Managing Infections Associated With Atopic Dermatitis

Valerie A. Fadok, DVM, PhD, Diplomate, ACVD
North Houston Veterinary Specialists
Spring, TX
fadokv@aol.com

Atopy represents the inherited tendency to mount a skewed and flamboyant immunological reaction to environmental antigens such as pollens, molds, danders, and mites. In atopic dermatitis, there is also a skin barrier defect, with decreased ceramides in the stratum corneum and changes in structural proteins in the corneocytes. These changes make the skin more porous and thus allergenic proteins can penetrate more deeply into the skin, activating the immune response. The defective barrier also makes dogs more susceptible to secondary infections with Staphylococci and Malassezia.

Developing atopic dermatitis is dependent on genetic components and environmental exposure. A number of gene polymorphisms affecting innate and acquired immunity, as well as skin structure, have been identified. We know that the immune system is skewed toward a T helper 2 response, at least initially, and that cytokines released during the allergic response can bind directly to nerves to stimulate itch. Atopic dermatitis is a lifelong inflammatory disease that when uncontrolled progresses to a disease difficult to control.

CLINICAL SIGNS: Classical clinical signs of atopic dermatitis in the dog include face rubbing, foot chewing, and axilla and belly scratching, lending support to the idea that most atopic dogs experience their allergenic exposure through their skin, rather than through the mucus membranes of the nasal passages. Many dogs will have itch and inflammation in their ears. Secondary infections in the skin and ears are common, and they often make the itch 10X worse!

DIAGNOSIS: The diagnosis of atopy and/or atopic dermatitis is based on appropriate history and clinical signs, and ruling out other causes of itch, including occult scabies, flea allergy dermatitis, and in some cases, food allergy. Intradermal skin testing and/or blood allergy testing are used to select allergens for immunotherapy.

TREATMENT: Owners must understand that atopic dermatitis is not curable, but it can be managed and the key to success increases exponentially if we combine multiple therapeutic approachs, including topical. Basically we avoid allergens if we can (usually foods, fleas), use allergen-specific immunotherapy to modify the immune response (subcutaneous injection therapy or sublingual drops), control infections and ectoparasites, repair the skin barrier, and control itch.

INFECTION CONTROL IN ATOPIC DOGS: The major infections associated with atopic dermatitis are those caused by Staphylococcal species and those caused by Malassezia yeast. Often these infections are combined, and we must treat them effectively to keep atopic dogs comfortable.

Staphylococcal pyoderma: There are a number of reasons why dogs are more susceptible to skin infections than cats or horses or other animals with whom we work. Their hair follicles lack a lipid plug, they have a thin stratum corneum with

little intercellular lipid, their skin has a relatively high pH and in atopic dogs, the natural skin antibiotics, defensins, are decreased. Up to 90% of atopic dogs are colonized with their pathogen, Staphylococcus intermedius, in their noses, around their mouths and perianal area, and sometimes in the groin. So they are poised to develop staphylococcal infections whenever their skin barrier is disrupted or their cutaneous skin immune system is dysregulated. It has been shown in humans with atopic dermatitis that repeated staphylococcal infections drive the abnormal immune response, and some patients will make IgE against Staphylococcal proteins. The same is likely true for dogs.

Managing staphylococcal pyoderma in dogs should always involve bathing. Bathing makes dogs look, feel, and smell better faster, and it may enable us to shorten the duration of antibiotic therapy. We must pick the correct antibiotic, use it at the correct dose and interval, and for the correct duration. We know what antibiotics are helpful and we know how to dose them; however, we really lack any tangible evidence as to how long to treat pyoderma. Most of what we have learnt is dogma passed on through the generations. Simply, we should treat pyodermas until they are resolved and no longer! We don't want to use antibiotics for long periods of time because the risk of selecting resistant mutants will increase. Likely the rate to cure will be affected by the individual dog, the strain of Staphylococcus and its virulence, and the antibiotic used.

