DIAGNOSING AND TREATING CANINE BACTERIAL PYODERMA

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Bacterial pyoderma is more common in the dog than any other mammalian species. As opposed *Staphylococcus aureus* infections that occur in humans, virulence factors such as protein A, leukocidin, hemolysins, epidermolytic toxin have not been shown to play a role in the pathogenesis of canine pyoderma. Numerous studies have failed to identify any differences in toxin profiles between staphylococcus from normal dogs and dogs with pyoderma[i]. Because *Staphylococcus pseudintermedius*, the most common organism that causes canine pyoderma, is a normal commensal of the dog it appears that abnormal "host factors" is the cause of pyoderma in dogs. These include hypersensitivities, endocrinopathies and cornification abnormalities. .

Bacterial pyoderma can be classified based on the depth of the lesion(s).[ii] The different classifications are:

Surface pyoderma
1. Pyotraumatic dermatitis
2. Mucocutaneous pyoderma
3. Skin fold dermatitis

Superficial bacterial folliculitis (SBF)

Deep pyoderma
1. Deep folliculitis and furunculosis
2. Cellulitis (SQ involvement)

Pyotraumatic dermatitis is diagnosed based on a history of a peracute onset and the appearance of the lesions (alopecia, crusts, and erosions +/- pain). Treatment involves clipping and scrubbing the lesion. It is painful to remove the tightly adherent crusts. Historically the author would sedate the dog prior to clipping the lesion. Instead the author now injects a local anesthetic into the lesion and then clips it. Sedation is used if needed but many times is unnecessary. By injecting the lesion clipping can be performed with minimal to no pain. The injection is a mixture of lidocaine/bupivacaine/sodium bicarbonate. This drug combination has both a quick onset (lidocaine) and a prolonged effect (bupivacaine). After clipping, the lesion is gently scrubbed with a chlorhexidene based shampoo. This is followed by a subcutaneous injection of dexamethasone (2 mg/ml) – 2 mg/30#. A topical antibiotic/steroid cream is dispensed with the instructions to apply it bid for 5-10 days along with gentle cleansing of the lesion. It is important to identify and either treat or eliminate (if possible) the underlying cause (flea allergy dermatitis (FAD), environmental allergen induced atopic dermatitis (atopy) or cutaneous adverse food reactions (CAFR). Please note that Golden Retrievers and Saint Bernards have a unique form of a pyotraumatic dermatitis involving the cheeks. This cheek "pyoderma" is NOT a surface pyoderma but rather a deep folliculitis and furunculosis and needs aggressive antibiotic therapy for 30 days along with an e –collar to prevent self-trauma- NOT steroids!

Mucocutaneous pyoderma is a crusting disease that may affect the lips, nasal planum (exclusively), the bridge of the nose, periocular region, genitals or anus. Clinically it is indistinguishable from DLE. There is no identifiable cause for this disease and the diagnosis is based on signalment (adult dog, most commonly in German Shepard Dogs (or mixes)), clinical appearance and distribution of the lesions and most importantly, response to antibiotic therapy. In the past it was differentiated from DLE based on histopathologic findings. DLE was diagnosed when a lymphocytic to lymphoplasmacytic lichenoid interface dermatitis with hydropic degeneration and/or individual necrotic keratinocyte involving the basal cell layer was present along with pigmentary incontinence and a thickened basement membrane. Mucocutaneous pyoderma would be diagnosed histologically when a plasmacytic to lymphoplasmacytic lichenoid infiltration was present without an interface change and without basal cell damage. HOWEVER, this criterion has been called into question with

a recent study that reported that mucocutaneous pyoderma and DLE may be indistinguishable histologically![iii] In that study, dogs were separated, based on histologic findings, into 3 groups, a lymphocytic lichenoid interface dermatitis with hydropic degeneration group; a plasmacytic lichenoid dermatitis group, and lastly a mixture of the first 2 patterns- lymphoplasmacytic lichenoid, interface dermatitis with hydropic degeneration group. The authors then evaluated whether each group responded to antibiotics or immunomodulating therapy. At the end of the study, it was determined that there was no statistical difference when histopathologic features were compared between the 2nd and 3rd groups!

This author now is proposing a new classification that encompasses both diseases (MCP and DLE) into 1 disease. This disease is name after the histiologic changes found in both MCP and DLE- lymphoplasmacytic lichenoid dermatitis (LPLD). LPLD is therefore a reaction pattern, that is sometimes responsive to antibiotic therapy and other times requires immunomodulation. Since clinically and histiologically it is impossible to determine which cases will require antibiotics and which will require immunomodulation, the author believes that all cases of canine nasal dermatitis should have a 30 day course of cephalexin prior to immunomodulating therapy- in fact a 3-4 week course of a cephalosporin prior to biopsy is appropriate and may establish a diagnosis without the need for a biopsy!

