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## Hostage to history – questioning the duration of systemic antimicrobial therapy for the treatment of canine superficial bacterial folliculitis

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### ABSTRACT

Current guidelines for the use of systemic antimicrobials for the treatment of superficial bacterial folliculitis in dogs include the recommendation that the disease be treated for a minimum of 3 weeks and for at least 1 week beyond clinical resolution. With increasing antimicrobial resistance being noted for bacteria involved in this condition, as well as the increased use of evidence-based medicine, this dogma needs to be reevaluated.

For decades, veterinarians have been treating dermatologic diseases in companion animals with varying drug regimens. Some recommendations are based on opinion, some are based on tradition or experience, and some are evidence-based. Increasing availability and awareness of evidence-based reviews help drive a more scientific approach to treatment guidelines for some clinical conditions, frequently improving safety and clinical outcomes. Yet anecdotal and tradition-based treatment approaches for many conditions, particularly dermatologic conditions, persist in the veterinary field despite lack of supporting data. This is particularly evident in the face of increasing concern for antimicrobial resistance. Duration of antimicrobial therapy remains a critical component for clinical case resolution as well as antimicrobial resistance.

Superficial bacterial folliculitis (SBF) is a common dermatologic condition diagnosed in dogs. In most cases, an underlying or predisposing cause can be identified that then needs to be managed to result in a successful treatment outcome or to minimize recurrences. *Staphylococcus pseudintermedius* is a part of the normal microflora of most dogs<sup>1</sup> and is the most common bacterial species identified in dogs with SBF; thus, it is an opportunistic pathogen. Underlying conditions such as allergies (atopic dermatitis, flea allergy, or

cutaneous adverse food reactions), endocrinopathies (hypothyroidism or hyperadrenocorticism), parasitic infestations (*Demodex spp* or *Sarcoptes scabiei*), cornification defects, and conformational abnormalities (skin folds, particularly in overweight dogs) are a few of the many possibilities. Since dogs will never be cured of *Staphylococcus*, as staphylococci are normal mucosal and cutaneous inhabitants, the goal of treatment is clinical cure, not microbiological cure. The chance of recurrent SBF exists, especially if the underlying or predisposing cause cannot be identified or controlled.

Treatment of dogs with SBF has been studied for many years, and evidence-based guidelines addressing the appropriate laboratory diagnostic approach, topical versus systemic therapy, empirical antimicrobial choices, and duration of therapy have been published.<sup>2,3</sup> However, these guidelines, in regard to duration of systemic antimicrobial therapy, are predominantly based on expert opinion due to limited published data, particularly randomized controlled trials. Regarding the duration of antimicrobial therapy, the ISCAID guidelines<sup>2</sup> state the following:

Most studies evaluating the efficacy of AMDs (antimicrobial drugs) indicate that SBF infections are resolved after 3 weeks or more of systemic AMD treatment ... In the absence

of evidence to the contrary, continuation of treatment for at least 7 days beyond clinical resolution of lesions is recommended in all cases, because the inflammatory process and lesions will subside and become inapparent as the infection is eliminated. This extended duration of treatment is based on clinical experience. Further research is required to confirm the need for such additional therapy, whether a 7-day period is sufficient or necessary, and to determine methods that will confirm whether infection has been eliminated when clinical lesions have resolved.

The Beco et al guidelines<sup>3</sup> state the following:

Superficial pyodermas typically need two to three weeks of treatment ... 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 case of superficial infections, ... although the evidence for this is largely anecdotal, and overly long treatment regimens may increase selection pressure for resistance among commensal bacteria.

To the authors' knowledge, there have been no published therapeutic trials to validate the necessity for 21 days of oral antimicrobial treatment for SBF and certainly not for continuing therapy beyond a clinical cure. In contrast, similar evidence-based guidelines for treating skin and soft tissue infections in humans state that there are no guidelines to dictate a specific duration of therapy.<sup>4</sup> Those guidelines recommend topical therapy for 5 days or oral therapy for 7 days for impetigo, which may be the condition closest to canine SBF. They also state that, following initiation of antibiotic treatment, if there is no response in 5 days, there should be a search for the reason of nonresponse or other investigations to verify the diagnosis. While veterinary patients fundamentally differ from human patients in some respects—fur covering most of the skin, inability to control the urge to scratch, etc—the pathophysiology and clinical course of these dermatologic conditions are not different enough that dogs should require a drastically longer course of therapy than human patients.

### **Where did the veterinary recommendations originate?**

In the second edition of *Small Animal Dermatology*, published in 1976, Muller and Kirk state that deep pyoderma should be treated for at least 3 weeks and make no further comments on duration of therapy for superficial bacterial folliculitis.<sup>5</sup> There is no reference for this statement, and there are no good comments on the duration of antibiotic therapy for superficial infections.

