial therapy, ensuring a high likelihood of cure while minimizing resistance concerns. **Narrow-spectrum antimicrobial agents are less susceptible to promote the selection and propagation of resistance in the commensal flora**. Their use however requires an appropriate identification of the causal pathogen, interpretation of bacterial sensitivity testing and knowledge of the PK/PD characteristics (e.g. distribution to the infection site) of the selected narrow-spectrum agent. ■



The use of narrow-spectrum antibiotics is recommended but it requires identification of the causal pathogen and interpretation of antibiotic sensitivity testing.

R.14 Which therapeutic approach is recommended while awaiting results?

- The results of common bacterial analyses of aerobic microorganisms are generally known after 48-72 hours. It takes longer for anaerobic bacteria or if the bacteria are less viable (e.g. sample taken from an animal already taking antibiotics, see recommendation R.5).
- If bacterial infection is clinically suspected, empirical antibiotic therapy is only justified in emergency cases, in life-threatening conditions or in non-emergency situations where delay would compromise the clinical outcome.
- 48 to 72 hours after the start of treatment, it is reassessed on the basis of the clinical improvement observed and the results of analysis.

Therapeutic approach while awaiting results

For an accurate diagnosis and an appropriate treatment, clinicians should perform cytology and ensure that specimens for culture and antibiotic susceptibility testing are properly sampled and promptly submitted to the laboratory. Premature initiation of antimicrobial therapy can suppress bacterial growth and preclude the opportunity to establish a microbiological diagnosis. The time required for results of bacterial culture and sensitivity testing depends on the laboratory technique used. It is generally 48-72 hours for aerobic bacteria (often longer for anaerobic bacteria), but may be prolonged according to the viability of the pathogens (previous antimicrobial treatment before sampling can delay bacterial growth) and their natural growth rate (from 24 hours to several days).

While awaiting results, small animal patients should be risk-assessed for treatment decisions. There are two options (Figure 1):

- In life-threatening (or potentially life-threatening) infections (e.g. septic shock), empirical antimicrobial therapy must be initiated as quickly as possible (''hit hard and hit fast'') to limit the development of infection and its complications. Other potential testing (e.g. imaging) should not delay antimicrobial therapy.
- For other infections, it is recommended to wait for the microbiological diagnosis before starting antimicrobial treatment. In non-emergency settings, the practitioner should take the time to tailor therapy to the individual patient based on the best clinical judgment and laboratory information. Such a short delay of treatment is not harmful and helps in reducing the amount of unnecessary or ineffective antibiotics.

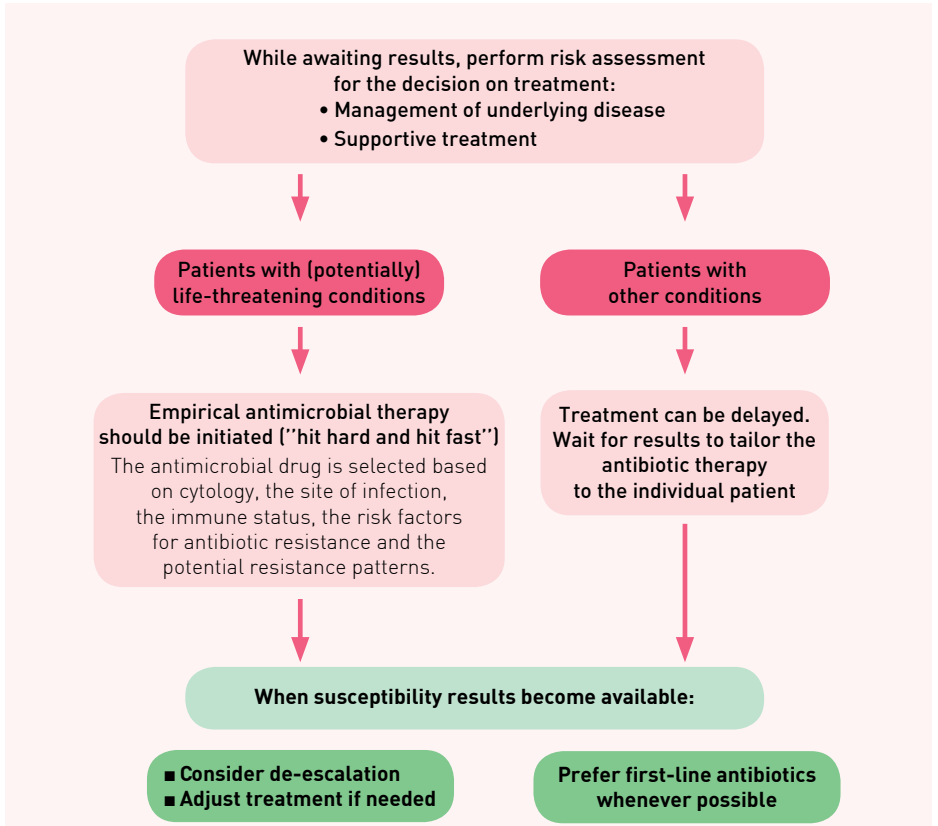


Figure 1 *- Risk-assessment for decision on treatment while awaiting laboratory results.*

In potentially lethal infections, empirical treatment implies that the antibacterial agent should be selected appropriately according to the site of infection, the patient's immune status (e.g. geriatric or cancer patients), the risk factors for antimicrobial resistance (e.g. prior hospitalization, recent antimicrobial use), and the potential resistance patterns to different antibiotic classes for the given infection[3].

Although the microbiological diagnosis is ideally based on laboratory data, frequently the "most likely" pathogen cause can be inferred from the clinical presentation and the site of infection based on epidemiological considerations, and from cytology results. For example,

Which therapeutic approach is recommended while awaiting results?

about 70% of isolates in complicated urinary tract infections in dogs are Gram-negative. *E. coli* is isolated in about 60% of cases[4]. Immune suppression and co-morbidities should be also considered as they may affect the response to the antimicrobial treatment, e.g. 35% and 30% of dogs with complicated urinary tract infection have, respectively, immune suppression and renal disease[4].

For these reasons, broad-spectrum antibiotics are recommended for empirical treatment in critically ill patients with the intent to cover multiple possible pathogens commonly associated with the infectious disease. This therapeutic approach improves the likelihood of appropriate antimicrobial coverage while waiting for the laboratory results. Antimicrobial treatment will be adjusted when the pathogen has been identified and its susceptibility evaluated. To reduce the risk for development of antimicrobial resistance, a strict policy of therapy de-escalation based on antimicrobial susceptibility testing should be followed (see recommendation R.11).

Antibiotic dosing during critical illness

Dosing of antimicrobials during critical illness is generally problematic as antimicrobial concentrations are subject to alterations and may fail to reach appropriate therapeutic levels. Five main issues can be detected in critically ill patients regarding altered pharmacokinetics (PK): increased volume of distribution, altered protein binding, augmented renal clearance, impaired renal clearance and hepatic dysfunction. There is no easy way to predict PK parameters in such conditions. However, from the available data in human patients, underdosing appears much more frequent than overdosing[2]. An intravenous loading dose is generally recommended to achieve appropriate concentrations more rapidly[3]. In emergency and critical care clinics, it is recommended to establish and use a specific empirical antimicrobial protocol for the treatment of life-threatening infections to improve time to antimicrobial administration[1]. ■

For non-emergency situations and non-life-threatening situations, it is recommended to wait for the microbiological results prior to initiating antibiotic therapy.

LONG-ACTING ANTIMICROBIALS

R.15 What is the benefit/risk ratio of (very) long-acting antimicrobials?

- Time-dependent drugs (e.g. ß-lactams) are slowly bactericidal. Serum concentrations therefore should exceed the minimum inhibitory concentration (MIC) for as long as possible during the dosing interval, either by continuous infusion or by frequent dosing.
- Time-dependent antimicrobials with a long elimination half-life (t1/2) (e.g. cefovecin) have a prolonged treatment efficacy following a single administration. Subsequent administration, if any, should be carried out before or at the time when concentration drops below the MIC. The immediate benefits of such a treatment are that it ensures the full course of therapy is properly administered (especially in uncooperative cats) and so avoids the risks of owner non-compliance.
- However, a very slow decrease in drug concentration exposes these bacteria to sub-inhibitory concentrations (lower than the MIC) for a longer period than with a short elimination half-life antibiotic. Consequently, the risk of resistant mutant selection and adverse effects on commensal bacteria may be greater.
- Before administering long-acting antimicrobials, the risks should be discussed with the owner and **the benefits to the patient should clearly out-weigh the risks, especially when it is a critically important antibiotic.**

Time-dependent drugs, like ß-lactams, are slowly bactericidal. The serum concentration therefore should exceed the minimum inhibitory concentration (MIC) for as long as possible during the dosing interval, either by continuous infusion or by frequent dosing. Time-dependent antimicrobials with a long elimination half-life (t1/2) have the advantage of prolonged treatment efficacy following a single administration. The subsequent antimicrobial administration should be performed when concentrations approach the MIC.

Optimal antimicrobial therapy not only involves maximizing therapeutic outcome but also minimizing the risk of emerging resistance during treatment. Discontinuation of the long-acting antibiotic administration will lead to a progressive decrease in its concentration. If pathogenic bacteria persist, re-growth of bacteria will start again once serum drug levels fall below the MIC value. A very slow decrease exposes these bacteria to sub-inhibitory concentrations (lower than the MIC) for a longer period than with a short elimination half-life

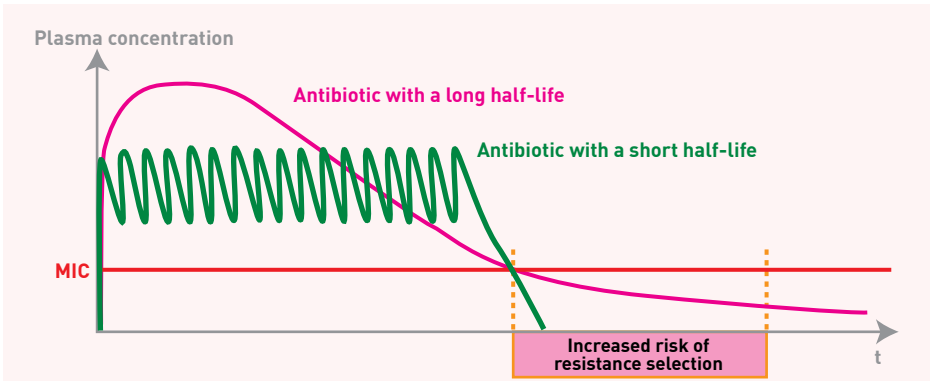


Figure 1 *- Comparison of the plasma vs. time concentrations of antibiotics with a long or a short elimination half-life in relation to the MIC and to the risk of resistance selection.*

antibiotic (Figure 1), and consequently **the risk of resistant mutant selection is greater**. Once the cure has been achieved and the pathogens have been killed, it is important to consider that antibiotics do not only target pathogenic bacteria but can also have damaging effects on the ecology of commensal species (skin, gut...). **This exposure can lead to decreased susceptibility and the development of multidrug-resistant bacteria**[5].

A well–documented example of a long-acting antimicrobial widely used in small animal medicine is cefovecin, a semi-synthetic 3rd generation long-acting cephalosporin authorized for use by subcutaneous administration in dogs and cats. However cefovecin is a critically important antibiotic so should be used with care under very specific conditions (see recommendations R.16 and R.17).

Cefovecin is a very broad-spectrum antimicrobial, with *in vitro* activity against both Gram-positive and Gram-negative (aerobic and anaerobic) pathogens associated with skin, urinary tract and periodontal infections in dogs and cats[12]. Clinical efficacy and safety of cefovecin in cats and dogs was demonstrated in urinary tract infections[8,9], abscesses and infected wounds[10,11,15,16], and more recently in canine Lyme disease[18]. However, in cats with clinical signs of upper respiratory tract disease, a single SC injection of cefovecin appears less effective than repeated oral administrations of amoxicillin + clavulanate or doxycycline[4].

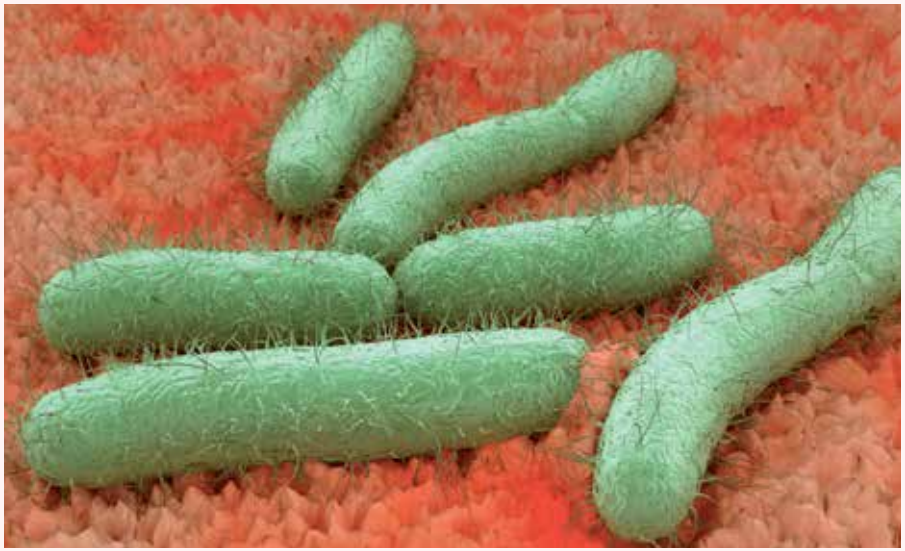
Cefovecin is rapidly and completely absorbed and fully bioavailable following SC administration[13,14]. Most of the dose is excreted unchanged in the urine. The exceptionally long elimination half-life of cefovecin (5.5 and 6.9 days, respectively, in dogs and cats), partly explained by high protein binding (95-100%), allows

What is the benefit/risk ratio of (very) long-acting antimicrobials?

treatment with a single injection every 14 days[13,14]. Therefore, administration of cefovecin by the practitioner ensures that the full course of therapy is properly administered and that the patient (especially uncooperative cats) receives a full dose. **Rather than covering for a hypothetical risk of owner non-compliance, the vet should restrict these treatments to animals where there is an acknowledged problem with compliance: appetent tablets or solutions that can be put in the food will solve the problem in many cases**. This distinct advantage probably explains the widespread and frequent use of cefovecin in small animals, especially in cats, up to 17% of non-topical antimicrobial prescription[2,6,7].

As previously explained, **one of the major risks of such long-acting antimicrobial therapy is that antimicrobial resistance and perturbation of the commensal flora may occur**. ß-lactam resistance was reported to be more common in faecal *E. coli* after cefovecin treatment in healthy dogs[3]. Further investigations are needed to determine the potential adverse effects of other antimicrobials on the gut microflora and resistance emergence in clinically ill patients.

It can be currently recommended that, **when prescribing long-acting antimicrobials, the benefits to the patient should clearly outweigh the risks** (Figure 2). ■



Prolonged-action antibiotics have an increased risk of resistance selection.

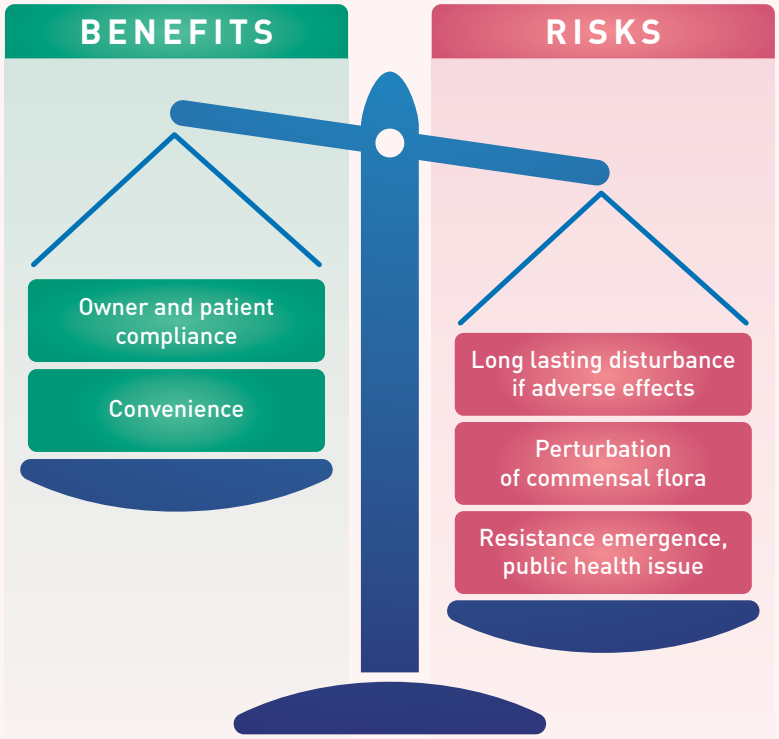


Figure 2 *- Risk-benefit balance of long-acting antimicrobials.*
When prescribing a long-acting antimicrobial therapy, the practitioner should perform an individual benefit/risk evaluation based on the drug's potential benefits outweighing the potential risks.

RECOMMENDATIONS

CRITICALLY IMPORTANT ANTIBIOTICS

RECOMMENDATIONS

R.16 Under which circumstances may 3rd and 4th generation cephalosporins and fluoroquinolones be prescribed?

- 3rd generation cephalosporins (e.g. cefovecin) and 3rd and 4th generation fluoroquinolones (e.g. enrofloxacin, marbofloxacin, pradofloxacin) must not be prescribed as a first-line treatment to avoid the emergence of resistance which is potentially dangerous for animal and human health.
- These antibiotics are only recommended if culture and sensitivity results demonstrate the need for such a prescription.
- However, these antibiotics can be indicated as first-line empirical treatment for life-threatening infections (e.g. sepsis) or specific conditions requiring their pharmacokinetic specific factors (e.g. prostatitis, rhinitis).
- The recommendations to be followed are:
  - carry out a bacteriological examination before starting treatment,
  - reduce the risk for development of antimicrobial resistance by "de-escalating" (down-staging) if antimicrobial susceptibility testing shows that a narrower spectrum antibiotic can be used,
  - use the recommended dose and avoid prolonged antimicrobial treatment.

Why are 3rd generation cephalosporins and 3rd and 4th generation fluoroquinolones so popular?

Fluoroquinolones offer many advantages for the treatment of infectious diseases. They have good to excellent *in vitro* activity against a wide range of aerobic Gram-positive and Gram-negative bacteria, as well as *Mycoplasma* spp. All fluoroquinolones (except pradofloxacin) approved in veterinary medicine are considered ineffective against the strict anaerobes. They have high oral bioavailability and an extensive tissue distribution in dogs and cats. Particularly high concentrations are found in the kidneys and liver, while therapeutic concentrations are also achieved in prostatic fluid, bone and cerebrospinal fluid. Fluoroquinolones are considered as relatively safe antimicrobial agents, although arthropathies in juvenile dogs and retinal degeneration with high doses of enrofloxacin in cats have been reported[12].

Third and fourth-generation cephalosporins are also characterized by a very broad spectrum of activity against Gram-negative and Gram-positive bacteria (though activity on Gram-positive bacteria may not always be as good as 1st and 2nd generation cephalosporins).

Cephalosporins are usually highly resistant to ß-lactamase enzymes, but pathogens are increasingly developing resistance through production of extended spectrum ß-lactamases that target 3rd and 4th generation drugs. Fourth generation cephalosporins may be effective against anaerobic bacteria. Third and fourth generation cephalosporins are well absorbed and have a wide tissue diffusion. Cephalosporins are among the safest antimicrobial drugs[10].

For all these reasons, fluoroquinolones and 3rd and 4th generation cephalosporins have become increasingly popular classes of antibiotics for prescription for a variety of infections in both human and veterinary medicine.

What evidence is there for their over-use and what problems does that cause?

Conversely, this widespread use has led to more prevalent resistance to these antimicrobial agents. Increasing resistance trends for cefovecin and enrofloxacin were reported in clinical isolates of *Staphylococcus intermedius* group (including *Staphylococcus pseudintermedius*) isolated from UK dogs and cats between January 2002 and December 2012[1]. In the US, a substantial rate of resistance (20%) to enrofloxacin in pathogenic *E. coli* isolates[3] and an increased frequency of *S. intermedius* isolates with resistance to fluoroquinolones[7] have been reported.

More than any other antibiotics, prescription of 3rd generation cephalosporins and quinolones must follow prudent use guidelines.

"Critically important antimicrobials": what does it mean?

Third and fourth generation cephalosporins and fluoroquinolones are classified among the most critically important antimicrobials for humans by the World Health Organisation[16], as they meet the two criteria required for this categorization (Table 1). Use of antimicrobials that are critically important for human health

Under which circumstances may 3rd and 4th generation cephalosporins and fluoroquinolones be prescribed?

in companion animals is an additional risk factor for the emergence and transmission of antimicrobial resistance. Although this risk has been observed for 15 years, above all in livestock, it should not be underestimated in dogs and cats. An important aspect related to antimicrobial resistance in companion animals is their close contact with humans potentially increasing the risk of interspecies transmission of (multidrug) resistant bacteria, as pets can act as reservoirs[8,14]. MDR bacteria in dogs and cats (MRSP, MRSA and ESBL-producing *E. coli*) are resistant to 3rd generation cephalosporins and therefore are likely to be selected by the use of these drugs. The current recommendation of the Committee for Medicinal Products for Veterinary Use (CVMP)[4] is that **"The use in companion animals of substances regarded as critically important antimicrobials (CIA) for human medicine should be carefully assessed considering the importance of those substances for public health, and possible limitations on the use of human last resort (life-saving) antimicrobials for treatment of companion animals should be considered."** To avoid regulatory restrictions or prohibition of use of such antimicrobials in the future, responsible and prudent use ("the precautionary principle") of 3rd and 4th generation cephalosporins and fluoroquinolones in small animals should therefore be promoted and practised by the veterinary profession[14].

How can these antimicrobials be used "prudently"?

Prudent use means the optimal selection of drug, dose and duration of antimicrobial therapy along with reduction of inappropriate and excessive use, as a means of slowing the emergence of antimicrobial resistance[13] (Figure 1). The current knowledge relating to prudent use of antibiotics is limited and direct evidence of the benefit is often lacking. Some recommendations however have been endorsed by national veterinary organizations[13]. It is essential to remember that **1st line (or primary use) antimicrobial agents are often useful for the treatment of most bacterial infections**. In most circumstances, they are just as effective as 3rd and 4th generation cephalosporins and fluoroquinolones, which are generally assigned to the secondary use category[9]. **Limited use of fluoroquinolones and 3rd and 4th generation cephalosporins is now widely accepted. These antimicrobials should be reserved for use in specific conditions requiring their specific pharmacokinetic factors (e.g. prostatitis, rhinitis), when culture and sensitivity results indicate that primary use drugs are not appropriate[9,13] or when compliance cannot be achieved**. As written in the 2005 ACVIM consensus statement[9], these drugs should not be employed in patients that are likely to recover without treatment, in patients that are as likely to be managed through treatment with primary use drugs, or in patients that are unlikely to survive regardless of the therapeutic regimen. In some life-threatening diseases (e.g. sepsis, patients with immune suppression and serious comorbidities) or in specific conditions requiring specific pharmacokinetic factors (e.g. prostatitis, rhinitis), fluoroquinolones and 3rd and 4th generation cephalosporins may be initially prescribed as empirical antimicrobial treatment. De-escalation should be considered whenever possible, as more targeted treatment can often be achieved once culture and susceptibility testing results are available[14]. Fluoroquinolones and 3rd and 4th generation cephalosporins may be inefficient in such clinical settings. A recent study in dogs with abdominal sepsis[5] demonstrated that empirical antimicrobial treatments

Selection of fluoroquinolones and 3rd or 4th generation cephalosporins	Should not be employed in patients that are: - likely to recover without treatment, - likely to be managed throught treatment with primary use drugs, - unlikely to survive regardless of the therapeutic regimen. Should be reserved when culture and sensitivity results indicate that primary use drugs are not appropriate. May be prescribed in life-threatening conditions as empirical antimicrobial treatment. De-escalation should be considered once culture and susceptibility testing results are available.
Selection of the dose	Use the label dose and dosing interval, but be aware that underdosing may occur in critically ill patients.
Selection of the treatment duration	Avoid prolonged treatment.

Figure 1 *- Prudent use of fluoroquinolones, 3rd and 4th generation cephalosporins. Prudent use means the optimal selection of drug, dose and duration of antimicrobial therapy along with reduction of inappropriate and excessive use, as a means of slowing the emergence of antimicrobial resistance[13].*

First-line antimicrobial agents are as effective as 3rd and 4th generation cephalosporins and fluoroquinolones in most circumstances. Their use should be preferred in 1st intention.

were inappropriate (based on the resistance pattern of bacteria according to culture and sensitivity results) in 47.4% of cases, the most commonly used inappropriate antimicrobials being amoxicillin + clavulanate and cefuroxime, but also a fluoroquinolone.

How does use of a licensed veterinary 3rd generation cephalosporin or fluoroquinolones fit into this?

The label dose and dosing intervals of fluoroquinolones and 3rd and 4th generation cephalosporins are generally consistent with current guidelines about antimicrobial use. However, these doses may be inappropriate during critical illness as drug metabolism and excretion may be altered. In critically ill human patients, underdosing appears to be much more frequent than overdosing, leading to poor clinical outcomes and resistance emergence[2]. Currently, in small animal medicine, the effect of critical illness on efficient dosing has not been evaluated. Prolonged treatment with fluoroquinolones or 3rd and 4th generation cephalosporins should be avoided, as shortening the duration of therapy is considered to be one of the strategies to reduce the increasing antibiotic resistance by decreasing the exposure of commensal bacterial populations to antimicrobial drugs[14]. In humans, 7 days of treatment for acute pyelonephritis is for example equivalent to longer treatment in terms of clinical failure and microbiological failure, including in bacteraemic patients[6,11]. Limited data are available in veterinary medicine. In dogs with urinary tract infections, the microbiological and clinical cure rates with a high dose (18-20 mg/kg PO q24h) of enrofloxacin for 3 days were 77.1% and 88.6%, respectively, and were not inferior to those following a 14-day treatment regimen with amoxicillin + clavulanate[15]. ■

Table 1 *- Criteria for categorization of cephalosporins (3rd and 4th generation) and fluoroquinolones as critically important antimicrobials in human medicine.*

Antimicrobial class	Criterion 1	Criterion 2
Cephalosporins (3rd and 4th generation)	Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children. Limited therapy for infections due to multidrug resistant *Enterobacteriaceae*, which are increasing in incidence worldwide. Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever.	Disease may result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella spp.* from non-human sources.
Fluoroquinolones	Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella* spp. and MDR *Shigella* spp. infections.	Disease may result from transmission of *Campylobacter* spp. and *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.

Criterion 1: An antimicrobial that is the sole agent or one of limited available therapy, to treat serious human disease.
Criterion 2: An antimicrobial agent that is used to treat diseases caused by either: (1) organisms that may be transmitted to humans from non-human sources or, (2) human diseases caused by organisms that may acquire resistance genes from non-human sources.

ANTIMICROBIAL CLASSIFICATION

RECOMMENDATIONS

R.17 Is it possible to rank antibiotics according to 1st or 2nd choice? Yes but...

- A consensus of the American College of Veterinary Internal Medicine defined four categories of antibiotics on the basis of their use: 1st line (or primary), 2nd line (secondary), 3rd line (tertiary) and restricted or voluntarily prohibited antibiotics.
- Secondary or higher use categories should only be used if primary use drugs are not appropriate and should be based on culture and sensitivity testing.
- It is difficult to classify antimicrobial drugs as there are not evidence-based categories.
- However, it is widely accepted that 3rd generation cephalosporins and fluoroquinolones should not be used as 1st line antimicrobials because they are critically important to treat life-threatening infections in humans.

To facilitate appropriate empirical selection of antimicrobial drugs by veterinarians on a routine basis, a consensus statement of the American College of Veterinary Internal Medicine (ACVIM) proposed a categorization of antimicrobials into primary, secondary and tertiary use categories[4].

The primary (1st line) use category includes older antimicrobials and those with a narrower spectrum of activity (see Table 1 p.356 and recommendation R.13).

Drugs assigned to the secondary (2nd line) use category include newer antimicrobials with an extended spectrum of activity compared with primary use antimicrobials and those of added importance in the treatment of serious or frequently resistant infections in humans. Secondary or higher use antimicrobials should be used only if primary use agents are not appropriate based on culture and AST results.

Drugs that are very important for human and animal health care, especially those most recently developed and those that have extended spectra of activity and are efficient against the most resistant bacteria, should be classified for tertiary use (3rd line). **Tertiary use drugs should only be prescribed for animals with clinically important infections caused by bacteria that have been demonstrated to be resistant to all primary and secondary use drugs.**

The last category includes antimicrobial agents for which the clinical value to human medicine is so important that their use should be voluntarily prohibited in animals (e.g. drugs that are not licensed for veterinary use and are essential for treating resistant infections in humans)[4].

The prescription of an antibiotic should take into account its category: first-line or second-line.

Definition of use categories and examples are presented in Table 1. However, development of specific categories, taking into account the type of infection, the patient characteristics, antimicrobial resistance patterns and drug factors, are needed (see Disease fact sheets in part 1 of the book). Recently, such guidelines have been proposed for canine superficial bacterial folliculitis by the International Society for Companion Animal Infectious Diseases[2]. FECAVA has also developed a poster for recommended therapy of common clinical conditions (www.fecava.org/sites/default/files/files/AMR%20theraphy.pdf).

A common mistake is to consider that primary use antimicrobials are less efficient than those in secondary or tertiary use categories, when 1st line drugs are useful in most infections. In a veterinary teaching hospital, despite a caseload skewed toward critically ill referral cases, drugs designated as first-line accounted for > 90% of 21,152 prescriptions between 1995 and 2004[7].

Another reason explaining the empirical prescription of broad-spectrum 2nd line drugs is the delay in receiving appropriate therapy based on laboratory results, which may affect the clinical outcome and survival in critically ill patients. Patients classified as receiving inappropriate empirical antimicrobial therapy have indeed at least a 36–48 hour delay in receiving appropriate antimicrobial therapy (while awaiting culture results) when compared to those given appropriate empirical antimicrobial

R.17 Is it possible to rank antibiotics according to 1st or 2nd choice? Yes but...

Table 1 - Categorization of systemic antimicrobials.

Use category	Definition and guidance for use	Examples
Primary/ 1st line Licensed for companion animals	• 1st line antibiotics are antibiotics that are well established with good evidence of high efficacy and safety. Ideally, they should be narrow-spectrum. They are as potent as 2nd and 3rd line drugs used in the appropriate circumstances. • They should be used wherever appropriate and possible.	• Penicillins • 1st generation cephalosporins • Amoxicillin±clavulanate • Trimethoprim sulfonamides • Tetracyclines • Lincosamides
Secondary/ 2nd line Licensed for companion animals	• 2nd line antibiotics are often broad-spectrum antibiotics that are important for animal and human health and in which resistance is more likely to occur following use and/or is of greater concern in veterinary and human healthcare. • Critically important antibiotics should only be used where C&AST results or good clinical and epidemiological evidence indicate that 1st line antibiotics will not be effective. Wherever possible, the use of 2nd line drugs should be supported by C&AST. • Some antibiotics are classified as 2nd due to their toxicity, but not due to their activity (e.g. aminoglycosides).	**Narrow spectrum:** • Aminoglycosides • Metronidazole • Macrolides **Broad spectrum:** • Chloramphenicol **Critically important ABs:** • Fluoroquinolones • Cefovecin (3GC)

Table 1 (continued)

Use category	Definition and guidance for use	Examples
Tertiary/ 3rd line	• 3rd line antibiotics are antibiotics that are of great importance to animal and human health especially for the treatment of multidrug resistant bacteria, and where resistance is more likely occur following use and/or is of great concern in veterinary and human healthcare. Many of these drugs are not licensed for companion animals, and therefore data on clinical breakpoints, efficacy and safety may be lacking. • They must only be used where there is culture evidence to show that 1st or 2nd line antibiotics will not be effective and where topical therapy has been ineffective or is not feasible. • The use of 3rd line drugs must be supported by AST, although these drugs may be started in life-threatening conditions while waiting for the culture results.	• 3rd and 4th generation cephalosporins other than cefovecin • Rifampicin • Fosfomycin
Restricted, voluntarily prohibited	• These drugs are vitally important to human health so should never be used in animals.	• Glycopeptides: vancomycin, teicoplanin • Carbapenems and monobactams • Oxazolidones: linezolid • Lipopeptides: daptomycin • Riminofenazines: clofazime

Is it possible to rank antibiotics according to 1st or 2nd choice? Yes but...

therapy. It was shown that this delay did not affect mortality in dogs with pneumonia[5] or septic peritonitis[1]. Larger, prospective clinical studies that include various subgroups of patients are however needed to provide clear evidence of the benefit of early and appropriate antimicrobial therapy[3].