Impetigo is a NON-follicular surface pyoderma seen most commonly in puppies between 6 weeks and 4 months of age. This lesion is usually found as an incidental finding during a routine vaccination visit. An underlying cause is rarely identified but the puppy should be evaluated for intestinal parasites and the diet and environment of the puppy should be reviewed and changed if necessary. Diagnosis is based on signalment, clinical appearance and distribution of the lesions and response to topical +/- systemic antimicrobial therapy. If systemic antibiotics are used they should used for 10-14 days passed clinical resolution of the lesions. Most of the time an antimicrobial shampoo (containing chlorhexidene) +/- a topical antimicrobial product with residual activity (chlorhexidene containing spray or leave on conditioner or mupirocin ointment) applied for 10-14 days is sufficient.

Superficial bacterial infection of the hair follicle (folliculitis) (SBF) is the most common presentation for dogs with a bacterial skin infection. *Staphylococcus intermedius* and, less commonly, *Staphylococcus aureus* had been the most commonly isolated pathogens in dogs with SBF. To confuse matters, the microbiologist now state that all the organisms identified in the past as *Staphylococcus intermedius* are really *Staphylococcus pseudintermedius*.[iv] This name change is not really clinically important since the treatment, etc are the same. But it is important that you are aware of this name change so that you are not confused in reading current literature. In fact you may see the term Staphylococcus intermedius group- just be aware it encompasses *S. intermedius, S. pseudintermedius*, and *Staphylococcus delphini*. Again this change is not clinically relevant other than differentiating this group from the bacteria that causes human infections, *Staphylococcus aureus.*

Recently another staphylococcus organism has been associated with bacterial pyoderma. This staphylococcus - *Staphylococcus schleiferi* may be either coagulase positive (*Staphylococcus schleiferi coagulans*) or coagulase negative (*Staphylococcus schleiferi schleiferi*). In the past coagulase negative staphylococcus were consider contaminants when found on a culture from a superficial lesion in a dog. However coagulase negative *Staphylococcus schleiferi schleiferi* is a pathogen that is potentially zoonotic. Because of this, it is important that laboratories identify coagulase negative staphylococcus down to the species level (to differentiate nonpathogenic *S. epidermidis* from pathogenic *Staphylococcus schleiferi schleiferi)*.

Dogs with SBF may be non-pruritic to mildly or intensely pruritic. Clinically SBF appears differently in different breeds of dogs. Most dogs will have multifocal areas of alopecia, follicular papules or pustules, epidermal collarettes, and serous crusts involving the trunk, abdomen and axillary areas. Short-coated breeds often present with a moth eaten appearance to the hair coat due to alopecic lesions associated with the folliculitis. Cocker Spaniels have their own special presentation, vegetative plaques. These plaques are frequently mistaken for seborrheic plaques. Clinically and histologically they can be quite similar, so if plaques are found in a Cocker, the dog

should be treated for a bacterial pyoderma before condemning the dog to "idiopathic seborrhea". The diagnosis of SBF is usually based on clinical signs—alopecia, papules, pustules, and epidermal collarettes. Differential diagnoses for lesions (follicular papules) that resemble SBF include demodicosis, *Malassezia* dermatitis and dermatophytosis. If non-follicular papules are present ectoparasites need to be included in the differential diagnosis list. Pemphigus foliaceus should be included if epidermal collarettes or pustules are present.

Primary lesions seen in deep bacterial pyoderma include nodules, hemorrhagic bullae, and draining tracts consisting of a serosanguineous to purulent exudate. Distribution of these lesions includes the bridge of the nose, chin, elbows, hocks and interdigital areas. In some dogs lesions may also include the lateral stifles or the trunk. Acral lick dermatitis is a subset of deep pyoderma usually affecting the carpus, metacarpus, tarsus or metatarsal regions.

Any time a dog is diagnosed with a bacterial pyoderma it is essential that you approach the problem in a systematic manner. It is critically important to remember that there is NO such thing as a primary bacterial pyoderma in the dog- there is always a "due to". A dog presented for the first time with a SBF may only need to have a limited number of diagnostic tests performed while a recurrent or chronic case of SBF or ANY dog with a deep bacterial pyoderma will need to have the underlying cause aggressively pursued. The different causes of SBF (deep pyoderma causes are marked with an *) include[v,vi,vii,viii]

1. Hypersensitivities (atopy; cutaneous adverse food reactions; FAD)
2. * Endogenous (hyperadrenocorticism) or exogenous steroid exposure;
3. * Demodicosis;
4. * Hypothyroidism;
5. Follicular dysplasias (eg color dilution alopecia, Chinese crested dogs);
6. Cornification abnormalities (sebaceous adenitis, ichthyosis)

In approaching any dermatologic case, the first step is to review the signalment. Age and breed can help point you in the right direction.