In order to treat infection effectively, we need to characterize it, and we do that using cytology. This 5 minute test helps us identify whether the infection is caused by cocci or rods (some dogs will get infection with Pseudomonas or other gram negative rods) and whether Malassezia is also present. If cytology shows cocci only, then most dermatologists advocate for use of a cephalosporin. My personal preference is for cefovecin (Convenia, Zoetis), because it works quickly and close to 90% of superficial pyodermas in my patients will respond with one injection. We know that it is given, so compliance is under control! If cytology shows rods, then it is important to collect material for culture and sensitivity. We empirically start a fluoroquinolone, and my personal preference is for marbofloxacin (Zeniquin, Zoetis) at 5.5 mg/kg/day. This is the mutant prevention concentration for that drug, as opposed to enrofloxacin for which the MPC is 10-20 mg/kg, depending on the pathogen. If there is co-infection with cocci and yeast, then we want a cephalosporin and an antifungal agent.

Our recommendations for pyoderma management are changing due to the emergence of methicillin resistant Staphylococcus spp in our patients. We put an increased focus on identifying the underlying causes quickly and controlling them, so that we don't use repeated courses of antibiotics. For atopic dermatitis, it is much better to identify the condition when the dogs are young, so that they don't develop refractory disease that is difficult to treat. We want to prevent the recurrence of infections. In my opinion, we want to use antibiotics at high doses for short durations, rather than low doses for long durations. We want to use the best in class, consider compliance and efficacy, and avoid the use of pulse antibiotics. We have come back to the use of Staphage Lysate for atopic dogs to help control recurrent infections, along with bathing and topical lipids to repair the skin barrier.

The first question we should ask is whether a systemic antibiotic is needed. For surface pyodermas such as those associated with folds or bacterial overgrowth, topical therapy is best. For folds, we have a variety of wipes and pads we can use

(e.g. Dechra Miconahex Tris and Tris-Chlor 4, DOUXO chlorhexidine with climbazole). We can also use topical silver sulfadiazine cream in folds; it will kill gram positive and gram negative bacteria, as well as yeast. Bacterial overgrowth in common in atopic dogs and these dogs need lots of baths!

For deeper infections (folliculitis, furunculosis), we do use systemic antibiotics. Empirical treatment of staphylococcal pyoderma is helped when we know our pathogen. The average S. pseudintermedius is not sensitive to penicillin, ampicillin, amoxicillin, and tetracyclines. So we would avoid those choices. We also try to avoid the use of fluoroquinolones empirically for staphylococcal pyodermas. These antibiotics are more effective against gram negative infections, and at least for the older fluoroquinolones, there is good evidence that they may promote resistance. I prefer a cephalosporin, and whenever possible, injectable cefovecin, because it reaches high levels in the skin rapidly and the levels stay above the MIC in the skin for 2 weeks. I have found that one dose will resolve most superficial pyodermas, particularly when some bathing is used. It is efficacious, has minimal side effects, and it helps avoid compliance problems. If I can't use cefovecin, then I like cefpodoxime 5-10 mg/kg every 24 hrs. I find that cephalexin used twice daily is less effective in my area of practice, so it is rarely my first choice. It may be best to use it every 6-8 hrs, but then compliance goes out the window.

We want to recommend bathing as well. If owners can bathe at least twice weekly for the first one to two weeks, then go to once weekly, dogs get better faster. Our literature suggests that chlorhexidine is the most effective against Staphylococcus pseudintermedius, and miconazole also has some antibacterial activity. The combination of chlorhexidine and miconazole is a great choice! Benzoyl peroxide and ethyl lactate appear to be less effective, and chloroxylenol, often used in generic shampoos, is not bactericidal. When selectin a shampoo, it is critical to use a good product. Formulation is critical and it is a false economy to buy generic shampoos.