Moreover, the clinical seriousness of an infection in a dog or a cat is not a valid reason by itself to justify the immediate prescription of 2nd line antimicrobials as initial treatment.

While categorization has clearly contributed to the appropriate use of antimicrobials on a routine basis by veterinarians over the last 10 years, it is however difficult, as stated in the second ACVIM consensus statement[8], to assign drugs to different tiers as there are not evidence-based categories. Antimicrobials should be assigned to tiers according to the spectrum of activity, the effect on commensal microbiota, the likelihood of resistance emergence, and the clinical usefulness for treatment of serious infections in humans and animals. Currently, given the paucity of data available on these aspects in veterinary medicine, especially regarding the impact of the use of antimicrobials on resistance emergence, more information is required to adequately assign drugs to tiers[8]. It should be also emphasized that the list of Critically Important Antimicrobials for human medicine by the World Health Organization in 2011[9] includes some antimicrobials (e.g. amoxicillin, ampicillin...) considered as primary use drugs by veterinarians. It is however widely accepted that only 1st and 2nd line drugs should be used for treatment of canine and feline infections and that 3rd and 4th generation cephalosporins and fluoroquinolones should not be used as 1st line antimicrobials. Use of tier-based antimicrobial selection is clearly helpful for initial drug prescription, but more information is needed for appropriate categorization of antimicrobial drugs. ■

Why should the use of Critically Important Antibiotics be avoided?

Not all antibiotics have the same critical importance for human health.

National and European recommendations are based on the avoidance of selecting resistance to critical antibiotics in bacteria in animals that could be transmitted to humans, i.e. (in order of importance):

- Last-resort antibiotics for humans (e.g. carbapenems),
- 3rd and 4th generation cephalosporins (e.g. cefovecin),
- Fluoroquinolones.

The use of these Critically Important Antibiotics should therefore be limited to individual clinical cases that cannot be treated by other antimicrobials (e.g. multidrug resistant infections). Culture and AST should be performed to make sure that no other antibiotic can be used instead of a CIA.

CAUSES OF FAILURE

RECOMMENDATIONS

R.18 What are the key causes of antibiotic treatment failure and what is the importance of resistance? What to do in a case of antibiotic treatment failure?

- Treatment failure can be a result of different factors influencing the clinical efficacy of antibiotic therapy either alone or together.
- Key causes to be considered in case of treatment failure include:
  - an unjustified antibiotherapy, combined with a mistaken diagnosis of bacterial infection, or not accompanied by essential measures (abscess lancing, draining of infection sites...),
  - a bad choice of drug: spectrum or lack of efficacy at the infection site,
  - a wrong dose regimen: low dose, frequency or length, non-compliance by pet owners,
  - a suppressed host immune status.
- Bacterial resistance is involved in a bad choice of drug or a wrong dose regimen, but its relative importance among the other causes of failure is difficult to quantify. Based on studies in human medicine bacterial resistance is the main cause of treatment failure.
- The veterinarian can take a certain number of measures to avoid resistance-related failures:
  - carry out a microbiological diagnosis of the pathogenic agent rather than an epidemiological one,
  - measure the sensitivity to antibiotics of the strain responsible for the infection. Sample for culture and AST if the previous treatment was empirical or sensitivity results are unreliable,
  - adhere to the recommended doses and the optimal administration procedures for time-dependent or concentration dependent antibiotics,
  - verify that the owner complies with the prescription (see recommendation R.21).

Key causes of antibiotic treatment failure

The role played by bacterial resistance in treatment failure has not been quantified in veterinary medicine. Human studies have shown that clinical conditions do not improve in most patients treated with antibiotics to which the cultured strains are classified as resistant (50-80%), whereas the rates of treatment failure are markedly lower (3-10%) in patients infected with susceptible strains[3,1]. However, the correlation between treatment failure and resistance has been poorly investigated in veterinary medicine.

It is generally assumed that the immune status of the patient influences the outcome of antibiotic treatment, especially when bacteriostatic drugs are used because it requires the host immune response to cure infection.

Lack of drug efficacy at the infection site may be due to physiological (e.g. brain- or prostate-blood barrier) or pathological barriers (e.g. abscess wall, biofilm, presence of pus and other organic matter interfering with antibiotic activity or pathogen intracellular location).

Inappropriate dosages also affect treatment outcome by hampering the achievement of adequate drug concentrations at the infection site. **Thus it is essential that the patient is weighed to calculate accurately the correct dosage based on the actual body weight**. Prescription of tablets that are designed to facilitate dosage by the owner may be another approach to avoid underdosage.

Non-compliance is another important cause of antibiotic treatment failure. In human medicine, it has been estimated that approximately 40% of patients do not adhere to antibiotic treatment[2]. The patterns of non-compliance include failure to start the therapy, delay in the start of the therapy, omission of single doses, changes in time intervals between doses, premature stopping of treatment or use of left-over antibiotics. Uncooperative or aggressive pets are a recognized cause for a lack of compliance in veterinary medicine (see recommendation R.21). Based on research in human medicine[2], non-compliance may also be due to owner's beliefs, cost of antibiotic, antibiotic bad taste, frequent dosing, long treatment time, side effects, owner's forgetfulness and rapid improvement of symptoms.

Non-compliance is an important cause of antibiotic treatment failure.

What to do in case of antibiotic treatment failure?

Treatment failure may be consequent to a variety of factors influencing the clinical efficacy of antibiotic therapy acting alone or in combination. Thus it is essential first to identify the most likely cause of failure taking into consideration both anamnestic and clinical data. Assuming that the prescribed drug is known to penetrate and be effective at the infection site and was not underdosed

in the prescription, the following steps should be taken:

• The possible causes of treatment failure are reviewed based on anamnesis and clinical records. A microbiological diagnosis (e.g. cytology) should be carried out.

• An appropriate sample is taken and submitted to a microbiology laboratory for culture and sensitivity testing if the previous treatment was empirical or based on sensitivity results that are regarded as old or unreliable.

• Another antibiotic is chosen based on available sensitivity results if the previous treatment was based on sensitivity results that are regarded as reliable.

• In case of suspected non-compliance, the owner is educated about the importance of compliance and a new treatment course is established using the least demanding treatment option (i.e. short-course antibiotic therapy with infrequent dosing, convenient dosage form and minimal adverse effects). Good communication and a trusting relationship with the pet owner is key to secure compliance. The pet owner should be comfortable enough with the vet to express his/her concerns if not able to deliver the proposed therapy to their animals (see recommendation R.21).

In case of suspected non-compliance, the owner is educated and a new treatment course is established using the least demanding treatment option.

• A bactericidal drug is chosen if the previous treatment was bacteriostatic and the immune status of the patient is suppressed.

• If none of the possible causes can be excluded, all the actions listed above should be implemented in the new treatment. ■

MULTIDRUG RESISTANT INFECTIONS

How to deal with multidrug resistant infections?

- Use clinical signs and cytology to determine the extent and severity of the infection.
- Use bacterial culture and antibiotic susceptibility testing of representative samples.
- Obtain minimum inhibitory concentrations (MICs) wherever possible.
- Always use topical antiseptic therapy wherever possible – consider chlorhexidine-based shampoos, sprays, and wipes; medical-grade honey ointments and dressings; hypochlorous acid sprays and dilute bleach solutions (see Figures 1 and 2).
- Consider topical antibiotics – effective drugs include mupirocin, fusidic acid, silver sulfadiazine and silver sulfadiazine combined with gentamicin or marbofloxacin.
- Treat the underlying cause of the infection (see Figures 3 and 4).
- Only use systemic antibiotics if absolutely necessary, and never use drugs of critical importance to human health even if the infection is susceptible.
- Bacterial biofilms may need specific measures, including products with anti-biofilm activity (e.g. acetyl cysteine, TrizEDTA and detergents) and/or removal of implants.
- Use strict barrier nursing, hygiene and infection control measures to prevent spread of the bacteria to the environment and other patients.
- Give advice to the owners about effective hygiene measures to minimise the risk of zoonotic colonisation and infection.
- Stop antibiotic therapy as soon as the infection has resolved.
- Culture appropriate carriage sites (e.g. nose and perineum, urine or faeces) to determine whether the patient is still colonised with the antibiotic resistant bacteria.
- Allow colonised animals to recover in the community – avoid antibiotics and veterinary visits and give advice on routine care and hygiene.

What influences treatment choices?

The extent and severity of the infection strongly influence treatment choices. It is difficult to make precise treatment recommendations for these cases, as most systemic antimicrobial options will be inappropriate. **Clinicians must therefore carefully evaluate clinical signs, cytology and culture results** to select the appropriate antimicrobials, route of administration and duration of treatment.

The minimum inhibitory concentration (MIC) is the lowest concentration of an antibiotic that completely inhibits growth of the bacteria. MIC data reveals the exact concentration that must be exceeded at the target tissues. It may be possible to achieve this even for resistant isolates by increasing the systemic dose or using topical therapy.

Topical antiseptics can be highly effective, even against multidrug resistant bacteria (see Tables 1 and 2, Figures 1 and 2). MICs are reported in µg/ml ranges assuming that the antibiotic will be given systemically. **Topical therapy, which delivers mg/ml antibiotic concentrations, can overcome apparent resistance**. Using antimicrobial sensitivity tests to predict the response to topical therapy is therefore misleading.

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Figure 1 *- MRSP-associated infection and wound breakdown after a hind limb amputation in a cat.*

© courtesy Dr Stephanie Horne

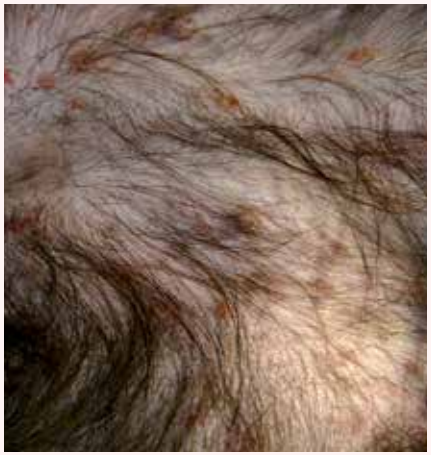
Figure 2 *- Three weeks later there was complete resolution of the infection following removal of the Penrose drain and sutures, and twice daily cleaning with a 0.011% hypochlorous acid solution.*

How to deal with multidrug resistant infections?

The identity of the organism guides the choice of antimicrobial, but decisions should be based on clinical signs and cytology. Topical antibiotics, moreover, may not be metabolised and excreted and may therefore have a much longer duration of activity compared to systemic drugs. Options include using antibiotic solutions to flush joints or cavities, nebulised solutions for respiratory infections, antibiotic creams, gels or ointments for ears, eyes, skin and wounds, and antibiotic impregnated beads and foams for joints, cavities and wounds (see Table 2).

Most antimicrobial resistant infections are opportunistic, involving commensal (e.g. MRSA, MRSP and *E. coli*) or environmental (e.g. *Pseudomonas*) bacteria.

These are not primary pathogens, and almost all infections are secondary to an underlying problem. **Successful resolution often requires management of the primary disease** (e.g. treating the atopic dermatitis, managing diabetes mellitus or removing foreign bodies, sutures and implants; see Figures 3 and 4). For example, in atopic patients with pyoderma, treatment with glucocorticoids alone or glucocorticoid-antibiotic combinations is more effective than the use of antibiotics alone. Antimicrobial resistant infections in dogs can rapidly improve following removal of foreign bodies, sutures and implants in conjunction with simple topical antimicrobial therapy.



Figue 3 *- MRSP-associated superficial bacterial folliculitis in a dog with atopic dermatitis.*

Figure 4 *- The infection completely resolved following management of the atopic dermatitis with cyclosporine and daily soaks with diluted bleach.*

Table 1 *- Effective topical antimicrobials.*

2-4% chlorhexidine shampoos	Superior *in vitro* efficacy than other antimicrobial shampoos. Effective as sole therapy in MRSP-associated canine pyoderma. Residual activity; can be used 2-3 times weekly for 5-10 minutes. 2% chlorhexidine and 2% miconazole show synergistic activity against *Staphylococcus pseudintermedius*.
0.15% chlorhexidine wipes	Highly effective *in vitro* compared to other antimicrobial and cleansing wipes. Little to no efficacy against *Pseudomonas* and ESBL-*E. coli*. No residual activity; use at least once daily.
0.15% chlorhexidine and TrizEDTA	Broad spectrum *in vitro* activity. High concentration of TrizEDTA potentiates chlorhexidine but there is no evidence of synergistic antimicrobial activity.
0.011% hypochlorous acid	Highly effective *in vitro*. No residual activity; use at least once daily.
Diluted bleach	Highly effective *in vitro*. Use higher concentrations with care.
TrizEDTA	Little to no antimicrobial activity by itself. High concentrations potentiate the antimicrobial activity of gentamicin and marbofloxacin but there is no evidence of synergistic antimicrobial activity.

Use of 2nd line and last resort systemic antibiotics

Second-line and last-resort systemic antibiotics (e.g. rifampin, chloramphenicol, aminoglycosides, 3rd or 4th generation cephalosporins, anti pseudomonal penicillins and fosfomycin) **should only be used where absolutely necessary**, i.e. when no first or second-line drugs are appropriate and topical therapy has not been effective or is not feasible. The choice of drug (see Table 3) should be made following culture of representative material, taking into account underlying conditions, concurrent medication and penetration to the target tissue. The underlying condition must always be managed, as treatment may otherwise just select for more resistance among pathogenic and commensal bacteria. It is questionable whether third-line antibiotics should be used if antibiotic therapy will not affect the overall clinical outcome. **Drugs that are vitally important for human health (e.g. vancomycin, teicoplanin, linezolid and carbapenems) should not be used in animals.** Stop antibiotic therapy as

Table 2 - *Topical antibiotics (combinations with another antibiotic / antifungal not included).*

1% silver sulfadiazine	Broad spectrum antimicrobial activity. Potentiates gentamicin (0.3%), amikacin (0.1%) and marbofloxacin (0.2%) but no evidence of synergistic antimicrobial activity.
Neomycin Gentamicin	Broad spectrum; usually combined with a glucocorticoid.
Fusidic acid	Narrow spectrum; topical application highly effective against MRSA and MRSP.
Mupirocin	Mupirocin may be reserved for use against MRSA in humans in some countries.
Antibiotic dilutions in TrizEDTA: **0.6% enrofloxacin** **0.2% marbofloxacin** **2.7% ticarcillin** **1.7% ceftazidime** **0.3% gentamicin** **0.1% amikacin**	Effective against *Pseudomonas*; gentamicin and amikacin solutions can be effective against *Pseudomonas*, MRSA/MRSP and ESBL-*E. coli*.

soon as the infection has resolved. This decision should be based on:

- the complete resolution of clinical signs associated with the infection (remembering that clinical signs associated with the primary disease may still be present),
- normal cytology,
- where appropriate, negative cultures (remember that animals may still be culture positive for commensal bacteria such as MRSP or *E. coli* in the absence of infection).

Importance of biofilms in treatment

Many antimicrobial resistant bacteria produce biofilms, which can complicate otitis, bacterial overgrowth syndrome and urinary tract infections. **Biofilm forms on implants, catheters and sutures, and protects the bacteria against topical and systemic antimicrobials leading to treatment failure, development of resistance and/or relapse after treatment**. Where possible biofilms should be removed by thorough bathing, wound cleansing and ear flushing. Triz-EDTA may facilitate antimicrobial penetration into biofilms and can be used before applying topical antibiotics where appropriate. Acetyl cysteine liquefies biofilms, facilitating removal and penetration by antimicrobials. Nevertheless, biofilms remain a significant clinical challenge and may necessitate removal of sutures, catheters and implants.

Minimising the spread of resistant bacteria

Great care should be taken to prevent dissemination of antimicrobial resistant bacteria in veterinary healthcare environments. Similarly, while most antibiotic resistant bacteria are opportunists and pose little risk to healthy people and animals, owners should be given clear and effective advice on hygiene and infection control. Clinically healthy animals that have recovered are often colonised with antimicrobial resistant bacteria. However, they should not be treated with antibiotics, as this may select for further resistance, reduce the diversity of commensal bacteria and lead to persistent carriage. Simple hygiene measures are enough to limit spread and most animals will lose colonisation with multidrug resistant bacteria without the need for any further measures (see recommendation R.24). ■

Consider topical antiseptic products for multidrug-resistant infections.

RECOMMENDATIONS

How to deal with multidrug resistant infections?

Table 3 *- Systemic antibiotics that may be effective in antimicrobial resistant bacterial infections.*

Antibiotic	Dose	Notes
Clindamycin	11 mg/kg q 12-24h PO	Check for inducible clindamycin resistance (PCR, D-zone test or concurrent resistance to erythromycin).
Chloramphenicol	50 mg/kg q 8h PO (dog) 50 mg/cat q 12h PO (cat)	Non-regenerative anaemia; inhibits hepatic microsome enzymes.
Florfenicol	25-50 mg/kg q 8h SC	
Amikacin **Gentamicin** **Tobramycin**	15-30 mg/kg q 24h SC 9-14 mg/kg q 24h SC 9-14 mg/kg q 24h SC	Ototoxic and nephrotoxic.
Trimethoprim-sulfadiazine	15-30 mg/kg q 12-24h PO or SC (dose may differ for other potentiated sulphonamides)	Effective against MRSA; most MRSP isolates are resistant. Adverse effects include kerato-conjunctivitis sicca, hypothyroidism, blood dyscrasias, immune-mediated reactions and urine crystals.
Doxycycline **Minocycline**	5-10 mg/kg q 12-24h PO 5-15 mg/kg q 12-24h PO	Effective against MRSA; most MRSP isolates are resistant. May cause oesophageal irritation.
Ceftazidime **Cefoperazone**	20-50 mg/kg q 8h IV/IM 22 mg/kg q 8 hours IV/IM	Anti-*Pseudomonas*.
Nitrofurantoin	4 mg/kg q 8h PO	ESBL-associated urinary tract infections.
Rifampin	5-10 mg/kg q 12-24h PO	Hepatotoxic.
Fosfomycin	40-80 mg/kg q 12h PO	Effective against MRSA and MRSP; ESBL-associated infections, especially in the urinary tract. Appropriate dose in dogs not yet fully validated.

Please note that some countries prohibit the use of some human antibiotics not licensed for animals, the off-label use of licensed drugs and/or the use of certain critical drugs even if there is evidence of sensitivity or efficacy.

PREVENTION OF RESISTANCE

RECOMMENDATIONS

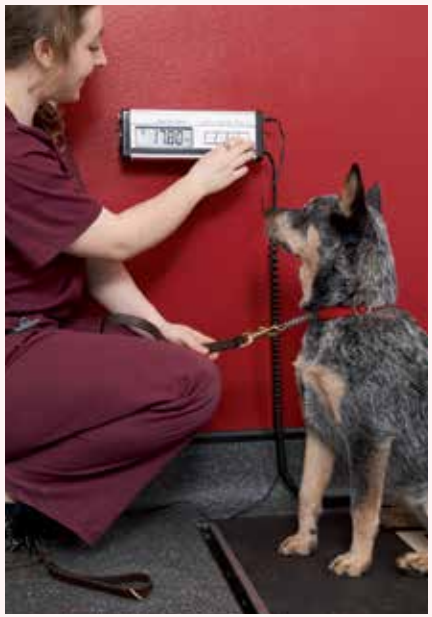
R.20 How can the development of resistance be limited when using antibiotics? (timing, dosage, duration)

- **Limit use of antibiotics to only as necessary. Avoid them whenever possible (e.g. superficial pyoderma, abscesses).**
- **Whenever possible, the antibiotic choice should be guided by cytology or sensitivity testing.**
- **When treating empirically, first-line antibiotics should be preferred over second-line agents with broad spectrum of activity (e.g. fluoroquinolones and third generation cephalosporins).**
- **Concentration-dependent drugs such as fluoroquinolones should be administered using the highest dosage possible to prevent selection of resistant mutants as well as to enhance clinical efficacy.**
- **Underdosing and irregular administration intervals should be avoided for all antibiotics.**

Sensitivity testing is useful to tailor therapy to the susceptibility profile of the infecting strain, therefore avoiding use of ineffective antibiotics. The information provided by cytology to guide antibiotic choice is not as accurate as for sensitivity testing but assists the decision on whether antibiotic therapy is needed. Furthermore, cytology results can also be used to select drugs active against specific groups of organisms based on the morphology of the infecting strain (Gram-positive cocci *vs.* Gram-negative rods). This is why cytology should be performed routinely to guide antibiotic choice in the treatment of pyoderma, otitis or urinary tract infections[1].

The broader the spectrum of an antibiotic, the wider the impact on the commensal flora and on selection of resistance.

This is why empirical use of broad-spectrum antibiotics, in particular fluoroquinolones, cefovecin or other third generation cephalosporins, should be avoided. Various studies in dogs[2-5] and livestock animal species[6-10] indicate that these drugs are likely to promote selection of multidrug-resistant bacteria of high clinical relevance such as MRSA, MRSP and ESBL-producing strains. These bacteria are per definition resistant to third generation cephalosporins and display relatively high rates of fluoroquinolone resistance. This is why we recommend that veterinary fluoroquinolones (enrofloxacin, marbofloxacin and pradofloxacin) and cefovecin, which is the only extended-spectrum long-acting cephalosporin authorized for use in companion animals in the EU, should only be used as second or third-line agents to preserve their efficacy for treatment of complicated infections. Dosing regimens should be carefully selected on the basis of pharmacokinetic and pharmacodynamic properties that prevent emergence of pre-existing and newly formed mutants. The concentration that restricts the emergence of resistant mutants within a susceptible population is defined as Mutant Prevention Concentration (MPC). There is increasing evidence that higher dosages allow the MPC to be reached at the site of infection and contribute to slowing down development of resistance to concentration-dependent drugs for which resistance mainly evolve by chromosomal mutations (e.g. fluoroquinolones). There is no consensus on whether a similar approach may be useful to prevent resistance to time-dependent antibiotics for which resistance mainly evolves by horizontal gene transfer. Some studies indicate that acquisition of resistance by horizontal gene transfer may also be avoided to some extent when the MPC is reached[11].



Underdosing should be avoided to limit resistance. Weighing the patient is essential to calculate accurately the correct dosage.

There is a lack of scientific evidence to recommend how long the duration of treatment should be in order to limit development of resistance. **As a matter of principle, unnecessary treatment should be avoided after the patient has recovered from the infection**. In humans there is an increasing consensus that treatment duration can affect the selection of antibiotic resistance. When comparing recommendations between human and veterinary medicine, it is evident that for some infections (e.g. urinary tract infections) duration of treatment is longer in animals[12]. More research is needed to optimize treatment duration in relation to both clinical efficacy and prevention of resistance development.

For more information on rational antimicrobial use and prevention of resistance development, please refer to Synopsis chapters. ■

COMPLIANCE

R.21 How to obtain good client compliance (to limit the development of resistance)?

Good communication

Good communication is important to engage clients and ensure compliance with prescribed therapies. Veterinarians should allocate time during the consultation to discuss and agree a therapeutic plan with their client and explain:

- the risk of treatment failure, disease recurrence and development of antimicrobial resistance if the therapeutic plan is not followed correctly,
- the frequency of dosing (e.g. explicitly explaining every 12 hours instead of twice a day),
- the correct dose,
- how to monitor the animals for any potential adverse effects,
- the requirement to:
  - complete the full therapeutic course,
  - contact the vet if the client needs to discuss any issues or queries they might have during the therapeutic course,
  - attend follow-up consultations (e.g. for therapy effectiveness assessment and discussion of possible further therapeutic options if required),
  - ensure leftover drugs are not used to treat recurrent conditions and/or new conditions in their animals or someone else's; these should be disposed of safely.

Veterinarians should allocate time during the consultation to discuss and agree the therapeutic plan with their client.

Good prescribing

- Select the antimicrobial that is the most appropriate for the likely/confirmed pathogen involved, condition and organ or system affected. However, also consider the level of compliance you are realistically likely to achieve (taking into account the route of administration, dose, dosing frequency and duration of therapy, animal characteristics and after discussion with the client what they are able or willing to do).
- Prescribe palatable tablets or tools e.g. pill poppers to aid tablet or drug administration.
- Select formulations with the correct dosing and for ease of administration.
- Prescribe only the quantity necessary for the duration of the therapeutic course.
- Opt for shorter therapeutic course durations whenever possible.
- Minimise the number of drugs included in the therapeutic plan.
- Select the most convenient frequency of dosing for the client, taking into account their availability and willingness to administer medications.
- Show how to administer the treatment to the animal.

Good service and follow-up

Consider offering:

- Administration of therapy by a member of staff (e.g. nurse consultations),
- Reminder phone calls or SMS messages for the frequency of dosing,
- Reminder phone calls or SMS messages for follow-up consultations,
- Follow-up calls to discuss progression of therapy.
- Provision of detailed written instructions to pet owners regarding the type of medication prescribed and method of administration.

How compliant are pet owners in the administration of medications?

In veterinary medicine, compliance is defined as "the extent to which owners adhere to instructions when giving prescribed drugs to their animals"[6]. There is scarce data regarding compliance levels in pet animals; studies focused on assessing compliance in small animal practice have reported varied levels between 27%

and 84%, depending on the definition of compliance applied, frequency of dosing and duration of therapy considered, species and country where the study was conducted[6,7,9]. **Veterinary surgeons often assume high levels of compliance by pet owners**[9]. Lack of compliance to prescribed therapies, either through failure to complete a treatment course, missed or incorrect dosing frequencies or by underdosing, can result in treatment failure, recurrent conditions and the development of antimicrobial resistance due to selective pressure upon microbial populations[2,8]. This may additionally lead to inaccurate assessment of therapeutic efficacy and mistrust in the initial diagnosis of the condition being treated[2].

What are the barriers to compliance?

There are several factors that can affect compliance in veterinary settings that may act as barriers (Table 1). Most of these factors are client-related. Nevertheless, the veterinarian and veterinary team play an important role in the education of pet owners regarding the importance of being compliant with instructions provided for prescribed therapies[6,7,9]. The ability of a client to administer a medication is often over-estimated. In a recent study focused on pets and horse owners, it was reported that none of the participating veterinarians (n=57) provided written information on drug administration and only 5% of them demonstrated how to administer tablets to animal owners[8]. Education of the owner in techniques of medication administration is one factor that can be easily addressed with demonstrations and provision of resources that can be referred to at home (prepared resources are readily available e.g. BSAVA drug information sheets and International Cat Care YouTube videos demonstrating administration of medications to cats via various routes www.youtube.com/user/iCatCare).

Good communication is clearly a key factor in the establishment of a relationship of trust and promoting compliance by clients. It has been reported that pet owners valued the time committed by vets to the consultation, which might indicate that their level of compliance might be affected by the perceived dedication of the vet to the care of their pets[6]. Active involvement of clients in the decision-making of a suitable therapeutic regimen is essential and should be adjusted to their availability[1,5]. This factor has been associated with non-compliance rates of up to 50% in a short-therapy study in dogs[5]. **Provision** of **explanations of the condition** suffered by their animal[4], **repeated instructions** on therapy prescribed and **explanation of effects** of prescribed therapy have been shown to improve compliance amongst animal owners, with the former improving client compliance by 31% (i.e. compliance levels reached 76.9%)[8].

Table 1 - *Barriers to compliance with prescribed therapy in veterinary practice.*

- Owner inability to effectively administer medication:
  - Owner cannot master technique to administer the treatment,
  - Due to dosing frequency or duration (e.g. unavailability, forgetfulness),
  - Dog or cat not amenable.
- *Owner interrupts treatment course because:*
  - Adverse effects are observed (drug is perceived as "harmful" to pet),
  - The animal gets better (pet perceived as "cured"),
  - No improvement is observed during the treatment (drug perceived as "ineffective").
- Cost of the therapy is too high (client unable or unwilling to pay).
- Inadequate consultation time to discuss prescribed therapeutic plan.
- More than one individual involved in the care of the animal.
- Animal fails to return to the clinic for follow-up assessment and further medication.

Compliance has been reported to decrease considerably (up to a nine-fold) with increased frequency of dosing of antimicrobials[1] and it is also known to be a particular issue when dealing with conditions that require long-term therapy, such as deep pyoderma in dogs[7], formulations that are not easy to administer due to the route of administration or due to animal behaviour (e.g. tablets for cats or topical ear preparations in dogs)[4,7]. Complex therapeutic protocols can also impact the level of compliance as these may be difficult to remember or implement by clients which may lead to loss of engagement[3,4].

Completion of prescribed therapy is a major issue, as clients might be tempted to "self-assess" the health of their animals and decide to stop therapy if they perceive that their animal's condition has improved[7]. The occurrence of unexpected adverse effects can also be a cause for non-compliance; although antimicrobials are often perceived as being "safe" drugs in animals, adverse or side effects include allergic reactions, gastrointestinal signs (e.g. vomiting and diarrhoea), pyrexia, cartilage abnormalities and tooth discoloration in young animals (e.g. fluoroquinolones and tetracyclines, respectively), amongst others[3].

It is therefore necessary to maintain **good communication** with clients **throughout the duration** of the therapeutic course in order to be able to **identify potential barriers to compliance** that might compromise therapeutic success and may result in the emergence of antimicrobial resistance[7,9]. ■

R.22

How do I get the pill into the animal? Top ten tips.

Veterinarians and nurses have an important practical role to play, beyond simply dispensing the medication, by ensuring that the owner will be able to administer the medication correctly.

1. Involve the owner from the start; it is important to realistically assess owner willingness, availability and ability to treat their pet.

2. Look for antibiotics that have been developed to be palatable; some feline products may have an International Cat Care "Easy to give" award.

3. Find out how the owner will plan to administer the medication i.e. either directly by tableting the pet or by disguising within food or treats. Give specific suggestions of suitable palatable food and treats to hide medication in e.g. fish pate, canned tuna or sardines for cats, soft cheese or small pieces of meat for dogs.

4. Consider the use of gelatine capsules, these can be helpful if the tablet has a bitter taste e.g. metronidazole, or if more than one medication needs to be given at a time.

5. If the owner is planning to administer the medication directly to the animal demonstrate how to do this effectively, particularly considering the restraint required and provide explanatory supports.

6. If a pill popper is recommended ensure the owner knows how to use this safely and without causing oropharyngeal or laryngeal trauma.

7. Discuss the importance of building a positive association with administration of the medication (e.g. always follow tableting with a treat or something the pet will enjoy such as a brush or play with a favourite toy). This simple act will reduce stress for the pet and owner and help the owner to more successfully administer medications.