Obtaining a detailed history is the next step. This starts by getting a copy of the dog's medical record. If the dog has had previous skin or ear disease, getting a copy of the medical records may help in developing a differential diagnosis list. Questioning the owner can help pinpoint the primary cause of the pyoderma. Questions that should be asked include:

1. Distribution of lesions initially and currently.
2. When did these symptoms first occur?
3. Has the dog had previous ear or skin disease before and if so when did it occur and how was it treated?
4. Where does the dog live- indoor, outdoors, both?
5. Which, if any heartworm and flea preventative is being used and how is it used
6. Are there any other pets in the household? If so, what kind and are they symptomatic.
7. Are any of the humans in the household showing "new" skin problems? If so, what kind
8. Do they board the dog, take him to obedience school, training or to the groomers?
9. What does the dog eat?
10. Is the dog pruritic
11. Is today's clinical presentation the best, worse or average since the problem began?
12. How was the progression of the lesions? Gradual or sudden?
13. If the dog is pruritic was there a "rash" first or itching first? Or did they occur simultaneously?

After reviewing signalment and thoroughly questioning the owner, the next step is to do a complete physical and dermatologic, including an otoscopic, examination. When performing the dermatologic examination, in addition to identifying primary and secondary lesions, be sure to evaluate the patient for ectoparasites, evidence of self trauma, the quality of the hair coat and the appearance of the skin (scaly, erythematous, etc).

After your examination you should have a list of differential diagnoses that may be the underlying cause of the SBF (or a deep pyoderma) in the patient. ALL dogs with lesions consistent with SBF or deep pyoderma must have deep skin scrapings performed to identify demodex mites if present. More recently a superficial demodectic mite has been identified in dogs- *Demodex cornei.*[ix,x] This short-bodied canine mite inhabits the surface layer of the skin as does the similar *Demodex gatoi* of cats. The biology of this new canine mite and its pathogenesis is poorly defined. It has been associated with a pruritic dermatitis.

An impression smear of a lesion should be evaluated for infectious agents, inflammatory cells and acantholytic keratinocytes (found in pemphigus foliaceus pustules). Dermatophyte cultures should be considered depending on the signalment, distribution of the lesions and the extent of the lesions.

Bacterial culture and susceptibility (c/s) testing should be performed in cases of poorly responsive (NOT recurrent) SBF. If a deep pyoderma has exclusively rods on cytology, has been treated with antibiotics recently or the dog is systemically ill then a culture and susceptibility test should be performed on the first visit. If a c/s is submitted, the MIC (broth microdilution technique) method should be used to determine the susceptibility rather than the disc diffusion method (Kirby-Bauer). The disk-diffusion susceptibility test (DDST) is semiquantitative in that the drug concentration achieved in the agar surrounding the disc can be roughly correlated with the concentration achieved in the patient's serum. It will only report the organism's susceptibility (susceptible, intermediate or resistant) based on an approximation of the effect of an antibiotic on bacterial growth on a solid medium. Tube dilution (MIC) is quantitative, not only reporting SIR but also the amount of drug necessary to inhibit microbial growth. It is reported as the amount of antibiotic (in µmg/ml) necessary to inhibit 90% of the tested bacteria (the lowest concentration in the tube that is clear). This allows a clinician to not only decide susceptible or resistant but also the proper dosage and frequency of administration of the antibiotic. Please be aware that a susceptible designation alone does not necessarily imply efficacy. Other factors as such as the location of the infection and the immunologic status of the host are also determining factors in the ability to clear an infection. The advantage of the MIC method is that not only does it indicate susceptibility, but it also implies the relative risk of emerging resistance and thus the need for a high dose.

