Antibiotics

A consensus statement has been released with the purpose of guiding practitioners in the diagnosis, treatment and prevention of superficial bacterial folliculitis (SPF). These guidelines, like the previous guidelines published concerning antibiotic use for treating urinary tract infections, are the result of a committee consisting of veterinary internists, pharmacologists, microbiologists and dermatologists. In this article it is stated that “there is concern among some members of this panel about the potential selective effects of third generation cephalosporins (cefpodoxime and cefovecin) on the Gram-negative microflora, due to their broader spectrum of activity compared with first generation cephalosporins”. The following is the author’s position on the use of these broad spectrum antibiotics in the treatment of SPF.

Cefpodoxime is a 3rd generation cephalosporin (broad spectrum) effective for most Staphylococcus infections that occur in dogs. The company believes that this drug should be a first line antibiotic instead of using the narrower spectrum antibiotic, cephalaxin, in the treatment of SPF. The concern about using a broad-spectrum antimicrobial is that they affect a wider variety of microorganisms and their use may select relatively resistant strains of non targeted microorganisms. Even if these microorganisms are non pathogenic, they can be a source of resistance genes for pathogens. A cited advantage of cefpodoxime over cephalaxin is that it is a once a day antibiotic leading to better owner compliance. This belief of higher compliance rate with once daily medication vs. twice daily has been dispelled in a study that revealed there is no difference in compliance with once daily versus twice daily dosing. Also be aware that there are numerous studies showing that once daily cephalaxin at 30-40 mg/kg is as effective as splitting this dose and administering q 12 hours. However these were not peer reviewed studies so this is NOT my recommendation. But these studies do suggest that missing 1 dose of cephalaxin is not catastrophic. Recognizing that missing one dose of a once daily pill would be the same as missing TWO doses of a twice daily pill the author believes that there is no advantage of medications that are given once daily vs. twice daily. Note if once daily dosing is important there are other antibiotics that would be more appropriate to dispense when treating SPF such as clindamycin (5-10 mg/#) or one of the potentiated sulfas. Another advantage mentioned is that the cefpodoxime pill is easier to administer than cephalaxin capsules. Cefalaxin is now available as a chewable tablet (Rilexine® Virbac) that helps make administration of cephalaxin much easier. Other concerns about cefpodoxime as a 3rd generation cephalosporin will be discussed below.

Cefovecin is a parenterally administered 3rd generation cephalosporin that has tremendous value when used properly (selectively). It too is a broad spectrum antibiotic when compared to cephalaxin. In New Zealand it is approved for infections due to Staphylococcus intermedius, β-haemolytic Streptococci, Escherichia coli and/or Pasteurella multocida and Proteus spp. In Canada it is approved for skin infections in dogs due to Staphylococcus (pseudo)intermedius, Streptococcus canis and Escherichia coli. It is also approved for canine urinary tract infections caused by Escherichia coli and Proteus mirabilis. In cats it is for skin infections caused by Pasteurella multocida, Prevotella bivia, Bacteroides fragilis, and Staphylococcus (pseudo)intermedius. This wide spectrum is in contrast to is compared to chewable cephalaxin (Rilexine® Virbac) which is only approved for the treatment of superficial bacterial pyoderma caused by Staphylococcus (pseudo)intermedius. Because of the previously mentioned issues, the author believes that this drug should be reserved for cases where the owner is unable to orally medicate the dog or cat or the animal can’t tolerate oral antibiotics. The concern about using this medication is that therapeutic drug concentrations (above MIC) are only maintained for 7-14 days post injection, depending on the infectious agent, while sub-MIC tissue levels persist for up to 65 days. The question is whether this prolonged subtherapeutic blood (tissue?) level will enrich the environment for the proliferation of resistant bacteria. Will adverse reactions require prolonged treatment due to the prolonged systemic drug clearance? What are the long-term effects on injection sites, especially in cats? Most of these questions have not been answered, even by the company. The following is from the Convenia drug insert (New Zealand)

“Cefovecin is a long acting broad spectrum fourth group cephalosporin. Cefovecin may persist in the body for approximately 4 to 5 weeks; therefore, adverse event monitoring should be carried out for a similar amount of time”. (note USA insert states that reactions may require prolonged treatment due to the prolonged systemic drug clearance (65 days) “Prudent Use: It is prudent to reserve third generation cephalosporins for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials including first generation cephalosporins. Use of the product should be based on susceptibility testing and take into account official, and local, antimicrobial policies. Indiscriminate use of Convenia could contribute to the development of antibiotic resistance.”

