Opportunities and challenges with antibiotic use

Antibiotic guidelines and consensus statements exist in veterinary medicine, but practitioners' awareness of these guidelines is generally poor. Use and prescription of antibiotics is still, in some cases, based on anecdotal evidence or old dogmas. Antibiotics are an essential, scarce resource that must be used judiciously in order to preserve them for future generations. Education of the veterinary care team and pet owners about the issues with antibiotic resistance needs to be a fundamental aspect of stewardship. Understanding that antibiotic resistance is a global One Health issue that needs multidisciplinary collaboration to be addressed is paramount.

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Antimicrobial resistance is a progressive process by which microorganisms, via evolutionary, environmental and social factors, develop the ability to become resistant to drugs that were once effective in de-activating them (Littmann, 2020). It is a threat from which no one can escape and inflicts enormous health, economic and social consequences (Littmann, 2020). Resistance to antimicrobials is a global public and veterinary health crisis, and if not addressed in a multidisciplinary way it will have negative impacts on patient care and animal welfare, incurring a huge economic burden. A recent report from the United Nations places the importance of antimicrobial resistance on par with the triple planetary crisis of climate change, biodiversity loss and pollution and waste, and states that it cannot be understood separately from these (United Nations, 2023). This recognition at the highest levels is fundamental to raise awareness and direct resources to tackle such a complex and serious threat.

Antibiotic resistance, due to its complexity, must be addressed with a One Health framework (Xie et al, 2017; WHO, 2021). The goal of One Health is to improve the understanding of and address complex health problems arising from the intricate relationship between humans, animals and the environment (King, 2008; Xie et al, 2017). One Health has been defined as an integrated, unifying approach that aims to sustainably balance and optimise the health of people, animals, plants and ecosystems, recognising their inter-dependence as a system (WHO, 2021). It promotes integrative health management at the systemic level to provide a comprehensive, strategic approach to future health challenges (Hasler et al, 2014).

The need for interdisciplinary governance, collaboration, communication and co-ordination across complex systems at the local, national and global levels is key in order to wrestle challenging health problems such as antibiotic use and resistance (King, 2008; Xie et al, 2017; WHO, 2021). Linking humans, animals and the environment can help to address the full spectrum of disease control, from disease prevention to detection, preparedness, response and management, and improve and promote health and sustainability (WHO, 2021).

In veterinary medicine, antibiotic use is a key driver for the promotion and transmission of resistance. Companion animals play a key role in the development, carriage and transmission of resistance among animals and people, due to their close interaction with their owners (Singleton et al, 2020).

Antibiotic stewardship

Injudicious prescription and use of antibiotics is the main driver for the increase in resistance in human and veterinary medicine around the globe (Kpokiri et al, 2020; Taylor et al, 2020). Therefore, the central focus to address the antibiotic resistance is to implement stewardship programs (Kpokiri et al, 2020). Antibiotic stewardship in human healthcare and veterinary medicine is crucial to slowing the emergence of resistance and extending the efficacy of antibiotics.

In veterinary medicine, antimicrobial stewardship has been defined as the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public and environmental health (American Veterinary Medical Association, 2018). From a value-based point of view, antimicrobial stewardship is the co-ordinated effort to optimise the use of antimicrobials to minimise adverse events, excess costs

and the development of resistance while improving health outcomes (Feyes et al, 2021; Sjoberg et al, 2023).

The American Veterinary Medical Association has put forward five core principles to be used by veterinary practices to develop stewardship programs (American Veterinary Medical Association, 2018):

1. Commit to stewardship
2. Advocate for a system of care to prevent common diseases
3. Select antibiotics judiciously
4. Evaluate antibiotic use practices
5. Educate and build expertise.

The US Center for Disease Control and Prevention outlined the seven core elements of antibiotic stewardship: leadership commitment, accountability, drug expertise, action, tracking and reporting and education (Center for Disease Control, 2019). Not all these elements would need to be implemented at once for a stewardship program to be successful. Identifying the priorities based on available resources, program interests and patient health and safety, as well as using a stepwise implementation approach can lead to an effective implementation in veterinary hospitals (Klepser et al, 2017).