To interpret and use a susceptibility test based on MIC requires the following information

1. MIC of the antibiotic in relationship to the organism. This is reported on the culture results.
2. Breakpoint MIC or in other words at what concentration is the bacteria consider susceptible (if the MIC is lower than this value) or resistant (if the MIC is higher than this value). This value should be available from your laboratory. Currently MSU's DCPAH website has a breakpoint chart available (see below for chart or go to www.dcpah.msu.edu/sections/bacteriology/WEBCD.BACT.REF.011)
3. You then look at the culture results and list all the antibiotics that are reported as $\leq$ X where X can be any number
4. For the next step you need to be aware that within a population of susceptible bacteria there is a mixture of strains (heterogeneity). Some of the strains are very sensitive to a given antibiotic while others are less susceptible. The less susceptible ones would be the ones w/the MIC closer to the breakpoint (resistant MIC level). From the list you made in step 3 you need to rank the antibiotic based on which have the most susceptible bacteria. You do this by calculating the efficacy ratio. This number is the breakpoint of the antibiotic divided by the MIC of the bacteria. The higher the number the more susceptible the bacteria is to that antibiotic.
5. You will need to take the list from step 4 and decide which antibiotic fulfills your needs based on
    a. High efficacy ratio
    b. Ability to penetrate the infected tissue
    c. Side effects of the drug
    d. Ease of administration (consider both route and frequency required)

e. Cost of the medication

6. If there are no antibiotics w/ $\leq$ X or the ones that do are either too toxic or too expensive you should then look at the remaining antibiotics that are reported as susceptible. From this list you need to calculate the efficacy ratio. Remember this number is the breakpoint of the antibiotic divided by the MIC of the bacteria. The higher the number the more susceptible the bacteria is to that antibiotic. For example if you have a staph bacteria that has a MIC of 1 umg/ml to enrofloxacin and has a MIC of 4 umg/ml to cephalexin. Which antibiotic is the population of bacteria most susceptible to? To determine this you take the breakpoint of enrofloxacin (4) and divide it by the MIC (1) and the efficacy ratio is 4. Doing the same to cephalexin you get (32/4) 8. Remember the higher the number the more susceptible the bacteria is to that antibiotic. So cephalexin would have the highest number of susceptible bacteria
7. With this list of antibiotics and their efficacy ratio, apply the criteria listed in step 5 to determine the most appropriate antibiotic

Samples from a pustule or intact nodule should be used for culturing however, if an intact pustule is not available, culturing an epidermal collarette has also been shown to be reliable for sampling a SBF[xi]. Use a minitip culturette to sample a draining tract or collect a macerated tissue sample if you are culturing a deep bacterial pyoderma or a nodule.

In the past oxacillin was used to identify all methicillin resistant staphylococcus (MRS). If the staphylococcus was a MRS then it would be resistant to ALL of the beta lactams. The incidence of methicillin resistant *S. pseudintermedius* (MRSP) has been increasing over the last decade[xii] eliminating treatment using common antibiotics. Complicating management of MRSP is that these bacteria are frequently multi-drug resistant (MDR). In a study by Bemis, et al[xiii] it was found that more than 90% of the MRSP were MDR. MDR was defined as being resistant to $\geq$4 additional antimicrobial drug classes. The cause of the increased frequency of MRSP has not been clearly established but one of the many risk factors for MRSA and MDR staphylococcus is the administration of fluoroquinolones. Reducing the administration of antibiotics and particularly fluoroquinolones and 3rd generation cephalosporins may help prevent persistent carriage of MRSA in humans.[xiv,xv] In humans the overuse of third-generation cephalosporins for long periods has caused MRSA outbreaks.[xvi] Additional information about the administration of 3rd generation cephalosporins or fluoroquinolones is discussed below.

The new protocol for identifying MRS in humans is to use cefoxitin. In humans the organism is *Staphylococcus aureus*. In animals the staphylococcus responsible for infection usually belongs to the staphylococcus intermedius group (*S. intermedius, S. pseudintermedius*, and *Staphylococcus delphini*). The problem is that certain strains of methicillin-resistant *S pseudintermedius* (any in the SIG?) may be falsely identified as methicillin susceptible if the laboratory uses cefoxitin susceptibility as the indicator. This is because cefoxitin may not induce the *mecA* gene as reliably in *S pseudintermedius* as it does in *Staphylococcus aureus*. The most recent protocol is that oxacillin susceptibility testing should be retained for *S pseudintermedius* isolates (all SIG?) and that the break point is lowered from the previous level of 2.0 umg/ml down to 0.5 umg/ml. How is this clinically important? If you are using a human laboratory or a local laboratory they may not be aware of this difference in testing between *Staphylococcus aureus* and *S pseudintermedius*. Because of this, the author strongly recommends using a veterinary laboratory that uses Clinical and Laboratory Standards Institute (CLSI) guidelines AND is aware of and has current knowledge of veterinary pathogens.