An additional concern about 3rd and 4th generation cephalosporins is that they are a risk factor for developing extended spectrum beta- lactamase (ESBL) producing bacterial infections. Extended-spectrum beta-lactamases (ESBLs) are mutant beta lactamases found in Enterobacteriaceae (E. coli, K. pneumoniae, etc) and are a concern in human medicine because they cause serious, potentially
life threatening infections. These bacteria are not only resistant to beta lactam antibiotics but are frequently multi- drug resistant being resistant to non beta lactam antibiotics such as aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and sulfamethoxazole-trimethoprim. This wide ranging resistance greatly limits effective treatment options. The genes encoding this resistance are mediated by plasmids and/or mobile elements which allows horizontal transfer between the same and different species of Enterobacteriaceae. Horizontal transmission allows wide spread dissemination between human bacteria or between human and animal bacteria. In contrast to FQ and 3rd generation cephalosporins, first generation cephalosporins have not been reported to be a risk factor for such resistance.

Bottom line – we should be very selective when dispensing any antibiotic but especially third- and fourth-generation cephalosporins in the treatment of SPF. The most convincing argument against using these newer drugs as a first line antibiotic is since there are disagreements about the long term impact of these drugs on bacteria, and since cephalaxin works well in most cases, why would you change?

**Antipruritic**

Oclacitinib is a JAK inhibitor approved for the treatment of canine pruritus. Cytokines bind to unique cell membrane receptors and activates specific intracellular pathways. JAK is one such intracellular pathway. Once triggered, the JAK pathway activates, via phosphorylation, intracellular proteins call Signal Transducer and Activator of Transcription (STAT). These proteins bind to specific DNA regulatory sequences in the nucleus to activate or repress cytokine production. JAK 1 is involved in the production of cytokines (IL-2, IL-4, IL-6, IL-13 and IL-31) that trigger and perpetuate the clinical signs of pruritus and cutaneous inflammation. Oclacitinib inhibits the activation of JAK 1 thereby decreasing the amount of pro-inflammatory and pruritogenic cytokines produced. It is approved for use in dogs as an antipruritic agent. This oral medication is dosed at 0.4-0.6 mg/kg bid for 14 days then sid. It appears that this drug, when effective, works very quickly, sometimes within hours. However a noticeable number of dogs will become pruritic when switching from bid to sid. In those cases, make sure you are using the 0.6 mg/kg dose- if not, then increase to that dose. If that dose is not effective when given sid, then try splitting the daily dose into bid. Please be aware that this drug will mask pruritic diseases such as sarcoptes, flea allergy dermatitis, pyoderma and *Malassezia* dermatitis. These are diseases that should be treated with ectoparasitcides for the former 2 or antimicrobials for the latter 2 rather than masking the pruritus with medication. As is true with any drug used in the treatment of atopic dermatitis, it should be used as a temporary therapy as you are trying to identify and manage the underlying cause (eg adverse food reaction (food trial), ASIT for environmental atopic dermatitis). The author monitors cbc, serum chemistry profile, urinalysis and urine culture q 6 months for dogs on prolonged treatment. To date only a few dogs have had adverse events (neutropenia/leucopenia) that resolved with discontinuation of the drug.

**Sublingual immunotherapy**

Recently sublingual immunotherapy (SLIT) has become available to veterinarians for the treatment of canine atopic dermatitis (cAD). The author has some reservations about the use of this therapy for cAD. Recognizing that SLIT has been used for many years in Europe for the treatment of human asthma we can review the information that is available in that species. The vast majority of studies and protocols in humans are for rhinitis/asthma and NOT atopic dermatitis. A review in human medicine (2006) found the following

1. Dosing summary
   a. The studies included doses that varied by 30,000-fold
   b. Frequency of dosing varying from daily to weekly
   c. Duration of treatment varying from 2 months to 5 years

   Their conclusion was that SLIT is an effective treatment (for rhinitis or asthma) but it was unclear what the proper dose, treatment schedule and overall duration of treatment was to be effective.

   Other review articles found that the cumulative monthly dose varied between 0.017 and >500 times the customary subcutaneous maintenance dose. In addition that each manufacturer uses its own standardization, formulation, and administration schedules. In a review of SLIT for human atopic dermatitis the authors could only find 1 DBPCR. That study evaluated the efficacy and safety of SLIT using housedust mite containing drops. They concluded that for mild–moderate disease there was significant improvement but there was no improvement in cases of severe disease. But it went on to say that standardized treatment was essential to ensure therapeutic efficacy. They used 80 umg protein concentration/day once daily with instructions to Patients were instructed to keep the drops under the tongue for 1–3 minutes and then swallow. Note in this study the treatment group had a total efficacy rate of 77.78% (cured + marked improvement) vs. 53.85% in the control group. These were statistically significant but look at the placebo effect! The other important finding was that during the first year of immunotherapy there was no difference between placebo and SLIT response and the difference was only noticeable at 2 years. In 2015 there was a systematic review to evaluate the evidence supporting the use of SLIT for hAD? They could only find 5 studies to fit their criteria. They found that in 4/5 studies there was an improvement in AD but in 2/4 there was a substantial placebo effect making the true effect of SLIT difficult to determine. They found serious
shortcomings such as lack of control group, lack of randomization, data analysis was not by intention to treat. The group graded 1 of the studies to have moderate quality, 2 to have low quality and 2 to have very low quality.