However, when the next edition of the same textbook was published in 1983, despite no references cited in support, the recommended therapy was altered to increase duration of treatment for pyoderma, as follows: "Pyoderma should be treated for

14 to 21 days, pruritic superficial folliculitis should be treated for 30 to 60 days, superficial pustular dermatitis (impetigo) for 10 to 14 days and superficial folliculitis for 30 days."<sup>6</sup>

The fourth edition of the same reference text published in 1989 marks the inclusion of the "treated for 7 to 10 days after clinical cure" concept, indicating that such a threshold is typically reached in 3 to 4 weeks.<sup>7</sup> Yet again the text provides no supporting data for such a recommendation.

In the fifth edition of *Small Animal Dermatology*, published 6 years later in 1995, Scott, Miller, and Griffin recommend 14 to 21 days of systemic antibiotics for the treatment of superficial infections and 30 to 60 days for complex infections. On a different page, the authors state that SBF should be treated for 21 to 28 days. Lastly, there is the recommendation to administer antibiotics for 7 days after surface healing.<sup>8</sup> Once again, these recommendations are not referenced with any original study or publication.

Even in the seventh and most current edition of this reference text, published in 2013, the still-unreferenced recommendation continues to be advocated, where Miller, Griffin, and Campbell state that "to prevent relapses ... it is recommended that antibiotic treatment be continued for 7 days after surface healing."<sup>9</sup> There is no reference supporting the statement that continuing antimicrobial therapy would prevent relapses.

Other textbooks continue with these same recommendations: "A common 'rule of thumb' for duration of initial antibiotic treatment is to treat for 1 to 2 weeks past complete clinical resolution of signs. For superficial pyoderma, a 3- to 4-week course usually suffices, with 6 weeks occasionally necessary."<sup>10</sup> More recently published books repeat the statement that superficial pyoderma or bacterial folliculitis should be treated for a minimum of 3 weeks of antimicrobial therapy, with therapy extending 1 week beyond clinical lesion resolution, concluding that this would help prevent recurrence or relapse and even minimize the development of antimicrobial resistance.<sup>11-13</sup> Even veterinary textbooks that are not specifically written for dermatologists state this same, unreferenced statement. "Antibiotic therapy should be maintained for at least 1 week after the clinical cure for superficial pyoderma...."<sup>14</sup> Very current papers continue to include the same or similar statement, that traditional advice, based on clinical expertise, is to treat superficial pyoderma for 3 weeks (or 1 week beyond clinical cure).<sup>15,16</sup>

A review of the published literature that fostered these guidelines revealed that early studies investigating the use of various antibiotics to treat canine pyoderma, either superficial or deep, were designed with treatment to be continued for 7 or 14 days after all active lesions disappeared.<sup>17-21</sup> The stated hypothesis was that terminating antibiotic therapy prior to or at clinical resolution leads to a higher relapse rate. In some cases, response to therapy was assessed by physical exam, but in others, the assessment was conducted via telephone. In all cases, posttreatment follow-up was approximately 3 months and approximately 20% (18% to 29%) of dogs experienced a relapse within that time. None of these studies had

a control group treated with a shorter duration for comparison so the recommendation for duration of therapy could be validated to result in either a more successful outcome or fewer recurrences.

A single, double masked investigation<sup>22</sup> evaluated 14 days of oral systemic antimicrobial therapy (cefadroxil, 22 mg/kg, q 12 h) compared to a single injection of a long-acting cephalosporin (cefovecin, 8 mg/kg, SC) for treatment of naturally occurring secondary superficial pyoderma, abscesses, and infected wounds in dogs. Treatment success was defined as reduction of clinical signs to mild or absent 2 weeks after the discontinuation of therapy. At the final assessment, 14 days following the completion of treatment, 92.3% (108/117) of the cefadroxil group and 92.4% (109/118) of the cefovecin group were successfully treated. There was no report of long-term follow-up as to recurrence in this investigation. This single study provides the only evidence that a 2-week course of systemic antibiotics may be sufficient to provide a clinical cure for canine SBF, with no need to extend the treatment course “beyond a clinical cure.” Whether a shorter course (ie, 7 days) would work as well still needs to be studied.

Some of the deleterious effects of prolonged courses of antimicrobial treatment include the potential for adverse reactions, problems with client adherence, higher cost, and selection of antimicrobial-resistant organisms.<sup>23</sup>

There are studies that have provided good evidence that topical therapy can be effective as the sole antibacterial for treatment of superficial bacterial pyoderma or can also be used in combination with systemic treatments to potentially reduce the duration of systemic therapy.<sup>16</sup> Topical therapy may be challenging as it requires pet owners’ time and effort, and its use also relies on patients’ temperament.<sup>15</sup> However, different formulations such as shampoos, sprays, foams (mousse), wipes, creams, ointments, and gels are currently available, facilitating topical therapy recommendations and potentiating compliance and residual effects in different situations. To the authors’ knowledge there are no studies supporting the use of topical antibacterials post clinical cure as is recommended for the use of oral antibiotics.

