Staphylococcus, Antibiotics, Resistance: Knowledge is Power

Staphylococcal bacteria are normal inhabitants of the skin of humans and pets. *Staphylococcus pseudintermedius* is responsible for approximately 96% of superficial pyodermas on dogs. There must be some break in barrier function or change to skin biology for these commensals to become pathogens. Diseases such as atopic dermatitis, food allergy, hypothyroidism, cushing’s disease are commonly complicated by secondary staph infections.

Scientist Alexander Ogston first coined the term Staphylococcus in 1882 for the spherical organisms he viewed under the microscope from suppuration associated with abscess in the skin. Modern scientific techniques have allowed investigators to determine that these seemingly simple organisms have quite complex characteristics. Of concern is the bacteria’s extensive arsenal of virulence factors and its ability to overcome antibiotic therapy. Antimicrobial resistance was documented in the human medical literature shortly after the introduction of antibiotics.\(^1\) The first published report of antimicrobial resistant staph in companion animals was in 1999.\(^2\) A recent review listed 18 genes responsible for contributing to antimicrobial resistance in staph bacteria.\(^3\) One such gene is the mecA gene which confers resistance to the beta lactam class of antibiotics. The mecA gene is contained in a genomic island called the SCCmec.. Under normal wild type conditions, a beta lactam antibiotic will impair the staph bacteria’s ability to build a cell wall thus killing the bacteria. A staph bacteria will no longer be susceptible to degradation once the the SCC mec gene island containing the mecA gene has been incorporated into a bacteria’s DNA. The bacteria then replicate and share the resistant genetics. Simply put, the current threat of acquiring methicillin-resistant strains of Staphylococcus is from exposure to a MecA positive Staphylococcus. Our patients are acquiring resistant bacteria strains from exposure to a carrier or fomite. The mecA gene is just one example of acquired antibiotic resistance that leads to methicillin resistant strains of staph bacteria. Bacteria can acquire higher levels of genetic resistance leading to multidrug resistant strains of bacteria.

Recurrent staph infections are frustrating for the practitioner and pet parent. Methicillin and multi-drug resistant strains can be downright distressing. As veterinarians we have a responsibility to be good stewards of antibiotic use so as to reduce contributions to the increasing incidence of antimicrobial resistance. The first and most important step is to prove a staph bacterial infection is present and that antibiotics are warranted. The author sees cases frequently in which antibiotics are administered for Malassezia dermatitis, pemphigus foliaceus or sarcoptic mange. Simple derm diagnostic tests such as tape and scrape can help you make informed therapy decisions. This is beneficial for everyone involved.

Second, utilize topical therapy as often as possible for focal infections such as otitis externa, facial or tail fold pyoderma, puppy impetigo of the ventral abdomen, etc. A series of studies was published in 2010 and 2011 and a review published in 2012 that provide evidence based medicine for topical therapy. Good evidence exists for using shampoos that contain 2-3% chlorhexidine for
bacteria, 2% chlorhexidene + 2% miconazole for bacteria & yeast and 2-3% Benzoyl peroxide for bacteria. Based on one study that included both owner and investigator observations, a 2% chlorhexidine acetate was shown to be as effective as a 4% chlorhexidine gluconate formula when dogs were bathed using 5 ml per 150 cm² body surface (~ 1.5 ml for 22 # dog) using the following protocol: gently wash with warm water, soak for 5 min, rinse & towel dry, bathe twice weekly. This publication included a second set of results which demonstrated efficacy of topical therapy against resistant strains of staph in 8 dogs. In an open trial study, dogs with a suspected methicillin resistant staph pyoderma were bathed with 2% chlorhexidene (Malseb: 50 ml per 30 kg (0.95 m²) by the following method: gentle washing, soak for 5 min, rinse and towel dry, every other day for 2 weeks pending C/S results. The dogs were evaluated 2 weeks later and scored by the investigator. Methicillin resistant Staphylococcus pseudintermedius was isolated from all 8 dogs. Results of the study showed that 5/8 dogs improved without the need for oral antibiotic, 1/8 improved with some need for oral antibiotic, 2/8 had no apparent improvement while 0/8 had worsening of clinical signs during treatment. A follow up to that study was published the following year which investigated the effective dose/volume of shampoo to use. Briefly, 27 dogs were divided into three groups of 9 dogs each. The dogs in each group were bathed every other day with Nolvasan surgical scrub with a different volume: 57 ml/m², 29 ml/m² or 19 ml/m². All groups showed statistically significant improvement. The best response per owners and blinded investigators was group 2 in which 89% showed excellent to good improvement. Only 2 dogs in group 3 showed deterioration.