As you review the studies in veterinary medicine concerning SLIT and eAD you will note that all studies except for 1 have the same very serious limitations- they are open studies, there are no placebo groups and only the study only applies to mite sensitive dogs. Also the studies state that there are statistically significant changes in CADESI and PVAS but don’t state if this translated into CLINICAL improvement- for example pruritus may go from +10/10 to a +7/10- statistically different but not clinically different. In the 1 DBPCR study that has been done to date in veterinary medicine, they found that overall the percentage of dogs that improved >40% were 50% in the control and 66% in the active group. Once again look at that placebo response! Two problems with this study- 1 they don’t state if the response rate is statistically different and also the criteria that has been establish states there must be at least a 50% improvement to be considered clinically significant- so why did that study use a 40% cutoff?

Lastly, things that give the author great pause about this whole subject is that there are some companies that refuse to tell the veterinarian what is in the SLIT formula that they expect us to give to our patients. In addition the different antigen companies are using different strengths in their SLIT (one company offers a dilution of 20,000 pnu or 40,000 pnu whichever you want – but doesn’t give guidelines how to chose), different volumes and different frequency (sid vs bid). So how can they all be effective? The author uses SLIT in very limited, specific situations such as when owners are absolutely adamant that they won’t give SCIT and won’t bring the pet in for you to give the injection, an animal that has had a severe reaction to SCIT or if the animal fails to respond to SCIT after 1-1 ½ years. I tell the owner that we really don’t know how successful this method is but that it is very safe to try.

**Antifungal**

Itraconazole (Sporonax ®-Janssen Pharmaceuticals- 100 capsules and 10 mg/ml oral solution)) is a member of the azole family of antifungal agents. Imidazoles (Imidazole family (thiabendazole, clotrimazole, ketoconazole, miconazole and enilconazole) and triazoles (itraconazole and fluconazole) make up this family of drugs. All azoles are potent inhibitors of ergosterol synthesis (a main membrane lipid of fungi) via inhibition of a microsomal cytochrome P450 enzyme (14 sterol demethylase) (see table 1). Since mammalian cytochrome P450 is involved in glucocorticoid and sex hormone synthesis (androgens), depending on which azole, the dog’s cortisol and androgen levels may decrease during therapy. This is more of a potential problem w/ketoconazole then w/itraconazole (ITZ) because ITZ is more selective for the fungal enzyme than the mammalian form. Itraconazole has been used in veterinary dermatology for many years to treat subcutaneous (eg Sporotrichosis) or systemic (eg cryptococcus, histoplasmosis) mycotic infections. More recently it has been used for treating cats (and occasionally dogs) for dermatophyte infections. It has also been found to be very effective for the management of Malassezia dermatitis. For cats w/dermatophytosis the author uses "pulse" therapies (i.e., daily therapy for 1 week, then one week off, then one week on, etc) at a dosage of 5-10 mg/kg/day. It is better absorbed if given with food. Side effects of itraconazole in dogs or cats include anorexia, GI disturbances, hepatopathies and in dogs (when using higher doses (10 mg/kg)) vasculitis. It is teratogenic so it is not to be used in pregnant animals. For dog’s w/Malassezia dermatitis, 5 mg/kg, 2 consecutive days/week is as effective as daily administration.

Fluconazole (Diflucan®, Pfizer Pharmaceuticals) is another alternative for the systemic treatment of Malassezia but until recently has been more expensive than either ketoconazole or itraconazole. The dosage is similar to ketoconazole 5-10/kg once daily- GI absorption is unaffected by food intake. The residual effect of fluconazole is similar to itraconazole. Fluconazole is eliminated primarily via the kidneys so administering this drug to a dog w/hepatic disease could be advantageous over the other azoles. Dosage adjustments for dog’s w/renal compromise are necessary.

Terbinafine is an allylamine antifungal agent used in human medicine for the treatment of dermatophyte infections. An advantage of terbinafine over the azoles is that terbinafine has minimal effect on the cytochrome P450 enzyme system as opposed to the azoles. Clinically this translates into fewer drug interactions especially compared to ketoconazole. This drug is effective for dermatophytes (when used w/lime sulfur) and Malassezia and can be used in both cats and dogs. The dose is cats and dogs is 30-40 mg/kg sid however there is a study that used the following dose for dermatophytosis (used w/lime sulfur dips)= cats < 2.8 kg = 62.5 mg, 2.8-5.5 kg- 125 mg and in cats > 5.5 kg 1 tablet.