8. Following any tablet or capsule with a treat (or liquid) will reduce the risk of oesophageal irritation which is especially important when administering clindamycin capsules or doxycycline hyclate/hydrochloride to cats, both of which have been associated with the development of oesophageal strictures[1,2]. This also applies to dogs.

9. Urge the owner to contact the clinic if they have any queries or experience problems administering the medication.

10. Provide the owner with reliable resources to refer to at home covering information about the type of medication given and methods of administration e.g. BSAVA medicine information sheets or web link to videos (www.youtube.com/user/iCatCare).

Palatable presentations will help compliance.

Whilst medication choices and prescribing habits are critical in antibiotic stewardship one fundamental aspect is ensuring the antibiotic actually reaches the patient at the right dose, frequency and for the correct duration. A course of medication can be stressful for both the owner and pet and this is undoubtedly more often problematic in cats.

Step 1: Making medication choices

Pet owner involvement is key to ensure compliance with prescribed therapy. Time should be allocated during the consultation to determining whether there is a choice of appropriate antibiotic formulation e.g. tablet versus capsule or liquid, and to discuss which will be easiest for the owner to administer. Establish realistic expectations about owner availability when considering whether to dispense a medication that requires dosing every 8 or 12 hours. Consider whether the ability of the pet owner may also be compromised by other factors for e.g. elderly or disabled clients may be less dexterous and fearful or aggressive pets may not tolerate restraint at home, which could endanger the owner-pet bond. In the case where pet owners are unable to administer treatment, an option could be offered to have the service provided by the veterinary staff. If not possible, revision of the therapeutic course or route of administration (e.g. injectable versus oral) might need to be considered, in order to ensure that the animal receives adequate treatment.

Step 2: Owner education

Training and demonstration of tablet administration by veterinary staff should be offered to pet owners; this is often overlooked. Instructions on the safe oral administration of tablets (and other formulations such as pastes and liquids) should be provided to avoid the risk of biting and scratching by pets and to prevent human injuries and infections e.g. *Bartonella* infection (cat scratch fever[3,4]).

Gelatine capsules might be perceived to be easier to administer by some pet owners; they are available in various sizes; tablets can be placed within an empty capsule for administration (Figure 1).

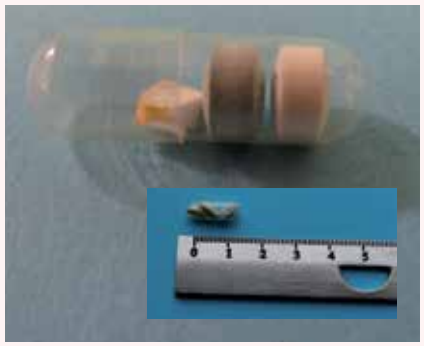


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Figure 1 *- Gelatine capsule prepared to administer three medications in a cat that is difficult to pill repeatedly; co-administration enables dosing, however the effect on pharmacokinetics is unknown.*

This could be the difference between successful administration versus none at all. The effect of using gelatine capsules on medication pharmacokinetics is unknown and it may be sensible to discuss planned use with the medication manufacturer. A loss of efficacy of the drug may also occur if the pet owner decides to crush the tablet and deliver it to the animal as a suspension for ease of administration[3].

If the owner is planning to disguise the medication in a food or a treat, provide specific suggestions of suitable treats or foods to use e.g. meat or fish pastes (strong smelling), soft cheese or specifically designed products (e.g. treat sticks and yoghurt paste). Some small tablets can be easily hidden in soft malleable treats or small meatballs[4]. For the latter, it is usually useful for the pet owner to assess how the animal eats the meatball (e.g. as a whole or in small pieces) before hiding a dose within[4]. Consider the use of a pill crusher if disguising the tablet within food and advise the owner to mix the powder with a small portion of food (e.g. one teaspoon) before giving the rest of the meal.

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Figure 2 *- A pill popper may enable easier administration of tablets or capsules in some pets.*

Step 3: Overcoming problems with administration of medications

It is important to maintain good communication with the pet owner during the therapeutic course, particularly if the veterinarian considers that there is the risk of non-compliance. Encourage pet owners to contact the clinic if they have any difficulties with drug administration to their pets. Simple reiteration of administration techniques or providing tips for disguising the food may enable the owner to overcome initial problems; alternatively bringing the pet back into the clinic for a nurse appointment for pilling may be helpful.

Demonstrating an understanding of the challenges of medicating cats and dogs is important for the owner, especially when initial efforts are problematic. In this situation the owner may feel that medicating the pet at home is impossible, however spending time discussing attempts, providing support and encouragement may enable the owner to find a successful method. ■

Figure 3 *- Tasty paste formula treats can be useful to hide crushed medication within or can be used as a treat following administration of medications, to help develop a positive association with pilling. Soft malleable treats can be used to disguise tablets.*

ZOONOTIC IMPACT

R.23 In which cases can resistance selected in dogs and cats cause a problem for human health?

- Companion animals can act as a source and reservoir of resistant bacteria such as Gram-negative (e.g. *Escherichia coli*, *Campylobacter* spp., *Salmonella* spp.) and multidrug-resistant bacteria (e.g. ESBLs, MRSP) that are known zoonotic pathogens. This is due to the regular use of antimicrobials in everyday practice and to the close contact of pets with their owners and other animals within the household and the community.
- Responsible use of antimicrobials should be promoted among veterinarians in order to prevent and contain the spread of antimicrobial resistance in animals under their care. Of particular importance is the moderation of use of antimicrobials deemed of critical importance in human medicine to treat severe, life-threatening infections such as cefovecin and fluoroquinolones.
- Veterinarians have an important role in the education of pet owners and the general public in the prevention and control of potential zoonotic risks derived from companion animals. Pet owners and members of the same household with diseased or colonised animals, where there is a likelihood of having an impaired immune system (e.g. young children, elderly people, pregnant women, immunocompromised or immunosuppressed individuals), should not be directly involved in the care of the animal. When visiting hospitalised pets, clients should follow good hygiene and infection control measures; where possible the veterinarian should explain the practice protocol for hospitalised patients.
- Veterinary staff are also at risk and could be exposed through direct contact with colonised and infected animals under their care or through the contamination of their workplace environment.

The role of companion animals in society has changed in recent years; pets are often perceived as family members by owners in high income countries[15]. Animals can become colonised and/or infected with resistant bacteria. **Colonisation** refers to when there is the presence and multiplication of microorganisms on a body surface (e.g. skin, mouth, intestines) without tissue invasion; the animal is clinically healthy.

In **infections**, microorganisms invade and cause damage to tissues and organs often leading to the occurrence of clinical signs.

Companion animals can act as a source and reservoir of resistant bacteria such as Gram-negative (e.g. Escherichia coli, Campylobacter spp., Salmonella spp.) and multidrug-resistant bacteria.

Antimicrobials, a risk factor

Use of antimicrobials is a known risk factor for AMR emergence and spread in companion animals, as excessive and misuse of these drugs can result in **selective pressure** upon bacterial populations[6,12]. In a recent study in dogs with pyoderma, Weese et al[22] reported that animals with a recent **history of antimicrobial use** were **10 times more likely to be infected with resistant strains** of meticillin-resistant *Staphylococcus pseudintermedius* (MRSP). This pathogen has also been isolated in clinically healthy dogs[21]. Veterinarians should follow current existing guidelines and recommendations for responsible use of antimicrobials whenever possible. Use of substances belonging to antimicrobial groups deemed as critically important for human medicine[23] should be evidence-based, and supported by antimicrobial susceptibility results whenever possible as it is important to preserve the efficacy of these antimicrobials to protect both animal and public health[12].

Pets act as a reservoir

The acquisition of resistance by pathogenic and commensal bacteria in pets can pose a **serious risk for public health**: pets can act as a reservoir of resistant bacteria and resistance determinants to humans and other animals within the same household and in the community[7,9]. Pets can also acquire resistant bacteria and resistance determinants **via foodborne sources**; the increased popularity of raw meat diets in companion animals can result in colonisation

of clinically healthy pets and infection with resistant zoonotic pathogens[10,19]. There is currently scarce surveillance data on levels of antimicrobial resistance in pathogenic and commensal bacteria in companion animals[5,12,21]. Healthy pets have been found to be carriers of resistant commensal bacteria. Commensal enterococci, which are part of the normal gut flora of both companion animals and humans have zoonotic potential and can cause opportunistic infections. A study conducted in Denmark reported lower levels of carriage of resistant gut bacteria in healthy dogs compared to food-producing animals. Nevertheless, the same study detected ampicillin-resistant *Enterococcus faecium* strains. This could have public health significance as *Enterococcus faecium* can cause bacteraemia and endocarditis in humans and ampicillin is one of the drugs of choice for treatment. Carriage of infection (e.g. UTIs in dogs) with resistant strains of this bacteria, by companion animals, could pose a risk for individuals in contact with these animals[6]. Concurrent carriage of and infection with resistant pathogens in companion animals can also occur. In a recent study in Canada, Beck et al.[3] reported MRSP isolation in the skin and carriage (in nostrils and rectum) in 40.5% and 34.1% of dogs affected with pyoderma (n= 173), respectively. The study also reported the persistence of carriage in 35.3% of animals after clinical resolution of the condition, which poses serious public health risks.

Contact with pets is a known risk factor for the transmission of resistant bacteria[5]. Frequent social interactions and shared environment has been shown to contribute to the transmission of resistant commensal and pathogenic bacteria between animals and humans. **Children are particularly at risk** of colonisation or infection by resistant pathogens from companion animals within the household due to their close interactions with pets and the environment and also as they are less likely to follow good hygiene practices and hand washing[12]. **Pets can become infected with resistant bacteria from human origin** (anthroponosis) such as MRSA and act as a reservoir in the household and the veterinary clinic[12,14,20]. Colonised or infected pets can also be a risk for the general public by contaminating the environment (e.g. faeces and urine)[4,5,14].

Figure 1 *- Multidrug resistant bacteria in companion animals are an emerging public health issue that should not be overlooked.*

Frequency of resistant bacteria

Occurrence of multidrug resistant (MDR) bacteria in companion animals is currently an emerging public health issue that should not be overlooked[5]. Vancomycin-resistant enterococci (VRE)[21] and ESBLs[9] are of particular relevance due to the lack of therapeutic options and the risk of therapeutic failure[8,9,17]. The level of carriage and infections caused in companion animals by VRE bacteria is currently low but they can cause severe infections in humans[21]. Levels of carriage and infection by **ESBLs in companion animals seem to be on the rise,** which can pose a serious risk to animal health and welfare as well as public health[9]**.** Other bacteria with zoonotic potential, in which MDR has been reported occurring sporadically in companion animals, are *Pseudomonas* spp. (e.g. ear and skin infections), *Salmonella* spp. and *Acinetobacter baumannii*[21]. MDR *Salmonella typhimurium* DT104 has been isolated in dogs associated with pet treats of animal origin (e.g. pig ears)[12]. **MDR bacteria** have been isolated from dog faeces collected in urban areas, suggesting the **potential risk for zoonotic transmission through environmental contamination**[4,12]. In a recent study in Italy, enterococci were isolated in 16.3% of faecal samples collected from the environment (n=418); from these, 67.1% were resistant to three or more antimicrobial substances[4]. The recent isolation in companion animals of MDR bacteria usually observed in healthcare settings (e.g. hospitals) such as MRSA (e.g. human clones 15, 16, 300)[14,20], carbapenem-resistant *Escherichia coli*[5] and *Acinetobacter baumannii*[21], also suggests anthroponotic transmission of MDR bacteria. **Of particular concern are animals belonging to households where humans have a previous history of hospitalisation within the last six months[7] or** pets that are used as **therapy animals** in healthcare facilities or nursing homes[13]. ■

Veterinarians play an important role in the education of pet owners in relation to zoonotic risk associated with resistant bacteria in companion animals[1,5], even when dealing with clinically healthy pets[5]. Recommendations for infection control practices when caring for pets are important in order to protect clients from potential zoonotic bacteria[2].

Good hygiene practices should be followed, including when caring for healthy pets, as these could also act as carriers for resistant bacteria even in the absence of clinical disease[1,2]. This is in order to prevent and limit the transmission of zoonotic pathogens to humans and other animals in the household and the contamination of the shared environment.

NOSOCOMIAL INFECTIONS

RECOMMENDATIONS

R.24

How to prevent and deal with nosocomial infections in a veterinary practice?

The prevention and control of nosocomial infections are based on:

- **effective hand hygiene,**
- **effective cleaning and disinfection,**
- **appropriate protective clothing,**
- **high standards of clean surgery,**
- **effective isolation and barrier nursing measures,**
- **high standards of staff training and motivation,**
- **effective surveillance,**
- **effective protocols for managing patients with antimicrobial resistant infections.**

The main risk pathways for colonisation and infection with antimicrobial resistant bacteria are within veterinary clinics (see Figure 1). These organisms readily colonise healthcare environments where they can be disseminated to vulnerable patients. These infections are of great concern as they **harm the practice reputation, limit the procedures that can be performed and increase morbidity, mortality and the cost and complexity of treatment**. Improving hand hygiene and infection control measures have reduced colonisation rates in human hospitals. **Effective infection control is a professional responsibility for veterinary clinicians**. For example, in the UK this is a key part of the Royal College of Veterinary Surgeons (RCVS) Practice Standards Scheme and Guide to Professional Conduct. Infection control guidance is available for veterinary practices from a variety of sources (see further resources).

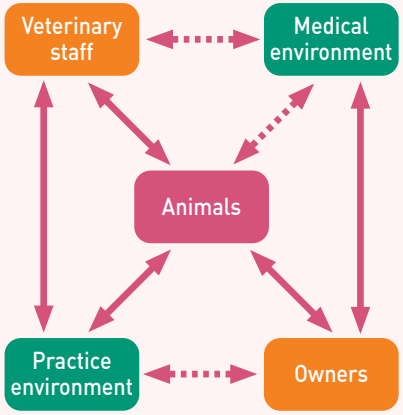

***Figure 1** - Risk pathways for colonisation and infection with antimicrobial resistant bacteria in veterinary practice.*

Improving infection control measures

Veterinary practices must develop instructions and guidelines to reduce colonisation and dissemination of antimicrobial resistant bacteria and other infectious organisms (see box at the end of the chapter). Everyone has a role in effective biosecurity and infection control and staff should work together to develop a culture where hygiene and cleanliness are foremost.

Sources of contamination include animals, fluids, tissues, bedding, kennels, floors, walls, tables, equipment, food and water. Hand touch sites are the most commonly contaminated and important in transmission. **Hand washing is the single most important measure to prevent the spread of hospital-acquired infections.** Alcohol gels on uniforms and kennels can be quickly used after handling an animal, but are only effective if hands are visibly clean. Practice design should therefore allow access to hand washing facilities without having to touch anything.

Effective cleaning and disinfection is key to prevent nosocomial infections.

Effective surveillance

Passive surveillance is the most practical type of monitoring. Medical records and laboratory data can be used to assess wound breakdowns, infection rates, antibiotic sensitivity tests, changing patterns of disease and in-patient status, etc. Systematic collection and analysis of this information allows early identification of problems and facilitates prompt action. Reception staff can also use similar data to screen patients for potential contagious or other risks on admission.

Active screening of patients, staff or the environment is only indicated as part of an epidemiological investigation of a specific outbreak. Active surveillance must have clear aims, a defined protocol and specific action in light of the findings.

How to prevent and deal with nosocomial infections in a veterinary practice?

Table 1 *- Key steps in effective infection control.*

Hand hygiene	• Clean and disinfect hands before and after touching animals or their surroundings (see Figure 2). • Train staff in effective hand washing and disinfection techniques (see Figures 3 and 4). • Visibly soiled hands must be washed before using disinfectant gels. • Arms should be bare; avoid watches, jewellery and nails that could interfere with cleaning.
Gloves	• Gloving is not a substitute for hand washing and disinfection. • Wear gloves for clean and/or aseptic procedures and/or when there is increased risk of transmission of infectious organisms. • Wash and/or disinfect hands before and after wearing gloves. • Remove gloves before touching equipment that is non-sterile or not immediately involved in the procedure.
Protective clothing	• Wear clean appropriate protective clothing at all times. • Change out of protective clothing when leaving the premises. • Long hair should be tied up and back when working. • Ties should not be worn. • Excessive equipment, pockets and pouches should be avoided; where necessary these should be cleaned and disinfected regularly.
Cleaning and disinfection	• Equipment and surfaces must be thoroughly cleaned and disinfected between patients; disinfectant wipes can be used if surfaces are visibly clean. • Stethoscopes should be cleaned and disinfected between patients. • Use approved detergents and disinfectants. • Cleaning should be performed according to strict rotas and protocols - visual assessments are highly unreliable. • Cleaning should be divided into daily, weekly and monthly tasks depending on the potential contamination and risk. • Identify and separate clean and soiled items. • Dispose of clinical waste promptly and correctly. • Avoid materials that can't be cleaned in high risk sites – consider waterproof keyboards or keyboard covers, laminated instructions and posters, white boards and impervious seats in clinical areas. • Clean leads, ropes, harnesses, collars, muzzles or rugs, etc. should be allocated to each animal on admission; these should remain with the animal during hospitalisation, must not to be shared and must be replaced if soiled.

Table 1 *(continued)*

Barrier nursing	• Use extra protection for high risk cases; change between patients gloves, aprons, masks, eye protection, etc. may be necessary for contact with body fluids, lesions and other contaminated materials.
Surgery	• Use a high standard of preparation, cleanliness and surgical skill. *See Prevention of surgical complications, p.258 for more details.*
Training	• Train and encourage all staff to follow infection control guidelines. • Adopt written infection control protocols. • Appoint an infection control champion (or team).
Surveillance	• Encourage clinical audit and review of infections and resistance patterns. • Discuss results with your microbiology laboratory. • Consider joining clinical surveillance programmes (e.g. SAVSNET in the UK).

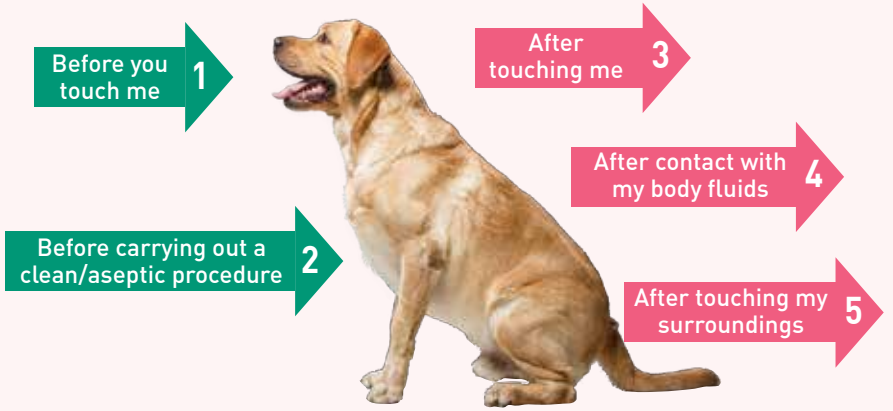

Figure 2 *- The key moments for hand hygiene (courtesy of the University of Edinburgh Royal [Dick] School of Veterinary Studies).*

RECOMMENDATIONS

Figure 3 *- UK National Health Service guidance for effective hand washing (Crown Copyright 2007 283373 1p 1k; adapted from World Health Organisation Guidelines on Hand Hygiene in Healthcare).*

Figure 4 *- Effective hand disinfection – effective if hands are visibly clean (Crown Copyright 2007 283373 1p 1k; adapted from World Health Organisation Guidelines on Hand Hygiene in Healthcare).*

Managing patients with antimicrobial resistant infections

Screening all cases prior to admission is not usually feasible in most practices. Specific risk factors for Healthcare-Associated Infections (HAIs) and antibiotic resistance include:

- animals that have received one or more broad-spectrum antibiotic courses,
- animals with an on-going infection despite antibiotic treatment,
- antibiotic treatment within the previous 3 months,
- non-healing wounds,
- post-operative infections,
- nosocomial infections. ■

Further resources

- *British Veterinary Association - www.bva.co.uk/public/documents/bva_antimicrobials_poster.pdf*
- *British Small Animal Veterinary Association - www.bsava.com/Resources/PROTECT.aspx www.bsava.com/Resources/MRSA.aspx*
- *British Equine Veterinary Association - www.beva.org.uk/useful-info/Vets/Guidance/AMR*
- *Responsible Use of Medicines in Agriculture Alliance (RUMA) - www.ruma.org.uk*
- *Federation of European Companion Animal Veterinary Associations (FECAVA) - www.fecava.org*
- *International Society for Companion Animal Infectious Diseases (ISCAID) – www.iscaid.org*
- *The Bella Moss Foundation - www.thebellamossfoundation.com*
- *Antibiotic treatment support materials and other resources - www.itsinfectious.co.uk*
- *Antibiotic Action and Antibiotic Guardian campaigns www.antibiotic-action.com and www.antibioticguardian.com*
- *SAVSNET - The Small Animal Veterinary Surveillance Network - www.savsnet.co.uk*

Managing patients with antimicrobial resistant infections

- Admit known or suspected cases directly into a consultation room to avoid the waiting room.
- Take samples for culture as soon as possible, but treat all suspect cases as positive until culture results are available.
- Minimise movement and procedures; where possible schedule last in the day.
- Discharging wounds should be covered with an impermeable dressing.
- Use trolleys to minimise contamination of corridors etc.
- Contaminated trolleys, rooms or corridors should be disinfected before further use.
- Avoid contact between infected patients and other animals and staff.
- Use strict barrier nursing precautions and where necessary, isolation facilities.
- Pens/pencils, stethoscopes, thermometers etc. should be used with the affected patient only and then disposed of or disinfected.
- Patients should be discharged as soon clinically fit. Samples should be taken from appropriate sites to detect persistent colonisation (e.g. mucosal swabs and/or faeces). The sites, type and frequency of culture should be addressed on a case by case basis, following advice from clinical specialists and microbiologists where necessary.
- If the animal remains colonised potential risks and precautions, including hygiene, must be discussed with the owner; give clear written guidance.
- Animals with persistent colonisation are best left to decolonise in the community; antimicrobial shampoos or wipes may be beneficial but may not be feasible, and the pros and cons of this approach should be discussed with the owners.
- Antibiotics should be avoided, as these may facilitate persistent colonisation.
- Active decolonisation of the household (including animals and humans) should only be considered where necessary with the full consultation and cooperation of medical healthcare services.

ANTIMICROBIAL PROPHYLAXIS FOR SURGERY AND CRITICAL CARE

RECOMMENDATIONS

R.25

How can infections be prevented when using indwelling devices (e.g. urinary catheter, IV catheter...)?

- Strict aseptic techniques of implantation.
- Prevention of patient interference.
- Shortest contact period as possible.
- Monitoring for clinical signs of infection.

All invasive devices provide open access from the patient's own microflora and environment to the body system. Eventually all these devices will be colonised by bacteria. In the right environment, these bacteria may be a source of infection, even if they are not pathogenic.

Implantation

The first rule when using an invasive device is to adhere to strict aseptic techniques. The area to be treated needs to be clipped and the skin should be prepared as for a surgical intervention with scrubbing and application of an antiseptic solution. The mucosa (for urinary catheterisation) should be irrigated with saline and diluted antiseptic solutions (povidone iodine 0.02%, chlorhexidine diacetate 0.05%).

Great care should be taken to avoid contamination at the time of insertion. Operators should use gloves and/or scrubbed/decontaminated hands (sterile gloves are mandatory for a central IV line).

If the device needs to stay in place, a protective dressing is placed to limit ascending contamination. For critical implants such as a central IV line, local application of antibacterial ointment is recommended. For urinary catheters, closed collection is set up.

Handling and monitoring

Once in place, implants should be handled while wearing clean disposable gloves or scrubbed/decontaminated hands All exits should be kept capped unless continuous drainage is expected. Closed drainage units are recommended as they prevent accumulation of "stagnant" organic liquids (seroma, urine) within the body which can favour bacterial growth.

The first rule when using an invasive device is to adhere to strict aseptic techniques.

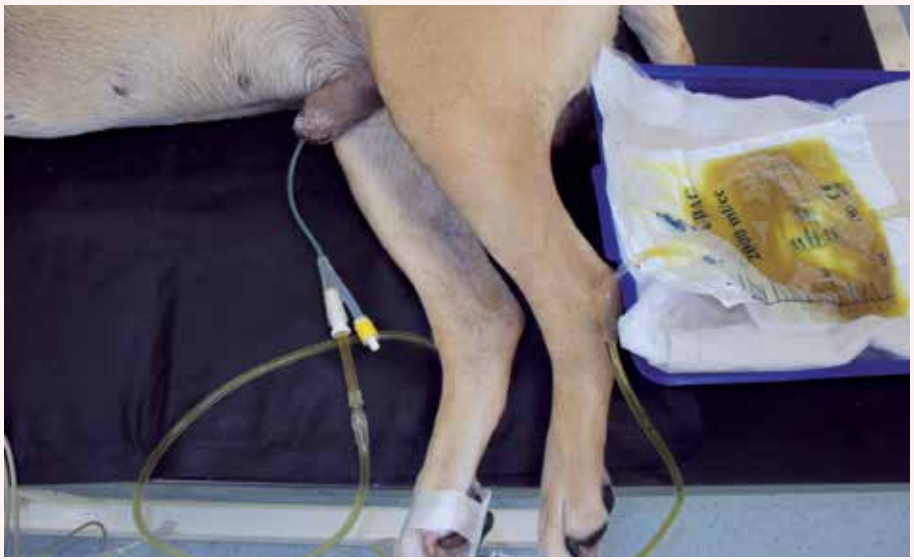

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Figure 1 *- An indwelling urinary catheter has been placed in this paraplegic mastiff. A soft Foley catheter has been placed aseptically and is connected to a collection bag to void the urinary bladder. The bag is drained periodically. Ideally, it is placed lower than the body to increase gravity drainage and prevent ascending contamination. Note that the collection bag is placed on an inco sheet within a tray to avoid contact with the ward floor.*

Regular flushing is advised for intravenous catheters but not for bladder catheters as this may cause a uretero-vesical reflux and ascending nephritis.

The patient should be assessed at least once daily (four times daily for critical devices such as jugular catheters) for signs of local inflammation/infection, such as fever, local redness at the point of insertion or a modified appearance of the drained fluids.

Dealing with contamination

Two problems may be observed with indwelling devices: phlebitis (IV catheter) and cystitis (long-term catheterisation). Usually, removal of the IV catheter suffices to resolve the problem and antibiotics are rarely necessary. Cystitis may simply be due to inflammation secondary to the foreign material; therefore, removal will resolve the problem. Although urine contamination may be observed on cytology, antibiotic therapy is not recommended unless there are

R.25 How can infections be prevented when using indwelling devices (e.g. urinary catheter, IV catheter...)?

clear clinical signs of infection.

If colonised, implants will be covered by a biofilm produced by the bacteria, which will protect them from the immune system and from the action of the antibiotics. This is why treatment of an implant infection with antibiotics will only reach the bacterial overgrowth associated with the infection but no longer attached to the implant. It will never sterilise the focus of infection. Therefore, infection will return as soon as treatment is discontinued and the antibiotics used will select for more resistant bacteria. Eventually, multiresistant bacteria will be selected. Especially in critically ill patients, it is recommended to use the tip of the implant for culture and sensitivity testing. In the case of indwelling urinary catheters, urinanalysis might be more relevant than culture of the tip of the catheter. In cases of life-threatening infection, broad-spectrum antibiotics against Gram+ and Gram- may be considered empirically until results are known. In critical cases, IV administration of ß-lactams or first-generation cephalosporins is indicated. In healthy patients, antibiotic treatment may be delayed until culture and sensitivity results are known.

In cases where the implant cannot be removed or changed, infection should be treated for as short a time as possible and with the least critical antibiotic as possible to keep the therapeutic options open after removal of the implant. ■

If the device needs to stay in place, a protective dressing is placed to limit ascending contamination.

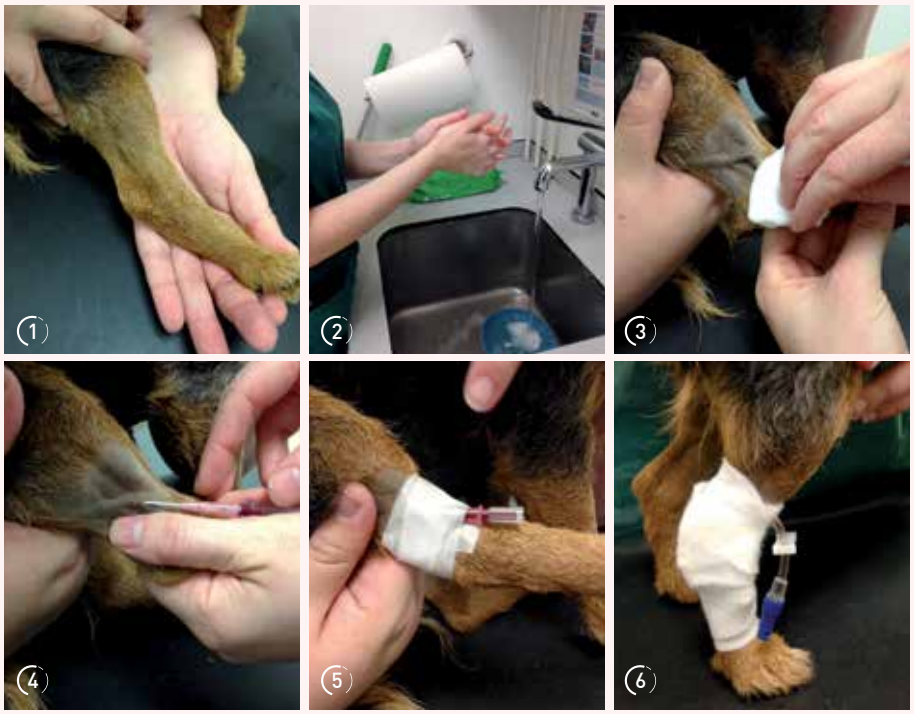


Figure 2 *- Placement of an over-the-needle IV catheter.*

1. *The chosen vein is identified while the limb is restrained by an assistant (here a lateral saphenous vein).*
2. *Wash hands before catheter placement (scrubbing or hydro-alcoholic hand rub).*
3. *Clip and prepare skin around the vein (scrubbing and application of an antiseptic solution).*
4. *Puncture and catheterise the vein.*
5. *Fix the catheter with adhesive tape.*
6. *Place a short extension set (T-port) to prevent direct action on the catheter that may increase the risk of contamination. The entire system catheter-T-port is bandaged to only leave access to the T-port. Catheters should be flushed with heparin saline when not used every 4 to 6 hours. Catheters should be changed if local inflammation/infection is suspected or as a rule minimum every 3 to 5 days pending on hospital policy and patient condition.*

R.26

How can surgical infections be prevented?

- Identification of patient risk factors (see Table 1).
- Identification of surgical risk factors (Altmeyer's classification, surgical time, peri-operative hypothermia, delayed for enteral feeding; see Table 2).
- Good "surgical footprint": protect healthy tissue, limit surgical trauma and help restore normal function and biology.
- Quality of non-surgical treatment (wound care, antibiotic prophylaxis and/or post-operative antibiotic treatment if needed). See also Prevention of surgical complications (including peritonitis and abscesses), p.258.
- Clean surgery <90 minutes and without implant does not require antibiotic prophylaxis.
- When antibiotic prophylaxis is scientifically indicated, respect the 5 rules of antibiotic prophylaxis (see box The 5 rules of antibiotic prophylaxis p.411).

Identification of patient and surgical risk factors

Post-operative infection (POI) is the result of a favourable environment for bacteria to grow and to overcome local host response. There are multiple factors involved in surgical infection.

Patient status is important, e.g. immune deficiency, poor body condition, age, endocrine disorders (especially diabetes) and gender–male animals have an increased risk of POI.