Recently, the European Union designated antimicrobials that can only be used for humans, hence prohibiting their use in veterinary medicine. Some of the antibiotics included in the regulation are: carbapenems, glycopeptides, combinations of cephalosporin with beta-lactamase inhibitors and oxazolidinones (Commission Implementing Regulation (EU) 2022/1255, 2022). In the UK, The Veterinary Medicines Directorate states that veterinarians should follow manufactures recommendations for the dose and duration of antibiotic therapy. However in specific cases the veterinarian could prescribe an antibiotic that is not authorized, particularly when culture and sensitivity supports such selection, with the understanding that the prescriber is fully responsible for that decision. In that case the veterinarian should be able to fully justify their decision making process with evidence from reliable sources (Mosedale and Harris, 2023). Contrasting with the regulatory environment in Europe, in the US small animal veterinary medicine sector there is currently no regulatory oversight, and the use of medically important antibiotics in companion animals is unrestricted. Despite this, the veterinary profession is recognising the importance of safeguarding antibiotics and many voluntary stewardship programs are being implemented in veterinary hospitals across the US. However, there is still room for continuous improvement and to expand stewardship more broadly. Engaging and collaborating with regulatory agencies will be key in working together to understand each other's point of views and more fundamentally implementing oversight without compromising animal welfare.

Antibiotic use

A study in the UK showed that 25% of 963 463 dogs and 21% of 594 812 cats seen at veterinary practices received at least one antibiotic over a two-year period and 42% of these animals were given repeated antibiotics (Buckland et al, 2016). In dogs, skin infections (pyoderma) are the principal reason for antimicrobial use in small animal veterinary practice (Hillier et al, 2014). Cats are more likely to be treated with injectable antibiotics than dogs (Singleton et al, 2020). It is probable that cat owners prefer injectable antibiotics because cats in general are harder to administer oral antibiotics, but it could also be possible that veterinarians encourage the administration of injectable antibiotics. Third generation cephalosporins are considered by the World Health Organization to be a highest priority critically important antibiotic. Despite this, third generation cephalosporins are frequently use in companion animal medicine, such as cefovecin which is commonly prescribed for cats (Stein et al, 2022). In the United Kingdom, the prescription of fluoroquinolones and third generation cephalosporins (particularly for cats) is relatively common, although current antimicrobial drug prescribing guidance strongly discourages such practices (Singleton et al, 2020). In the US, third generation cephalosporins were found to be commonly used in canine upper respiratory disease and urinary tract infections, deviating from the current guidelines from the International Society for Companion Animal Infectious Diseases (Banfield, 2017).

Duration of antibiotic therapy

In human medicine, the concept that antibiotic treatment should continue past the time when signs and symptoms have resolved can be traced back to 1945 and based on the statement that doctors administered penicillin to patients with pneumonia 'until there was definite clinical improvement and the temperature had remained below 100°F for 12 hours...then given for another two to three days' (Spellberg, 2016). Additionally, this dogma has been reinforced by the equally illogical statement that to prevent antibiotic resistance, it is necessary for patients to complete the entire prescribed course of therapy, even after resolution of symptoms. However, there is no evidence that taking antibiotics beyond the point at which a patient's symptoms are resolved reduces antibiotic resistance (Spellberg, 2016). These outdated dogmas could equally be applied to veterinary medicine.

In human and veterinary medicine, there is limited knowledge of the required lengths of antibiotic treatment in most cases (Rice, 2008; Sousa et al, 2022). Today, it is understood that the best strategy for reducing the emergence of antibiotic resistance is to treat infections for as long as it is necessary (Rice, 2008). A shorter antibiotic treatment regimen would benefit the patients appropriately treated with a narrow-spectrum antibiotic drug and reduce exposure associated with patients treated inappropriately or with longer courses of antibiotics than necessary (Rice, 2008). Since the evidence for reducing the length of antibiotic therapy is, in general, poor or evolving, it is common for clinicians to use antibiotic courses even beyond clinical improvement 'just to be sure' (Rice, 2008; Sousa et al, 2022). Due to the emergence of antibiotic resistance and the side effects of unnecessary antibiotic therapy, this dogma must change.

It has been suggested that a short duration of antibiotic therapy can have several advantages (Uranga et al, 2016). First, among respiratory pathogens, a short duration of antibiotic therapy has been associated with lower rates of antibiotic resistance. Low doses of β-lactam antibiotics for more than 5 days were associated with an

increase in *Streptococcus pneumoniae* penicillin-resistant nasopharyngeal carriers in people. Second, shorter duration of antibiotic treatments likely leads to cost savings. Third, unnecessarily long treatments with antibiotics increases the risk for side effects. Fourth, compliance could improve if treatment duration is shortened (Uranga et al, 2016).