Methicillin resistant staphylococcal pyoderma: If a pyoderma fails to resolve to two different classes of antibiotic, we have to worry about methicillin resistance. In my opinion, if the skin lesions do not respond to cefovecin, then either the infection is methicillin resistant, or the lesions are not due to staphylococcal infection. When MRS is suspected, we have to collect samples for culture and sensitivity, because we can't predict what will work. The happy news is that these are not MRSA (methicillin resistant Staph. Aureus), the human pathogen. Most dogs are infected with MRSP (methicillin resistant S. pseudintermedius) or MRSS (MR S. schleiferi). MRSP is not more contagious or more virulent; it is just harder to treat. We pick antibiotics based on culture and sensitivity but there are a few hints. If your sensitivity shows that the MRSP is sensitive to clindamycin, check the sensitivity to erythromycin. If the bug is resistant to erythromycin, then clindamycin is much less likely to work. This is a simple way to estimate the presence of clindamycin-inducible resistance. The dogs may initially look better with clindamycin but then they relapse. Also a good tip for doxycycline is to check the MIC. Dr. Papich and others have determined that the breakpoints used by our microbiology labs for doxycycline and S. pseudintermedius may not be correct. If the MIC is higher than 1 microgram/ml, don't use it as it likely will not work.

Usually we are left with three choices: chloramphenicol, amikacin, and rifampin. Chloramphenicol is used at 30-50 mg/kg every 8 hrs; it commonly causes nausea,

vomiting, and diarrhea. When used for 30 days, it may induce a rear limb paresis as well, that goes away when we stop the drug. It can cause bone marrow suppression in some patients, although not the aplastic anemia that occurs in humans. We recommend that our owners handle the drug with gloves. Amikacin, an aminoglycoside, has the potential for renal toxicity, but it is safer to use than gentamicin. It is given subcutaneously at 15 mg/kg every 24 hrs. For healthy dogs, we recommend monitoring a urinalysis once to twice weekly, checking for casts, proteinuria, or a drop in specific gravity. Many dogs tolerate this antibiotic very well, although it doesn't always work well for superficial pyodermas. We have had some success with using amikacin in Tris EDTA as a topical spray twice daily. Injectable amikacin is added to Tris EDTA to a final concentration of 5 mg/ml. This mix can be used in ears as well. Rifampin can be used as the sole antibiotic if necessary. It has the potential for liver toxicity, and we recommend that we keep the dose at 10 mg/kg every 24 hrs. Higher doses may be more likely to induce hepatic problems. Monitoring liver enzymes every 10-14 days is recommended.

Bathing dogs with MRSP is critical. I have found that bathing dogs 2-3 times a week with chlorhexidine shampoos allows me to keep the duration of rifampin at two weeks. When no antibiotics are feasible, we can resolve MRSP with daily bathing for 3-4 weeks with chlorhexidine shampoos.

Topical mupirocin can be used on focal areas when MRSP is present. We have had success mixing it in HydroPlus brand of Burow's + hydrocortisone to use as a lotion for feet and also in the ears when MRS are present. 11 grams of mupirocin are added to a 2 oz squeeze bottle then HydroPlus added to 2 oz. The mix is shaken until the material is compltely emulsified, then used twice daily.

Once MRSP has been documented in a dog, we have to culture the infection each time we see it. We can't rely on old sensitivity tests as new resistances can develop.

Staphage Lysate: This product fell out of favor when pulse antibiotic therapy became commonplace. We no longer recommend pulse antibiotic therapy for dogs with recurrent pyoderma. We emphasize finding and treating the underlying cause, using bathing and other topical therapy, and using oral fatty acids and topical lipids to help repair the skin barrier. Some atopic dogs though still get recurrent infections and these dogs may be helped by Staphage Lysate. SPL is also useful for dogs with itchy pyodermas where the itch completely resolves with antibiotics, but the pyodermas come back quickly. When no underlying cause is found SPL is worth using. Dogs can show positive skin test reactivity to SPL, as well as anti-staphylococcal IgE in their serum. These findings suggest that dogs do have staphylococcal hypersensitivity. In that case, SPL might actually work as an allergy vaccine. The schedule that I use is as follows:

Week 1: 0.25 cc subcutaneously
Week 2: 0.5 cc subq
Week 3: 0.75 cc subq
Week 4: 1.00 cc subq then 1 cc weekly.

SPL will not resolve an active infection; dogs should be given an appropriate antibiotic to resolve the pyoderma as the SPL is started.