Surgical risk factors: Altmeyer's classification (Table 2) is routinely used to identify patients needing pre- or post-operative antibiotics. Post-operatively, patients should not be starved as this will decrease the effectiveness of the immune system and may favour the translocation of bacteria from the intestinal lumen into the general circulation. Therefore, the intestinal tract should be used even after gastro-intestinal surgery. If required, a tube-feeding strategy (naso-oesophageal tube or oesophagostomy, gastrostomy or jejunostomy tubes) should be considered during surgery and post-operatively.

Good surgical footprint

The "**surgical footprint**" represents the ability of the surgeon to protect healthy tissue, to limit surgical trauma and to help restore normal function and biology. The accumulation of fluid, dead space or necrotic/devitalised tissues in the surgical

Table 1 *- ASA (American Society of Anesthesiologists) score: assessment of the anaesthetic risk of the patient.*

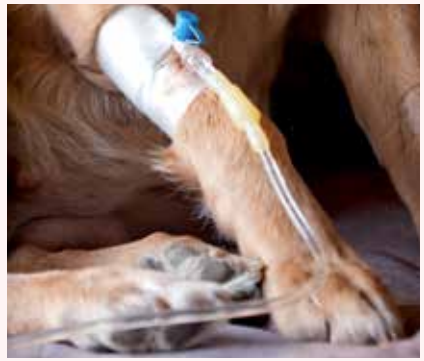
Category	Physical status	Infectious risk
I	Normal healthy patient	0 / no ABs needed
II	Patient with mild systemic disorder	0 / no ABs needed
III	Patient with severe systemic disorder	+ / consider preventive ABs
IV	Patient with severe systemic disorder engaging survival	++ / use preventive ABs
V	Moribond, not expected to survive without surgery	++(+) / use preventive and postoperative ABs

Increasing risk of infection

sites will increase the risk of infections that may be a challenge to treat with antibiotics.

In surgery, hypothermia and operating time are closely linked to each other. Studies showed that the risks of infection in clean surgeries increased by 30% every hour.

Clipping just before the surgery, reducing air circulation in theatres during surgeries and taking active measures to maintain normothermia may help in limiting the infection risks.



Disinfection of the site of catheter insertion is an essential point in limiting the risk of phlebitis.

Why and when

Antibiotic prophylaxis aims to achieve an active concentration (above the MIC) in the tissue during surgery. Any bacteria getting into contact with the surgical site will be readily deactivated or killed by the antibiotics. However, antibiotics are only needed at the time of the surgery and should be discontinued immediately

Table 2 - Altmeyer's classification and infectious risk associated with the type of surgical procedure. This classification aims to help surgeons in the assessment of the risk for postoperative infection and the rational use of antibiotics. The antibiotic choice is based on the bacteria to be likely present in the surgical field (see Prevention of surgical complications (including peritonitis and abscesses), p.258).

Classification	Type	Antibiotic treatment
Clean	Non traumatic. Non inflammatory. No breach of asepsis, procedure shorter than 90 minutes.	No antibiotics. Antibiotic prophylaxis may be performed in case of clean orthopaedic procedures involving implants.
Clean-contaminated	Clean, longer than 90 minutes. Minor opening without spillage of the respiratory, urogenital, biliary or intestinal tracts. Minor breach of asepsis.	Targeted antibiotic prophylaxis. No post-operative antibiotics.
Contaminated	Traumatic wound (less than 4 to 6 hours). Major opening of respiratory, urogenital, biliary or intestinal tracts with or without obvious infected content. Controlled spillage of the tract content.	Antibiotic prophylaxis and post-operative antibiotics (short duration). Possibly, sampling for culture and sensitivity testing.
Dirty	Surgical site with pus. Surgical site with faecal contamination, foreign material, devitalized/necrotic tissue. Traumatic wound (older than 6 hours).	Pre- and post-operative antibiotics (long term). Recommend sampling for culture and sensitivity testing.

after surgery or within the following hours. This protocol is indicated for long clean and clean contaminated procedures (see Altmeyer's classification). **Clean surgery <90 min and without an implant does not require antibiotic prophylaxis**.

Which antibiotics?

ß-lactams and first generation cephalosporins are generally recommended for antibiotic prophylaxis. They should be injected IV 30 to 60 minutes before the initial incision to ensure that active concentration will be found locally at the time of surgery. As the tissue concentration should remain higher than the MIC during the time of possible contamination, repeated administration is required: every 90 to 120 minutes. Cephalosporins are generally administered every 90 minutes in case of orthopaedic procedures. Whittem et al[7] showed that antibiotic prophylaxis for clean orthopaedic surgery decreased post-operative infection. He also showed that there was no benefit of cefazolin over penicillin G regarding the decreased risk of complications. In view of the likely bacteria (*Staphylococcus* spp.) able to contaminate the surgical site, narrow-spectrum antibiotics should be used to limit selection for resistance and to keep therapeutic options open.

Rational for antibiotic choice is discussed in Prevention of surgical complications (including peritonitis and abscesses), p.258. ■

The most likely bacteria to be encountered are commensals from the skin (mainly Gram-positive: *Staphylococcus* spp.) and possibly from the environment (Gram-negative: *E.coli*).

The 5 rules of antibiotic prophylaxis

- Scientifically indicated (not a clean procedure <90 min without implants)
- Targeted (monotherapy toward the bacteria most likely to contaminate the surgical site)
- Bactericidal
- Appropriate tissue concentration (above the MIC) at the time of surgery; this concentration should be maintained until the end of the procedure*
- Administer IV 30 to 60 minutes prior to incision; discontinue 24 hours after surgery.

First-generation cephalosporins are commonly used in veterinary practice (e.g. cefazolin or cefalexin 20mg/kg). The risk of infection is lower for soft tissue procedures (where drugs will be administered every 2 to 3 hours) compared to orthopaedic surgery where a higher administration frequency (e.g. every 90 minutes) and dosage (30 mg/kg) are generally recommended.

**The drug should be re-administered after a period equivalent to one to two times the drug's half-life. Ex: cefazolin IV has a half-life of 1h; if used for antibiotic prophylaxis, it should be re-injected every 2h.*

RECOMMENDATIONS

R.27

Am I doing it right? Five tools to assess my surgical site infection prevention protocol.

1. Definition of surgical site infections (see Table 1).
2. Systematic assessment of all surgical wounds at suture removal.
3. Recording of all bacterial culture and antibiotic susceptibility test results.
4. Up-to-date and accurate records for clinical cases, antibiotic use, cleaning and training in infection control.
5. Effective clinical audit.

Veterinary practices must be able to assess the effectiveness of their antibiotic stewardship programmes and infection control measures. This facilitates early detection of problems allowing prompt and effective action. Practices can then modify their protocols to better suit their structure, facilities and caseload. Good record keeping and effective use of clinical audit are a professional responsibility and some hospitals have included them in their Practice Standard Scheme (e.g. UK Royal College of Veterinary Surgeons).

This approach requires careful planning, recording and review of all available and appropriate data. No system will work in each situation and practices will have to develop their own arrangements appropriate to their size and activity. Nevertheless, a properly planned and executed system does not need to be overly complicated or time consuming. Individual members of staff should keep their records up to date and computerised record keeping will facilitate data capture. A small team should therefore be able to review data and make recommendations on a regular and scheduled basis.

• **Assessment of surgical site infections** (SSIs) is an easy and important set of data to record. However, there is no widely accepted definition or classification for SSIs and therefore practices must adopt their own criteria. Turk et al.[1] proposed a thorough definition differentiating superficial, deep and organ/space SSIs with assessment done at 1 and 12 months postoperatively. This provides an adequate start for a practice to develop its own protocol.

• Besides SSIs, it is also important to **record any other possibly infectious process** observed during or just after hospitalization. This will allow detection of any non-surgical hospital-acquired problems such as kennel cough, dermatophytosis, MRSA, MRSP or *E. coli* colonisation, Salmonella etc. Prompt sampling of animals with post-operative and/or hospital-acquired coughing, skin lesions, diarrhoea and/or urinary tract monitoring and sampling of animals after discharge from the veterinary practice.

Table 1 - *Definition of Surgical Site Infection (SSI)*[6].

Classification	Criteria
Superficial SSI	Within 30 days. Skin / subcutis. 1 or more of the following: - Pus. - Bacteria on cytology. - Local signs of inflammation (heat, redness, pain) justifying surgical re-exploration. This has to be classified as infection unless culture/sensitivity is negative.
Deep SSI	Within 30 days, up to a year if implants *in situ*. Soft tissues deeper than the incision. 1 or more of the following: - Pus. - Spontaneous dehiscence or surgical re-exploration due to suspected infection unless culture/sensitivity is negative. - Abscess or any evidence of infection on imaging/history.
Organ or space SSI	Within 30 days, up to a year if implants *in situ*. Any part of the body that has not been opened/manipulated during surgery. Abscess or any evidence of infection on examination, exploration or imaging/history.

• The results of **bacterial culture and antibiotic susceptibility tests** should be recorded and periodically reviewed. Special attention should be given to antimicrobial resistant, post-operative and hospital-acquired infections. However, monitoring resistance trends provides useful information for choosing effective antimicrobials: the prevalence of different organisms and the frequency of resistance among the hospital population. This can help inform good clinical practice and antimicrobial stewardship.

• **Regular and routine reviews of the data** by appropriate staff should be established. The frequency of this will depend on the importance of the activity, type of data and speed of response that would be required. Reviews in important areas should be done not less than monthly,

but reviews in less critical areas and/or reviews of trends could be done every 6-12 months. It is important to review the data against comparable figures to provide a benchmark for the location and type of practice. Benchmark figures may be earlier data from the same practice, regional information from clinical audit and surveillance schemes and/or data from the veterinary literature.

• All staff should be trained and encouraged to record data routinely and participate in **clinical audit**. They should be reassured that this is not a way to apportion blame, but is to identify and correct problems to improve patient care. These "no blame" approaches have greatly enhanced reporting and outcomes in veterinary and medical healthcare, food safety, engineering and a wide range of other areas.

• Clinical audit should identify precise **areas for improvement**. Overly complex and ambitious aims become overwhelming and often defeat their objectives. People find it much easier to focus on small-scale, specific and achievable aims. In time, these can lead to profound improvements in practice. This has been demonstrated in a very wide range of fields including healthcare, science, engineering, education and sports.

• Passive surveillance for clinical audit and infection control are fairly straight forward and inexpensive procedures. They facilitate the "no-blame" approach, which encourages a committed and supportive culture (Figure 3).

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Figure 1 *- This dog had an extra-articular stabilisation of his stifle after cranial cruciate ligament rupture. He presented 3 weeks later with a deep SSI. In this case, sampling the pus is not relevant; sampling should be performed on the deep sutures.*

• Active surveillance measures are more expensive, time consuming, and may be misleading. Active targeting of staff and work areas can lead to a defensive "blame-centred" culture that discourages involvement in clinical audit and infection control. Nevertheless, specific problems highlighted by passive surveillance may require more active investigation of patients, wounds, material, equipment and, possibly, staff to determine the cause of the infections. Active surveillance should be carefully planned to answer a precise problem, and avoid the risks of appearing to apportion blame. ■

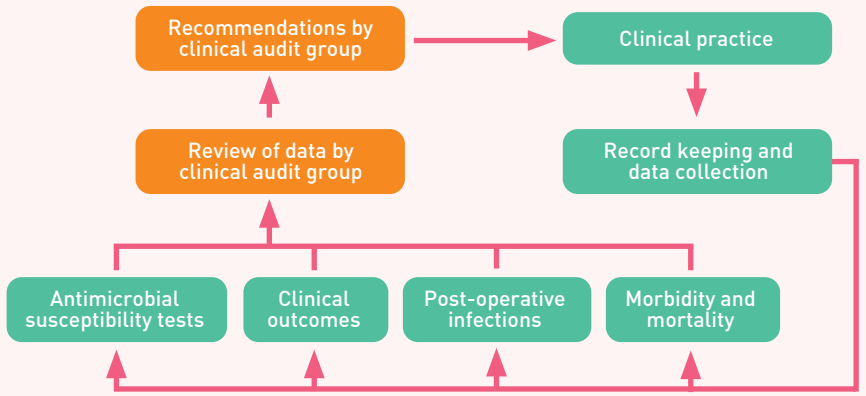

Figure 2 *- Example of a clinical audit procedure.*
The exact nature of the data recorded, reporting procedure, reviews and action, as well as the make-up of the clinical audit group, will depend on the type, size and caseload of the practice.

Surgical site infection prevention must follow a strict procedure.

Am I doing it right? Five tools to assess my surgical site infection prevention protocol.

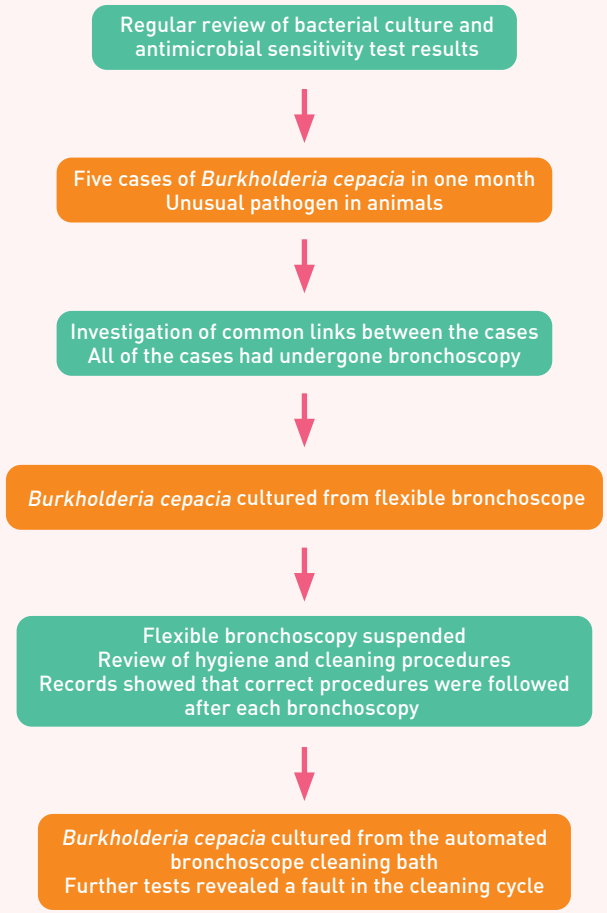

Figure 3 *- Real-life example of passive surveillance and clinical audit in veterinary practice. In this (real) example, passive surveillance quickly identified an unusual cluster of infections. The focused investigation resolved the problem within five days, minimising the impact on clinical services and the risk to patients. Good record keeping and a "no blame" approach lead to a rapid resolution.*

RECOMMENDATIONS TO PET OWNERS

R.28 What are the recommendations and advice that can be given to the pet owner?

Veterinarians have an important role in the education of pet owners. It is therefore essential to allocate time during the consultation to explain the treatment plan to the client and be ready to answer any questions they might have regarding the therapeutic course and the condition of their animal;

- Recommendations for pet owners are similar to those observed by human patients. Where possible pet owners should:

• only undertake antimicrobial treatment under prescription from a veterinarian,

• not continue treatment without veterinary advice,

• not treat the same condition or another condition with the same drugs without veterinary advice,

• dispose of unused medicines correctly and not re-use without veterinary advice,

• not purchase antimicrobials over the counter (including those purchased via the internet without a prescription) or use leftover antimicrobials that were originally prescribed for themselves (human drugs), other animals or different conditions,

• follow the instructions provided by the veterinarian, including:

- administration of the recommended dose and frequency,

- completion of the course of antimicrobial therapy prescribed - this should not be discontinued unless stated otherwise by the veterinarian,

- report to the veterinarian any adverse effects or anomalies observed during the treatment course,

- attend the follow-up consultations, as this will allow the veterinarian to assess the effectiveness of the therapy prescribed.

- Veterinarians should:

• make arrangements to follow-up the progress of the animal during therapy and re-assess the treatment plan; this could be through a phone call or a consultation. For the latter, it is recommended to remind the pet owner (letter, phone call, SMS...),

• remind pet owners to follow good hygiene and infection control practices when caring for their sick pet.

One of the key recommendations for owners is to give the appropriate dose and frequency of an anti-infective treatment.

Poor compliance to prescribed therapy can lead to treatment failure and recurrence of infectious conditions and can therefore compromise animal health and welfare[1] and increase veterinary costs to pet owners[2,14]. Furthermore, it can also lead to distress for pet owners due to the prolonged suffering of their pets, particularly when in the presence of untreatable infections caused by multidrug resistant pathogens[2].

Pet owners should be discouraged from stopping the antimicrobial course, assuming that because an animal appears to be getting better, it is cured. It should be explained to them that early discontinuation of antimicrobial therapy, even in the absence of clinical signs, may have a negative impact on their animal's health and welfare due to the risk of relapse and lead to the occurrence of antimicrobial resistance. The veterinarian should therefore **stress the importance of finishing the prescribed course of therapy** to pet owners. In the recommendations made to pet owners, the veterinarian should also discuss the possibility of occurrence of adverse reactions, as this may discourage the client from complying with the prescribed course of therapy due to the perceived risk to the animals health and welfare. The pet owner should be encouraged to seek veterinary advice in the presence of adverse reactions in order to allow revision of the therapeutic plan and possible change to a more suitable and effective antimicrobial therapy if required.

What are the recommendations and advice that can be given to the pet owner?

Underdosing, inadequate frequency of dosing or duration of therapy can result in antimicrobial resistance through selective pressure upon commensal and pathogenic bacteria[1,6]. This may result in colonisation and infection of companion animals with resistant strains which may compromise animal health and welfare[3]. This can pose a zoonotic risk to both pet owners and veterinary staff[8,9,12]. Transmission of zoonotic resistant pathogens such as MRSA from colonised and/or infected pets through colonisation of humans and other animals and contamination of the environment within the household can occur. This is also true for the horizontal transfer of resistant genetic determinants between resistant pathogens and environmental bacterial populations and human gut flora[4,8].

It is important that pet owners follow the veterinarian's advice in order to **prevent self-medication with either licensed veterinary or human antimicrobial products**, as this may compromise the efficacy and safety of treated animals and lead to the occurrence of antimicrobial resistance. Off-label use of antimicrobials should only be conducted under the supervision and recommendation of the veterinarian if no licensed veterinary drugs are available, as stated by the Cascade principle[5].

Follow-up consultations are important as they allow the veterinarian to re-assess the clinical condition of the animal and the effectiveness of the therapy. In the presence of treatment failure, the veterinarian should investigate the potential causes for this occurrence. Lack of compliance is a common cause for treatment failure and recurrence. **Good communication with the pet owner** is essential to establish a good relationship of trust with clients in order to ensure compliance[10]. Poor communication of zoonotic risks by veterinarians has been previously reported as a relevant issue in practice by pet owners[13]. The veterinarian should allocate time to discuss the prescribed therapy during consultation[11] and the potential zoonotic risks of resistant bacteria. This is particularly important when dealing with client pressure for antimicrobial prescriptions or dealing with possible non-compliance.

Follow-up of cases, either through consultation or via the phone will allow the veterinarian to assess the effectiveness of the treatment and the progression of the condition of the animal. The veterinarian will then be able to advise the pet owner if the therapy should be stopped, changed or continued, depending on the progression of the condition affecting the animal. Failure to attend the follow-up consultation may result in treatment failure and recurrence of the condition. If the failure is due to a suspected occurrence of resistance, the veterinarian should consider sampling the site of infection and carry out antimicrobial susceptibility testing (AST)[3,7]. This could have serious animal health and welfare implications and additional costs for the animal owners. ■

R.29 What are the recommendations and advice for owners of premises where pets are kept in groups (breeders, kennels, catteries...)?

■ Breeders, kennels and catteries should follow similar recommendations for pet owners with slight modifications:

- antimicrobial treatment of their animals should only be undertaken under veterinary prescription and supervision,
- individuals should not purchase antimicrobials over the counter (including those purchased via the internet without a prescription) or use leftover antimicrobials that were originally prescribed for themselves (human drugs), other animals or different conditions,
- develop and implement animal health schemes and infection control protocols in collaboration with their veterinarians,
- train staff to follow good hygiene and infection control practices,
- Educate staff to raise awareness regarding potential zoonotic risks.

■ Breeders, kennel and cattery staff should follow the instructions provided by the veterinarian, including:

- administer at the recommended dose and frequency,
- complete the course of antimicrobial therapy prescribed; this should not be stopped unless otherwise stated by the veterinarian,
- report to their veterinarian any adverse effects or anomalies observed during the treatment course,
- attend the follow-up consultations or agree to follow-up phone calls or emails, as these will allow the veterinarian to assess the effectiveness of the therapy prescribed,
- carry out vaccination and worming programmes in order to prevent the occurrence and spread of infectious diseases in the animals under their care,
- isolate and quarantine suspect or diseased animals to avoid spread of disease across the animal population and treat on a case-by-case basis,
- avoid mass prophylactic or metaphylactic treatment of animals with antimicrobials,
- good hygiene practices (cleaning and disinfection, hand hygiene...).

When dealing with breeding centres, catteries or kennels, the veterinarian is dealing with population medicine, but must still care for the health and welfare of the individual animal. There are also economic considerations to take into account, due to the monetary value of the animals (e.g. purebred breeding animals)[7] and the potential loss of business (e.g. catteries and kennels).

The close proximity of animals sharing the same physical space, sometimes kept at high-density levels leading to overcrowding, can facilitate the spread of infectious diseases in susceptible populations. Particularly in premises where there is the mixing of animals from different origins (e.g. catteries and kennels), unknown health and vaccination status and large turnover (e.g. animal shelters), **the risk of introduction and spread of infectious diseases is higher** than in households with only one pet[1,11]. Furthermore, the keeping of large groups can also result in stress for the affected animals which may compromise the animal's immune system and therefore make it more prone to infection and colonisation by bacteria and other pathogens[3]. Therefore, it is important to put effort into the prevention of infectious diseases commonly observed in animals kept in these systems. Development of infection control protocols and animal health plans are essential to prevent and control disease in environments where risk of infectious diseases is high[12]. **Good hygiene** should be observed by staff to prevent the spread of infectious diseases. **Training programs** should be in place to ensure responsible antimicrobial use and good hygiene practices by staff (see Table 1).

Table 1 *- Recommendations and advice regarding zootechnical measures in canine and feline breeding establishments.*

	Zootechnical measures
Premises	- Premises layout (quarantine, hospital, infirmary, nursery...). - Cleaning, disinfection and depopulation protocol.
Individuals	- Incoming patient management (state of health, vaccinations, testing, adaptation to microbial environment...). - Short term management of suspect or sick animals: identification, isolation, veterinary care. - Long term management of suspect or sick animals in reproduction: artificial insemination, withdrawal from breeding.
Staff	- Continuous education about: respect of isolation, compliance with antibiotic treatment (doses, duration, veterinary control). - Continuous education about: zoonosis, respect of usual and reinforced hygiene measures (gloves, masks...).

Cleaning and disinfection of premises

Disease transmission in shelters and kennels often occurs through direct contact with infected animals, aerosols and fomites[13]. Cleaning and disinfection of the environment is important to contain spread of disease; only licensed products for the effect required should be used in the premises[1,3]. Breeding centres, kennels and catteries should design and implement protocols for cleaning and disinfection of their premises in order to ensure the protection of both animal and human health[19].

There are four levels of cleaning in group-housed environments:

- **physical cleaning** (e.g. removal of organic materials and waste from the environment),
- **sanitation** (e.g. application of a chemical substance to reduce bacterial contamination),
- **disinfection** (e.g. use of a licensed disinfectant that will kill the viruses and bacteria, but not spore-forming organisms), and
- **sterilisation** (e.g. will kill all viruses and bacteria, including spore-forming organisms)[13].

Good cleaning and disinfection of equipment and surfaces and following good hand hygiene should be practised at all times. **Cleaning and disinfection of equipment and facilities should be performed daily** and more frequently in premises where occurrence of infectious diseases is common or where turnover of animals is high[13]. Animals should be moved into empty cages or held by staff while their cage is being cleaned and disinfected. Mops should not be used to clean the floors in areas with animals, as these tend to spread pathogens around. Instead, hard bristle brushes with disinfectants should be used. Good hand

The risk of introduction and spread of infectious diseases among group-housed animals is higher than in households with only one pet.

***Table 2** - Efficacy of disinfectants in known small animal pathogens[21].*

Categories	Examples	Pathogens							
		Gram-positive bacteria	Gram-negative bacteria	Mycobacteria	Envelopped viruses	Large non enveloped viruses	Small enveloped viruses	Fungi	Spores
Acid	Acetic acid, citric acid, lactic acid.	+	+	-	+	-	+/-	+/-	+/-
Alcohols	Ethanol, isopropagol, methanol.	+	+	+	+	+/-	+/-	+/-	+/-
Aldehydes	Glutaraldehyde, formaldehyde, orthophtalaldehyde.	+	+	-	+	+	+	+	+
Alkalis	Sodium hydroxide (caustic soda), calcium hydroxide (slaked lime), sodium carbonate, ammonium hydroxyde.	+	+	+	+	+	+/-	+	+/-
Biguanides	Chorhexidine diacetate and gluconate.	+	+	-	+/-	+/-	+/-	+/-	-
Chlorine releasing agent	Sodium hypochlorite (bleach, Clorox), calcium hypochlorite, chlorine dioxide.	+	+	+	+	+	+	+	+/-
Iodine Iodophors	Iodine solutions (tintures) or iodophors (complex of iodine with neutral polymers), such as povidone iodine.	+	+	+	+	+/-	+/-	+	+/-
Oxydizing agents	Hydrogen peroxide, accelerated hydrogen peroxide, peroxyacetic acid, peroxymonosullfate.	+	+	+	+	+	+	+/-	+/-
Phenolic compounds	Various phenols (2-phenylphenol, benzyl phenol, 4-chloro-3,5-dimethyl phenol...).	+	+	+	+/-	+/-	+/-	+	-
Quaternary ammonium compounds	Various ammonium salts (benzalkonium chloride, benzethonium chloride, cetalkonium chloride...).	+	+	+/-	+/-	-	-	+/-	-

hygiene should be promoted amongst the staff, volunteers and visitors; hand sanitizers and hand washing facilities should be made available throughout the premises. Footbaths with approved disinfectants may also be required for disease control purposes when outbreaks occur[13]. Staff involved in the cleaning and disinfection of premises should move from healthy to sick areas to avoid the spreading of disease[13].

Moist heat treatment (> 60°C) can be used to sterilise equipment in close contact with animals (towels and blankets, feeding and water bowls). These measures are essential to control and prevent environmental dissemination of multidrug resistant pathogens such as MRSA[3]. Ultraviolet light devices have also been found to be relevant in the reduction of environmental levels of resistant bacteria such as *Clostridium difficile* and VRE, that can pose a serious risk for both animal and public health[3].

Formaldehyde, bleach (sodium hypochlorite) at 1:32 dilution, quaternary ammonium compounds (note that some may not be effective in destroying parvoviruses)[13], peracetic acid or sodium peroxide have also been recommended for use in breeding premises, kennels, catteries and animal shelters. These disinfectants are effective against viruses that can survive in the environment (e.g. canine and feline parvoviruses) that are often complicated by secondary bacterial infections (Table 2)[23]. It is important to adhere to the contact times recommended for disinfectants in order for these to be effective[13].

Vaccination

Adoption of animal health schemes is key in preventing disease introduction and spread. Most infectious diseases occurring in group-housed animals are viruses affecting the respiratory tract. In animal shelters, upper respiratory disease and 'kennel cough' are the most common syndromes observed. The most common infectious diseases in group-housed dogs and cats are shown in Table 3. Animals affected by viral infections are more susceptible to secondary opportunistic bacterial infections.

Vaccination can reduce the burden of disease and therefore of antimicrobial use in companion animals. In premises where companion animals are housed in groups, vaccination should be promoted not only for prevention but also for disease control in the presence or suspicion of an outbreak[1,11]. Vaccination contributes both to the protection of the individual animal but also of the population, through the effect of herd immunity. In this case, vaccination provides indirect protection of a large proportion of individuals (non-immune) to infectious disease from susceptible individuals (e.g. non-vaccinated) within a given population[23]. Vaccination programs should be developed as part of the health management programs of shelter kennels and catteries, where the health and vaccination status of animals is often unknown due to the potential risk of infectious diseases, already mentioned above[11]. Owners of boarding kennels and catteries should require core vaccination of animals under their care as a precondition for boarding[11] (see Table 4).

Table 3 *- Common infectious diseases in dogs and cats housed in group conditions, adapted from WSAVA[23].*

System	Dogs	Cats
Respiratory	Canine Upper Respiratory Disease "Kennel cough" (multifactorial- Canine Herpes virus, Canine Distemper virus, Canine Parainfluenza virus, Canine Adenovirus virus type 2, *Bordetella bronchiseptica*, *Mycoplasma* spp.)	Feline Upper Respiratory Disease (e.g. Feline Rhinotracheitis, Feline Calicivirus) *Bordetella bronchiseptica* *Chlamydophila felis* *Mycoplasma* spp.
Gastrointestinal	Canine Distemper (Canine Distemper virus) Infectious Canine Hepatitis (Canine Adenovirus type-1) Canine Parvovirosis (CP) Canine Coronavirus Salmonellosis Campylobacteriosis Protozoa (*Giardia lamblia*, *Cryptosporidium parvum*)	Feline Panleukopenia (FP) Feline Enteric Coronavirus (FECV) Salmonellosis Campylobacteriosis Protozoa (*Cryptosporidium felis*, *C parvum*)
Gastrointestinal, opportunistic	*Clostridium difficile*	*Clostridium difficile*

R.29 What are the recommendations and advice for owners of premises where pets are kept in groups (breeders, kennels, catteries...)?

Table 4 *- Core vaccinations recommended for dogs and cats housed in group conditions[23].*

Dogs	Cats
Canine Distemper virus (CDV)	Feline (panleukopenia) parvovirus (FPV)
Canine Adenovirus type-1 (CAV-1) and Canine Adenovirus type-2 (CAV-2)	Feline calicivirus (FCV)
Canine Parvovirus type-2 (CPV-2)	Feline herpes virus-1 (FHV-1)
Rabies virus*	Rabies virus*

**Only in countries where rabies is endemic and poses an animal and public health issue.*
Note: Bordetella bronchiseptica may be indicated in some shelters to be used as part of the core vaccination.

Animal shelters may also consider the use of "non-core" vaccines, e.g. against Feline Leukaemia Virus (FeLV), and canine Lyme disease, if the risk of exposure is high (see Table 5)[12].

Table 5 *- Non-core vaccinations recommended for dogs and cats[3].*

Dogs	Cats
*Bordetella bronchiseptica** ± (Canine Parainfluenza virus and/or Canine Adenovirus-2)	*Bordetella bronchiseptica**
Lyme borreliosis *(Borrelia burgdorferi)*	Feline Leukaemia Virus (FeLV)
Leptospirosis (e.g. *Leptospira canicola, L. icterohaemorrhagiae, L. grippotyphosa, L. pomona)*	*Chlamydia psittacci*

** Bordetella bronchiseptica may be indicated in some shelters to be used as part of the core vaccination.*

Quarantine and isolation

Quarantine is recommended for new animals arriving at animal shelters, due to unknown health status of the animals and the risk of introducing disease into the animal population[23]. For example, new cats in shelters with asymptomatic, subclinical infections may be disease carriers and can develop upper respiratory disease or diarrhoea due to stress and shed the pathogens in the environment.

Isolation of diseased animals is important to prevent the spread of disease and to allow treatment of severely affected individual animals; for this purpose, the shelter or kennel should have appropriate isolation facilities[14].

Quarantine of new arriving animals and isolation of diseased animals are recommended to prevent the introduction and the spread of disease.

