Suggested guidelines for using systemic antimicrobials in bacterial skin infections (2): antimicrobial choice, treatment regimens and compliance

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Systemic antimicrobials are critically important in veterinary healthcare, and resistance is a major concern. Antimicrobial stewardship will be important in maintaining clinical efficacy by reducing the development and spread of antimicrobial resistance. Bacterial skin infections are one of the most common reasons for using systemic antimicrobials in dogs and cats. Appropriate management of these infections is, therefore, crucial in any policy for responsible antimicrobial use. The goals of therapy are to confirm that an infection is present, identify the causative bacteria, select the most appropriate antimicrobial, ensure that the infection is treated correctly, and to identify and manage any underlying conditions. This is the second of two articles providing evidence-led guidelines to help practitioners address these issues. The first article (*VR*, January 19, 2013, vol 172, pp 72-78) discussed the use of clinical signs, cytology and culture in diagnosis. This second article covers the rationale for topical and systemic antimicrobial therapy, including choice of first-, second- and third-line drugs, the dose, duration of therapy, compliance and identification of underlying predisposing conditions. In addition, there is guidance on cases of therapeutic failure and environmental hygiene. These guidelines should help veterinarians avoid the development and propagation of antimicrobial-resistant bacterial strains.

Therapy: selecting an appropriate antibiotic
Systemic or topical treatment?

Once a pyoderma has been diagnosed, it is important to consider if the infection is deep, severe and/or generalised enough to warrant treatment with systemic antibiotics. Preferred alternatives for mild, surface and/or focal infections include topical antimicrobial shampoos and sprays, or even topical antibiotics if topical antiseptics do not clear the infection. Topical antiseptic treatments can hasten clearing the infection, or will greatly reduce the need for systemic therapy (Scott and others 2001, de Jaham 2003, Murayama and others 2010).

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Systemic antibiotics

If systemic antibiotics are considered the best approach, there are five relevant points to take into consideration:

- The vast majority of skin infections are associated with coagulase-positive staphylococci.
- The skin is the largest organ of the body, and its blood supply is comparatively poor.
- The length of treatment will depend on the depth of the infection.
- Most cases of canine pyoderma are secondary to other pathologies, which must be addressed to obtain a clinical cure.
- Using topical antiseptic treatment will hasten clearing the infection.

Choice of antibiotic

The vast majority of skin infections in companion animals are associated with coagulase-positive staphylococci, with *Staphylococcus pseudintermedius* (part of the *Staphylococcus intermedius* group [SIG]) the most common causative agent in canine pyoderma (Devriese and others 2005, Bannoehr and others 2007).

There have been many studies describing the antibiotic susceptibility of SIG isolates (eg, Medleau and others 1986, Ihrke 1987, 1996, Piriz and others 1996, Pellerin and others 1998, Ganiere and others 2005, Jones and others 2007, Norström and others 2009, Yoon and others 2010, Ghidini and others 2011). These show that the antibiotic sensitivity of SIG isolates vary. In particular, the number of drug-resistant, multidrug-resistant (ie, resistant to three or more classes of antimicrobial), and meticillin-resistant isolates has increased over time. Regular updates on susceptibility patterns to antimicrobials used in veterinary medicine are therefore required (Authier and others 2006). In addition, antimicrobial susceptibility patterns vary between countries, and clinicians

should use data relevant to their location. A recent systematic review of systemic antibiotic therapy for canine pyoderma evaluated 17 clinical trials (Summers and others 2012). The authors concluded that there was good evidence supporting the high efficacy of subcutaneously injected cefovecin in superficial pyoderma and for oral clavulanate-amoxicillin in deep pyoderma. There was fair evidence for moderate to high efficacy of oral clavulanate-amoxicillin, clindamycin, cefadroxil, trimethoprim-sulfamethoxazole and sulfadimethoxine-ormetoprim in superficial pyoderma, and oral pradofloxacin, oral cefadroxil and subcutaneously injected cefovecin in deep pyoderma. It is possible to use this efficacy data and SIG susceptibility data to estimate the probability of successful management of staphylococcal skin infections with different antibiotics, and classify them into first-, second- and third-line antibiotics.

