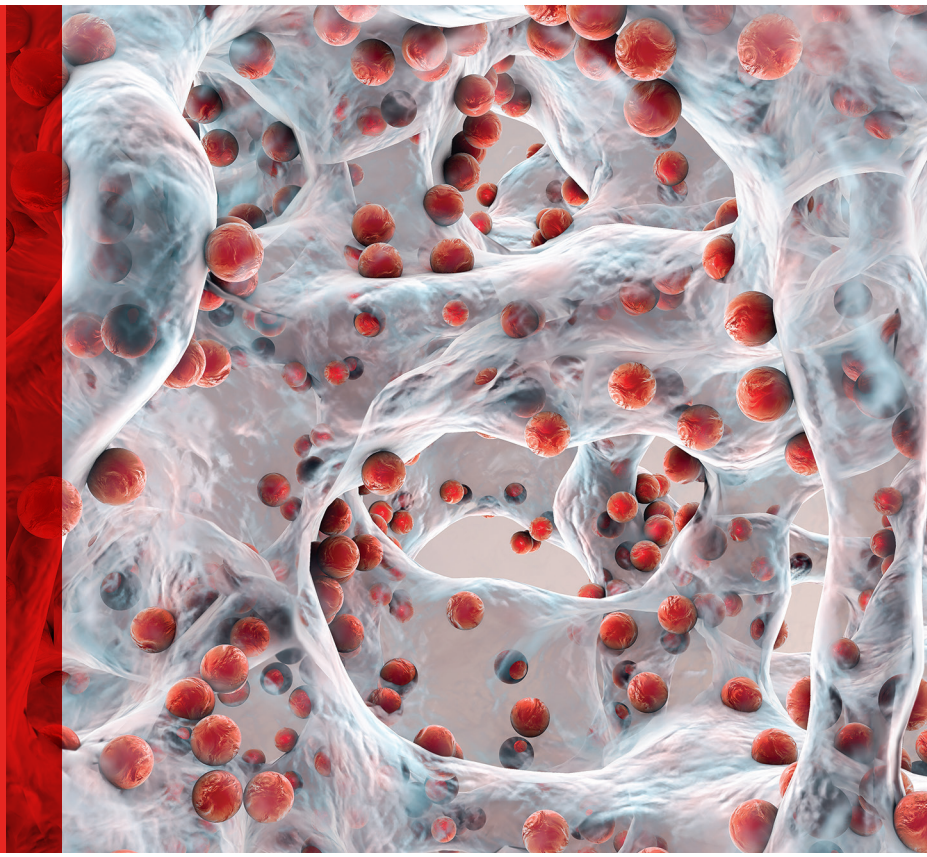
Responsible Antimicrobial Stewardship



Jill Maddison, BVSc, DipVetClinStud, PhD, FACVS, SFHEA, MRCVS
Royal Veterinary College
London, United Kingdom

Antimicrobial resistance is a substantial threat to human health. Annually, ≈700,000 humans die of drug-resistant microbial infections; this number could rise to 10 million by 2050 unless current antimicrobial drug use trends are reversed.[1]

Bacterial resistance as a cause of therapeutic failure is less recognized in veterinary medicine because many clinicians in general practice do not have experience caring for patients with drug-resistant UTIs or drug-resistant skin or wound infections.

Antimicrobial drugs are frequently prescribed for companion animals. A study surveying the records of dogs and cats over a 2-year period at a subset of clinics in the United Kingdom found that 25% of dogs and 21% of cats received antimicrobial treatment.[2] Of the antimicrobial drugs administered, 34% of those given to cats and 6% of those given to dogs were drugs determined by the World Health Organization to be of critical importance to human health (ie, fluoroquinolones, macrolides, third-generation cephalosporins).[2,3]

Methicillin-resistant *Staphylococcus pseudintermedius* can be resistant to all antimicrobial drugs used in veterinary medicine, and many other pathogenic organisms (eg, methicillin-resistant *S aureus*, extended-spectrum β-lactamase–producing *Escherichia coli*, carbapenemase-producing *E coli* and *Klebsiella pneumoniae*, multidrug-resistant enterococci) can colonize and infect both farm and companion animals.[4] Because pet owners and veterinary staff have close connections with companion animals, there is also an increased risk for organism transfer between species[5-7]; young children and immunocompromised pet owners are at the greatest risk.