Malassezia dermatitis: The presence of Malassezia is always a complicating factor. Daily bathing with an imidazole-containing shampoo (DOUXO chlorhexidine with climbazole, Malaseb, Miconahex-Tris, Mal-A-Ket, KetoChlor) will reduce yeast numbers without having to resort to systemic therapy but not many people are willing to bathe their dogs daily. Therefore, we use a combination of ketoconazole 5 mg/kg once daily or fluconazole 5 mg/kg once daily with once to twice weekly bathing with Malaseb or one of the other shampoos. Itraconazole (5 mg/kg/day) and terbinafine (30-40 mg/kg/day) can also be used. In particular, terbinafine has been useful for canine Cushing's disease patients being treated with trilostane. The use of pledgets or pads impregnated with chlorhexidine and an antifungal agent (e.g. DOUXO chlorhexidine pads, Dechra's Miconahex-Tris or Mal-A-Ket pads, TrisChlor 4 pads) on feet and focal areas of bacterial/yeast colonization has been a wonderful addition to allergy management! Some dogs are allergic to their yeast, and for these dogs we can add Malassezia allergen to their allergy injections or drops. Because it takes some time for the allergy vaccine to work, we can use pulse therapy with an oral antifungal agent 2-3 times weekly for 3-6 months.

SOURCE FOR GOOD INFO ON MRS and other infectious diseases

Worms And Germs Blog
http://www.wormsandgermsblog.com/promo/services/

Table of Antibiotic Doses for Canine Pyoderma

Cefovecin (Convenia)	**8 mg/kg subQ; repeat in 2 weeks if necessary**
Cefpodoxime (Simplicef)	**5-10 mg/kg QD (higher doses best)**
Cephalexin	**22-30 mg/kg TID**
Lincomycin (Lincocin)	**20 mg/kg BID**
Clindamycin	**11 mg/kg QD to BID**
Amoxicillin-clavulanate (Clavamox)	**20 mg/kg BID to TID**
Ormetoprim-sulfadimethoxine (Primor)	**27.5-30 mg/kg QD**
TMP-sulfa	**20-30 mg/kg BID**
Doxycycline (if sensitive)	**10 mg/kg BID**
Minocycline (if sensitive)	**5-10 mg/kg BID**
Marbofloxacin (Zeniquin)	**5.5 mg/kg QD**
Enrofloxacin (Baytril)	**20 mg/kg QD**
Ciprofloxacin (not recommended)	**30 mg/kg QD*** **
Chloramphenicol	**50 mg/kg TID**
Amikacin	**15 mg/kg subQ QD**
Rifampin	**5-10 mg/kg QD****

*** Ciprofloxacin, while inexpensive, is a second generation fluoroquinolone with less activity against gram + bacteria than we would like. It has been shown in 2 different studies to be very inconsistent in absorption. If used, use at the high dose. It may be helpful to crush the tablets to help promote absorption but we really don't know as much about this antibiotic in dogs as we would like (This from data provided by Dr. Mark Papich, NCSU, soon to be published).

****Keep dose at a max of 10 mg/kg/day to reduce risk of hepatic damage, including necrosis and death.

REFERENCES

1. Olivry T, DeBoer DJ, Favrot C, Jackson HA, Mueller RS, Nuttall T, Prelaud P, and International Task Force on Canine Atopic Dermatitis. 2010. Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the international task force on canine atopic dermatitis. *Veterinary Dermatology* 21:233-248.

   (this article is available for download at no charge at the following URL)
   http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3164.2010.00889.x/full
   it is also available at ExcellenceinDermatology.com

2. Marsella R, Sousa CA, Gonzales AJ, Fadok VA. 2012. Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. J. Amer. Vet. Med. Assoc. 241:194-207.

3. Bexley J et al. 2013. Serum anti-Staphylococcus pseudintermedius IgE and IgG antibodies in dogs with atopic dermatitis. Vet Dermatol. 24:19.

4. Farver K et al. 2005. Humoral measurement of type-1 hypersensitivity reactions to a commercial Malassezia allergen. Vet Dermatol. 16:261.

5. Draize, J. H. 1942. The determination of the pH of the skin of man and common laboratory animals. *J. Invest. Dermatol.* 5: 77-85.

6. Meyer, W., and K. Neurand. 1991. Comparison of skin pH in domesticated and laboratory animals. *Arch Dermatol Res* 283: 16-18.