First-line antibiotics

First-line antibiotics include established and well-tolerated narrow- and broad-spectrum drugs with antistaphylococcal activity. They are no less potent than higher-tier drugs in the correct circumstances, and are appropriate for empirical treatment of uncomplicated canine pyoderma. First-line drugs include cefadroxil, cefalexin, clavulanate-amoxicillin, clindamycin and lincomycin. Cefpodoxime and cefovecin can be included as first-line antibiotics where medication may be difficult, and/or compliance is, or likely to be, poor (Van Vlaenderen and others 2011). Long-term injectable or once-daily palatable oral antibiotics are useful if there is, or is likely to be, poor adherence to the treatment regimen, problems with communicating the treatment regimen to the owner, and/or multiple therapies within a treatment regimen.

Inherent resistance of staphylococci limits the usefulness of tetracyclines (Kim and others 2005, Yoon and others 2010), some sulfonamides (Papich 1988) and simple penicillins (Abraham and Chain 1988, Yoon and others 2010). Tetracyclines and sulfonamides, however, may be useful for meticillin-resistant *Staphylococcus aureus* or *S pseudintermedius* infections when their use is indicated by in vitro sensitivity tests (Morris and others 2006).

Second-line antibiotics

Second-line antibiotics should only be used when there is culture evidence that first-line drugs will not be effective. These antibiotics are not appropriate for empirical antibiotic treatment (Authier and others 2006). Second-line antibiotics include newer broad-spectrum drugs important to animal and human health where the development of resistance is of greater concern. Second-line antibiotics include cefovecin, cefpodoxime, difloxacin, enrofloxacin, marbofloxacin, orbifloxacin and pradofloxacin. The recent decline in staphylococcal susceptibility to fluoroquinolones is probably due to the common use of these drugs (Prescott and others 2002). To limit the emergence of resistance, fluoroquinolones should only be used where second-line antimicrobials are necessary (Authier and others 2006).

Third-line antibiotics

Third-line antibiotics are very important to animal and human health, especially for treatment of multidrug-resistant organisms. Resistance towards these drugs is of great concern and/or they have greater potential for adverse effects. Most of these drugs are not licensed for animals, and there are few safety and efficacy data. Third-line antibiotics must only be used when there is culture evidence of sensitivity, no first- or second-line antibiotics are effective, and topical antimicrobial therapy is not feasible or effective (Authier and others 2006). Third-line antibiotics include aminoglycosides, azithromycin, ceftazidime, chloramphenicol, clarithromycin, florphenicol, imipenem, phosphomycin, piperacillin, rifampin, tiamphenicol and ticarcillin.

The development of resistant bacteria in human health is a big concern. In their ethical role of healthcare professionals, veterinarians should never use drugs deemed critically important to human health (eg, vancomycin, teicoplanin, linezolid, etc) in animals. Some countries, moreover, expressly prohibit the use of human antibiotics not licensed for animals (eg, azithromycin, ceftazidime, clarithromycin, imipenem, phosphomycin, piperacillin, rifampicin, ticarcillin and others), so those antibiotics should preferably be avoided, even if there is evidence of sensitivity. Clinicians are responsible for ensuring that it is legal to use non-licensed drugs in their countries.

Escalation and de-escalation of treatment

Ideally, treatment should not be started until the results of bacterial cultures and antimicrobial sensitivity tests are available. If immediate treatment is necessary, the selection of an appropriate drug should be based on clinical signs and cytology, bearing in mind the most likely organisms and their likely antimicrobial sensitivity patterns in each case. When culture results become available, clinicians should be prepared to escalate treatment by selecting a higher-tier drug, or de-escalate treatment to a lower-tier drug, as indicated.

Antibiotic dose, duration, adverse effects and compliance issues
Antibiotic dose

The skin is the largest organ of the body, and its blood supply is comparatively poor (Scott and others 2001). Antibiotics should, therefore, be used at the upper end of their dose range in pyoderma. Animals should always be weighed to allow accurate dosing. If necessary, slightly overdose – never underdose.