Urinary tract infections

In human medicine, guidelines for the treatment of urinary tract infections are used as part of stewardship programs to improve prescription practices (Gupta et al, 2011). In healthy young women, there is evidence that short antibiotic courses of 1–3 days are effective for the treatment of urinary tract infections (Rice, 2008; Gupta et al, 2011).

In companion animals, urinary tract infection is common with a prevalence as high as 27% in the canine population (Foster et al, 2018). The prevalence of subclinical bacteriuria in healthy dogs ranges between 2–12%. (Foster et al, 2018; Weese et al, 2019) In young cats, urinary tract infection is rarer, affecting 1–2 % of the population. However, in older cats, urinary tract infections can occur in as much as 45% of the population (Dorsch et al, 2019). It is important to differentiate infection from subclinical bacteriuria – the latter refers to the identification or isolation of bacteria from the urinary tract of an animal showing no signs of urinary tract disease (Weese et al, 2019). Subclinical bacteriuria has been reported at rates of between 2–12% in healthy dogs (Weese et al, 2019).

Urinary tract infections or subclinical bacteriuria are an important cause of antibiotic over-prescriptions in small animal medicine, hence contributing to the development of antimicrobial resistance (Weese et al, 2019). Adherence to treatment guidelines and limiting the use to a few first-line antimicrobial agents when prescription is necessary and imperative to control antibiotic resistance (Dorsch et al, 2019; Weese et al, 2019).

The decision to treat with antibiotics should be based on the presence of clinical signs, urine analysis, urine cytology and urine culture and susceptibility. Current veterinary guidelines for sporadic cystitis call to treat the inflammation with anti-inflammatory drugs for 3–4 days. If antibiotics need to be added afterwards, then a lower tier drug for a short duration of therapy of 3 days, is adequate in most cases (Weese et al, 2019). A recent paper evaluating prescribing practices for primary care veterinarians belonging to a corporate practice group revealed a small but positive trend towards improvement in antibiotic prescriptions for sporadic urinary tract infections (Bloch et al, 2022).

Dermatologic infections

Superficial bacterial folliculitis is a common condition in dogs, and veterinarians use different approaches to diagnose and treat it (Hillier et al, 2014). The emergence of multi-drug and extensively-drug resistant skin infections is of great concern for veterinarians practicing in general or specialty settings (Morris and Cole, 2023).

Veterinarians could base their treatment recommendations on tradition, experience or evidence (Sousa et al, 2022). Following treatment decisions based on evidence or published guidelines improves antibiotic stewardship, safety and patient outcomes (Sousa et al, 2022). Duration of antibiotic treatment for pyoderma is a well-established dogma in the veterinary literature, which calls for the treatment of skin infections for 21 days with oral antibiotics plus 7 days beyond resolution of clinical signs. However, there is no evidence to validate these recommendations (Sousa et al, 2022). These long treatment courses of antibiotic therapy for superficial infections should be strongly discouraged and topical treatment of non-antibiotic medications must be used instead. One study has shown that topical therapy can be effective as the sole antibacterial for treatment of superficial bacterial pyoderma, and can also be used in combination when systemic treatments are needed to reduce the duration of antibiotic therapy (Sousa et al, 2022). The International Society for Companion Animal Infectious Diseases published guidelines for the diagnosis and use of antibiotics in superficial pyoderma in dogs – this document is currently being updated to reflect the most current trends and recommendations (Hillier et al, 2014).

A recent study found that only 10.4% of the veterinarians surveyed always performed cytology for suspected bacterial infections before initiating treatments (36.4% reported often, and 45.5% stated they sometimes perform cytology) (Yudhanto and Varga, 2023). Training veterinarians and technicians on the proper way to obtain, process and interpret samples for cytological examination should be a key part of stewardship. Cytological examination before starting antimicrobial treatment is an inexpensive and important tool that the veterinary care team should use to better guide antibiotic prescription – this is especially true for dermatological infections. Furthermore, the use of culture and sensitivity and the development of other novel rapid testing would further improve stewardship (Morris and Cole, 2023).

Intestinal diseases

Gastrointestinal disease leading to diarrhoea are common in different veterinary species and another common cause for antibiotic over-prescription in veterinary practices. Today, there is emerging evidence that the treatment of diarrhoea with antibiotics can cause more harm than benefit, further worsening the risk for the emergence of bacterial resistance.