7. Meyer, W., K. Neurand, and T. Bartels. 1991. The "protective acid coat" of the skin of our domestic animals. *Deutsche tierarztliche Wochenschrift* 98: 167-170.

8. van Damme, C. M., T. Willemse, A. van Dijk, H. P. Haagsman, and E. J. Veldhuizen. 2009. Altered cutaneous expression of beta-defensins in dogs with atopic dermatitis. *Mol Immunol* 46: 2449-2455.

9. Griffeth, G. C., D. O. Morris, J. :. Abraham, and S. C. Rankin. 2008. Screening for skin carriage of methicillin-resistant coagulase-positive staphylococci and Staph. schleiferi in dogs with healthy and inflamed skin. *Vet. Dermatol.* 19: 142-149.

10. Foster, G., and J. Barley. 2007. Staph scheiferi subsp coagulans in dogs. *Vet Rec.* 16: 496.

11. Rich, M., M. Jones, and V. Young. 2007. Staph schleiferi subspecies coagulans in companion animals. *Vet Rec.* 16: 107.

12. Igimi, S., E. Takahashi, and T. Mitsuoka. 1990. Staphylococcus schleiferi subsp. coagulans subsp nov. isolated from the external meatus of dogs with external ear otitis. *Int. J. Syst. Bacteriol.* 40: 409-411.

13. Baxter, C. G., and L. J. Vogelnest. 2008. Multifocal papular deep bacterial pyoderma in a Boxer dog caused by Pseudomonas aeruginosa. *Aust Vet J* 86: 435-439.

14. Hillier, A., Alcorn, L. K. Cole, and J. J. Kowalski. 2006. Pyoderma caused by Pseudomonas aeruginosa infection in dogs:20 cases. *Vet Dermatol.* 17: 432-439.

15. Ihrke, P. J. 1987. An overview of bacterial skin disease in the dog. *Br Vet J* 143: 112-118.

16. Pin, D., D. N. Carlotti, P. Jasmin, D. J. DeBoer, and P. Prelaud. 2006. Prospective study of bacterial overgrowth syndrome in eight dogs. *Vet Dermatol.* 158: 437-441.

17. Bassett, R. J., G. G. Burton, and D. C. Robson. 2004. Antibiotic responsive ulcerative dermatoses in German Shepherd Dogs with mucocutaneous pyoderma. *Aust Vet J* 82: 485-489.

18. Ihrke, P. J., and T. L. Gross. 2006. Warning about postgrooming furunculosis. *Journal of the American Veterinary Medical Association* 229: 1081.

19. Adams, V. J., J. R. Campbell, C. L. Waldner, P. M. Dowling, and C. L. Shmon. 2005. Evaluation of client compliance with short-term administration of antimicrobials to dogs. *J Am Vet Med Assoc* 226: 567-574.

20. Muto, C. A., J. A. Jernigan, B. E. Ostrowsky, H. M. Richet, W. R. Jarvis, J. M. Boyce, B. M. Farr, and SHEA. 2003. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of Staphylococcus aureus and enterococcus. *Infect Control Hosp Epidemiol* 24: 362-386.

21. Dalhoff, A, and Schubert. 2010. Dichotomous selection of high-level oxacillin resistance in Staphlyococcus aureus by fluoroquinolones. *Int J Antimicrob Agents* 36: 216-221.

22. Hanssen, A. M., and J. U. Ericson Sollid. 2006. SCCmec in staphylococci: genes on the move. *FEMS Immunol Med Microbiol* 46: 8-20.

23. Deurenberg, R. H., C. Vink, S. Kalenic, A. W. Friedrich, C. A. Bruggeman, and E. E. Stobberingh. 2007. The molecular evolution of methicillin-resistant Staphylococcus aureus. *Clin Microbiol Infect* 13: 222-235.

24. Weese, J. S., and E. van Duijkeren. 2010. Methicillin-resistant Staphylococcus aureus and Staphylococcus pseudintermedius in veterinary medicine. *Vet Microbiol* 140: 418-429.