The following are effective doses for the most common antibiotics used in canine pyoderma:

- Clavulanate-amoxicillin: 12.5 to 25 mg/kg every 12 hours orally (Lloyd and others 1997).
- Cefalexin: 22 to 30 mg/kg every 12 hours, or 30 to 40 mg/kg every 24 hours orally (Toma and others 2008).
- Cefadroxil: 22 to 30 mg/kg every 12 hours orally (Angarano and MacDonald 1989, Frank and Kunkle 1993), or 30 to 40 mg/kg every 24 hours orally (Noli and Scarampella 1999).
- Lincomycin: 22 mg/kg every 12 hours orally (Harvey and others 1993).
- Clindamycin: 11 mg/kg every 12 to 24 hours orally (Harvey and others 1993, Saridomichelakis and others 2011).
- Cefovecin: 8 mg/kg every 14 days subcutaneously (Stegemann and others 2007, Six and others 2008).
- Cefpodoxime: 5 to 10 mg/kg every 24 hours orally (Brown and others 2007, Papich and others 2010, Kumar and others 2011).
- Enrofloxacin: 5 to 20 mg/kg every 24 hours orally (DeManuelle and others 1998, Frazier and others 2000, Bidgood and Papich 2005, Boothe and others 2006).
- Marbofloxacin: 2.5 to 5 mg/kg every 24 hours orally (Schneider and others 1996, Carlotti and others 1999, Frazier and others 2000, Paradis and others 2001, Horspool and others 2004, Boothe and others 2006).
- Difloxacin: 5 mg/kg every 24 hours orally (Boothe and others 2006).
- Orbifloxacin: 2.5 to 7.5 mg/kg every 24 hours orally (Boothe and others 2006, Scott and others 2006).
- Pradofloxacin: 3 mg/kg every 24 hours orally (Mueller and Stephan 2007, Restrepo and others 2010).
- Azithromycin: 10 mg/kg every 24 hours orally (Girard and others 1987, Shepard and Falkner 1990).
- Chloramphenicol: 50 mg/kg every eight hours orally.
- Rifampin: 5 to 10 mg/kg every 12 to 24 hours orally.
- Tobramycin: 9 to 14 mg/kg every 24 hours subcutaneously.
- Netilmicin: 9 to 14 mg/kg every 24 hours subcutaneously.
- Amikacin: 15 to 30 mg/kg every 24 hours subcutaneously.
- Gentamicin: 9 to 14 mg/kg every 24 hours subcutaneously.

Duration

The duration of treatment will depend on the depth of the infection. Superficial pyodermas typically need two to three weeks of treatment. Deep pyodermas can be greatly improved after two weeks, but full resolution often takes four to six weeks or longer (Carlotti and Ovaert 1988, Angarano and MacDonald 1989, Guaguère and Marc 1989, Paradis and others 1990, Scott and others 1994, 2006, Carlotti and others 1995).

Treatment has to be continued until the infection is visually and palpably cured, and cytology is normal. It is conventional to continue treatment for another seven days in the case of superficial infections, and 14 days if there was deep infection (Scott and others 2001), although the evidence for this is largely anecdotal, and overly long treatment regimens may increase selection pressure for resistance among commensal bacteria. Treated cases should be checked every one to two weeks. If there is any doubt that complete resolution has not occurred, treatment

should be continued, checking cytology and/or culture to confirm that remission is progressing. It is important to note that the clinical signs associated with an underlying disease may still be present and must be differentiated from the clinical signs of the pyoderma.

Owner compliance

Poor compliance or adherence to treatment is likely to compromise efficacy and encourage resistance. Compliance problems include underdosing, missed doses and stopping treatment early (Barter and others 1996, Grave and Tanem 1999), and compliance declines with twice daily or more frequent dosing and treatment regimens with more than one drug. Furthermore, owners may find it difficult or dangerous to administer drugs to some animals. Thus, discussing potential problems openly and honestly with owners helps to select the most appropriate drug and dosing regimen. Compliance can be improved by:

- Using long-duration injectable drugs.
- Using once-daily drugs.
- Using palatable drugs.
- Using drugs that the owner is able to administer safely.
- Convincing the owner of the importance of correct treatment.
- Giving written instructions.
- Using precise terminology – for example, 'every 12 hours' instead of 'twice daily'.
- Good follow-up and communication.
- Minimising the number of different drugs or treatments.

Adverse effects

Owners should be warned about common and mild adverse effects, such as transient gastrointestinal tract upsets, to avoid them prematurely ceasing treatment. Adverse effects arise from effects on non-target bacteria, pharmacological activity (usually predictable and dose-related) or immune-mediated drug reactions (usually unpredictable and not dose-related). Adverse effects can be age-, breed- and species-associated. Common adverse effects of antibiotics include, but are not limited to:

- Gastrointestinal tract upsets – vomiting and diarrhoea may be associated with broad-spectrum antibiotics. This is usually mild and of short duration in dogs and cats, but may be more severe in hindgut-fermenting species (eg, rabbits, rodents, horses, etc).
- Fluoroquinolones can cause neurological problems (especially enrofloxacin in cats and in dogs with a history of seizures) (Ihrke and others 1999), and cartilage abnormalities in skeletally immature dogs (Gough and others 1992).
- Sulfonamides can be metabolised into immunologically reactive derivatives that cause skin reactions, polyarthritis, anaemia, thrombocytopenia and glomerulonephropathy, especially in dobermans (Noli and others 1995, Trepanier 1999). Keratoconjunctivitis sicca (Berger and others 1995) and hypothyroidism (Hall and others 1993) can also be seen, particularly with long-term treatment.
- Penicillins and cephalosporins occasionally trigger allergic and immune-mediated drug reactions (Torres and Blanca 2010). Cross-reaction between penicillins and cephalosporins occurs in 1 to 10 per cent of human patients (Adkinson 1998).
- Cefalosporins can induce positive Coomb's tests, but haemolytic anaemia is rare (Johnson and others 2007).
- Cefalosporins can induce renal tubular damage, but clinical toxicity is very rare (Barza 1978).
- Chloramphenicol can induce dose- and time-dependent bone marrow suppression (Holt and others 1993), although irreversible aplastic anaemia is not generally recognised in animals.
- Aminoglycosides may cause renal toxicity (Martínez-Salgado and others 2007), and renal function should be checked before and during treatment (Noli and Morris 2011). For this reason, systemic aminoglycoside antibiotics should only be considered when there is evidence from bacterial culture and sensitivity testing that other antimicrobials would not be appropriate, and when topical antimicrobial or antibiotic therapy is not appropriate (eg, in deep pyoderma) or has not been effective.
- Tetracyclines may cause hepatotoxicity, photosensitivity, discoloured teeth in young animals and teratogenicity.

- Rifampin may cause hepatotoxicity, so hepatic function should be checked before and during treatment.

The potential for drug interactions and/or dose adjustments should be considered in animals on multiple drugs, and/or with renal or hepatic impairment. Reduced metabolism and/or excretion and extended half-life can cause cumulative dosing and increase the potential for adverse effects. It is therefore advisable to use drugs with an alternative route of excretion in animals with impaired renal and/or hepatic function, or to decrease the dosing interval and/or the dose. However, this may compromise efficacy if adequate tissue levels are not achieved and maintained.

Identification of the underlying cause

The vast majority of skin infections are secondary to a primary condition, such as a hypersensitivity, ectoparasitic infestation, endocrinopathy or keratinisation defects and so on. Successful long-term management requires that these are addressed. It is therefore important that the history and clinical signs are evaluated for clues to the underlying condition. These should then be investigated and managed as appropriate. It is beyond the scope of this article to discuss potential primary problems, and clinicians should consult other texts where necessary.

Treatment failures and recurrence
Poor response to treatment

In cases of poor response to treatment, a variety of reasons should be carefully considered:

- Is there a bacterial skin infection? Carefully re-evaluate the clinical signs, cytology and bacterial culture.
- Are resistant organisms present? Perform or repeat bacterial culture and antibiotic sensitivity.
- Was the antibiotic given correctly? Was the owner compliant? Improve communication with the owner.
- Were the dose and the duration correct? Re-evaluate the treatment regimen.
- Was there concurrent inappropriate use of immunosuppressive drugs, especially systemic glucocorticoids?
- Poor distribution to the target tissue: deep pyodermas often feature extensive necrosis, scarring and debris that may limit penetration and activity of some antibiotics. Clindamycin, cefovecin and fluoroquinolones penetrate well to sites of skin infection and inflammation and could be used in these cases.

Recurrent pyoderma

In recurrent pyoderma, it is important to evaluate the time between drug withdrawal and relapse of the skin infection. If the pyoderma relapses after a few days, then the antibiotic course was too short. A longer course, following bacterial culture and sensitivity testing to check that the drug will still be effective, should be administered. If the pyoderma relapses weeks or months after antibiotic withdrawal, then there probably is an undiagnosed or uncontrolled underlying cause. In order to decrease the number and frequency of pyoderma relapses, topical antimicrobial shampoos or rinses can be used until the underlying cause is controlled.