Responsible antimicrobial stewardship reduces inappropriate antimicrobial use,[4] improves appropriate antimicrobial use, and reduces the risk for transfer of drug-resistant pathogens between humans and animals.

How Does Bacterial Resistance Develop?

Bacterial resistance did not start with the discovery of penicillin. Antimicrobial-resistance mechanisms developed in bacteria >2 billion years ago.[8] Antimicrobial drugs preferentially target resistant populations of bacteria. Selection and clonal amplification of resistant bacterial strains are more likely to occur at sites associated with lower and variable antimicrobial concentrations (ie, sites other than the infection site)—either the gut and skin microbiome or the inanimate environment following excretion of the therapeutic agent or its metabolic breakdown products.[9] Resolution of infection following antimicrobial therapy does not indicate resistance has not occurred.[10] Resistance always occurs to some degree in the normal flora in the skin and gut but can also emerge at the site of infection if treatment was inadequate or inappropriate.[9]

The microbiome is the collection of microorganisms living in or on a human or animal body. A healthy immune system is able to keep the microbiome in balance.[11] Understanding the impact antimicrobial use has on the microbiome is crucial to comprehending the effects of prescribing antimicrobial drugs inappropriately. Human and animal immune systems have developed the ability to cohabit with and control microbiota.[11] Dysbiosis occurs when control of these microbiota is lost. The structure of the microbial community can be influenced by various factors (eg, host genetics, diet, infection, antimicrobial use).[12] Many antimicrobial drugs have long-lasting effects, which can lead to permanent loss of some organisms and proliferation and persistence of other bacteria.[12]

A substantial increase in chronic inflammatory and autoimmune disorders in humans has been attributed, at least in part, to the use of antimicrobial drugs, changes in diet, and a reduction in intestinal parasitism. These changes have profoundly affected human microbiota and, as a direct result, the immune system and are believed to be a factor in a variety of diseases associated with abnormal immune responses toward environmental antigens and self-antigens (eg, inflammatory bowel disease, multiple sclerosis, type 1 diabetes, allergies, asthma).[12,13] It is not yet known if similar changes are occurring in animals. The prevalence of antimicrobial use in companion animal practice may contribute to the increase in potentially resistant bacteria in the microbiome of pets and pet owners and the increased risk for immune-related disorders in pets.

Choosing Appropriate Antimicrobial Therapy

Antimicrobial therapy should eliminate infectious organisms without harming the host and is most effective when supplementing endogenous defense mechanisms rather than acting as the sole means of infection control. The patient's natural defense mechanisms (eg, mucociliary escalator in the respiratory tract, flushing effect of urination, unique defenses of the microbiome) are of primary importance in preventing and/or controlling infections.

Antimicrobial therapy should be used only if a bacterial infection is a likely diagnosis or has been definitively diagnosed and should not be prescribed in place of a diagnosis. If antimicrobial therapy is used for prophylaxis (eg, perioperatively), the nature of the likely infecting organism should be carefully considered and an appropriate antimicrobial therapy chosen.

Antimicrobial therapy may not be needed for many common clinical presentations that rarely have a bacterial cause, such as in dogs with acute vomiting (with or without diarrhea) caused by dietary indiscretion. In addition, antimicrobial therapy may not be needed in healthy dogs with diarrhea that contains fresh blood (unless an infectious cause is suspected); routine use of metronidazole in these patients has not been shown to be effective.

In young cats (<10 years), signs of lower urinary tract disease are more likely to be caused by stress and calculi,[14] which should not require antimicrobial therapy. Although no good evidence-based studies have been conducted, routine antimicrobial therapy in dogs and cats before, during, and/or after treatment for periodontal disease is typically not justified; scaling, polishing, and extractions (when necessary) are generally sufficient in these patients. Healthy cats and dogs undergoing routine surgical procedures <90 minutes in duration, that do not involve the respiratory or GI tracts, and in which asepsis has been properly maintained do not typically warrant antimicrobial therapy; if prophylactic perioperative antimicrobial therapy is indicated, continuation of therapy for >24 hours postoperation is typically not necessary unless there is evidence of infection.