### **Possible problems with extended systemic antimicrobial treatment beyond a clinical cure for dogs with SBF**

The coagulase-positive and coagulase-negative staphylococci, which are normal commensals of the skin and mucosa of most dogs, are typically susceptible to most of the commonly used antimicrobials (ie,  $\beta$ -lactams, sulfa drugs, lincosamides, and fluoroquinolones).<sup>24,25</sup> When a dog with SBF is treated with a systemic antimicrobial, the susceptible bacteria are rapidly killed, potentially leaving behind resistant bacteria. These are usually controlled by the immune system.<sup>26</sup> Though if the underlying cause for the infection isn’t controlled and the antimicrobial continues to be administered, there is an increased chance that subsequent infections will be caused by these resistant or even multidrug-resistant patho-

gens.<sup>27</sup> One study demonstrated that the longer the course of  $\beta$ -lactam therapy and the more frequent the treatment was administered to dogs, the more likely the subsequent infection was caused by a methicillin-resistant *Staphylococcus*.<sup>27</sup>

First, in addition to antibiotics’ curative power, their use naturally selects for preexisting resistant populations of bacteria in nature. Second, it is not just “inappropriate” antibiotic use that selects for resistance. Rather, the speed with which resistance spreads is driven by microbial exposure to all antibiotics, whether appropriately prescribed or not.<sup>28</sup>

Another study<sup>29</sup> showed that dogs that were treated with a “short duration” of antibiotic therapy (< 21 days) were less likely to have methicillin-resistant *S pseudintermedius* when the infection recurred than those that had received treatment for a longer time. Despite this, the authors still concluded that an appropriate treatment duration for canine superficial pyoderma is 1 to 2 weeks past clinical resolution.

In addition to rational drug selection, the correct dose and length of treatment should be prescribed. Therapy should be continued until at least one week past clinical resolution. This usually requires a minimum of three weeks of therapy and it can take up to six or eight weeks to achieve this endpoint. Discontinuation of therapy has potential consequences on selection of resistant bacteria, re-colonization and re-infection.<sup>30</sup>

Since dogs with complex dermatologic conditions may be referred to a specialist once 1 or more treatment efforts fail, veterinary dermatologists see a skewed population of patients compared to the general pet population and are more likely to culture antimicrobial-resistant pathogens than general practitioners.

### **What should happen in veterinary medicine now?**

Overtreating human patients who have an established infection is likely a major source of selective pressure that drives antibiotic resistance.<sup>31</sup>

Spellberg<sup>32</sup> proposed that the old dogma of continuing therapy past resolution of symptoms be replaced with a new, evidence-based dogma of “shorter is better” with the following finding: “short-course therapy was just as effective as longer courses and often with better point estimates of clinical success, fewer adverse events, and/or diminished emergence of resistance at the site of infection.”

To effect change as a veterinary profession, the term “cure” in the context of SBF needs to be defined. Bacteria that are part of the normal microflora cannot be eliminated from the patient; therefore, the concept of “cure” is misleading and should not be the clinical goal. Rather, resolution of clinical signs is appropriate.

Newer FDA outcomes for clinical trials of skin infections in humans focus on early response (eg, improvement of clinical manifestations such as area of erythema at 72 hours after initiation of study). Moving forward, blinded clinical investigations to determine noninferiority should proceed to establish any benefit to systemic antimicrobial treatment for 7, 10, 14, or 21 days or beyond a clinical cure as well as the frequency of relapse or time to recurrence. Such a trial is currently

being conducted by the University of Illinois School of Veterinary Medicine, where dogs are being evaluated every other week for up to 2 months after clinical resolution (C Souza, DVM, MS, PhD, DACVD, College of Veterinary Medicine, University of Illinois, personal communication, February 13, 2022). There would also need to be agreement on when a subsequent infection would be classified as recurrent or a relapse (eg, within a month of discontinuation of systemic antibiotics) or a new infection. In all cases, the underlying cause of the SBF (eg, atopic dermatitis, hypothyroidism, cornification defect, etc) would need to be controlled or cured when looking at recurrent infections.

## Age of responsible use of antimicrobials

With the current knowledge of the increased prevalence of antimicrobial-resistant *Staphylococcus* in dogs and current guidance on responsible use of antimicrobials in human medicine, now is the time to reexamine dogma and develop scientific, evidence-based recommendations for the systemic treatment of canine SBF—which antibiotic, at what dose, and, most importantly, for what duration.

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