Use of antimicrobials

Prophylactic and metaphylactic use of antimicrobials as the main means of disease prevention in breeding, catteries and shelter facilities should be discouraged as it may lead to the emergence and spread of resistant bacteria and resistance genes[19]. Prophylactic use of antimicrobials at parturition in breeding kennels has been associated with the emergence of multidrug resistance in Gram-positive bacteria in treated bitches[16]. Antimicrobials are routinely used in breeding kennels in bitches, in order to reduce stillbirths and neonatal morbidity and mortality due to transfer of pathogens (e.g. *Staphylococcus* spp., Streptococcus spp. and *Escherichia coli*) via the genital tract and through lactation[18]. However, in the study by Milani et al.[16], no impact was observed on neonatal mortality in treated animals.

A Belgian study found that healthy cats kept in catteries had higher levels of carriage of resistant indicator enteric bacteria (i.e. 33.3% of *Escherichia coli*, 92.3% of *Enterococcus faecalis* and 56% of *Streptococcus canis* isolates) compared to cats kept as single pets (15.8%, 66.7% and 22.2%, respectively)[17]. This study underlined the potential role of the shared environment, group housing[17], animal density[9] and widespread use of antimicrobials in particular age groups (e.g. kittens) in the transmission of resistant bacteria[17]. ESBLs have also been isolated in dead, sick and healthy dogs and cats privately owned or held in kennels in a survey conducted in Rome[9].

Furthermore, community-acquired strains commonly observed in humans were also isolated in dogs in the same study (e.g. SHV-12-positive *Escherichia coli*)[9].

Colonisation with a human clone of MRSA (EMRSA-15) has also been reported in 7.8% of clinically healthy dogs recovered in a shelter kennel in the Southeast of England in a recent study by Loeffler et al.[15], at levels higher than usually observed at community level. Nevertheless, most colonisation was only transient and transmission was not sustained in the shelter environment probably due to implementation of effective cleaning and disinfection protocols[15].

Common conditions observed in kennels include the Canine Infectious Respiratory Disease Complex (CIRDC) also known as kennel cough that is often caused by multiple viral and bacterial pathogens (e.g. *Bordetella bronchiseptica*, *Streptococcus zooepidemicus*). *S. zooepidemicus* can harbour resistance, often to doxycycline and can cause serious disease in both pets and humans[10].

Neonate animals in breeding centres can be susceptible to bacterial infections if they have a poor passive immunity due to either insufficient colostrum uptake or low antibodies (lack of exposure or compromised immune status) in the bitch or queen. Culture and AST may not be useful in individual cases as very young animals may die before a diagnosis is obtained but can aid in the management of future cases in affected litters. Post-mortem examination of deceased animals in an affected litter may also help to reach a diagnosis and aid in the disease management on the premises. Oral antimicrobials may not always be recommended in neonates and young animals due to the potential disruption of the development of the gut flora[20].

In animals that have received colostrum, infections may occur at 5-6 weeks of age when passive immunity from the mother has waned. **In young animals, diarrhoea is rarely due to bacterial infections and therefore antibiotic therapy is rarely required**; protozoal and parasitic infections are more common[20]. Empirical worming of kittens and puppies is usually recommended[12]. Upper respiratory tract infections caused by *Bordetella bronchiseptica* can occur and can be fatal particularly in neonates; in older kittens mixed respiratory infections are common[20] (for therapeutic options, see Feline rhinitis and tracheobronchitis, p.96). Viral infections through vertical transmission from the dam may be observed; in kittens, Feline Immunodeficiency Virus (FIV), Feline Leukaemia Virus (FeLV), Feline Infectious Peritonitis (FIP), Feline Parvovirus (causative agent for Feline Panleukopenia and Feline Infectious Enteritis) and in puppies, Canine Herpes virus and Canine Distemper virus may occur[20].

Zoonotic risk for animal owners and staff

Individuals working in kennels, catteries and breeding facilities may also be at risk of occupational infections caused by resistant pathogens. An outbreak of gastrointestinal infection due to multi-drug resistant *Salmonella typhimurium* DT104 was reported in the USA amongst animal shelter staff and diseased cats with subsequent spread into humans in the close community via adopted pets from the same shelter and secondary human-to-human transmission[22]. ■

Disease transmission in shelters and kennels often occurs through direct contact with infected animals, aerosols and fomites.

PART 3
SYNOPSIS

HYGIENE AND ANTISEPSIS IN VETERINARY SURGERY

The best way to prevent surgical infection is to prevent contamination of or access to the surgical site by bacteria, either actively during surgery or later during hospitalisation. This simple principle covers different aspect of the management of the patient and its environment: disinfection, antisepsis, asepsis and hygiene.

Disinfection

This includes the means and techniques of the **destruction of the microflora** (bacteria, fungi, viruses, spores) **from the surface of non-biologic material**: instruments, implants and environment. The ultimate form of disinfection is sterilization when all floras are destroyed. In veterinary practice, this is only available for small material (surgical kits, implants). The reality of disinfection is the control of the overall contaminants and bacterial population. Increasing levels of disinfection are recognised, ranging from **non-critical** (objects that can be cleaned but not sterilized: a building, a room) and **semi-critical** (objects that directly in contact with the patient: surgical table, kennels, which can be disinfected frequently if not fully sterilized) to **critical** (surgical material, implants) where sterilization is required.

Antisepsis

This includes the means and techniques for the **destruction of the microflora** (bacteria, fungi, viruses, spores) **from the surface of biologic material**: skin or mucosa, usually without full elimination of the residing flora. Antisepsis is performed by using antiseptics following a dedicated protocol to ensure contaminant removal without damaging the surface tissue and affecting its biology. In surgery, antiseptics are important for the preparation of the surgical site and of the surgeon's hands. Ideal antiseptics have a broad-spectrum action, a rapid activity, are not irritant or toxic and do not impair the healing process. They should not be inactivated by organic material and remain present and active for a long time after application. The most frequently use antiseptics in veterinary medicine are denatured (75%) alcohol, povidone iodine and chlorhexidine.

Asepsis

A condition by which a tissue or surface is free of micro-organisms. By extension, aseptic techniques include all techniques or strategies used in surgery to prevent bacterial contamination.

Hygiene

In a medical context, this includes all the techniques and practices aimed at the prevention of the carriage and spread of bacteria within the hospital and between patients, mainly by enforcing cleaning, disinfection and antisepsis.

Each veterinary practice should keep hygiene as a main focus of interest. Cleaning is the first line of any of the above practices. This means that an antiseptic or disinfectant should be applied to an uncontaminated area that has been thoroughly cleaned before application.

As antiseptics and sterilization will be altered or inhibited by residual organic tissues and secretion and as all organic material harbours microorganisms, cleaning is therefore the first line of hygiene. Strict cleaning protocols are paramount throughout the building but also apply to kennels, tables and clothes. Soap is a great antiseptic, and can dramatically reduce the degree of contamination and soiling: after cleaning, more than 99% of bacteria are removed. Basic hygiene measures that will decrease surgical sites contamination and possibly infection include clean clothes (scrubs), easy access to hand cleaning units in all the rooms of the practice, hand cleaning between patients and use of gloves whenever handling or dressing open wounds. Easy access to disposable gloves and aprons (as well as hand rub distributor or sinks and antiseptic soaps) is paramount to facilitate hygiene for all hospital staff. Practices should have written protocols regarding maintenance and cleaning of surgical theatres and kennels (frequency, type of disinfectant to use, environmental testing for any residual flora), protecting of sterile

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Figure 1 *- In this operating theatre, both surgeons are wearing sterile gloves and gowns. There is a limited team inside the theatre to prevent airborne contamination due to displacement within the room. All staff should wear masks and headwear as well as dedicated theatre shoes (washable orange and white clogs) that should not be used outside the theatre. Sterile drapes cover the non-scrubbed body parts of the patient and the instrument table. Note that the theatre is dedicated to surgery and is not used for the storage of equipment/material.*

material (closed cabinets, sterility indicators, dates of sterilization) and creation of areas of restricted access (such as surgical theatres) to prevent air turbulence and contamination of the surgical sites.

In the operating theatre, ensure the use of sterile material, large surgical drapes and the preparation of a large surgical site to limit the risk of contamination. The surgeons should wear sterile surgical gowns, gloves, a mask and headwear to prevent oronasal bacteria and body hairs from contaminating the wound.

Antibiotics should not be used as an alternative to proper disinfection and asepsis. Good asepsis and hygiene will reduce the need for antibiotics and markedly reduce the risks of surgical infection.

Cleaning should always be performed prior to disinfection.

Figure 2 - (a) Keep surgical theatres for surgical use only. After each procedure, the theatre is fully cleaned. Thorough disinfection is required on routine basis (e.g. weekly/monthly). All areas of the room should be treated, including the trolley wheels (b) and the ceiling lights (c). Swabbing the prepared surfaces (d) will help monitor the efficacy of the disinfection protocol.

Surgical site preparation

The first step consists of clipping the hair. Large areas should be clipped, allowing a wide margin from the surgical site to prevent wound contamination. Shaving should be avoided as this may cause trauma of the tissue and favour contamination by the inherent flora.

Skin cleaning and disinfection

The ideal antiseptic is non-toxic, has a rapid action, is efficient against bacteria, viruses, fungi and spores and remains active after application. Three antiseptics are commonly used in veterinary practice: spirit (alcohol), iodophores and chlorhexidine.

The area is first scrubbed, rinsed and dried with a soap to remove contaminants. Next, antiseptics are applied and left to act for a certain period of time. Chlorhexidine and iodophores can be associated with soaps, improving the contact time. Contact time should be a minimum of 5 minutes for alcohol (70%), chlorhexidine and iodophores.

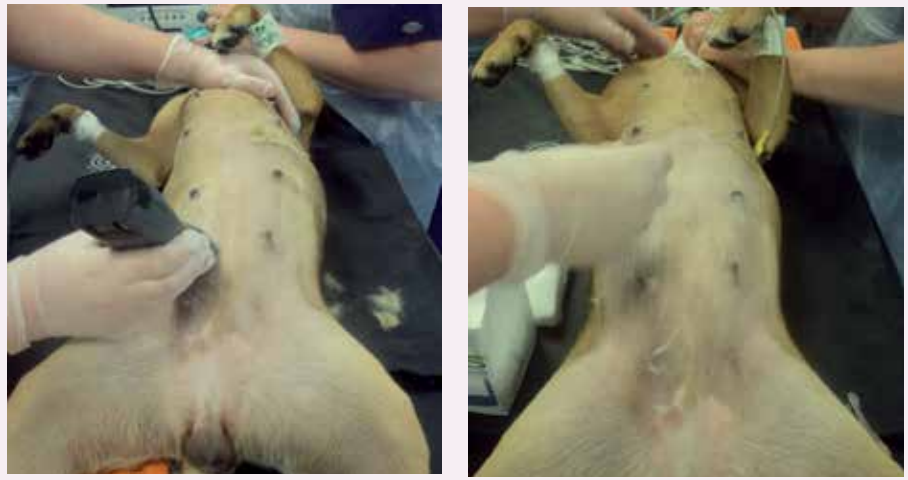


Figure 3 - Preparation of the surgical site before going into theatre includes wide hair removal (clipping) and scrubbing in a centrifugal motion to ensure good decontamination/initial antisepsis before the final preparation in theatre. Note the use of disposable gloves and the removal of all hair (vacuuming) before antisepsis.

The surgeon

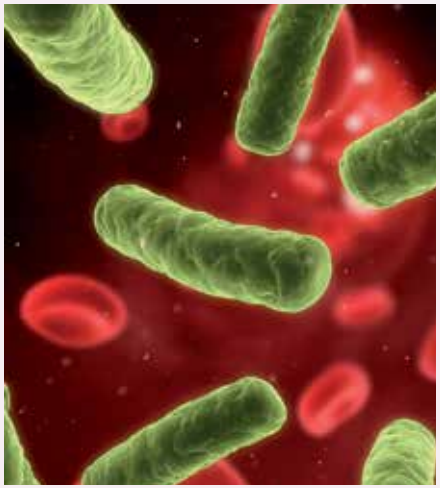
The surgeon's hands and forearms hands are prepared with the same antiseptics and soaps for the same duration of time. Care should be taken to clean and remove all contaminants from under the nails. Frequent scrubbing may cause skin dryness and irritation, which eventually may alter the normal non-pathogenic resident flora. Over the last years, the use of hydro-alcoholic rubs have been promoted and advocated for simple hand hygiene but also for "surgical hands". They act faster, are less aggressive for the skin and are potentially more efficient in delaying the recolonisation of hands inside the surgical gloves. ■

Figures 4 *- Surgical scrubbing may be replaced by a hydro-alcoholic rub. This is quicker and does not require the use of water. The antisepsis lasts longer and is less irritant to the skin.*

SYNOPSIS

KEY QUESTIONS BEFORE INITIATING ANY ANTIBIOTHERAPY

Antimicrobials are essential to cure bacterial infections but their use promotes selection of resistant bacteria, thereby contributing to reduced antimicrobial efficacy over time. Even though resistance is a natural phenomenon that exists regardless of antimicrobial use, resistant bacteria are selected (not created) by antimicrobial use. It is impossible to eradicate antimicrobial resistance unless we stop using antimicrobials. However, we can control and to some extent prevent clinical challenges related to antimicrobial resistance by using antimicrobials in a rational way.



Antimicrobials are essential to cure bacterial infections but their use promotes selection of resistant bacteria. We can limit this risk by using them in a rational way.

During recent years, *rational antimicrobial therapy* has gained considerable attention in companion animal medicine due to the emergence of meticillin-resistant *staphylococci* (MRSA and MRSP), *Escherichia coli* producing extended-spectrum ß-lactamase (ESBL) and other multidrug-resistant (MDR) bacteria in dogs and cats[5, 10].
Carriage and infection with MDR bacteria represent a major challenge for effectively managing bacterial infections as well as for preventing nosocomial infections and zoonotic risks to veterinary staff and pet owners.

The easiest way to prevent resistance is to **avoid systemic antimicrobials when they are not necessary**, e.g. in cases of upper respiratory and enteric infections that are self-limiting (i.e. infections that resolve spontaneously with or without specific treatment) or caused by viruses or parasites. Another way to reduce overall antimicrobial use is by **treating the primary cause since bacterial infections in companion animals are frequently secondary** to host-predisposing factors and may represent and require periodic antimicrobial therapy if the primary cause is not identified and treated whenever possible.
In otitis externa, superficial skin infections and wound infections systemic antimicrobials can be replaced by antiseptics, which have comparable therapeutic efficacy[2, 4] and are not supposed to select for resistance among commensal microbiota outside the application site, such as in the gut where most bacteria and opportunistic pathogens reside.

Rational antimicrobial therapy is a term that comprises any aspect of antimicrobial use that contributes to the optimisation of therapeutic efficacy and/or the prevention of resistance in the strain causing infection as well as in the patient's commensal microbiota. **Antimicrobial choice** is a cornerstone of rational antimicrobial therapy as both therapeutic efficacy and prevention of resistance are strongly influenced by the type of antimicrobial prescribed/used. Other essential aspects of rational antimicrobial therapy include **dose**, **administration interval** and **treatment duration**.

For otitis externa, superficial skin infections and wound infections systemic antimicrobials can be replaced by antiseptics

Critical decisions on antimicrobial choice are taken at two different steps in the diagnostic process: the first (empirical) during the clinical examination of the animal and the second two to three days later, once laboratory results (culture and sensitivity testing) have become available.

In the first step, during clinical examination, the veterinarian decides whether bacterial culture is indicated, selects the most appropriate specimen for submission to the laboratory, and evaluates the need for empirical antimicrobial

therapy. Subsequently, if samples have been submitted to the laboratory, they interpret antimicrobial susceptibility data to initiate therapy or correct empirical therapy if necessary (Figure 1).

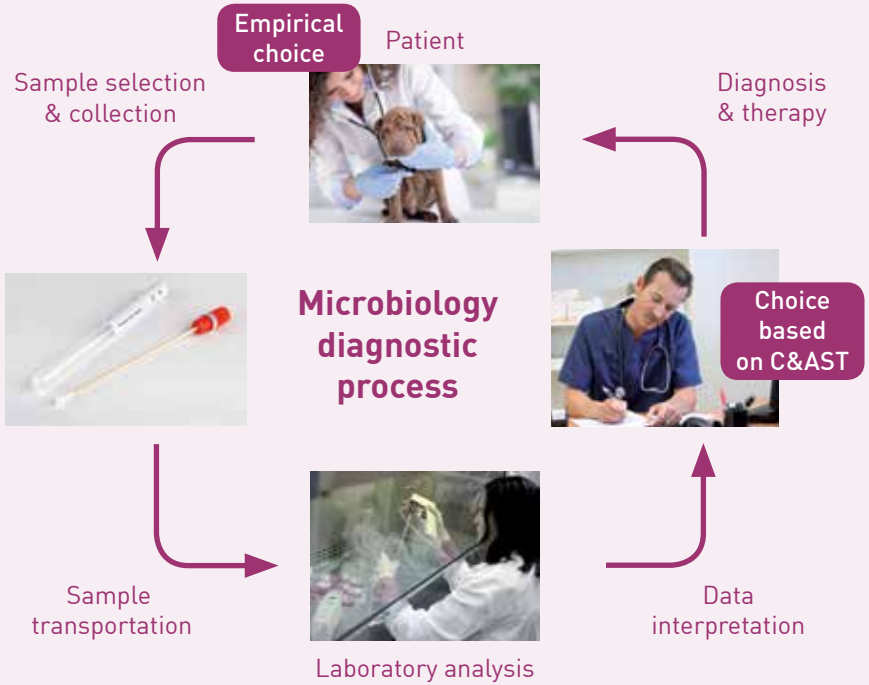


Figure 1 - During the microbiology diagnostic process, critical decisions on antimicrobial choice are taken by the clinician during the first visit (empirical choice) and when interpreting the results of antimicrobial susceptibility testing (choice based on C&AST).

First visit

The critical decisions to be taken during the first visit can be summarized in three questions (Q1 to Q3):

1- Is empirical antimicrobial therapy needed?

Empirical therapy is recommended if:

- bacterial infection is suspected on the basis of well-grounded clinical data,
- infection is life-threatening or causing pain or discomfort in the patient,
- delay in treatment could adversely affect the clinical outcome,
- collection of a suitable clinical sample requires invasive procedures that may complicate infection or patient stability,
- interpretation of the culture result is hampered by contamination with commensal bacteria, or
- infection requires topical antimicrobial therapy.

2 - If yes, which drug should be used/prescribed?

The drug(s) recommended as first choice for empirical therapy of specific infections are reported in the Disease Fact Sheets chapters. A qualified choice requires basic knowledge of the pharmacology of antimicrobial agents, of the causative agents of bacterial infections in companion animals and of the local patterns of antimicrobial resistance. In particular, the drug should be:

- able to penetrate and be active at the infection site,
- active on the most likely bacterial species suspected to be responsible for infection,
- be non-toxic to the patient,
- easy to administrate and
- as narrow spectrum as possible.

With regard to the last point, empirical therapy with broad-spectrum drugs such as 3rd generation cephalosporins or fluoroquinolones should be avoided unless the infection is life-threatening or is an infection for which one of these drugs is recommended as first choice (e.g. fluoroquinolones are recommended as first choice in the management of acute or chronic prostatitis due to their ability to pass the blood-prostate barrier).

In other situations, the narrower spectrum drugs should be chosen, since broad-spectrum cephalosporins and fluoroquinolones have a considerable impact on the commensal flora and promote selection of multidrug-resistant bacteria (see recommendation R.20). For certain types of infections (e.g. otitis, skin infections and UTIs), antimicrobial

choice should be guided by cytology (see recommendation R.2). Local patterns of resistance may be gathered from national reports, scientific articles or even better from retrospective analysis of the susceptibility data at the clinic level.

3 - Regardless of whether empirical therapy is initiated or not, should a clinical specimen be submitted to the microbiology laboratory?

Even if empirical therapy is initiated, **culture and antimicrobial susceptibility testing (AST) are recommended if**:

- there is suspicion of a complicated infection (i.e. an infection associated with structural or functional abnormalities or the presence of underlying disease, which increases the risks of failing therapy),
- the patient has not responded to therapy or has a history of relapse or re-infection,
- there is any reason to suspect infection with MDR bacteria on the basis of anamnesis and clinical records.

Culture and AST are indispensable if:

- the patient is immunocompromised,
- the infection is life threatening (see recommendation R.3).

Information on how samples should be collected is provided in recommendation R.4.

Broad-spectrum drugs such as 3rd generation cephalosporins or fluoroquinolones have a considerable impact on the commensal flora and promote selection of multidrug-resistant bacteria.

For an optimal prescription

Another set of critical decisions have to be taken in order to perform an optimal prescription (Q4 to Q7):

4 - What is the most appropriate dose?

As a matter of principle the dose should follow the label instructions provided by the antimicrobial drug manufacturer. If the label instructions indicate that the drug can be administered at different doses, the highest dose is recommended for concentration-dependent drugs such as the fluoroquinolones in order to enhance therapeutic efficacy and prevent selection of resistant mutants[3].

5 - What is the most appropriate administration interval?

The interval at which a drug is administered is particularly important for time-dependent antimicrobial drugs such as all ß-lactams since therapeutic efficacy is affected if these drugs are not prescribed according to the recommended interval (e.g. q12 or q8 hours). The administration interval also influences prevention of resistance to concentration-dependent drugs such as fluoroquinolones. Delayed administration may lower the drug concentration below the mutant prevention concentration (MPC), thereby increasing the risk of selecting resistant mutants during therapy[3].

6 - What is the most appropriate treatment duration?

This question is difficult to answer due to knowledge gaps. For some infections the recommended courses of antimicrobial therapy in veterinary medicine are significantly longer than for human medicine and this difference is not justified by scientific evidence (see recommendation R.20). The latest trend in human medicine is that unnecessary treatment should be avoided after clinical resolution of symptoms.

7 - Which antibiotic to choose?

A clear distinction should be made between empirical choice and choice based on susceptibility testing results. This important distinction is largely overlooked in most veterinary guidelines for antimicrobial use, which usually only provide recommendations on antimicrobial choice for empirical therapy.

When choosing an antimicrobial based on susceptibility data, the choice should fall on the drug that has the least possible impact on selection of multidrug-resistant bacteria, provided that the drug is clinically effective and non-toxic.

KEY QUESTIONS BEFORE INITIATING ANY ANTIBIOTHERAPY

Off-label use of products registered for human use should only be considered if the tested strain is resistant to all antimicrobial agents licensed for veterinary use.

When choosing an antimicrobial based on susceptibility data, the choice should fall on the drug that has the least possible impact on selection of multidrug-resistant bacteria, provided that the drug is clinically effective and non-toxic.

The priority system proposed by the Danish guidelines for antimicrobial use in animals ranks the antimicrobial classes into five categories (Figure 2):

- The lowest category, at the bottom of the pyramid includes drugs with narrow spectrum and limited risk for selection of multidrug-resistant bacteria found in small animals (e.g. penicillins, macrolides and streptomycin) or drugs that are not used for systemic therapy in human medicine (e.g. chloramphenicol).
- The higher to the top, drugs have an increasing importance in human medicine and higher potential for selection of clinically relevant resistance phenotypes. The fifth and highest category contains critically important antimicrobials (CIAs) in human medicine that are not licensed for veterinary use, namely carbapenems, vancomycin and linezolid.

- **Use of CIAs in small animals is only justified in rare cases of life-threatening multidrug-resistant infections that cannot be managed otherwise** and only after consultation with an infectious disease specialist. Specific requirements for the use of CIAs have been defined in the Danish guidelines[6] or, sometimes, in national regulations.

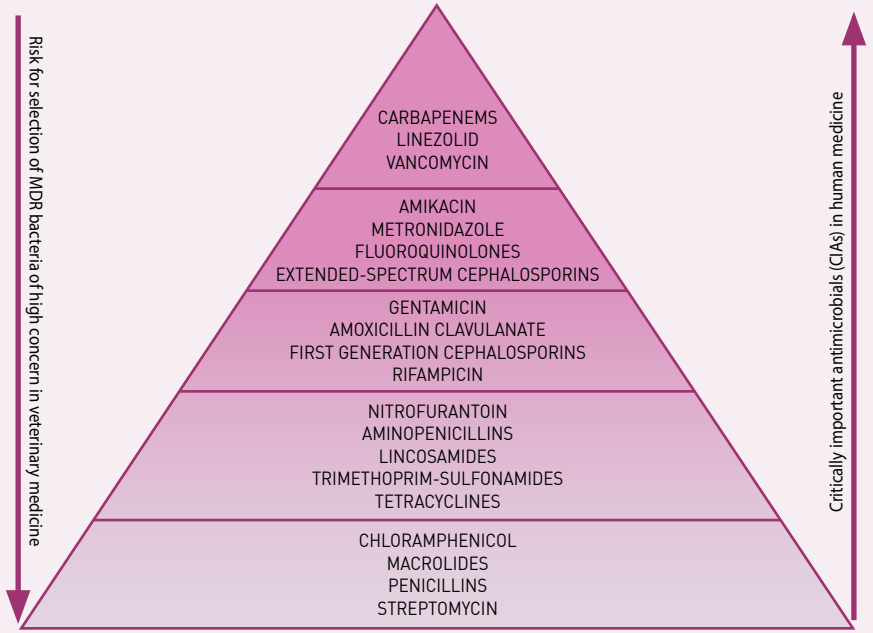


***Figure 2** - Danish classification of systemic antimicrobials based on their critical importance in human medicine and the risk of selecting multidrug-resistant (MDR) bacteria of high concern in veterinary medicine. Drugs with very limited or no therapeutic alternatives in human medicine and high risk of selecting MDR bacteria are located on the top layer of the pyramid. (From the Danish antimicrobial use guidelines for companion animals[6]).*

C&AST interpretation

Interpretation of C&AST reports is not as simple as it may appear on the surface. The critical decisions to be taken when interpreting C&AST reports can be summarized with five questions (Q8 to Q12):

8 - Why are some of the antimicrobials used in clinical practice not included in the panel of antimicrobials tested by the microbiology laboratory?

Clinical breakpoints (i.e. the threshold values used by diagnostic laboratories to categorize strains as resistant, intermediate or susceptible) are lacking for some antimicrobials that are used in clinical practice (e.g. cefalexin and cefovecin).

In the absence of clinical breakpoints, surrogate drugs belonging to the same antimicrobial class and displaying similar pharmacodynamics and pharmacokinetic properties may be used by microbiology laboratories as surrogate drugs for susceptibility testing (see recommendation R.8).

Clinical breakpoints are also lacking for some drugs that are used for topical treatment in veterinary medicine (e.g. fusidic acid).

For others (e.g. enrofloxacin and gentamicin) there are clinical breakpoints for systemic therapy but their use for predicting efficacy of topical therapy is questionable (see recommendation R.3).

9 - Why are some antimicrobials tested by the microbiology laboratory not available for use in clinical practice?

One of the most common problems encountered in the interpretation of susceptibility reports is the presence of antimicrobial agents that are not used in clinical practice. Some agents are used as indicators for testing susceptibility to clinically relevant drugs belonging to the same class or subclass. Others are used to detect specific resistance phenotypes of clinical relevance.

For example, oxacillin and cefoxitin are used for detection of MRSA and MRSP (meticillin resistant *Staphylococcus*). Information on how to interpret susceptibility data of drugs that are not used in veterinary clinical practice but are commonly included in the panels of antimicrobials tested by microbiology laboratories are provided in recommendation R.8.

10 - Which antimicrobial should be chosen when laboratory report includes susceptibility profiles of multiple strains?

Some infections, mainly wound infections, otitis externa and to a lesser extent UTIs, often result in culture of multiple bacteria. In these situations, cytology can be helpful in determining the relative abundance of cocci and rods. The clinical relevance of each organism reported by the laboratory should be considered based on its pathogenicity. For example, *Corynebacterium auriscanis* is unlikely to be a primary pathogen in otitis externa as it is never isolated alone[1]. Anecdotal evidence suggests that otitis externa associated with this organism resolves if the primary pathogen is targeted by antimicrobial therapy.

Targeting the primary pathogen is the most reasonable approach since targeting all the strains cultured may be difficult and lead to unnecessary use of broad-spectrum antimicrobials. Considering the most common infections in companion animals, *Staphylococcus pseudintermedius* should always be regarded as the primary pathogen in pyoderma, *Escherichia coli* in UTIs and *Pseudomonas aeruginosa* in otitis externa. Coagulase-negative staphylococci (skin contamination), *Bacillus* spp. (soil contamination) and enterococci (faecal contamination) are among the most common contaminants of clinical specimens that may complicate antimicrobial choice when interpreting C&AST results.

A good microbiology laboratory should not indiscriminately report everything that grows. It should indicate results that may be clinically insignificant due to likely contamination or even exclude those from the report. Reporting accurate but insignificant results can be as counterproductive as reporting inaccurate results and can have serious consequences to patient care and the development of resistance.

When multiple bacteria are cultured, cytology can be helpful in determining the relative abundance of cocci and rods.

11 - Should therapy be changed if the strain is reported as resistant to the antimicrobial that was prescribed empirically?

In theory, the initial therapy should be interrupted and a new drug should be chosen from among those to which the strain is susceptible. However, this is not necessarily a wise decision since various studies have shown that the therapeutic outcome is not always predicted by *in vitro* susceptibility testing and infection can be eradicated even if the causative agent is reported as resistant (see Recommendation R.10). Thus, the patient's condition and treatment outcome should always be checked before changing antimicrobial therapy based on C&AST results.

12 - Why must antibiotics such as carbapenems and vancomycin not be used in veterinary practice?

These antibiotics are "last resort" drugs for the therapy of life-threatening conditions in humans; currently there are no veterinary preparations available with these substances. Carbapenems are indicated for treating infections in humans caused by multidrug resistant *Enterobacteriaceae*, while vancomycin has been widely used to treat MRSA infections in humans[11]. Resistance to these antibiotics has been reported in recent years, with the emergence of resistance pathogens such as carbapenemase-producing bacteria that have also been isolated in companion animals[7,8]. Carriage of vancomycin-resistant enterococci has been reported in healthy companion animals[11]. Therefore, it is essential to prevent the further spread of these genetic determinants to other bacteria that could be potentially harmful to both public and animal health. ■

Carbapenems and vancomycin must not be used in veterinary practice because they are so-called last resort drugs for the therapy of life-threatening conditions in humans.

PHARMACOLOGICAL BASIS OF ANTIBIOTIC THERAPY

The likelihood of antibacterial efficacy depends on the potency of a drug against a pathogen (usually expressed as the MIC), patient exposure to a drug (the concentration of antimicrobial agent available for effect over time) and the host defences. Antibacterial drugs are needed only if the host defences are inadequate. The exposure to the antimicrobial agent is dependent on the drug pharmacokinetics and the dosing regimen. The beneficial effects on the host will depend on the killing or growth inhibition of the bacteria. The dosing regimen should be optimized so that the primary aims (clinical outcome, resistance suppression) of the antimicrobial therapy are reached. The treatment target should be the achievement of a good clinical outcome (clinical/bacteriologic cure and no relapse) with the least toxicity, but should also minimize the risk of bacterial resistance emerging during therapy. Antimicrobial agents should not be misused (Table 1).

The treatment target should be the achievement of a good clinical outcome with the least toxicity, but should also minimize the risk of bacterial resistance emerging during therapy.

Table 1 *- Common misuses of antibiotics*[adapted from 4].