25. Lee, S. M., M. Ender, R. Adhikari, J. M. Smith, B. Berger-Bächi, and G. M. Cook. 2007. Fitness cost of staphylococcal cassette chromosome mec in methicillin-

resistant Staphylococcus aureus by way of continuous culture. *Antimicrob Agents Chemother* 51: 1497-1499.

26. Faires, M., S. Gard, D. Aucoin, and J. S. Weese. 2009. Inducible clindamycin-resistance in methicillin-resistant Staphylococcus aureus and methicillin-resistant Staphylococus pseudintermedius isolates from dogs and cats. *Vet. Microbiol.* 139: 419-420.

27. Woods, C. R. 2009. Macrolide-inducible resistance to clindamycin and the D-test. *Pediatr Infect Dis J* 28: 1115-1118.

28. Kasten, M. J. 1999. Clindamycin, metronidazole, and chloramphenicol. *Mayo Clin Proc* 74: 825-833.

29. Wendt, C., S. Schinke, M. Württemberger, K. Oberdorfer, O. Bock-Hensley, and H. von Baum. 2007. Value of whole-body washing with chlorhexidine for the eradication of methicillin-resistant Staphylococcus aureus: a randomized, placebo-controlled, double-blind clinical trial. *Infect Control Hosp Epidemiol* 28: 1036-1043.

30. McConeghy, K. W., D. J. Mikolich, and K. L. LaPlante. 2009. Agents for the decolonization of methicillin-resistant Staphylococcus aureus. *Pharmacotherapy* 29: 263-280.

31. Landa-Solis, C., D. González-Espinosa, B. Guzmán-Soriano, M. Snyder, G. Reyes-Terán, K. Torres, and A. A. Gutierrez. 2005. Microcyn: a novel super-oxidized water with neutral pH and disinfectant activity. *J Hosp Infect* 61: 291-299.

32. DeBoer, D. J., K. A. Moriello, C. B. Thomas, and K. T. Schultz. 1990. Evaluation of a commercial staphylococcal bacterin for management of idiopathic recurrent superficial pyoderma in dogs. *Am J Vet Res* 51: 636-639.

33. Kloos, I., Straubinger, R.K., Werckenthin, C., and Mueller, R.S. (2013). Residual antibacterial activity of dog hairs after therapy with antimicrobial shampoos. Vet Dermatol *24*, 250-e54.

34. Loeffler, A., Cobb, M.A., and Bond, R. (2011). Comparison of a chlorhexidine and a benzoyl peroxide shampoo as sole treatment in canine superficial pyoderma. Vet Rec *169*, 249.

35. Murayama, N., Nagata, M., Terada, Y., Okuaki, M., Takemura, N., Nakaminami, H., and Noguchi, N. (2013). In vitro antiseptic susceptibilities for Staphylococcus pseudintermedius isolated from canine superficial pyoderma in Japan. Vet Dermatol *24*, 126-9.e29.

36. Murayama, N., Nagata, M., Terada, Y., Shibata, S., and Fukata, T. (2010). Comparison of two formulations of chlorhexidine for treating canine superficial pyoderma. Vet Rec *167*, 532-33.

37. Murayama, N., Nagata, M., Terada, Y., Shibata, S., and Fukata, T. (2010). Efficacy of a surgical scrub including 2% chlorhexidine acetate for canine superficial pyoderma. Vet Dermatol *21*, 586-592.

38. Murayama, N., Terada, Y., Okuaki, M., and Nagata, M. (2011). Dose assessment of 2% chlorhexidine acetate for canine superficial pyoderma. Vet Dermatol *22*, 449-453.

39. Young, R., Buckley, L., McEwan, N., and Nuttall, T. (2012). Comparative in vitro efficacy of antimicrobial shampoos: a pilot study. Vet Dermatol *23*, 36-40.

40. Stroh A, Werckenthin C, Luis CS, Mueller RS. 2010. Influence of a phytosphingosine-containing chlorhexidine shampoo on superficial bacterial counts and bacterial adherence to canine keratinocytes. Veterinary Microbiol. 141: 190-193.

41. Summers JF et al. (2012). The effectiveness of systemic antimicrobial treatment in canine superficial and deep pyoderma:a systematic review. Vet Dermatol 23:305.