Acute colitis is a common syndrome affecting dogs seen at veterinary clinics (Rudinsky et al, 2022). In the majority of dogs, the diarrhoea is self-limiting and identification of the initiating cause is normally not possible. These cases are managed with diet modifications, probiotics, antibiotics and supplementation of fibre (Rudinsky et al, 2022). Metronidazole is a popular treatment for acute diarrhoea in dogs due to its antimicrobial, anti-inflammatory and antiprotozoal properties (Rudinsky et al, 2022). This practice should be discouraged because infectious etiologies for canine acute colitis are rare, metronidazole has side effects and causes intestinal dysbiosis and over-prescription of antibiotics leads to increase resistance.

A recent randomised controlled trial clearly demonstrated that dietary management alone was superior to metronidazole and dietary management when treating acute colitis in dogs (Rudinsky et al, 2022). Dietary management can be accomplished with an easily digestible diet with or without psyllium enhancement, both of which outperformed metronidazole in terms of faster times to

remission and minimised impact on the canine dysbiosis index (Rudinsky et al, 2022).

The European Network for Optimisation of Veterinary Antimicrobial Treatment (ENOVAT) is currently developing guidelines for antimicrobial use in dogs with acute diarrhoea. The group concluded that antibiotic therapy was not beneficial in treating dogs with acute diarrhoea and mild to moderate disease, regardless of whether the diarrhoea was hemorrhagic or not (Jenssen, 2023).

Conclusions

Guidelines and consensus statements to help veterinarians improve the use of antibiotics have been published. However, in general, awareness and adherence to guidelines to improve stewardship remains low in veterinary practices. Additionally, information from human medicine could be utilised to improve stewardship in veterinary settings. More needs to be done to bring these recommendations to practicing veterinarians and deliver education programs that help the veterinary care team improve stewardship. Veterinary teaching institutions must improve their curriculum to train the veterinarians of the future to be better stewards of antibiotics. Key points and recommendations for practitioners should be based on:

- Improving prescription practices for antibiotics and finding alternatives therapies when possible
- Reserving clinically important antibiotics for specific clinical conditions and use first line antibiotics initially
- Utilising cytology, culture and sensitivity and other diagnostics to guide treatment
- Selecting the dose and duration of antibiotics based on evidence-based information and remembering a shorter duration is better.

In essence, continuous efforts should be made to educate practitioners and students on the importance of preserving antibiotics for future generations by using them judiciously.

As evidence continues to emerge, replacing the old thinking of continuing antibiotic therapy beyond resolutions of clinical signs with new, evidence-based views that shorter duration is better will improve the judicious use of antibiotics and decrease the risks of adverse effects, improve patient outcomes and reduce costs of care.

Infection prevention is paramount to decrease the disease burden – hence the need for antibiotic prescription. Primary care veterinarians have a key role to play by providing preventative care to pets. Furthermore, education of pet owners about the importance of disease prevention must be an intricate part of stewardship. For example, vaccinating against viral respiratory diseases has a direct impact in lowering the over-prescription of antibiotics to incorrectly treat viral infections; this is true for companion animals and humans.

Developing alternative therapies to directly attack bacteria in a manner that does not drive resistance will play a key role in veterinary medicine. Utilising alternatives to antibiotics for the treatment of dermatologic infections and re-introducing old remedies such as honey, silver or phage therapies could treat infections without inducing resistance. Additionally, alternatives such as dietary modification can spare the use of metronidazole in dogs with colitis.

KEY POINTS

- Antibiotic resistance is a global health crisis that, if not addressed in a multidisciplinary way, will have negative impacts on patient care and animal welfare, incurring a huge economic burden.
- Antibiotic use and over-use are key drivers for the emergence of resistance. Pets play a key role in the development, carriage and transmission of resistance among animals and people, due to their close interaction with their owners.
- Antibiotic stewardship programs are crucial to slow the emergence of resistance and extend the efficacy of antibiotics.
- Use diagnostic tools such as cytology, culture and sensitivity and other emerging diagnostics to guide antibiotic treatment

The veterinary care team has a fundamental role to play in slowing the emergence and spread of resistance in pets and people. As this is a problem that affects people, humans, plants and the environment, cross-discipline collaboration and learning is paramount for tackling such a complex problem. CA

Conflicts of interest

The author declares that there are no conflicts of interest.

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