Culture & Susceptibility Testing

Culture and susceptibility testing should always be performed in patients with life-threatening infections and/or deep or complex skin infections. Cultures should also be submitted if rod-shaped bacteria are seen on cytology (ie, skin, ears, urine), when empiric antimicrobial drugs are not effective, and when the risk for antimicrobial resistance is high.

Empiric Use

Although culture and susceptibility testing should ideally be performed before antimicrobial therapy is initiated, it may not be practical (often due to economic reasons). In these situations, an empiric choice should be made based on which pathogenic organisms are most likely present at the infection site. Culture and susceptibility testing are strongly recommended if therapy fails or infection immediately recurs after therapy has ceased. When possible, a gram stain should be performed on the exudate and microscopy performed on urine sediment to determine whether gram-positive or gram-negative bacteria are present, as these characteristics may influence empiric prescribing choices.

ANTIMICROBIAL PRESCRIBING CONSIDERATIONS

- Is the bacterial infection confirmed or probable?
- Will the infection cause critical illness?
- Will the infection progress without treatment?
- Is the patient's condition life-threatening, and can bacterial infection not be ruled out? Pyrexia and neutrophilia may indicate a bacterial infection, but they can also occur with stress, nonbacterial infections (eg, viral, fungal), immune-mediated inflammation, and neoplasia.
- Can the type of infection and antimicrobial susceptibility be predicted? The location of the infection and likely causal pathogens should be considered (eg, gram-negative aerobes and *Staphylococcus* spp for uncomplicated UTIs, *S pseudintermedius* for skin infections). Appropriate guidelines should be reviewed (see ***Suggested Reading***, next page).
- Is culture and susceptibility testing indicated and feasible for the patient? Can the infection site be accessed? Is the pet owner able to pay for testing?
- Will the drug's pharmacokinetic properties influence effectiveness (eg, can the drug get to the infection site)?
- Will infection-site factors (eg, purulent material, necrotic tissue, foreign material) impair drug action? How can infection-site factors be managed to enhance drug efficacy?
- Does the drug have any potential adverse effects for the patient? Patient species, breed, age, and concurrent disease should be considered.
- Is the pet owner able to administer the drug appropriately? Pet owners should understand dosage instructions, be able to administer prescribed medications, remain involved in treatment decisions, and be aware of the adverse effects of poor compliance with medication instructions.

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Empiric antimicrobial therapy is necessary for immediate treatment of life-threatening infections until culture results are received. An empiric approach is also appropriate for topical therapy.

Empiric antimicrobial therapy should only be used to treat other infections when the infection is not life threatening, the patient has not had an infection in the past 3 months, skin infection is superficial, the infection has a predictable antimicrobial susceptibility, and the patient does have signs of antimicrobial resistance.[15]

Signs of Antimicrobial Resistance

Antimicrobial resistance, or the risk that it may occur, should be suspected if a patient has received multiple broad-spectrum antimicrobial courses or antimicrobial treatment within the past 3 months. Signs of resistance include nonhealing wounds, postoperative infection, nosocomial infection, and ongoing infection in patients receiving continuing antimicrobial treatment. Urinary calculi, foreign bodies, and/or the need for surgical drainage can also impair therapy. See ***Antimicrobial Prescribing Considerations***, previous page, for a comprehensive list of considerations for prescribing antimicrobials.

Conclusion

Practicing responsible antimicrobial stewardship involves striving to prevent both antimicrobial resistance and an unecessary impact on the microbiome by prescribing appropriate drugs to treat infections and recognizing when antimicrobial treatment and prophylaxis are inappropriate. Resistance can occur at infection sites when treatment is inadequate or inappropriate. Resistance can also affect other sites (eg, the microbiome), which can result in the transfer of drug-resistant bacteria and dysbiosis.

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Suggested Reading

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