Recently the effectiveness of clindamycin against MRSA has been questioned[xvii]. There are 2 genes, *msrA* and *erm* that are responsible for *S.aureus'* resistance to macrolides (eg erythromycin). The *msrA* gene accounts for the resistance to only macrolides, while the *erm* gene codes for macrolides and lincosamides (lincomycin and clindamycin) resistant. The *erm* gene may be constitutive which means that it will be present in the bacteria from the onset and the culture will report resistance to clindamycin. It may be inducible in which case the MRSA will be susceptible initially to clindamycin and therefore reported as such. When MRSA has the inducible gene,

resistance to clindamycin will develop WHILE on treatment. As the susceptibility pattern to clindamycin of MRSA isolates possessing the *msrA* gene (truly susceptible to clindamycin) or the inducible *erm* gene (potentially resistant) are the same, it is important to distinguish between these phenotypes. This is accomplished by an additional culture technique called the Double-disc diffusion D-test. This test will detect the occurrence of the inducible *erm* gene. Since no commercial lab is currently doing this additional culture, resistance to erythromycin may be used as a clue to this inducible gene. This is because the *msrA* gene and the **erm** gene both encode staphylococcus resistance to erythromycin. So if the staphylococcus is resistant to erythromycin, there is a potential for the inducible *erm* gene to be present. In the study by Rich et al, 97.3% of erythromycin-resistant isolates of MRSA were truly resistant to clindamycin despite only 25.5% demonstrating clindamycin resistance by routine laboratory testing. Therefore based on this study it would prudent to avoid clindamycin on all *Staphylococcus aureus* infections that report resistance to erythromycin. However in a 2009 study, inducible clindamycin-resistance was present in only MRSA isolates NOT in MRSP[xviii]. The authors of the study concluded that since inducible resistance was not identified in any of the MRSP the use of clindamycin was a reasonable option for MRSP infections. Unfortunately, a subsequent study in 2010 did identify inducible clindamycin gene in 2 strains of MRSP[xix]. In 2011 this issue of inducible clindamycin resistance was identified in MSSP and methicillin susceptible *Staphylococcus aureus* (MSSA). Because of this the author will avoid clindamycin in any staphylococcus infection, regardless of the species and strain, if the organism is reported to be resistant to erythromycin.

In infections with MRSP or methicillin susceptible *Staphylococcus pseudintermedius* (MSSP), resistance to tetracycline is mediated by 2 genes, *tet(K)* and *tet(M)*[xx]. Resistance to tetracycline but not doxycycline or minocycline is mediated by *tet(k*), while *tet(m)* will confer resistance to all 3 members of the tetracycline family. Complicating the issue is that if a MRSA organism (at this time it is unknown whether this is true for MRSP) has the *tet(k)* gene, exposure to either tetracycline or doxycycline can induce doxycycline thereby leading to clinical failure of doxycycline. This inducible resistance doesn't occur with minocycline. This has lead to the recommendation that MRSA infections that are resistant to tetracycline should be considered resistant to doxycycline regardless of the *in vitro* test result. In cases of tetracycline resistant MRSA infections, minocycline should be tested since if the *tet(m)* gene is present will minocycline will be ineffective but if only the *tet(k)* gene is present, minocycline would be effective[xxi].

Because of the increasing incidence of resistant bacterial infections to orally administered antibiotics, topical therapy, either as a monotherapy or as part of polypharmacy, is becoming more important. Topical therapy may not only decrease or eliminate the need for systemic antibiotics but, since many of the dogs with SBF have atopic dermatitis, bathing to remove antigens from the skin can be useful in managing the allergies. The limitations of using topical therapy include time constraints of the owner and cost may be significant if treating a large area. Shampoo ingredients that are effective for treating bacterial pyoderma include chlorhexidene, benzoyl peroxide, ethyl lactate, triclosan and boric acid/acetic acid. In 2 different studies chlorhexidene was the most effective ingredient.[xxii,xxiii]

Topical therapy with mupirocin may be very useful.[xxiv] Not only is it a very effective antimicrobial agent against gram positive bacteria but because of its unique MOA cross-resistance with other antibiotics is very uncommon.

Silver sulfadiazine has traditionally been used for its effectiveness against gram negative bacteria, especially *Pseudomonas*.[xxv] However it is also effective against some gram-positive bacteria[xxvi] including *Staphylococcus aureus*.

When treating a dog with a SBF an antibiotic should be administered for at least 21 days, or 14 days past YOUR clinical examination that has determined the infection has resolved, whichever is LONGER. For dogs with deep pyoderma, treat for at least 6 weeks or 21 days beyond clinical resolution, whichever is longer. In SBF don't use GC when the pruritus is only at the lesions or when the pruritus is only mild at the nonlesional areas. If a dog with a SBF has intense pruritus at nonlesional areas then a tapering 21 days course of prednisone may be dispensed. Using GC in the presence of a pruritic pyoderma makes interpretation of response to therapy impossible (was it the

steroid or the antibiotic/antifungal therapy that resolved the pruritus?). It also makes it more difficult to resolve the infection. NEVER use GC in deep pyodermas!!