Common misuses of antimicrobial agents
Prolonged empirical antimicrobial treatment without clear evidence of infection (e.g. inflammatory syndromes can be present with signs that mimic infectious diseases).
Treatment of a positive clinical culture in the absence of disease (e.g. asymptomatic urinary tract infection).
Failure to use narrow spectrum antimicrobial therapy when a causative pathogen is identified (e.g. prolonged used of broad-spectrum antimicrobials).
Prolonged prophylactic therapy (e.g. pre and postsurgical prophylaxis).
Excessive use of certain antimicrobial agents (e.g. excessive prescribing of a single class of antibiotic).

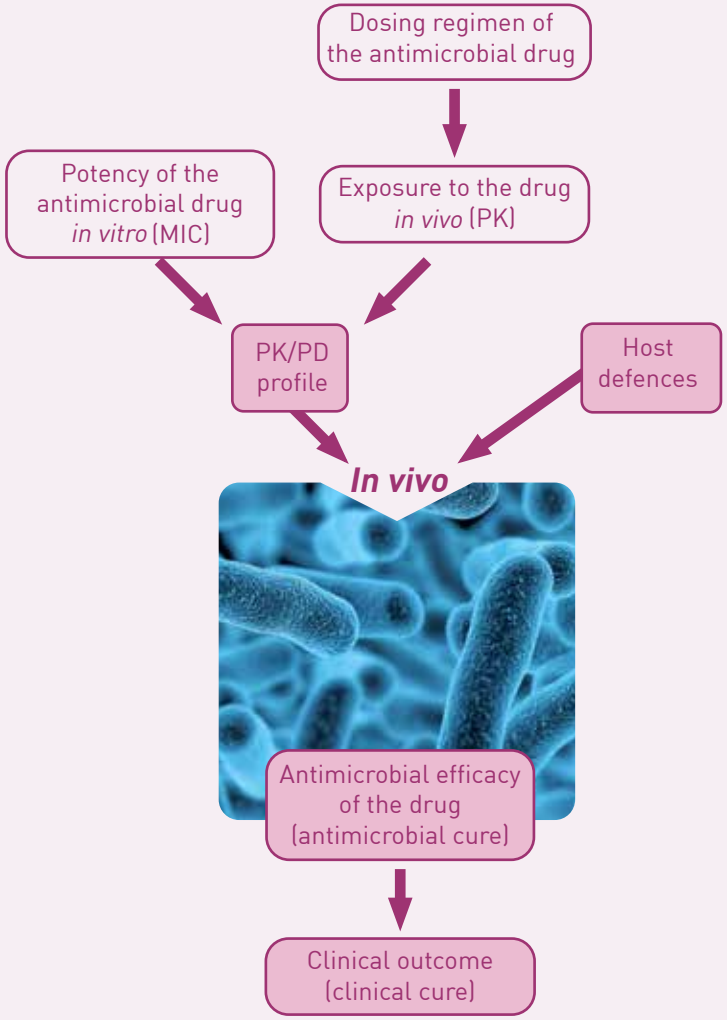


Figure 1 *- Determinants of clinical outcome. The PK/PD profile of the antimicrobial drug within the host can be used to predict the likelihood of antimicrobial efficacy*[adapted from 9].

Main principles for antibiotic therapy

Need for an accurate infectious disease diagnosis

Site of infection, characteristics of the host (e.g. immunocompromised, geriatric, comorbidities), and, whenever possible, cytological and microbiological diagnosis are requirements for appropriate antimicrobial therapy. Although the "most likely" microbiological aetiology can be frequently inferred from the clinical presentation, identification of the specific pathogen is critical in life-threatening infections and/or in case of prolonged antimicrobial therapy. Similarly, if an empirical antimicrobial therapy based on clinical presentation has failed, further laboratory investigations should be performed to determine the causal pathogen. Any possible non-infectious conditions should be excluded. The number of bacteria should be also estimated by the laboratory to distinguish colonization from infection.

Need for antimicrobial sensitivity testing

After identification of the pathogen by culture, the next step for the clinical microbiology laboratory is the antibiotic susceptibility testing (AST) of significant bacterial isolates. **AST measures the ability of the pathogen to grow in the presence of an antimicrobial agent *in vitro*, and therefore predict the clinical success or failure of the antibiotic being tested. Results are reported as minimum inhibitory concentration (MIC)** (i.e. the lowest concentration of an antibiotic that inhibits visible growth of a microorganism), **and are interpreted by the laboratory as "susceptible," "resistant," or "intermediate".**

The MIC is the best way of measuring an antibacterial effect *in vitro* and this knowledge can also be used to tailor treatment to an individual patient. Although AST results are quite helpful for the selection of the antimicrobial agent, other factors should be also taken into account, such as the nature and the site of infection and the tissue distribution of the antibiotic.

Culture and AST results are helpful for the selection of the antimicrobial agent, but the nature, the site of infection and the tissue distribution of the antibiotic should also be taken into account.

Bactericidal agents are not more efficient than bacteriostatic agents

A very common hypothesis in antimicrobial therapy is that agents with *in vitro* bactericidal activity should be preferred to agents with *in vitro* bacteriostatic activity (see Table 2 page 460). The rational is that bacteriostatic drugs, contrary to bactericidal drugs, require the aid of host defences to clear the infecting pathogen. Most antibacterials however, are potentially both bactericidal and bacteriostatic. Little to no suitable clinical data exist to address the potential superiority of bactericidal versus bacteriostatic activity. *In vitro* results should be combined with pharmacokinetic and pharmacodynamic data to provide more meaningful prediction of *in vivo* efficacy. Potentially adverse clinical consequences may also result from the rapid lytic action of bactericidal agents[10].

Inadequate penetration of the infection site can induce failure of antibacterial therapy

To be effective, the antimicrobial agent must be distributed to the site of infection, which most often is extravascular. The drug penetration depends on tissue-related factors, such as local blood flow, vascular surface area, type of vascularisation (fenestrated capillaries, tight junctions...) and drug-related factors (lipid solubility, pKa, molecular size, and plasma protein binding). In most tissues, free antibacterial concentrations in serum/plasma are directly related or equal to the concentration in the extracellular space.

However **in the central nervous system, eye, prostate, bronchial secretions and the mammary gland, drug distribution is limited because of membrane barriers. Lipophilic antibacterial drugs** (e.g. fluoroquinolones, metronidazole, chloramphenicol, tetracyclines, sulfonamides, trimethoprim) **can cross some of these barriers very readily**, in contrast to hydrophilic drugs (penicillins, cephalosporins, aminoglycosides).

Rational antibiotic combination therapy may be more effective to combat multidrug resistance

Antimicrobial monotherapy is generally preferred to combination therapy. However, in case of multidrug resistance the appropriate empirical therapy that can completely eradicate target microorganisms without leaving any mutants should be selected. In such clinical settings there is a higher possibility

of adequate antibacterial coverage by combining two antibacterial agents rather than a single agent. Combined antibacterial agents with their broad spectra of activity and multimodal action may prevent emergence of drug resistance. Synergistic action resulting from combination therapy leads to broader spectrum than the sum of activity of the two individual agents. Antibiotic combination therapies are also the mainstay of treatment of polymicrobial infections especially of mixed infection with each pathogen requiring a different drug. In patients where the nature of infection is not clear, empirical antibiotic combinations can be very useful to initiate the therapy[1,8,9].

However, combination therapies potentially have some disadvantages:

- encouragement of "shotgun therapy",
- failure to provide an optimum dose of individual drugs,
- increased drug resistance by providing empirically two agents if the organism is susceptible to a single agent,
- cost of the therapy.

Although data are missing in veterinary medicine, judicious and rational use of antibiotic combination therapy is recommended by various society guidelines in human medicine[8].

Timing of initiation and duration of antimicrobial therapy should be rationally guided by the clinical condition and laboratory results

The timing of initial therapy should be guided by the clinical condition. **In stable, non-urgent clinical settings, antimicrobial therapy should as much as possible be deliberately delayed until microbiology results are available**. This is not always easy to explain to an owner, who might expect immediate treatment. In critically ill patients, empirical antimicrobial therapy should be initiated immediately after or concurrently with the taking of samples for laboratory diagnosis. Once the pathogen and antimicrobial susceptibility are known, every attempt should be made to narrow the antibiotic spectrum (downscaling or de-escalation). Delay in the start of suitable antibiotic therapy may lead to treatment failure and increased drug resistance, although the impact on patient outcome remains poorly documented in veterinary medicine[3,4,8].

Short treatments reduce the risk of emergence of resistance.

Although recommendations regarding the duration of treatment exist in small animals, there is no evidence-based guidance on optimal duration of antimicrobial therapy. **Short (at least not abusively long) durations of treatment should be encouraged** as it is one of the simplest and most effective ways to reduce exposure of commensal bacteria to antimicrobial agents. Moreover they improve the owner's compliance, reduce the cost of the therapy and limit the risk of adverse effects. A very simple principle is that the longer the duration of therapy the higher the risk of resistance emerging. In practice, the treatment has to be carefully individualized and should be discontinued once there is evidence of clinical and microbiological cure[13].

Host factors should be considered before selecting the antimicrobial agent

In patients with renal (or hepatic) dysfunction, drug pharmacokinetics (PK) especially the elimination of drugs may be altered and lead to overexposure for drugs that are essentially cleared by the kidney (or the liver). Although in such situations the dosage regimen can be adjusted, it is preferable to select antimicrobial drugs cleared by the extrarenal (or extrahepatic) route. For drugs cleared by both hepatic and renal pathways, accumulation due to renal impairment may be compensated by increased hepatic elimination[6]. Age-associated physiological differences could also affect antimicrobial drug PK (e.g. excretion of antibacterial drugs in urine depends on the glomerular filtration

Surgical incision and drainage, and not antimicrobials, are the key treatment for abscesses.

rate, which is 87% higher in puppies than in mature dogs[5]). Antimicrobial drugs should be also prescribed with caution during pregnancy and lactation. Genetic diversity observed in dogs and cats may also cause variability in antimicrobial agent PK, even if insufficient data are currently available for breed-specific recommendations[7].

Adjunctive non-antimicrobial treatment (debriding necrotic tissues, removing foreign bodies and other sources, removing predisposing causes, nursing...) should not be neglected in the infected patient and may be equally or **even more important than antimicrobial therapy**[12].

Surgical incision and drainage, not antimicrobials, are for example the key treatment for abscesses.

The clinical history of antimicrobial therapy should be also documented, as prior administration of antimicrobials may induce development of strains of resistant bacteria through selective pressure. Avoiding recently used antimicrobials is therefore recommended when chosing the appropriate drug[2]. Patients with immune suppression (e.g. patients with cancer or neutropenia) should be also identified as they may respond poorly to the antimicrobial therapy.

Understanding how dosing affects the antimicrobial activities of different agents is required for appropriate antimicrobial therapy

An understanding of the relationships between pharmacokinetic (PK) and pharmacodynamic (PD) parameters allows a better correlation of *in vitro* potency and *in vivo* efficacy. MIC is the most frequently used PD parameter. However, it is not representative of the *in vivo* process involved in the antibacterial effect over time. Integration of PK and PD data can therefore predict the antibacterial efficacy against a given pathogen. PK/PD relationships are also essential for determining the dosage regimen.

Antimicrobial bactericidal drugs can be distinguished by their action mechanism: concentration dependent (e.g. aminoglycosides and fluoroquinolones) or time-dependent (e.g. ß-lactams).

Drugs with concentration-dependent effect have an enhanced bactericidal activity at high plasma concentration. With these agents, the peak plasma concentration (and not the frequency of administration) is more closely associated with efficacy.

In contrast, drugs with a time-dependent effect have relatively slow bactericidal action. It is therefore important that plasma concentrations exceed the MIC as long as possible during the dosing interval, either via continuous infusion or by frequent dosing.

Frequently used PK/PD indices for the assessment of antimicrobial efficacy are the time above MIC, peak plasma concentration to MIC ratio, and area under the curve (AUC) to MIC ratio (Figure 2).

- For ß-lactams, time>MIC values at least equal to 40-50% of the dosage interval have been proposed.
- For aminoglycosides, C_{max}/MIC of 8-10 is the most closely correlated with efficacy. This can be accomplished by a single dose once daily.
- For fluoroquinolones, AUC/MIC ratio >100-125 has proved to be the most predictive of efficacy.
- For bacteriostatic drugs (e.g. macrolides, tetracycline, clindamycin and chloramphenicol), time>MIC is used to predict efficacy[11]. ■

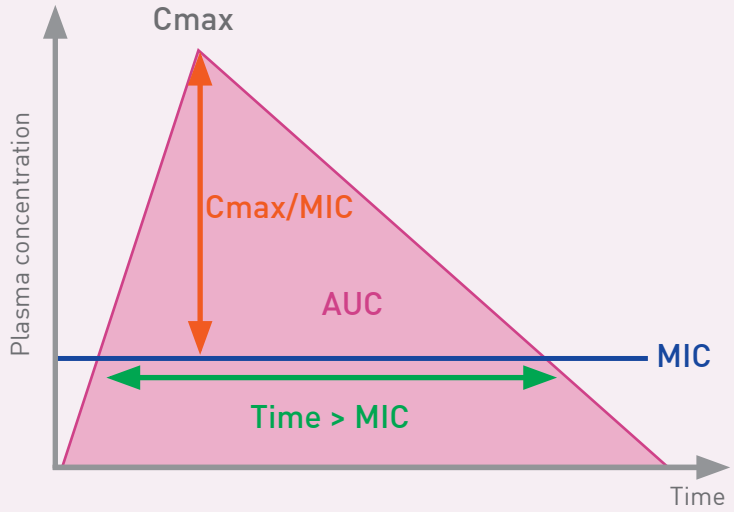


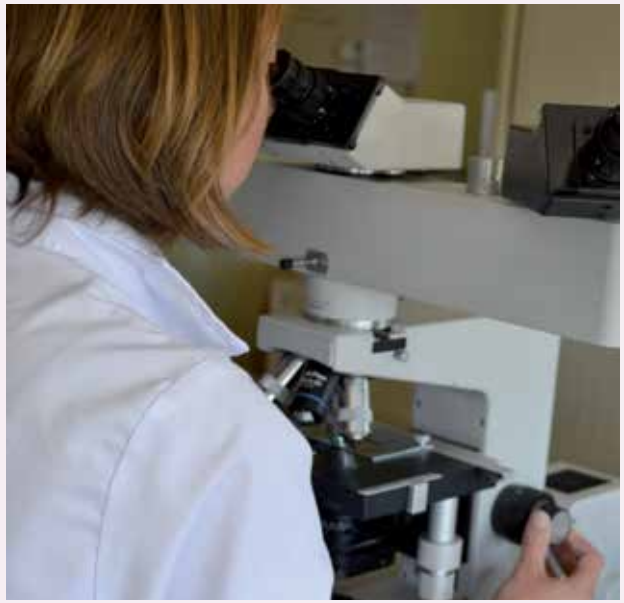
Figure 2 *- The most frequently used PK/PD indices for antibiotics.*
The Cmax/MIC and the AUC/MIC are indices of the efficacy of dose-dependent antibiotics.
The time above MIC (T> MIC) is used for time-dependent antibiotics.

Table 2 - Definition of bacteriostatic/bactericidal drugs, and current limitations of this categorization[10].

Bactericidal drug	Bacteriostatic drug	Comments
General definition		
The agent kills bacteria	The agent prevents the growth of bacteria (i.e. it keeps them in the stationary phase of growth).	Bactericidal agents usually fail to kill all bacteria, especially if the inoculum is large, while most so-called bacteriostatic agents kill some bacteria. *In vitro* conditions of testing (growth condition, test duration...) may influence whether an antimicrobial agent is considered bactericidal or bacteriostatic.
Microbiological definition		
The generally accepted definition of bactericidal is a 99.9% reduction in viable bacterial density in an 18-24-h period. The minimum bactericidal concentration (MBC) is the lowest concentration of an antibacterial agent that either totally prevents growth or induces a 99.9% decrease in the initial inoculum (i.e. a ^{3}log10 reduction in colony-forming units [cfu]/mL).	Bacteriostatic activity has been defined as a ratio of MBC to MIC of >4.	There is no evidence that a > or <99.9% decrease might not be equally useful in predicting clinical outcome. The extension of the incubation time from 18-24 h to 36 h or even 48 h could also change the classification of many antibacterial agents from bacteriostatic to bactericidal, or vice versa. MBC is the result of an *in vitro* test in which a static concentration of an antibacterial agent is being tested against an initially fixed concentration of pathogens in an aqueous medium. This differs from the *in vivo* situation, in which antibacterial and bacterial concentration in various body fluids and tissues may change considerably over time.

Table 2 (continued).

Bactericidal drug	Bacteriostatic drug	Comments
Examples of so-called bactericidal or bacteriostatic drugs		
Aminoglycosides, fluoroquinolones, ß-lactams	Tetracyclines, macrolides	At high concentrations, bacteriostatic agents may be bactericidal against some susceptible organisms. At low concentrations, bactericidal drugs may exhibit bacteriostatic activity. A high *in vivo* bacterial load may affect the activity of bactericidal drugs.



Cytological and microbiological diagnoses are requirements for appropriate antimicrobial therapy.

CURRENT SITUATION OF ANTIBIOTIC RESISTANCE IN DOGS AND CATS, EMERGING RESISTANCE PATTERNS

Veterinary care of companion animals has evolved in recent years[8,18]. In many countries, companion animals are now perceived as family members[3,8]. This has resulted in an increased use of veterinary services[3], and consequently of antimicrobial substance in these species[17,18]. Pet animals can act as both source and reservoirs of resistant bacteria and determinants. This poses a risk for pet owners due to the close social interactions and sharing of the same environment in the household[18]. It also poses an occupational risk to **veterinary professionals**, as they are at **higher risk of colonisation with resistant and multidrug resistant pathogens** than individuals in the community and increases the risk of nosocomial infections in the workplace[23,27]. Pets can become colonised or infected with resistant strains in many ways: contact with other animals, humans, contaminated environment (including that of the veterinary practice), food and treats of animal origin. Contaminated dog food and pig ear treats have been associated with multidrug-resistant *Salmonella* spp. in dogs[38]. The increased popularity of raw meat diets may also pose a risk to public health[22].

The epidemiology of antimicrobial resistance in companion animals is still not completely understood. Antimicrobial use is a known risk factor for the emergence of resistance and colonisation with resistant bacteria in pets, similar to what is observed in humans[8, 18, 23, 43]. All groups of antimicrobials used in veterinary practice are also routinely used in human medicine. Of particular interest is the growing use of veterinary approved cephalosporins and fluoroquinolones, to treat common infectious diseases in small animals, that are deemed as critically important antimicrobials (CIAs) for the treatment of life-threatening infections in humans[9,44]. Furthermore, besides the CIAs that are approved for veterinary use there are those approved for human use only (e.g. carbapenems, fosfomycin, vancomycin). Although currently a controversial issue, a veterinary surgeon may exceptionally prescribe the latter (CIAs for human use only), in particular to avoid unacceptable suffering, to treat the animal in accordance with the "Cascade" (Arts. 10 & 11 of Directive 2001/82/EC of the European Parliament and of the Council).

Pet animals have close social interactions with pet owners and can act as both source and reservoirs of resistant bacteria.

Resistance in companion animal bacterial pathogens

Data on susceptibility of canine and feline bacterial pathogens is **scarce and fragmentary** due to the **lack of surveillance programs** for antimicrobial resistance in these species.

Current resistance scenario in UTI bacterial pathogens

Recently, a multicenter study of urinary tract infection susceptibility was conducted in companion animals in 14 countries in Europe[24]. For all bacterial species, Southern European countries generally showed higher levels of antimicrobial resistance compared to Northern European countries. This may be associated with the various national antibiotic prescription habits in the countries concerned (Figure 1 and Table 1).

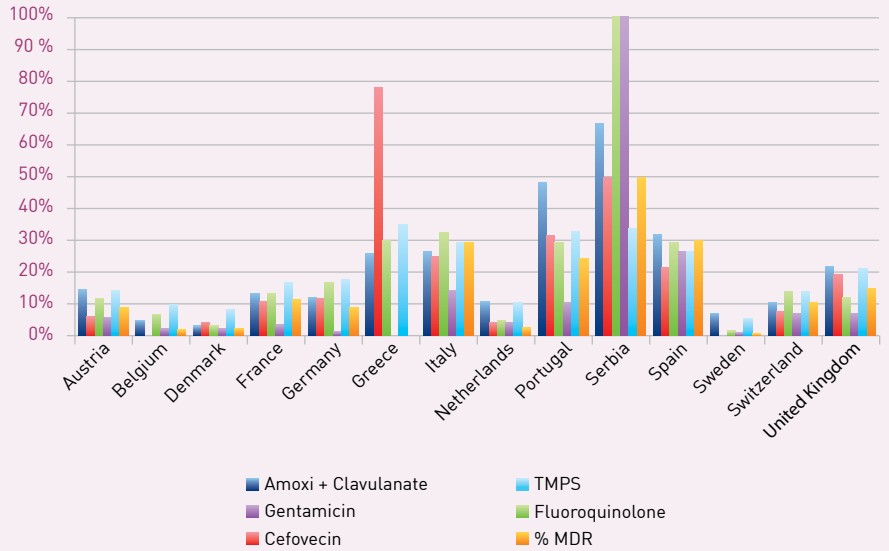


***Figure 1** - Percentage of resistance in urinary Escherichia coli by antimicrobial and country in 2012-2013[24].*

Amoxicillin-clavulanate resistance

Denmark (2.88%) and Belgium (4.29 %) had the lowest frequencies of amoxicillin-clavulanate resistance in *E. coli*. In Portugal, *E. coli* had a significantly higher amoxicillin-clavulanate resistance frequency (48.15%). Earlier studies conducted in dogs in Portugal prior to 2002[14,15] and in dogs and cats from Germany in 2004-2006[16] and Switzerland in 2000-2001[21] described lower frequencies of *E. coli* resistance.

Third-generation cephalosporins

E. coli resistance to third generation cephalosporins (3GC) had also the highest frequencies in southern countries: Portugal (31.25%), Italy (24.64%) and Spain (21.15%). **Being of critical importance to humans, prudent use of 3GC is of upmost importance**.

Trimethoprim-sulfamethoxazol

E. coli resistance to trimethoprim-sulfamethoxazol (TMPS) was over 25% in southern countries, and even over 30% in Portugal, Greece and Serbia.

Fluoroquinolones

Several authors have reported lower fluoroquinolones resistance frequencies[16,29,37,45] than the ones found in this study, especially regarding southern countries. In emergency cases, fluoroquinolones are considered a good first choice for pyelonephritis treatment and should otherwise be used as a second line antimicrobial for the therapy of lower UTIs.

Gentamicin

Resistance to gentamicin was low in *E. coli*, *Proteus* spp. and *Staphylococcus* spp. over Europe. Nevertheless, the distribution seemed to follow the same pattern, with increased resistance in southern over northern countries.

Multidrug resistance

Multidrug resistance (resistance to three or more categories of antimicrobials) was also higher in *E. coli* in Southern European countries. During the study period, the frequency of resistance to several antimicrobials including fluoroquinolones decreased significantly in *E. coli* isolates in Belgium, Denmark, France and the Netherlands[24].

Table 1 *- Percentage of resistance in urinary Escherichia coli by antimicrobial and country in 2012-2013[24].*

	Amoxi + clavulanate	Cefovecin	Fluoro-quinolone	Gentamicin	TMPS	% MDR	Zero R %
Austria	14,1 % (n=142)	5,6 % (n=142)	12,0 % (n=142)	5,6 % (n=142)	14,1 % (n=142)	8,4 % (n=142)	78,9 % (n=142)
Belgium	4,3 % (n=840)	(n=0)	6,6 % (n=769)	1,7 % (n=840)	10,4 % (n=839)	1,4 % (n=769)	85,1 % (n=769)
Denmark	2,9 % (n=206)	3,9 % (n=208)	2,9 % (n=208)	1,9 % (n=208)	8,2 % (n=208)	2,4 % (n=208)	88,9 % (n=208)
France	12,8 % (n=954)	10,8 % (n=933)	12,8 % (n=948)	3,4 % (n=951)	16,3 % (n=959)	11,0 % (n=909)	77,2 % (n=909)
Germany	11,8 % (n=153)	11,8 % (n=152)	16,3% (n=153)	1,2 % (n=153)	17,7 % (n=153)	8,6 % (n=152)	67,8 % (n=152)
Greece	25,8 % (n=31)	77,8 % (n=9)	30,0 % (n=30)	(n=0)	34,6 % (n=26)	(n=0)	(n=0)
Italy	26,1 % (n=69)	24,6 % (n=69)	31,9 % (n=69)	14,5 % (n=69)	29,0 % (n=69)	29,0 % (n=69)	63,8 % (n=69)
Netherlands	10,8 % (n=1461)	3,8 % (n=1380)	4,9 % (n=1457)	3,7 % (n=81)	10,2 % (n=1459)	2,2 % (n=1380)	81,3 % (n=1380)
Portugal	48,1 % (n=27)	31,3 % (n=31)	29,0 % (n=31)	10,0 % (n=30)	32,3 % (n=31)	24,0 % (n=25)	32,0 % (n=25)
Serbia	66,7 % (n=3)	50,0 % (n=2)	100 % (n=3)	100 % (n=3)	33,3 % (n=3)	50,0 % (n=2)	50,0 % (n=2)
Spain	31,7 % (n=60)	21,2 % (n=52)	29,6 % (n=61)	26,6 % (n=46)	26,7 % (n=60)	29,7 % (n=37)	43,2 % (n=37)
Sweden	7,0 % (n=2091)	0 % (n=2082)	1,1 % (n=2091)	0,2 % (n=2091)	5,0 % (n=2091)	0,2 % (n=2082)	90,2 % (n=2082)
Switzerland	10,5 % (n=133)	7,5 % (n=132)	13,6 % (n=132)	6,8 % (n=132)	13,7 % (n=131)	10,0 % (n=130)	83,1 % (n=130)
United Kingdom	21,7 % (n=143)	19,0 % (n=142)	11,9 % (n=143)	6,5 % (n=92)	21,1 % (n=142)	14,6 % (n=89)	69,7 % (n=89)

n: Total number of Escherichia coli tested for the considered antibiotic category.

MDR : multidrug-resistant isolates are defined as those resistant to three or more categories of antimicrobials in this table

Zero R: full-susceptibility is defined as an isolate being susceptible for all the above-mentioned classes of antimicrobials.

MDR and Zero R percentages do not include resistance to cefovecin for Belgium and gentamicin for the Netherlands.

Current scenario in Staphylococci resistance

Three studies evaluated antimicrobial resistance in *Staphylococcus pseudintermedius* over time[2,6,26].

The studies detected increasing resistance trends for ampicillin/amoxicillin/penicillin, cefovecin, cefalexin, enrofloxacin, clindamycin and trimethoprim/sulfamethoxazole[2,6,26]. One report evaluated the trends and molecular mechanisms of antimicrobial resistance in clinical staphylococci isolated from companion animals over a 16-year period[6]. Increasing resistance trends to the above antimicrobials were also observed, but also to cefoxitin in *S. aureus* and CoNS, oxacillin in *S. pseudintermedius*, and to amoxicillin-clavulanate, cefotaxime, ceftriaxone, ciprofloxacin, norfloxacin, ofloxacin, moxifloxacin, tetracycline, chloramphenicol, gentamicin, neomycin, tobramycin, kanamycin, streptomycin, erythromycin was seen in all staphylococci analysed[6] (see Figure 2 for resistance mechanisms). The increase over time of meticillin-resistant mecA-positive and multidrug-resistant strains is worrying. Several meticillin-resistant staphylococci (MRS) clonal lineages circulating in human hospitals and in the community were found in this study, suggesting that companion animals can become accidently infected with highly successful human MRS clones or may indicate that these clones are not host specific.

Thus, **companion animals can act as reservoirs of important bacterial clones and genes of human origin, perpetuating the transmission cycle of MRS**.

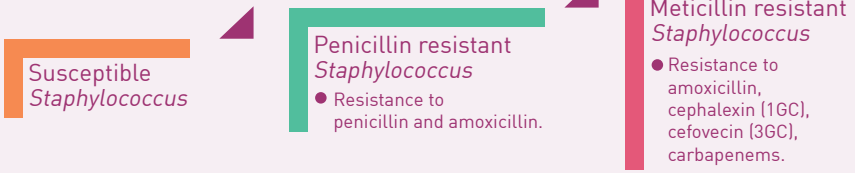


***Figure 2** - Stepwise mechanisms of ß-lactam resistance to meticillin resistance in Staphylococcus mediated by the mecA gene (resistance is mediated by the mecA gene that encodes penicillin binding protein 2a).*

Multidrug-resistant bacteria in companion animals

Recently, the European Medicine Agency (EMA) has voiced its growing concern over antimicrobial resistance by publishing a reflection paper on the risk of antimicrobial resistance. The document points out that MRSA, MRSP, extended-spectrum ß-lactamases (ESBL, *ampC*) producing *Enterobacteriaceae* and multidrug-resistant non-fermenting Gram-negative bacteria have emerged in both healthy and sick dogs and cats[13]. A potential risk of transmission of these bacteria to humans from infected or colonized companion animals is implied. In addition there is the possibility of transfer of genetic material coding for resistance from companion animals. The occurrence of multidrug resistant bacteria (e.g. MRSA, MRSP, ESBLs) in companion animals poses a serious threat to animal health and welfare due to the lack of treatment options and treatment failure that could lead to the euthanasia of the animal[3] – besides being a public health risk to those in contact with the animal[3,8,13,38].

Knowledge of the mechanisms involved in ß-lactam resistance among Gram-positive and Gram-negative bacteria may be very useful when choosing antimicrobial therapy (Figure 2).

Meticillin-resistant staphylococci (MRSA, MRSP) have been reported in companion animals with UTI in Europe[4, 6]. MRSP poses a particular risk for both animal and public health phenotype; exposure to antimicrobials has been associated with colonisation of small animals with this pathogen[1]. In Europe, the main circulating clones are ST71-SCCmec II-III and ST106-SCCmec IV[6, 30].

In Europe, acquired ampicillin resistance is a major phenotypic marker of hospital acquired *Enterococcus faecium* and experience has shown that the appearance of such resistance often precedes increasing rates of vancomycin resistant enterococci (VRE) with a delay of several years. Ampicillin resistance and also high level gentamicin resistance has been detected in *Enterococcus faecalis*

Multidrug resistant bacteria pose a serious threat to animal health and welfare due to the lack of treatment options and a public health risk to those in contact with the animal.

causing UTI[11]. Clones of resistant enterococci bacteria associated with nosocomial infections in humans have been isolated with increased frequency in healthy pets; Damborg et al[10] described the first isolates of ampicillin resistant *E. faecium* ST-192 (AREF) that were all similar to the human clonal complex 17 (CC17). This poses a serious risk for animal health, as *E. faecium* is a common pathogen in canine UTIs and is resistant to commonly used antimicrobials for the treatment of this condition (e.g. ampicillin, potentiated amoxicillins and sulphonamides, first generation cephalosporins, 3GC and fluoroquinolones)[10]. This is a potential public health risk, as the treatment options of AREF infections are limited to penicillin or penicillin/gentamicin combinations and, as a last resort, vancomycin[10]. The potential reservoir role of pets for resistant bacteria, even those of human origin, should not be ignored[10,18].