A small number of cases, however, will suffer relapsing pyoderma if an underlying cause cannot be found (primary pyoderma) or cannot be controlled. Immunostimulants, such as Staphphage Lysate (DeBoer and others 1990) or autogenous bacterial vaccines (Curtis and others 2006) can be used in these cases. Topical antibiotics can be suitable for focal lesions, and may be useful to treat mucosal reservoir sites (Saijonmaa-Koulumies and others 1998). Pulse therapy with systemic antibiotics is not recommended for managing idiopathic recurrent pyoderma, as long-term systemic antibiotic treatment is a risk factor for the acquisition of antibiotic-resistant organisms. However, as a last resort, full-dose bactericidal antibiotics, such as clavulanate-amoxicillin or cefalexin may be given on two to three consecutive days each week ('weekend therapy') (Carlotti and others 2004). Long-duration injectable antibiotics are not suitable for pulse dosing.

Hygiene measures

Antibiotic resistance is an emerging problem in veterinary and human medical care, and constitutes a threat to animal welfare and public

health. Good hygiene routines are necessary to prevent and control infections and minimise zoonotic risk. Suggested measures to improve hygiene standards in veterinary healthcare premises are based on minimising the risk of contamination of clothes, skin (especially the hands), instruments, clipper blades and the environment.

Work clothes should be changed at least daily (or more often if contaminated), and should not be used outside the clinical setting. Wearing short sleeves and restricting jewellery to simple wristwatches and wedding rings are important for proper hand hygiene. Alcohol-based (propanol 60 per cent w/w, ethanol 70 to 90 per cent w/w or isopropanol 60 to 80 per cent w/w) hand disinfection is effective in reducing transient microbial flora (Rotter and others 1998, WHO 2009, Kampf and Loffler 2010), but hand washing with warm water and a detergent is necessary if the hands are visibly soiled. To minimise the drying effect of alcohol, humectants and/or emollients can be added (Kampf and others 2005). Chlorhexidine should be avoided for hand disinfection of personnel, as chlorhexidine contact allergy can occur (Liippo and others 2011). Gloves do not substitute for hand hygiene. Hands should be disinfected before and after contact with a patient, before gloves are put on (as the integrity of gloves can be breached during the procedure), and after the use of gloves. After handling contaminated material, personnel should dispose of gloves and disinfect hands before touching a clean area. Unnecessarily frequent or prolonged use of gloves should be avoided as this can lead to development of hand eczema (Cleenewerck 2010).

Frequently touched surface areas in the environment, such as door handles, lamp handles and buttons, and microscope knobs need extra attention, and should be cleaned daily with non-corrosive disinfectants. As disinfectants can be partly inactivated when in contact with organic debris, mechanical cleaning (for example, with alcohol in combination with a surfactant/detergent) is important before disinfection. Spraying or pouring disinfectants on top of a dirty surface will not suffice in many instances. Non-disposable instruments should be cleaned and sterilised. Ear cones and clipper blades should ideally be autoclaved after use in veterinary practice. Computer keyboards have also been shown to be contaminated frequently with *Pseudomonas* and *Enterococcus* species, and should be disinfected regularly (Fraser and Girling 2009). Washable keyboards should be used in clinical areas.

Patients with known or suspected contagious diseases and infections with multiresistant bacteria should be booked last in a day if possible, and ideally evaluated in a special consulting room. Extra hygiene measures should be undertaken when handling the patient. After the consult, the room should be cleaned before the next patient is allowed in. At this point, it is unknown for how long a dog that had an infection with a multiresistant *Staphylococcus* species can be an asymptomatic carrier of the bacteria. Owners of such patients can be asked to shampoo the dog with an antibacterial shampoo before coming into the clinic. Those dogs should not spend time in the waiting room. If possible, the dog should wait in the car, or outside with the owner, and then go straight into the consult room (FECAVA 2010, BSAVA 2011).

Clinic hygiene measures will only be successful if the board of the clinic is supportive, and all members of the staff stick to the protocol. Correctly implemented hygiene routines are an important contribution to patient and staff welfare, and are mandatory for high-quality veterinary healthcare.

Conflicts of interest

The authors are all recognised specialists in veterinary dermatology who were given an independent brief to develop a comprehensive guide to the use of systemic antimicrobials in bacterial skin infections. The meetings of the authors to produce these guidelines were sponsored by Pfizer Animal Health. However, the guidelines are exclusively the opinion of the authors. The treatment options may include off-label or off-cascade suggestions. The authors believe that any decision on treatment protocols for a particular case remains the complete responsibility of the prescribing veterinarian. In particular, veterinarians must be aware of relevant medicines legislation and whether it is legal to administer certain treatments in their country of work.

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