In regards to systemic antibiotic the following are appropriate skin antibiotics

1. Cephalexin 10-15 mg/# bid-tid
2. Potentiated sulfa
    a. Trimethoprim/sulfonamide- Tribrissen® 15 mg/# bid
    b. Sulfadimethoxine and ormetoprim- Primor ® 25 mg/# sid on day 1 then 12.5 mg/# sid
3. Clindamycin- Antirobe® 5-10 mg/# sid-bid
4. Amoxicillin/clavulanic acid – Clavamox® 10 mg#/bid
5. Cefpodoxime proxeil- Simplicef® - 5-10 mg/kg sid 10-15 mg/# bid- SOMETIMES
6. Cefovecin (Convenia)- SOMETIMES

The author needs to make a few comments about cefpodoxime and cefovecin. Cefpodoxime (Simplicef®, Pfizer) is a 3rd generation cephalosporin effective for most of the staphylococcus infections that occur in dogs. This once a day antibiotic is useful in cases where the owner has difficultly administering medication. The once daily administration and the formulation in a pill rather than a capsule may make it easier for some owners to medicate their dog. Another instance where it may be of use is during a food trial. During this trial it is best, if possible, to avoid gelatin (animal protein) that is present in capsules. Using cefpodoxime tablets would solve this problem. The author also has an impression that there are fewer intestinal disturbances using cefpodoxime versus cephalexin. An additional reason to dispense brand name cefpodoxime (Simplicef®) is to support veterinary drug companies. These companies are the life line of new veterinary drugs and they must have the financial resources to continue R&D. However, consider when dispensing cefpodoxime there are some staphylococcus infections that will be resistant to cefpodoxime but susceptible to cephalexin[xxvii]. Also the stated higher compliance rate of once daily medication vs twice daily may not be true. Adams et al reported that in their study there was no difference in compliance with once daily versus twice daily dosing[xxviii]. Lastly there are numerous studies showing that once daily cephalexin at 30-40 mg /kg is as effective as splitting this dose and administering q 12 hours.[xxix,xxx,xxxi,xxxii,xxxiii,xxxiv,xxxv] HOWEVER these were not peer reviewed studies so this is NOT my recommendation. However these studies do suggest that missing 1 dose of cephalexin is not catastrophic. In addition remember missing one dose of a once daily pill would be the same as missing TWO doses of a twice daily pill. See comments about 3rd generation cephalosporin use below.

Cefovecin (Convenia®, Pfizer) is a parenterally administered 3rd generation cephalosporin that has tremendous value when used properly (selectively). 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 after the first injection therapeutic drug concentrations (above MIC) are only maintained for 7-14 days, depending on the infectious agent, while tissue levels persist for up to 65 days[xxxvi]. The question is whether this prolonged subtherapeutic blood (tissue?) level will encourage the incidence of methicillin resistant staphylococcus. 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? How clinically significant is the *in vitro* finding that cefovecin increases free concentrations of carprofen, furosemide, doxycycline, and ketoconazole. Will drugs with a high degree of protein-binding (e.g. cardiac, anticonvulsant, and behavioral medications) compete enough with cefovecin-binding to create adverse reactions. Most of these questions have not been answered, even by the company.

In the BSAVA Guide to the Use of Veterinary Medicines[xxxvii], it discusses the prudent use of antimicrobial agents. In regards to 3rd generation cephalosporins and all fluoroquinolones (FQ) it states "that in all species fluoroquinolones and third- and fourth-generation cephalosporins should be used judiciously and <u>never</u> considered as first-choice options".

The Europeans are also concerned about 3rd generation cephalosporin use and FQ use. The European Medicines Agency states (EMEA/CVMP/215997/2006) "Following advice given by the CVMP Scientific Advisory Group on Antimicrobials (SAGAM), the CVMP agreed the following

statements should be included in section 4.5 of the SPC (special precautions for 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 or first generation cephalosporins.” and “Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies”

The Swedes published guidelines in 2009[xxxviii] for the use of antibiotics in the treatment of dogs and cats. In this guideline it is stated very clearly that third generation cephalosporins should only be used to treat infections where there are no other suitable options. It goes on to state that injections with long-acting antibiotics should not normally be used to treat a pyoderma. Specifically in the guidelines it states that cefovecin should only be used if the treatment is “of the utmost importance” for the animal AND administration of other medications is not possible.