ESBL producing organisms have been identified in companion animals. The majority of isolates in these studies were *E. coli* isolated from UTIs, namely the CTX-M-15-producing *E. coli*[12,14,20]. This multidrug-resistant ESBL producing *E. coli* (resistance to 3GC, aminoglycosides and fluoroquinolones) belongs to the sequence type 131 and has recently emerged as a worldwide pandemic clone in humans which is now being detected in companion animal with UTI[33]. Carbapenem resistance has so far remained a rare phenomenon among Gram-negative bacteria isolated from companion animals in Europe. Carbapenems are not commonly used in small animal practice and should be avoided as these are considered "last resort" drugs in human medicine[46]. Carbapenems are not licensed for veterinary use, although off-label use has been reported occasionally associated with the treatment of infections caused by multidrug resistant pathogens in these species[42]. Recently, the emergence and clonal spread of *K. pneumoniae* and *E. coli* producing carbapenemase OXA-48 in dogs was reported in Germany[36]. An OXA-23-mediated carbapenem resistance in sequence type 2 multidrug-resistant *Acinetobacter baumannii* was associated with UTI in a cat in Portugal[32]. It is believed that carbapenemase resistant Gram-negative bacteria are likely from human origin, as these drugs are commonly used as last resort to treat multidrug resistant life-threatening infections in hospital settings[46]. New Delhi Metallo-ß-Lactamase (blaNDM) in *E. coli* isolates have also been recently detected in diseased small animals in the USA posing issues for animal and public health due to potential treatment failure due to lack to therapeutic options for both animals and humans in the close community[35]. ■

Pets can become colonised or infected with resistant strains by food and treats of animal origin.

Available data show that resistant bacteria emerge in companion animals and several problematic multidrug resistant organisms are shared between companion animals and humans. Thus the use of antimicrobials in companion animals contributes to the selection and potential spread of drug resistance which constitutes a potential risk to public health.

RELEVANCE OF MULTIDRUG-RESISTANT INFECTIONS FOR THE VETERINARY PROFESSIONAL

Senior healthcare leaders throughout the world have raised concerns about the danger antimicrobial resistance poses to modern healthcare. The World Health Organisation considers that this is one of the greatest threats that we are facing. This was highlighted by the recent award of the UK Longitude Prize to research in this field, with Catherine Ball of the Biochemical Society stating that "antibiotic resistance is the obvious choice" [for the award]; indeed, without antibiotics many of the discoveries in the other challenge areas could be rendered useless.

Humans and animals are exposed to the same drugs, bacteria and resistance genes. As they are often in close contact, bacteria can be transferred in both directions.

How real is the threat from antimicrobial resistance?

Evidence of clinically significant antimicrobial resistance in human healthcare is clear. The One Health Initiative recognises that humans and animals are intimately associated: we are exposed to the same drugs, bacteria and resistance genes. Humans and animals are often in close contact and bacteria can be transferred in both directions. For example, identical bacteria can be isolated from humans and animals in the same households, dog owners can become colonised with bacteria from their dog's pyoderma, and in-contact humans carry equine and farm animal specific MRSA strains. It would therefore be surprising if we did not see antimicrobial resistance in veterinary healthcare.

The development of antibiotic resistance was inevitable as antibiotic resistance genes are widespread in nature. Antibiotics favour the survival of bacteria carrying resistance genes, allowing them to spread. Resistance to penicillins was seen shortly after the introduction of these drugs; for example, meticillin was introduced in 1959 and MRSA first isolated in 1961. Since then, **the prevalence of antimicrobial resistance has increased, and it is estimated that this will result in an annual toll of 10 million deaths worldwide by 2050** (see Figure 1). This does not take into account the increased morbidity and costs associated with successful treatment and/or avoiding procedures where the risk of infection is too high. The impact on veterinary healthcare is likely to be similarly devastating.

The first companion animal MRSA isolates were also reported in 1961, with multiple case series emerging in the 1990s. Meticillin resistance also occurs in other staphylococci including *Staphylococcus pseudintermedius* (MRSP). MRSP was first recognised in Europe and North America in 2004, and has spread in domestic animals throughout Europe, USA and Canada. Meticillin-resistant staphylococci have been isolated from 0.5% to 10% of vet-visiting animals and clinical samples in Europe and Canada, but the prevalence can be higher. The prevalence was 46% among canine in-patients in Japan, and in the US they were found in 15-38% of dogs with pyoderma and up to 20% of clinical samples.

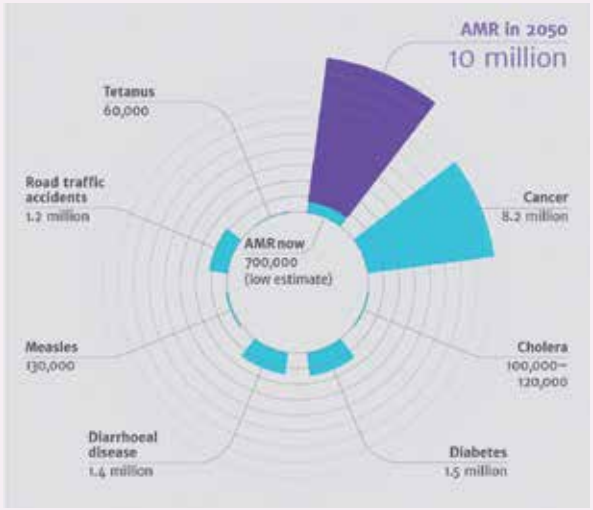


***Figure 1** - Estimates of current and future human deaths attributable to antimicrobial infections (From: Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014.).*

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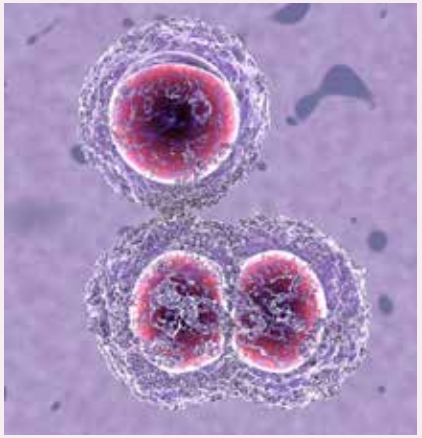
The first case series of MRSA in the UK were seen in the late 1990s and it became a prominent clinical concern in 2004. There has been a steady increase in the prevalence, with one laboratory seeing the proportion of meticillin-resistance among staphylococcal isolates increase from 3.8% to 8.9% in 2008-2012. However, this overall figure masks a subtle shift in the epidemiology of meticillin-resistant staphylococci. Over this period the number of MRSA isolates has been relatively stable and the increase in prevalence is accounted for by MRSP isolates (which have increased from 7.1% to 64.2% of the total). MRSP isolates are of concern as they have a wider resistance spectrum than MRSA isolates, and are more host-adapted to and persistent in animals.



Meticillin-resistant staphylococci (MRSA)

Fluoroquinolone-resistant, ESBL and AmpC producing E. coli have been found in 5-10% of faecal and environmental samples from veterinary hospitals in the UK.

Other bacteria of concern showing an increasing prevalence of antimicrobial resistance include multidrug-resistant (MDR; resistance to ≥3 antimicrobial classes) *Pseudomonas*, *Salmonella* and *Streptococcus*, and extended spectrum ß-lactamase (ESBL) and AmpC producing *E. coli* and *Klebsiella*. For example, fluoroquinolone resistant, ESBL and AmpC producing *E. coli* have been found in 5-10% of faecal and environmental samples from veterinary hospitals in the UK.

Does antibiotic use select for resistance?

There is no doubt that antibiotic use is the single biggest factor driving the emergence and spread of antibiotic resistance. Levels of resistance correlate well with antibiotic prescribing rates in human healthcare (e.g. rates of defined daily doses per 1,000 people/day of 11.4 in the Netherlands compared to 28 in Greece) (see Figure 2). Reducing antibiotic prescribing in Sweden was associated with lower levels of resistance. Glycopeptides, cephalosporins, and fluoroquinolones have been specifically associated with selection for MRSA in humans.

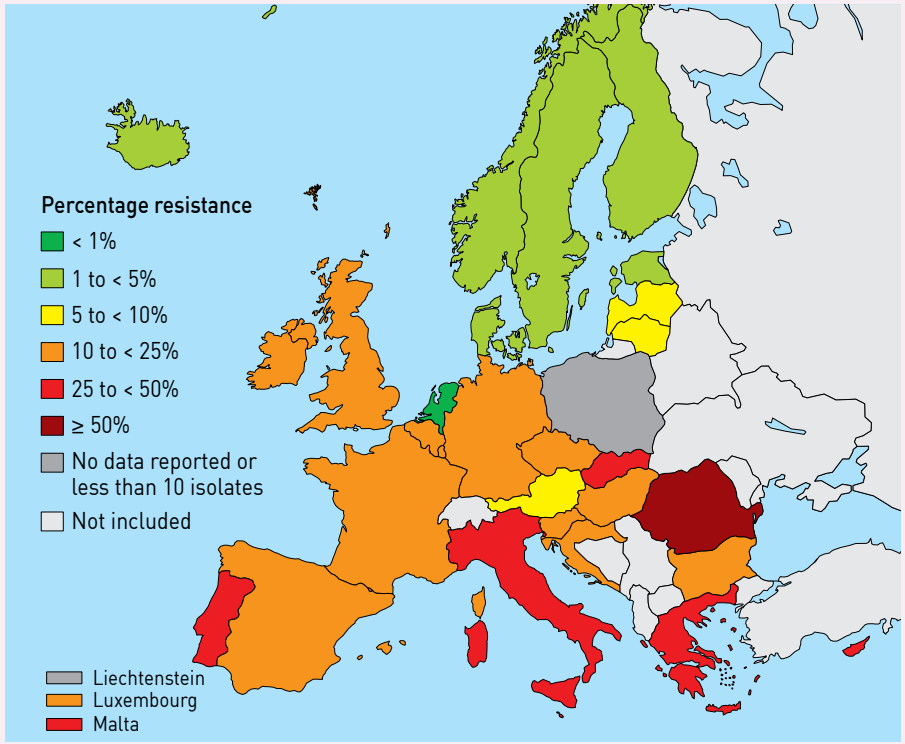


***Figure 2** - Proportion of MRSA human isolates in Europe in 2014 (source: European Centre for Disease Prevention and Control, ECDC).*

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It is therefore not surprising that the two main risk factors for infection or colonisation with antibiotic resistant bacteria in animals are contact with veterinary environments and multiple antibiotic courses. Studies of antimicrobial use in veterinary practices show that some 25% of dogs and 17% of horses receive antimicrobials, with broad-spectrum drugs the most commonly prescribed antimicrobials in both species. Systemic antimicrobial treatment in dogs increases the prevalence of antimicrobial resistance among commensal staphylococci and *E. coli*, and the effects generally last for three months after the end of treatment (Figure 3). However the evidence that specific antimicrobials particularly select for resistance is less clear.

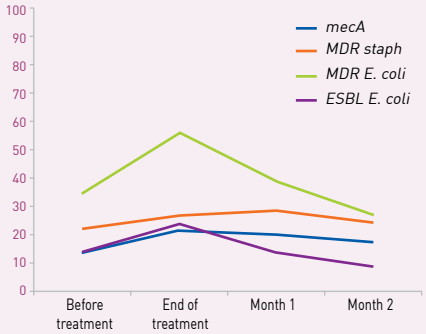

Figure 3 *- Prevalence of antimicrobial resistance (%) among commensal staphylococci and E. coli in dogs treated with systemic antibiotics (MDR, mecA, ESBL). Data from Dr Vanessa Schmidt and Dr Nicola Williams, The University of Liverpool School of Veterinary Science.*

Where do animals become colonised and infected?

Antibiotic resistance genes are natural and widespread in the environment. Antibiotic resistant bacteria can also be isolated from healthy animals in the community. For example, nearly 40% of healthy horses and 18-29% of healthy dogs carry MDR *E. coli*, and 29% of horses and 6-40% of dogs carry meticillin-resistant coagulase-negative staphylococci (MR-CoNS). The clinical significance of these isolates is uncertain; they are rarely isolated from infections although they may act as reservoirs of resistance genes.

Clinically significant antimicrobial resistant bacteria are much less common in healthy community based animals. ESBL *E. coli* are only carried by 6.3% of horses and 4% of dogs, and AmpC *E. coli*, MRSA and MRSP by less than 1% of animals. Colonisation with antimicrobial resistant bacteria increases with veterinary contact, particularly hospitalisation, surgery and systemic antimicrobials. Animals that have had multiple antibiotic courses and/or have post-operative or nosocomial (healthcare-associated) infections are significantly more likely to have antimicrobial resistant infections than animals with community acquired wounds and infections.

Studies have shown that 7-13% of veterinary staff are colonised with meticillin-resistant staphylococci, and that these isolates reflect their area of work. Meticillin-resistant staphylococci can also be isolated from up to 10% of environmental samples in veterinary practices, particularly hand touch sites, and ESBL and AmpC *E. coli* can be isolated from 5-10% of ward floor, table and keyboard samples.

It is therefore likely that most colonisation and infection with antibiotic resistant bacteria is associated with veterinary contact and treatment. The risks of this can be reduced by adopting responsible antimicrobial use policies and adhering to strict infection control.

Key professional responsibilities

Veterinarians must exercise greater antimicrobial stewardship. Recent studies found that only 3.5% of small animal practices and 0.8% of equine practices in the UK had an antimicrobial use policy. These are key to helping veterinarians use these drugs less often and more effectively, thereby preserving their efficacy for the future. A variety of antimicrobial use guidelines have been produced (see further resources) for practice use. Similarly, improving hand hygiene and infection control measures have reduced colonisation and infection rates in human and veterinary healthcare. It is essential that veterinary practices adopt and adhere to strict infection control guidelines. Guidance to help veterinary practices develop their infection control measures is available from several sources (see further resources). Regular clinical audit to monitor trends in antimicrobial resistance and hospital acquired infections is vital in identifying potential problems in infection control and improving measures to counter these.

Regular clinical audit is essential to monitor trends in antimicrobial resistance and identify potential problems.

Responsible antimicrobial use is now considered a professional responsibility by the UK Royal College of Veterinary Surgeons (RCVS). Effective infection control is also a key part of the RCVS Practice Standards Scheme. While most

RELEVANCE OF MULTIDRUG-RESISTANT INFECTIONS FOR THE VETERINARY PROFESSIONAL

practices will encounter occasional antimicrobial resistant infections, wound breakdowns, and/or hospital acquired infections it is unlikely that these would be regarded as negligent provided that appropriate measures have been taken and adherence to these can be documented.

However, practices that do not adopt appropriate antimicrobial use guidelines and infection control measures or that cannot document this could be considered negligent with all the consequences that this entails. ■

Antibiotic resistance is a clear threat to modern veterinary healthcare. New drugs are not the answer; if we do not learn to use antimicrobials more wisely we will at best merely push the problem forward for a few years. We can help by improving infection control, reducing antimicrobial use, and using these drugs more effectively. We should encourage owners to expect less antibiotic treatment and to follow instructions carefully when they are prescribed. Finally, we can work with policy makers to develop effective guidelines and regulation to further responsible antimicrobial use without compromising animal welfare.

Further resources for antimicrobial stewardship and infection control

- *British Veterinary Association - www.bva.co.uk/public/documents/bva_antimicrobials_poster.pdf*
- *British Small Animal Veterinary Association - www.bsava.com/Advice/PracticePack/PROTECTPoster/tabid/1500/Default.aspx www.bsava.com/Resources/MRSA.aspx*
- *British Equine Veterinary Association - www.beva.org.uk/useful-info/Vets/Guidance/AMR*
- *Responsible Use of Medicines in Agriculture (RUMA) - www.ruma.org.uk*
- *Federation of European Companion Animal Veterinary Associations (FECAVA) - www.fecava.org*
- *International Society for Companion Animal Infectious Diseases (ISCAID) – www.iscaid.org*
- *Bella Moss Foundation - www.thebellamossfoundation.com*
- *Infection control guidelines - www.thebellamossfoundation.com/practice-guidelines/*
- *Antibiotic treatment support materials and other resources - www.itsinfectious.co.uk*
- *Antibiotic Action and Antibiotic Guardian campaigns - http://antibiotic-action.com/ and http://antibioticguardian.com/*

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TABLES COMPARING EXISTING GUIDELINES

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)	France (AFVAC)	International (ISCAID)	Vet. Rec. 2013
Skin and ear disorders							
Superficial pyoderma	Cytology, Culture & sensitivity testing if possible. Topical AS (chlorhexidine...). Topical AB (fusidic acid, SF). Systemic ABs (different according to countries). 1st choice: 1GC (cefalexin, cefadroxil), amoxi-clav, TMPS, clinda. 2nd choice: FQ (enro, marbo, prado...), aminosides, TC (doxy). No consensus on 3GC (cefovecin). AB reserved for human medicine: not recommended. In case of MRSA or MRSI: alternative AS, fusidic acid...	Cyto, C&ST if possible. Clinda, or cefalexin or TMPS.	Topical AS: chlorhexidine. Topical AB, fusidic acid, SF. General antibiotherapy: amoxi-clav, cefalexin, cefadroxil, clinda, cefovecin (if compliance problems). FQ (2nd intention). MRSA, MRSI: depending on C&ST or chlorhexidine, fusidic acid, doxy, TMPS.	Cyto, C&ST if possible. Topical AS generally suffice for superficial pyoderma 1. Clinda. 2. Cefalexin (cefadroxil), amoxi-clav, TMPS, doxy.	C&ST in case of failure 1. Topical AS (shampoo). 2. Amoxi-clav, cefalexin (BID) or fusidic acid. 3. Clinda or TMPS	**1st choice:** Lincosamides (clinda or linco). 1GC (cefalexin, cefadroxil). Amoxi-clav. **1st or 2nd choice:** (no consensus). 3GC (cefovecin, cefpodoxime). **2nd choice:** (after 1st choice and C&ST). Tetracyclines (doxy), chloramphenicol, FQ (enro, marbo, orbi, pradofloxaxin), aminosides (genta or amikacin), ± TMPS, ± lincosamides (clinda). **3rd choice:** (if 1st and 2nd choice inappropriate and after C&ST). AB reserved for human medicine: linezolide, teicoplanin, vancomycin.	**1st choice:** 1GC (cefalexin, cefadroxil). Amoxi-clav Lincosamides (clinda or lincomycin). 3GC (cefovecin, cefpodoxime) can be 1st choice AB if administration proves difficult. **2nd choice:** FQ (enro, marbo, orbi, pradofloxaxin) or 3GC (cefovecin, cefpodoxime). **3rd choice:** aminosides, azithro, clarithro, ceftazidime, chloramphenicol, florfenicol, thiamphenicol, rifampicin, piperacillin, ticarcillin, imipenem.
Deep pyoderma		Cyto, C&ST. Cefalexin (while awaiting C&ST results).		Cyto + C&ST. 1. Clinda. 2. Cefalexin (cefadroxil), amoxi-clav, TMPS, doxy, 3. FQ or 3GC (cefovecin).	Topical AS + Amoxi-clav, cefalexin (BID), fusidic acid, clinda or TMPS. In case of failure and after C&ST, FQ.		

TABLES COMPARING EXISTING GUIDELINES

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)	France (AFVAC)	International (ISCAID)	Vet. Rec. 2013
Skin and ear disorders							
Wound, abscess, soft tissue infection	Cleaning and disinfection of wounds, in general without topical AB. Systemic ABs not recommended if no general clinical signs (fever) or severe infection. AB if necessary: see above.	Cyto (+ C&ST in case of surgical complication and/or suspicion of ESBL, MRSA, MRSI). Topical AB not routinely recommended. Cleaning and disinfection of the wounds. In case of fever or severe infection, systemic AB.	Amoxi-clav. or 1GC (cefalexin) or FQ (2nd choice).	As above (deep pyoderma) if AB necessary.			
Otitis externa	No systemic ABs. Topical AS or AB If cocci: fusidic acid or other. If bacilli: polymyxin B, FQ, or aminosides (genta). Anti-*Malassezia* ttm+ corticoids.	Cyto without C&ST. Systemic ABs not needed. Topical AS or fusidic acid (cocci), or polymyxin B (bacilli). Anti-*Malassezia* ttm+ corticoids.	Ceruminous otitis: Topical: fusidic acid, framycetin, genta; marbo, orbi, polymyxin B, miconazole + cleaning. Suppurative otitis: Topical: FQ or aminoside.	Cyto + C&ST if possible. Otitis due to cocci (or mixed infections): Fusidic acid and framycetin, or genta. Otitis due to bacilli (except *Pseudomonas*): polymyxin B, genta or marbo. *Pseudomonas*: idem + FQ or genta by systemic route if severe infection.			

TABLES COMPARING EXISTING GUIDELINES

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)	France (AFVAC)	International (ISCAID)	Vet. Rec. 2013
Skin and ear disorders							
Systemic AB not recommended		Wounds with granulation tissue. Deep or superficial pyoderma. Hyperseborrheic skin disorder, Otitis externa, Uncomplicated wounds and lesions. Cat-bite abscess.	Skin surgery (mass excision) without major reconstruction. Dermatitis due to *Malassezia*, pruritus, desquamation, nodules, crusts.				
Urinary disorders							
Lower urinary tract infection (cystitis or UTI)	Cyto + C&ST (if recurrence). Amoxi-clav or TMPS Cat: non-infectious UTI: AB not recommended (or after C&ST).	Cyto + C&ST (if recurrence). Amoxi-clav or TMPS (while awaiting C&ST results).	Cystitis Cat/Dog: Amoxi-clav or TMPS. UTI often not infectious in cats. Struvite dogs: Amoxi-clav or TMPS.	Cyto + C&ST. Cat/Dog: Amoxi or TMPS (while awaiting C&ST results).	Dogs (no C&ST if uncomplicated): amoxi-clav, cefalexin or TMPS. Cats according to C&ST.	Amoxi or TMPS (while awaiting C&ST results if complicated infection).	
Upper urinary tract infection, Pyelonephritis	Cyto + C&ST (cystocentesis). Amoxi-clav, TMPS or FQ while awaiting C&ST results. In case of general signs, see sepsis.	Cyto + C&ST (cystocentesis). Amoxi-clav or FQ while awaiting C&ST results. In case of general signs, see sepsis.	TMPS (and C&ST in chronic cases). Suspicion of *Leptospira*: ampi, amoxi, peni G, doxy.	Cyto + C&ST (cystocentesis). Amoxi-clav or FQ while awaiting C&ST results.	Cyto + C&ST (cystocentesis). Amoxi-clav, FQ, TMPS, nitrofurans.	Pyelonephritis: FQ while awaiting C&ST results.	
Subclinical bacteria, Urinary catheterism	No ABs recommended if no clinical signs.				Antibiotic prevention in case of catheter is contra-indicated.	AB not recommended.	
Systemic AB not recommended		Feline urolithiasis.	Urinary incontinence. Feline urolithiasis. Metabolic disease (polyuria/polydipsia...).				

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TABLES COMPARING EXISTING GUIDELINES

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)	France (AFVAC)	International (ISCAID)
Genital disorders						
Orchitis and epididymitis	Castration. Amoxi-clav or TMPS.			Castration. Amoxi-clav or TMPS. (+ Brucellosis serology).		
Prostatitis	C&ST if possible. FQ or TMPS + Castration.		FQ or TMPS. + C&ST in chronic cases	C&ST if possible. Enro or TMPS + Castration.	FQ, TMPS.	FQ, TMPS.
Mastitis	C&ST if possible. Amoxi, amoxi-clav or TMPS.		Amoxi-clav. or TMPS.	C&ST if possible. Amoxi.		
Acute metritis	C&ST if possible. In case of general signs: amoxi-clav or TMPS.		In case of general signs: amoxi-clav or TMPS.	C&ST if possible. In case of general signs: amoxi-clav or TMPS.		
Endometritis	C&ST if possible. 1. TMPS or amoxi-clav 2. FQ.		Amoxi-clav or TMPS.	C&ST if possible. 1. TMPS 2. Enro		
Pyometra	Medical treatment (aglepristone and Pg) and in severe cases: TMPS or FQ. Surgical treatment with perioperative AB.	Surgical treatment. In severe cases, FQ.	Amoxi-clav or TMPS.	Medical treatment (aglepristone and Pg) and in severe cases: TMPS or enro. Surgical treatment with perioperative AB (ampicillin IV).		
Systemic AB not recommended		Juvenile vaginitis, Balanoposthitis, Prostatic hyperplasia (or cysts).				

TABLES COMPARING EXISTING GUIDELINES

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Respiratory diseases				
Rhinitis	AB not recommended. Except chronic purulent rhinitis: doxy or amoxi/ amoxi-clav.	AB not recommended. Except chronic purulent rhinitis: (doxy). No C&ST, but look for the (non infectious) cause of the chronic purulent rhinitis.	Amoxi-clav.	If necessary 1. Doxy. 2. Amoxi.
Acute bronchitis	No AB unless fever. In case of complication: doxy or amoxi-clav. In case of mycoplasm: doxy.	AB not recommended. No C&ST (commensal flora).	In severe cases: amoxi-clav, doxy or OTC. In case of mycoplasm: azithro, doxy or OTC (dogs).	AB if complication (fever): 1. doxy (active against mycoplasm). 2. Amoxi.
Pneumonia	C&ST is difficult (BAL). Amoxi-clav/ ampi IV route (or cefalexin, doxy...) ± metronid. In severe cases (large spectrum): FQ + Peni G/ amoxi/ ampi (IV route).	No C&ST (sampling is difficult, BAL). Doxy, cefalexin, amoxi-clav (TID). In severe cases: FQ + Peni G/ amoxi/ ampi (IV route).	Dog: aminosides + metronid, amoxi + FQ, amoxi + metronid, doxy or OTC Cat: amoxi-clav or doxy.	C&ST recommended. 1. Amoxi-clav (or ampi IV route). 2. FQ (enro) + ampi (IV route).

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Respiratory diseases				
Pyothorax	Cyto + C&ST (thoracocentesis). Drainage and lavage of the pyothorax. In case of cocci: amoxi-clav (or ampi IV) or other. In case of bacilli, FQ (while waiting for the C&ST results). Association to large spectrum AB (FQ +...) while waiting for the C&ST results.	Cyto + C&ST (thoracocentesis). Drainage and lavage of the pyothorax. In case of cocci: amoxi-clav q8 hours. In case of bacilli FQ (while waiting for the C&ST results).	Dog: Ampi + FQ, clinda + FQ, metronid + FQ. Cat: Amoxi-clav.	Cyto + C&ST (thoracocentesis). Drainage and lavage of the pyothorax. FQ (enro) + Ampi (IV route).
Systemic AB not recommended		Kennel cough, Chronic bronchitis, Viral disease, viral rhinitis and cat flu.		

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Digestive, hepatic and oral diseases				
Oral infection (gingivitis, stomatitis, periodontitis)	No AB. In case of systemic signs (fever…): clinda, spira + metronid, ampi/ amoxi/ amoxi-clav.	No AB. In case of systemic signs (fever…): clinda.	Ampi, amoxi, amoxi-clav. clinda, spira + metronid.	No AB. C&ST recommended in case of AB therapy. In case of systemic signs (fever…): clinda (second choice: amoxi/clav).
Gastro-enteritis	No AB if no clinical signs (see sepsis). Specific gastro-enteritis (culture). *Campylob*: macrolides (FQ ?). *Cl. difficile*: metronid. *Cl. perfringens*: tylo or metronid. *Salm.* after C&ST. Gastritis resistant to other treatments (*Helicobacter*): omeprazole, amoxi + metro (or clarithro).	No AB if no clinical signs (see sepsis). C&ST if suspicion of *Salm.* or *Campylob.* or toxigenic *Clost.*	Acute complicated diarrhoea: amoxi-clav or cefalexin. Gastro-enteritis with blood: metronid + (amoxi-clav or cefalexin) ± FQ or aminosides against Gram negative agents. *Campylob.*: enro or erythro. *Helicobacter* gastritis: amoxi + metronid, azithro + tindizole, clarithro + metronid (+ antiulcer treatment).	No AB unless C&ST. C&ST if suspicion of *Salm.* or *Campylob.* or toxigenic *Clost.* *Campylob*: erythro or tylo. *Cl. difficile*: metronid. *Cl. perfringens*: tylo or metronid. *Salm.* after C&ST. Gastritis resistant to other treatments: omeprazole, amoxi + metronid (or clarithro).

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Digestive, hepatic and oral diseases				
Chronic enteropathy	Prednisolone alone. If necessary: association with tylo (or failing that, TC or metronid).		Prednisolone alone. If necessary: association with tylo (or failing that, TC or metronid).	Prednisolone alone. If necessary: association with tylo (or failing that, TC or metronid).
Anal gland abscess	No systemic AB. In case of severe infection: cyto + C&ST + TMPS or amoxi-clav while waiting for the C&ST results.	No AB. In case of severe infection: cyto + C&ST + TMPS (while waiting for the C&ST results).	Topical treatment. Amoxi-clav.	No AB. In case of severe infection: cyto + C&ST + TMPS (while waiting for the C&ST results).
Liver infection (cholecystitis, cholangitis, cholangio-hepatitis)	Cyto + C&ST (if possible, biopsy or FNA). Ampi/ amoxi/ amoxi-clav/ cefalexin or doxy.	Cyto + C&ST (if possible, biopsy or FNA). Doxy or cefalexin.	Ampi, amoxi, amoxi-clav. cefalexin, metronid.	Cyto + C&ST (if possible, biopsy or FNA). Doxy or cefalexin.

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Digestives, hepatic and oral diseases				
Systemic AB not recommended		Chronic inflammatory enteropathy. Anal sacculitis without abscess. Parodontal disease. Viral gastroenteritis (parvo), Gastroenteritis due to *Salmonella*, *Campylobacter* or *Cl. difficile*. Routine dental descale.	Acute diarrhoea or vomiting, Chronic gastroenteritis.	

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Sepsis and general diseases				
Peritonitis	Cyto + C&ST (paracentesis). While waiting for the C&ST results, large spectrum: FQ + ß-lactams/ clinda/ metronid (if anaerobes).	Cyto + C&ST (paracentesis). FQ + Peni G/ amoxi/ ampi (IV) while waiting for the C&ST results.	Amoxi-clav, ampi + FQ or genta or cefotaxime, Or clinda + enro. + metronid if anaerobes suspected.	
Sepsis	Cyto + C&ST (several blood samples). While waiting for the C&ST results, large spectrum: FQ + ß-lactams/ clinda.	Cyto + C&ST on several blood samples. FQ + Peni G/ amoxi/ ampi (IV) while waiting for the C&ST results.	Amoxi-clav + FQ, ampi + FQ or genta or cefotaxime, clinda + enro.	Cyto + C&ST on several blood samples. Enro + ampi (IV) while waiting for the C&ST results.
Neutropenia	See UK.		Mild neutropenia: No AB. Severe neutropenia without clinical signs: TMPS. Severe neutropenia with clinical signs: 1GC (cefalexin) + FQ.	
Endocarditis	See UK.		Amoxi-clav + enro or amoxi-clav + metronid.	

TABLES COMPARING EXISTING GUIDELINES

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Sepsis and general diseases				
Vector-borne diseases	Hemobartonellosis: doxy or FQ. *Anaplasma* spp.: 1. doxy; 2. rifampicin or enro Ehrlichiosis: 1. doxy; 2. imidocarb. Borreliosis: 1. doxy; 2. amoxi.		Hemobartonellosis: doxy or FQ.	*Anaplasma* spp.: 1. doxy; 2. rifampicin or enro. Ehrlichiosis: 1. doxy; 2. imidocarb. Borreliosis: 1. doxy; 2. amoxi.
Systemic AB not recommended		Healthy animals without contact to sick animals. Viral disease (FeLV, FIV...) or non-infectious disease.	Cardiovascular disease. Metabolic disease (polyuropolydipsia, weight loss).	

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Eye diseases				
Conjunctivitis	No systemic AB Topical AS or AB. Cat, if *Chlamydophila*: doxy (± FQ).		Topical cloxacillin, fusidic acid, genta. Cat, if *Chlamydophila*, doxy or enro.	Topical. Cat, if *Chlamydophila*, doxy.
Blepharitis, non-ulcerative keratitis	No systemic AB. See Denmark.			Topical. 1. Fusidic acid. 2. Chloram-phenicol.
Dacryocystitis	No systemic AB. See Denmark.			If necessary, chloramphenicol eye drops.
Corneal ulcer	See Denmark.			If ulcer with risk of perforation: chloramphenicol (drops) + amoxi-clav (per os). Melting ulcers: FQ (cipro) and amoxi-clav per os.
Uveitis	See Denmark.			AB if necessary (depending on diagnosis). Chloramphenicol eye drops.
Retrobulbar and eye infection	See Denmark.			C&ST recommended Clinda while waiting for the C&ST results.