The concern with using FQ is that, according to information from the CDC website, “none of the fluoroquinolones are FDA-approved for treatment of MRSA infections. A major limitation of fluoroquinolones is that resistant mutants can be selected with relative ease, leading to relapse and treatment failure”. MRSA strains are especially adept at developing fluoroquinolone resistance, and such resistance is already found among MRSA isolated from patients with CA-MRSA infections. In addition it has been reported that there is a significant association between total fluoroquinolone use within human hospitals and percentage of *S. aureus* isolates that were MRSA and between total fluoroquinolone use in the community and percentage of *E. coli* isolates that were fluoroquinolone-resistant *E. coli*.[xxxix] Association between the action of fluoroquinolones on *mecA*-positive *S. aureus* and the increase in the resistance index for methicillin resistance has been reported.[xl] Lastly it has been widely reported that there is an association between FQ use and clinically significant MRSA[xli,xlii,xliii]

Bottom line – we should be very selective when dispensing any fluoroquinolones or any third- and fourth-generation cephalosporins in the treatment of canine bacterial pyoderma.

SUMMARY- if the dog has papules, pustules and/or epidermal collarettes a skin cytology and deep skin scraping should be performed. Consider fungal culture and/or bacterial culture depending on the history and clinical presentation. In cases of SPF, if cocci are seen on cytology and there is not a recent history of antibiotic use, dispense antibiotics and shampoo therapy as mentioned below. Be sure to recheck the dog after 14-21 days of antibiotics to assess response to therapy. Remember to treat any identified underlying disease.

1. Antibiotics- Remember for SBF 21 days is the minimum and 6 weeks is the minimum treatment time for dogs with deep pyoderma. Use an appropriate skin antibiotic as previously listed.
    a. The author’s initial antibiotic will be cephalexin.
        i. If there is no response to the initial appropriate given at an appropriate dose and frequency, then culture and susceptibility testing should be performed
2. Antimicrobial +/- antifungal shampoo is important

If the dog was pruritic when first presented with the SBF and the pruritus and lesions resolve when you have only treated the secondary infection continue the antibiotic for 14 more days. In this case the SBF was the major (only?) cause of the CURRENT pruritus and it was secondary to one of the following:

a. Seasonal atopy and the season has changed;
b. An endocrinopathy

If the dog was pruritic when first presented with the SBF and the pruritus did NOT resolve with antibiotics but the lesions did, then continue the antibiotic for 14 more days. Atopy, CAFR or ectoparasites need to be pursued as the underlying cause.

If the dog was pruritic when first presented with the SBF and the pruritus and lesions did NOT resolve with antibiotics then ectoparasiticidal therapy, fungal culture and bacterial culture and susceptibility testing should be performed (+/- skin biopsy).

If the dog was NOT pruritic when first presented with the SBF then either the dog has seasonal atopy and the season has changed or the dog has an endocrinopathy. Rarely CAFR or nonseasonal atopy may present with recurrent non-pruritic SBF as the only clinical sign. If the lesions

resolve with antibiotics then continue the antibiotics for 14 more days and continue to investigate the underlying cause. If the lesions DON'T resolve with antibiotics then fungal culture and bacterial culture and susceptibility testing should be performed (+/- biopsy).

Unfortunately there will be cases of recurrent SBF that have been properly evaluated and managed. In recurrent cases with no definable cause the author will treat with antibiotics for a minimum of 6 weeks and begin immunotherapy with Staph Phage Lysate (SPL) (Delmont Labs, Swarthmore, PA, USA). However the following criteria need to be met to maximize the success of SPL

1. The disease responds to antibiotic and topical antimicrobial therapy ALONE (NO steroids have been used)
2. The dog should have a history of recurrent SBF that has been treated appropriately (14 days past clinical resolution – minimum of 21 days)
3. All underlying causes should be ruled out (i.e., demodicosis, flea allergy dermatitis, CAFR, hyperadrenocorticism (iatrogenic and spontaneous) and hypothyroidism).

If in spite of these therapies the SBF continues to recurrent the author will "admit defeat" and treat with a long term, low dose antibiotic therapy. The risk with this treatment is the possibility of developing a resistant infection, even though this has not been recognized in cases managed by the author in this manner.

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Resistance Breakpoints for Antimicrobials Used in Animals

Drug	Species or Organism*	Resistant Breakpoint MIC
Amikacin		≥64
Amoxicillin/Clavulanic acid (Skin and soft tissue isolates) **Note:** Breakpoints for amoxicillin-clavulanic acid based on amoxicillin dosage of **11 mg/kg (dogs)** or **12.5 mg/kg (cats)** every 12 hours orally.	Coagulase-positive staphylococci (canine) *E. coli* (canine) Staphylococci (feline) Streptococci (feline) *E. coli* (feline) *Pasteurella multocida* (feline)	≥1/0.5
Amoxicillin/Clavulanic acid (Urinary tract or large animal isolates)	Staphylococci Other bacteria	≥8/4 ≥32/16
Ampicillin* (Skin and soft tissue isolates) **Note:** Breakpoints for ampicillin based on amoxicillin dosage of **22 mg/kg (dogs)** every 12 hours orally. **Note:** Breakpoints for ampicillin based on ampicillin sodium dosage of **22 mg/kg IM q12 (horses)** *(Predicts susceptibility to Amoxicillin)	*E. coli* (canine) Staphylococci Coag-positive staphylococci (canine) Streptococci (not *S. pneumoniae*) Group G (*Streptococcus canis)* (canine) *Streptococcus zooepidemicus* (equine) Enterococci	≥1 ≥0.5 ≥0.5 ≥8 ≥0.5 ≥0.5 ≥16
Ampicillin* (Urinary tract or large animal isolates) *(Predicts susceptibility to Amoxicillin)	Enterobacteriaceae Staphylococci Streptococci Group G Strep Enterococci	≥32 ≥0.5 ≥8 ≥0.5 ≥16
Azithromycin	*Haemophilus sp.* Staphylococci Streptococci	≥32 (No Resistant brkpt) ≥2
Cefazolin		≥32
Cefotaxime		≥32
Cefovecin		≥8
Cefoxitin		≥32
Cefpodoxime	Canine wounds & abscesses*	≥8
Ceftazidime		≥32
Ceftiofur	Bovine & Swine Resp. Disease Bovine Mastitis *S. zooepidemicus* (equine)	≥8 ≥8 (No Resistant brkpt)
Cephalexin	See Cephalothin	
Cephalothin	(predicts susceptibility to all first-generation cephalosporins)	≥32

Drug	Species or Organism*	Resistant Breakpoint MIC
Chloramphenicol	*Streptococcus pneumoniae* Other Streptococci All other organisms	≥8 ≥16 ≥32
Ciprofloxacin		≥4
Clarithromycin	*Haemophilus sp.* Staphylococci Streptococci	≥32 ≥8 ≥1
Clindamycin (predicts lincomycin susceptibility)	Dogs (Dermal & Soft Tissue)	≥4
Doxycycline (see Tetracycline)	Staphylococci + Enterococci	≥16
Enrofloxacin	Cats & Dogs (at dosage of 2.5-5 mg/kg) Cats & Dogs (at dosage of 20 mg/kg) Bov. Resp. Disease	≥4 ≥8 ≥2
Erythromycin	Streptococci Staphylococci + Enterococci	≥1 ≥8
Florfenicol	Bov. + Swine Resp. Disease *Salmonella cholerasuis*	≥8 ≥16
Gentamicin **Note:** For dogs, the dose of Gentamicin modeled was **10 mg/kg IM q24h (dogs)** and **6.6 mg/kg IM q24h (horses).**	Enterobacteriaceae(canine/equine) *P. aeruginosa* (canine/equine) *Actinobacillus sp.* (equine) Other bacteria	≥8 ≥8 ≥8 ≥16
Imipenem		≥16
Kanamycin		≥64
Marbofloxacin	Cats & Dogs (Dermal) Dogs (UTI)	≥4 ≥4
Oxytetracycline	See Tetracycline	
Penicillin	Staphylococci *Streptococcus pneumoniae* Streptococci—viridans grp Streptococci, β-hemolytic, Listeria Enterococci	≥0.25 ≥2 ≥4 (No Resistant brkpt) ≥16
Penicillin/Novobiocin	Bov. Mastitis	≥4/8
Pirlimycin	Bov. Mastitis	≥4
Piperacillin		≥128
Spectinomycin	Bovine Resp. Disease	≥128
Sulfisoxazole (and other sulfas)		≥512
Trimethoprim/Sulfamethoxazole	Urinary tract isolates Other bacteria	≥2/38 ≥4/76
Tetracycline** **(predicts susceptibility to doxycycline and oxytetracycline) **Note:** For BRD & SRD, derived from pk data of Oxytetracycline at 20 mg/kg, IM, once, injectable formulations only.	*Streptococcus pneumoniae* Other Streptococci All other organisms Bov. Resp. Disease Swine Resp. Disease	≥8 ≥8 ≥16 ≥8 ≥2