TABLES COMPARING EXISTING GUIDELINES

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Bone and joint diseases				
Septic arthritis	Cyto + C&ST (FNA of the synovial fluid or biopsy). Joint lavage. Clinda, or cefalexin, or amoxi-clav.	Cyto + C&ST (FNA of the synovial fluid or biopsy). Joint lavage. Clinda, or cefalexin, or amoxi-clav (TID).	Amoxi-clav or 1GC (cefalexin).	Cyto + C&ST (FNA of the synovial fluid or biopsy). Joint lavage. Clinda, or cefalexin, or amoxi-clav.
Osteomyelitis	X-ray and C&ST (bone biopsy). Look for the underlying cause (e.g. implant...). Clinda, amoxi-clav, cefalexin while waiting for the C&ST results.	X-ray and C&ST (bone biopsy). Look for the underlying cause (e.g. implant...). Clinda while waiting for the C&ST results.	Amoxi-clav or 1GC (cefalexin).	X-ray and C&ST (bone biopsy). Look for the underlying cause (e.g. implant...). Clinda while waiting for the C&ST results.

Disorder	Summary	Europe (FECAVA)	UK (BSAVA)	Denmark (SvHKS)
Surgery				
Surgery not requiring perioperative AB	Risk ASA 1-2 with clean surgery: No antibiotics. Examples: Routine dental descale, castration, caesarean section, laparotomy, fxcision of non-infected tumours, clean (non-infected) orthopaedic surgery < 90 min, reconstructive skin surgery on healthy tissue, neurosurgery.	Routine dental descale, caesarean section, laparotomy, excision of non-infected tumours, clean (non-infected) orthopaedic surgery < 90 min, reconstructive skin surgery on healthy tissue, neurosurgery.	Routine surgical castration, skin surgery (mass excision) without major reconstruction	Risk ASA 1-2 with clean surgery: No antibiotic prophylaxis.
Perioperative AB	AB required if: Animal already infected, immunodepressed, long surgery (> 90 min), involving an implant or dental disease. 1. Amoxi-clav/ampi (IV), cefalexin. 2. Digestive or uterine surgery: FQ or genta. 3. Parodontal disease: metronid.		Most commonly: amoxi-clav or 1GC (cefalexin), IV route. AB required if: long surgery (> 90 min), involving an implant, sick or immunodepressed animal, digestive surgery (genta or FQ), parodontal disease or dental surgery (+ metronid), infected wounds or pre-existing infection.	Only if risk ASA ≥ 3 or infected wounds, general infection, orthopaedic surgery. If risk of skin infection (*Staph* and *Pasteurella*): cefazolin (IV). If risk of infection via the digestive tract or the uterus (enterobact., enterococci, anaerobes): ampicillin (IV).

PART 4
APPENDICES

Classifications and drug index

Principal pharmacological parameters of antibiotics

ANTIBIOTICS	Distribution					Elimination	Use during pregnancy[4]
	Skin[1]	Lungs[2]	Secretions	Bone	CSF[3]	Main pathway	
Amoxicillin ± clavulanate	++	++	++	++	+++ If infl.	Urinary	Yes
Ampicillin	++	++	++	+	+++ If infl.	Urinary	Yes
Cefalexin	++	++	+	++	+++ If infl.	Urinary	Yes
Cefovecin*	++	++	++	++	+++ If infl.	Urinary	Yes
Clindamycin	+++	+	+++	+++	+	Urinary	Yes
Doxycycline	++	++	++	++	-	Mixed	No
Fluoro-quinolones*	+++	+++	+++	+++	+++	Urinary	No
Gentamicin	-	+/-	+/-	+	-	Urinary	No
Metronidazole	+	+	+++	++	+++	Mixed	With precautions
Spiramycin	+	++	+++	+++	++	Biliary	Yes
Tetracycline Oxytetracycline	++	++	++	++	-	Mixed	No
Trimethoprim - sulfonamides	++	++	+++	+	+++	Urinary	No

If infl.: in case of inflammation

** In bold: critically important antibiotics.*

Notes:
1. Note that tissue diffusion in the skin is poor in case of abscesses.
2. Lungs and other well-irrigated tissue.
3. Cerebrospinal fluid.
4. Based on information established in human medicine and the benefit/risk ratio for veterinary medicine.

Antibacterial spectrum of activity of selected antibiotics

	Aerobic bacteria		Anaerobic bacteria		
Spectrum	Gram +	Gram -	Gram +	Gram -	Examples
Very broad					Chloramphenicol
Very broad					3rd generation fluoroquinolones
Very broad					3rd and 4th generation cephalosporins
Very broad					Tetracyclines
Broad					Ampicillin, amoxicillin (± clavulanate)
Broad					1st generation cephalosporins
Broad					Trimethoprim - sulfonamides
Intermediate					Aminoglycosides
Intermediate					Macrolides, lincosamides
Narrow					Penicillins G (or M)
Narrow					Nitroimidazoles (metronidazole)
Narrow					Colistin

For more information, see recommendation R.13.

Excellent activity
Moderate activity
Limited activity
No or negligible activity

Classifications and drug index

Categorization of systemic antibiotics

Use category	Definition and guidance for use	Examples
Primary/ 1st line Licensed for companion animals	• 1st line antibiotics are antibiotics that are well established with good evidence of high efficacy and safety. Ideally, they should be narrow-spectrum. They are as potent as 2nd and 3rd line drugs used in the appropriate circumstances. • They should be used wherever appropriate and possible.	• Penicillins • 1st generation cephalosporins • Amoxicillin±clavulanate • Trimethoprim sulfonamides • Tetracyclines • Lincosamides
Secondary/ 2nd line Licensed for companion animals	• 2nd line antibiotics are often broad-spectrum antibiotics that are important for animal and human health, and in which resistance is more likely to occur following use and/or is of greater concern in veterinary and human healthcare. • Critically important antibiotics should only be used where C&AST results or good clinical and epidemiological evidence indicate that 1st line antibiotics will not be effective. Wherever possible, the use of 2nd line drugs should be supported by C&AST. • Some antibiotics are classified as 2nd line due to their toxicity, but not due to their activity (e.g. aminoglycosides).	**Narrow spectrum:** • Aminoglycosides • Metronidazole • Macrolides **Broad spectrum:** • Chloramphenicol **Critically important ABs:** • Fluoroquinolones • Cefovecin (3GC)

For more information, see recommendation R.17.

Use category	Definition and guidance for use	Examples
Tertiary/ 3rd line	• 3rd line antibiotics are antibiotics that are of great importance to animal and human health especially for the treatment of multidrug resistant bacteria, and where resistance is more likely to occur following use and/or is of great concern in veterinary and human healthcare. Many of these drugs are not licensed for companion animals, and therefore data on clinical break points, efficacy and safety may be lacking. • They must only be used where there is culture evidence to show that 1st or 2nd line antibiotics will not be effective and where topical therapy has been ineffective or is not feasible. • The use of 3rd line drugs must be supported by AST, although these drugs may be started in life-threatening conditions while waiting for the culture results.	• 3rd and 4th generation cephalosporins other than cefovecin • Rifampicin • Fosfomycin
Restricted, voluntarily prohibited	• These drugs are vitally important to human health so should never be used in animals.	• Glycopeptides: vancomycin, teicoplanin • Carbapenems and monobactams • Oxazolidones: lineazolid • Lipopeptides: daptomycin • Riminofenazines: clofazime

For more information, see recommendation R.17.

Classifications and drug index

Index of the main antibiotics available in companion animal medicine

Family	Antibiotic	Dosage forms (companion animals)	Special warnings/ Recommendations in specific conditions
ß-lactams Penicillin G	Benzylpenicillin	Injectable solution (IM)	Risk of ß-lactam allergy.
	Benzylpenicillin + dihydrostreptomycin	Inj. sol. (IM/SC)	
ß-lactams Amino-penicillins	Ampicillin	Tablets, Inj sol. (IM/SC)	Risk of ß-lactam allergy.
	Amoxicillin		
	Amoxicillin + clavulanate	Tablets Inj sol. (SC)	Risk of ß-lactam allergy. Adding clavulanate (ß-lactamase inhibitor) is justified in case of ß-lactamase producing pathogens.
ß-lactams 1st generation cephalosporins (1GC)	Cefalexin	Tablets, Inj sol. (IM)	Risk of ß-lactam allergy.
ß-lactams 3rd generation cephalosporins (3GC)*	**Cefovecin**	Inj. sol. (SC)	Risk of ß-lactam allergy. **Critical antibiotic.**
Sulfonamides +/- diamino-pyrimidines	Trimethoprim sulfonamides	Tablets, Inj. sol. (IV, IM, SC)	Risk of keratoconjunctivitis sicca (KCS) and nephrotoxicity. Schirmer tear testing is recommended if use > 3 weeks.

** In bold: critically important antibiotics.*

Family	Antibiotic	Dosage forms (companion animals)	Special warnings/ Recommendations in specific conditions
Fluoro-quinolones*	**Enrofloxacin**	Tablets, Inj. sol. (SC)	Risk of cartilage alterations in growing dogs (in particular large and giant breeds) Risk of retinal toxicity in cats in case of overdosage. **Critical antibiotics.**
	Marbofloxacin	Tablets, Inj. sol. (SC, IV)	Risk of cartilage alterations in growing dogs (in particular large and giant breeds). **Critical antibiotics.**
	Pradofloxacin	Tablets, oral solution	
Tetracyclines	Doxycycline	Tablets	Risk of calcium binding in teeth and bone.
Macrolides (+ nitro-imidazoles)	Spiramycin + dimetridazole	Tablets	See metronidazole.
	Spiramycin + metronidazole	Tablets	
Lincosamides	Clindamycin	Tablets, Capsules, Oral solution.	
Nitro-imidazoles	Metronidazole	Tablets	Risk of liver toxicity or central nervous system toxicity in case of overdosage.
Amino-glycosides	Gentamicin	Inj. sol.	Risk of kidney toxicity if administered by injection.
	Neomycin	Capsules	
	Framycetin (+ sulfaguanidine)	Tablets	

For more information, see the Synopsis chapters.

** In bold: critically important antibiotics.*

Classifications and drug index

Classification of antibiotics according to their mechanism of action

Bactericidal antibiotics		Bacteriostatic antibiotics
Concentration-dependent	**Time-dependent**	**Time-dependent**
Aminoglycosides Fluoroquinolones Colistin	Penicillins Cephalosporins Nitro-imidazoles	Macrolides Lincosamides Tetracyclines Sulfonamides Diaminopyrimidines Phenicoles

For more information, see the Synopsis chapters.

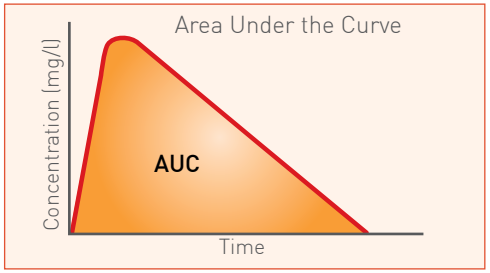
Classification of bacteria according to their GRAM staining

GRAM positive	GRAM negative	Bacteria that cannot be stained by Gram*
Aerobic organisms *Corynebacterium* spp. *Listeria* spp. *Staphylococcus* spp. *Streptococcus* spp. **Anaerobic organisms*** *Actinomyces* spp. *Bacteroides* spp. *Clostridium* spp. *Fusobacterium* spp.	**Aerobic organisms** *Bordetella* spp. *Brucella* spp. *Campylobacter* spp. *Escherichia coli* *Haemophilus* spp. *Klebsiella* spp. *Leptospira* spp. *Neisseria* spp. *Pasteurella* spp. *Pseudomonas* spp. *Salmonella* spp. **Anaerobic organisms*** *Borrelia* **Intracelullar organisms*** *Ehrlichia*	*Mycoplasma* **Intracelullar organisms*** *Rickettsia* *Chlamydia*

** In order to be identified by the laboratory, these bacteria generally require specific sampling, transport and culture conditions.*

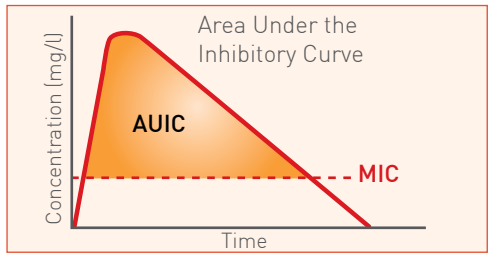
Glossary

1GC	1st generation cephalosporins (e.g. cefalexin, cefadroxyl)
3GC	3rd generation cephalosporins (e.g. cefovecin)
AB	Antibiotic(s) (synonym: antimicrobial)
ADM	Agar Dilution Method
AM	Antimicrobial (synonym: antibiotic)
AMK	Amikacin
Amoxi-clav / AMC	Amoxicillin + clavulanate
Amoxi / AMX	Amoxicillin
Ampi / AMP	Ampicillin
AMR	Antimicrobial resistance
AMS	Antimicrobial susceptibility
AMT	Antimicrobial therapy
AMU	Antimicrobial use
AS	Antiseptics
ASA	American Society of Anesthesiologists, which defined a widely used classification of anaesthetic risk
AST	Antibiotic Susceptibility/Sensitivity Testing
AUC	Area Under the Curve: the area under the plasma or blood concentration-time curve, i.e. the total drug expose over time. It is proportional to the amount of active substance absorbed. It is expressed in µg x h / ml or µg /ml x h.



AUC_{24h}	AUC for the first 24 hours.
AUC_{IV}, AUC_{IM}, AUC_{SC}, AUC_{oral}	These are the AUC obtained depending on the route of administration (see next page for the calculation of the bioavailability).

AUIC	Area Under the Inhibitory Curve: the part of the AUC for which the plasma concentration is above the MIC of the target pathogen. AUIC = AUC/MIC. For bactericidal concentration-dependent antibiotics the AUIC ratio should be at least 125, which corresponds to maintaining plasma concentrations five times higher than the MIC for 24 hours.

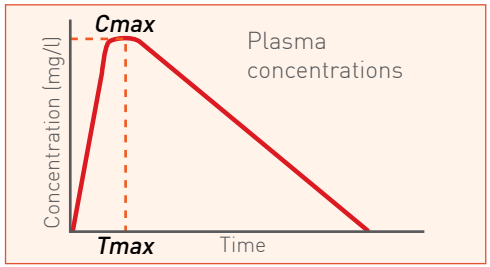


Azithro	Azithromycin
B. fragilis	*Bacteroides fragilis*
BALF	Bronchoalveolar Lavage Fluid
BID	Twice daily (*bis in die*)
Bioavailability	Amount (or fraction F, in %) of an administered dose of drug that reaches the systemic circulation. By definition, if a medication is administered intravenously, its bioavailability is 100%. Bioavailability is calculated by the AUC between two subsequent administrations. Absolute bioavailability is compared to the AUC for IV administration, e.g. AUC_{IM}/AUC_{IV}. Relative bioavailability compares the AUC to that of another, non-intravenous route, e.g. $AUC_{oral\ sol.}/AUC_{tablet}$. The relative bioavailability between two similar galenic forms is sometimes based on the Cmax rather than the AUC, e.g. $Cmax_{oral\ sol.}/Cmax_{tablet}$. Bioavailability also covers the speed with which the drug reaches the blood (see Cmax and Tmax).
(Clinical) breakpoints	Breakpoint: the concentration of an antibiotic which defines whether a species of bacteria is susceptible or resistant to the antibiotic. If the MIC is less than or equal to the susceptibility breakpoint the bacteria is considered susceptible to the antibiotic. If the MIC is greater than this value the bacteria is considered intermediate or resistant to the antibiotic. For the results of antibiotic sensitivity testing to be predictive of the therapeutic outcome, clinical breakpoints have been established according to dosages, pharmacokinetic data,

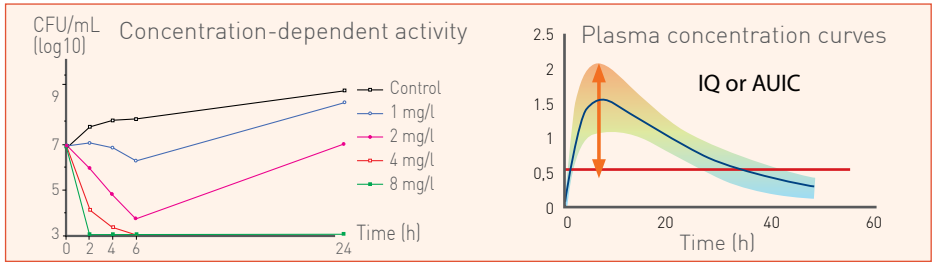
Glossary

	resistance mechanisms, MIC distributions, zone diameter distributions and pharmacodynamics and epidemiological cut-off values (ECOFFs).
C. difficile	*Clostridium difficile*
C&(A)ST	Culture and (Antibiotic) Sensitivity/Susceptibility Testing
CA	Companion Animals
Cascade use	Use outside the indications or target species as approved in the SPC
CEF	Cefalotin
CFF	Ceftiofur
CFO	Cefovecin
CFU	Colony Forming Units: the number of identified colonies, and is a measure of viable bacterial cells in the sample. Results are given as CFU/ml for liquid, CFU/g for solid samples.
CFZ	Cefazolin
CHL	Chloramphenicol
CIA	Critically Important Antibiotic. See also recommendation R.16.
CIP /Cipro	Ciprofloxacin
CKD	Chronic Kidney Disease
Cl	Clearance: the volume of plasma completely cleared of a substance (antibiotic), per unit of time. The unit is ml/min. Total body clearance is expressed in ml/min/kg. For a substance to be cleared completely after its first passage in the circulation, the clearance value equals that of the cardiac flow, which is the maximum clearance value. Different organs can eliminate the antibiotic, allowing the calculation of several difference clearance types: plasma clearance (formerly: body or total clearance), renal clearance, hepatic clearance. Renal clearance (Clr) is equivalent to plasma clearance for antibiotics that are completely eliminated via the kidneys. Hepatic clearance (Clh), also called extrarenal clearance (Clnr) is calculated by subtracting the renal from the total clearance. In cattle, this extrarenal clearance also includes elimination in the milk and saliva.
CLA	Clavulanic acid / clavulanate
Clarithro	Clarithromycin
CLI/Clinda	Clindamycin

CLSI	Clinical and Laboratory Standards Institute
Cmax/Tmax	Cmax: maximum (peak) plasma concentration after administration of the antibiotic. The Cmax is reached at a time after administration called Tmax (usually between 15 minutes and 6 hours, depending on the formulation and the route of administration). Cmax and Tmax indicate the speed of absorption in the blood. They do not apply to intravenous administration, for which absorption is immediate and complete.

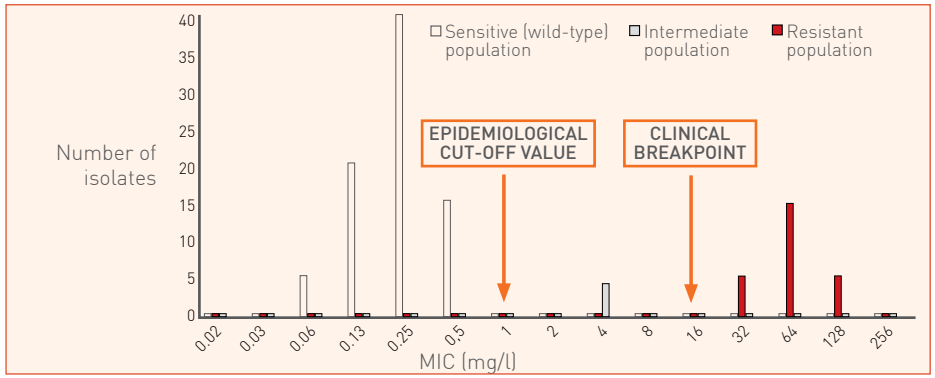


Colonisation	Development of bacteria in an infected animal, without showing clinical signs linked to the infection.
CVMP	Committee for Medicinal Products for Veterinary Use: committee at the European Medicines Agency.
Cyto	Cytology
DCD	Defined Course Dose (dosage required for a full course)
DDD	Defined Daily Dose (assumed average dose per day for a drug used for its main indication)
DDM	Disk Diffusion Method
Dose or concentration-dependent antibiotics	Antibiotics whose bactericidal activity is linked to the concentration, i.e. to the dose administered. Predictive criteria of concentration dependent antibiotics are the inhibitory quotient (IQ≥8) and the AUIC (≥125).



Glossary

DOXY / doxy	Doxycycline
DS	Disinfectants
DSH	Domestic Short Hair
E. coli	*Escherichia coli*
ECOFFs	Epidemiological cut-off values (ECOFFs) separate bacterial isolates with a high MIC value (with a resistance gene) from susceptible isolates (no resistance gene).



EMA	European Medicines Agency
ENR / Enro	Enrofloxacin
EPR	Electronic Patient Record
ERT	Ertapenem
ERY / Erythro	Erythromycin
ESBL	Extended-spectrum ß-lactamases (resistance to last generation cephalosporins, including 3GC)
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESGAI	ESCMID Study Group on Anaerobic Infections
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EUCAST	European Committee on Antimicrobial Susceptibility Testing
Extra-label drug use	Use other than those described in the SPC, in particular regarding indications (cascade use), dosage regimen, contra-indications or warnings.
FA	Fusidic acid
FDA	Food and Drug Administration
FLUTD	Feline Lower Urinary Tract Disease

FNA	Fine Needle Aspiration
FOX	Cefoxitin
FOX / CFT	Cefoxitin/Cefotetan
FQ	Fluoroquinolone
FRA	Framycetin
FVE	Federation of Veterinarians of Europe
GEN / Genta	Gentamicin
HAI	Healthcare-Associated Infections
HPLC	High-Performance Liquid Chromatography
HPLC / MS	High-Performance Liquid Chromatography with Mass Spectrometry
IM	intramuscular
Infection	Animal infected by a pathogen, showing clinical signs related to that infection.
IQ	Inhibitory Quotient (or inhibitory rate): denoted as the maximum plasma concentration divided by the minimum inhibitory concentration (Cmax/MIC). For bactericidal concentration-dependent antibiotics, the IQ should reach 8-10.
ISB	Index of Surviving Bacteria: this indicator measures the bactericidal speed during the early phase, between 0 and 6 hours, based on bactericidal kinetics measured *in vitro*. It compares the bactericidal AUC to that of the inoculum on a semi-logarithmic scale. The smaller the ISB (%), the greater the bactericidal action. An ISB of 0% reflects an intense, dose-dependent bactericidal action, while an ISB of 80% reflects a non-concentration dependent effect.
ISCAID	International Society for Companion Animal Infectious Diseases
IV	Intravenous
KAN	Kanamycin
KCS	Keratoconjunctivitis sicca
LC/MS	Liquid Chromatography with Mass Spectrometry
LEX	Cefalexin or cephalexin
LIN / Linco	Lincomycin
LUTD	Lower Urinary Tract Disease
MAR / Marbo	Marbofloxacin
MBC	Minimum Bactericidal Concentration: the lowest concentration of an antibiotic required to kill 99.99% of the initial bacterial population after 24 h. The calculation is made in broth.

Glossary

MDR Multi-drug resistance

MET Meticillin

METZ / Metronid Metronidazole

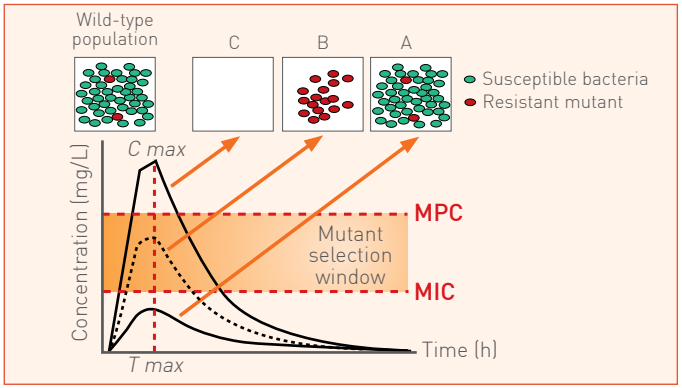
MIC Minimal Inhibitory Concentration: the lowest concentration of an antibiotic that will completely (100%) inhibit the growth of a microorganism. It is measured in µg/ml and is generally determined in a liquid (stock solution) environment by subsequent dilutions. MIC values generally follow a geometric evolution: 0.125 - 0.25 - 0.5 - 1.0 - 2.0 - 4.0 - 0.8 - 16 µg/ml etc.
For a single antibiotic, the collection of MICs for different bacterial strains of the same species provides a statistical estimate of the concentration that inhibits 50% (MIC_{50}) and 90% (MIC_{90}) of bacterial isolates. MIC can also be calculated on agar dilution plates.
The method is simple but requires prior calibration. For a bactericidal antibiotic, the MIC is very close to the MBC.

MIC_{50} or MIC_{90} Lowest concentration of antibiotics that inhibits at least half (MIC_{50}) or 90% of the tested isolates.

MLST Multi Locus Sequence Typing

modal MIC The most common MIC for the pathogens tested.

MPC Mutant Prevention Concentration: this corresponds to a higher concentration than the MIC_{90}. The MPC inhibits the so-called low (or first) level resistance, and is defined as the lowest concentration of an antibiotic that will inhibit the growth (*in vitro*) of a colony of resistant mutant strains.



MRCoNS Meticillin-resistant coagulase-negative staphylococci

MRS Meticillin-resistant staphylococci

MRSA Meticillin-resistant *Staphylococcus aureus*

MRSI Meticillin-resistant *Staphylococcus intermedius*

MRSP Meticillin-resistant *Staphylococcus pseudintermedius*

MRT Mean Residence Time: the average amount of time that each of the antibiotic molecules persist in the organism. This average persistence is a statistical approach (based on probabilities). It is usually expressed in hours.

MSSP Meticillin-susceptible *Staphylococcus pseudintermedius*

NA Nalidixic acid

NCT Non-randomised controlled clinical trials

NEO Neomycin

NIT Nitrofurantoin

NOV Novobiocin

NSAID Nonsteroidal anti-inflammatory drug

ORB / Orbi Orbifloxacin

OTC Oxytetracycline

OXA Oxacillin

P. aeruginosa *Pseudomas aeruginosa*

PAE Post-Antibiotic Effect: persistent suppression of bacterial growth after exposure even though antibiotic concentrations have dropped below the MIC. It usually lasts 1-4 hours for most antibiotics. It has mainly been assessed for macrolides and fluoroquinolones.

pAmpC Plasmidic AmpC ß-lactamases

PEN Penicillins

Peni G Benzylpenicillin or penicillin G

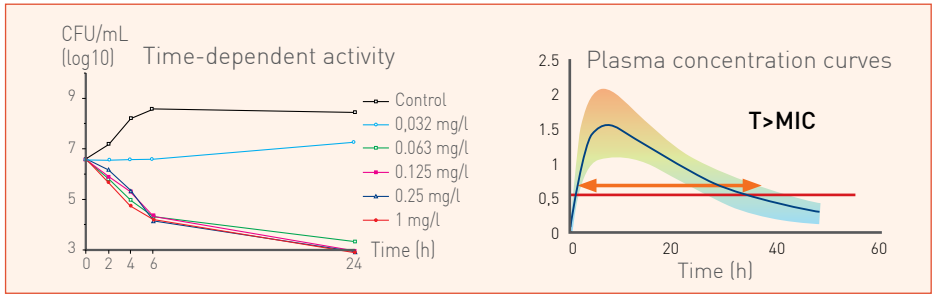
PK/PD Pharmacokinetics/pharmacodynamics of a drug reflect the relation between pharmacokinetic (PK) parameters such as the AUC and the Cmax, and pharmacodynamic (PD) parameters such as the MIC. AUIC, IQ and t>MIC are so-called "dual" PK/PD indicators as they take into account both pharmacokinetic and pharmacodynamic properties.

PO *Per os* (by mouth)

POLB Polymixin B

Glossary

Ppb	Parts per billion (1 ppb = 1 ng/g = 1 µg/kg)
Ppm	Parts per million (1 ppm = 1 µg/g = 1 mg/kg)
Prado	Pradofloxacin
PRI	Pristinamycin
RCT	Randomised controlled clinical trial
RIF	Rifampin, rifampicin
S. aureus / SA	*Staphylococcus aureus*
S. epidermis	*Staphylococcus epidermis*
S. haemolyticus	*Staphylococcus haemolyticus*
S. intermedius	*Staphylococcus intermedius*
S. pseudinter - medius / S. pseudint. / SP	*Staphylococcus pseudintermedius*
SC / SQ	Subcutaneous
SDR	Single drug resistance
SF	Sulfonamide
SIG	*Staphylococcus intermedius* group
SPC	Summary of Product Characteristics: the document approved by the medicines agencies and authorities, describing the drug and the use approved by the authorities, in particular regarding indications, dosage regimen, warnings, precautions and contraindications.
Spira	Spiramycin
SSI	Surgical Site Infection
STR	Streptomycin
t>MIC	The time the plasma concentration of an antibiotic remains above the MIC. It is expressed in time (hours) or in a percentage of the interval between two administrations (generally 12 or 24 hours in animals). For time-dependent antibiotics, the percentage should be as high as possible, i.e. at least 70%.
$t_{1/2}$	Half-life: the time it takes for the plasma concentration to be halved. During the so-called elimination phase, this value is independent of the concentration; the same amount of time is required for the plasma concentration to go from 2 to 1 µg/ml as from 0.5 to 0.25 µg/ml. This criterion, which is easy to understand as an elimination rate constant or persistence of the antibiotic in the body, should be interpreted with care. Indeed, the half-life does not only depend on the elimination but also on distribution. Clearance is a parameter that is more difficult to understand, but it provides a better representation of the drug elimination capacity. Elimination half-life (sometimes called $t_{1/2}ß$) corresponds to the half-life during the elimination phase. The term absorption half-life is sometimes used to describe the absorption of drugs into the blood stream.
TET	Tetracycline
TID	Three times daily (*tris in die*)
TIG	Tigecycline
Time-dependent antibiotics	Antibiotics for which the bactericidal (or bacteriostatic) activity is unrelated to the concentration. To increase the efficacy, it is necessary to prolong the exposure. The predictive criterion of efficacy is the t>MIC.



TMP/SMX	Trimethoprim-sulfamethoxazole
TMPS	Trimethoprim sulfonamide
TMS	Trimethoprim+sulfonamide, trimethoprim-sulfamethoxazole
Tylo	Tylosin
UTI	Urinary Tract Infection
VAN	Vancomycin
Vd	Apparent volume of distribution: the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that is observed in plasma in case of a uniform distribution. It is generally expressed in L/kg. Colistin and aminoglycosides are examples of antibiotics that do not distribute well throughout the organism; colistin does not pass phospholipid membranes and aminoglycosides have an extracellular distribution. Their distribution volumes are relatively low, between 0.6 and 1 L/kg.

Glossary

By definition, distribution volumes cannot be lower than the plasma volume in the organism (around 0.2 L/kg). Antibiotics that readily pass through phospholipid membranes and even accumulate inside cells will have distribution volumes exceeding 1L/kg, generally 2 to 4 L/kg. However, distribution volumes do not predict antibiotic tissue concentrations.

VRE Vancomycin-resistant *Enterococcus* spp.

WHO World Health Organisation

WOAH/OIE World Organisation for Animal Health

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Broad-spectrum AM, combinations, de-escalation

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Nosocomial infections

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