Not all patients and not all infections are candidates for topical therapy and systemic antibiotic therapy is often necessary. We often think of choosing an antibiotic based on a classification of first, second and third tiers. It is common practice to reach for Convenia®, Simplicef®, Clavamox® or cephalexin for first time infections. It is acceptable to continue to reach for these antibiotics for relapsing infections when previous infections cleared readily and completely. A recent systematic review article provided the following conclusions:

- **Good evidence for high efficacy:**
  - Subcutaneous injections of cefovacin at 8 mg/kg given 2 weeks apart

- **Fair evidence for moderate to high efficacy of the following:**
  - Amoxi-clavulanic acid at 12.5 mg/kg, BID, 21-28 d.
  - Cefadroxil, 22-35 mg/kg, BID, 28-42 d.
  - Clindamycin, 5.5 mg/kg, BID, 21 d.
    - The author would like to highlight another study and encourage the use of clindamycin at a higher dose of 11 mg/kg BID, especially since it is often employed for treating methicillin resistant strains of staph.
  - TMPS, 30 mg/kg, QD or BID, 42 d.
  - Sulfa-ormetoprim, 55 mg/kg day 1, 27.5 mg/kg thereafter, 21-42 d.

- **Comparing duration of treatments:**
- 80% considered cured 14 d after single cefovacin injection at 8 mg/kg
- 70% considered cured 14 d after course of cefadroxil at 22-35 mg/kg, BID

We want to set our clients up to succeed when treating a superficial pyoderma. Evidence based medicine published in 2011 lists the top barriers for owner compliance. The number one barrier to client compliance is frequency of dosing. We can help our clients by choosing therapies that need to be given less frequently. The 4th barrier to compliance is a long duration of treatment. Treating for the shortest period of time will not only make our clients happy but will also decrease the time our patients spend in the “mutant selection window” (a term that is defined later in these notes). Treating for the shortest period of time does NOT mean 7 or 10 days total. Use the practice of treating for 5-7 days past resolution of the infection, this way therapy is tailored to the individual. One final practice we can use to maximize successful resolution of superficial infection is to use antibiotics at their highest recommended dose. This utilizes a concept called the mutant prevention concentration (MPC). It is simply not enough to target killing 90/100 strains of a staph bacteria (MIC90) instead we want to use antibiotic doses that will achieve concentrations to quickly kill all bacteria and kill bacteria with decreased susceptibility. This mutant prevention concentration needs to exceed the MIC90 but needs to be lower than the maximum safe concentration (MSC). Between the MIC90 and the MPC is the mutant selection window (MSW). Placing antimicrobial concentrations inside the window is expected to enrich resistant mutant subpopulations selectively while placing antimicrobial concentrations above the window is expected to restrict resistant selective enrichment. Future studies are needed to find the concentration of each antibiotic with each bacterium at which no mutant is recovered both in vitro and in vivo. This will help us not only control infection, but decrease resistance.

The patient that has rapidly relapsing superficial pyoderma or an infection that is not responding to appropriate first line antibiotic therapy may have acquired a resistant strain of bacteria. The author highly encourages repeating skin cytology to confirm the presence of the bacteria followed by submission of a sample for aerobic culture and sensitivity testing. Use aggressive topical therapy pending C/S test results. Chose an appropriate antibiotic based on test results. Antibiotic commonly used for resistant staph infections are ormetoprim-sulfa, TMP-SMZ, Clindamycin, Marbofloxacin, Enrofloxacin and Chloramphenicol. Doxycycline is commonly identified as an appropriate choice for resistant staph but the author cautions anecdotally of multiple treatment failures when using this drug class.

Fluoroquinolones (FQs) should never be used as a first line choice for treating superficial pyoderma. Four FQs have been approved for use in veterinary medicine: enrofloxacin, orbifloxacin, difloxacin, and marbofloxacin. Laboratory reports of sensitive versus intermediate versus resistant are based on interpretive criteria provided by Clinical Laboratory Standards Institute (CLSI) and are based on pharmacokinetic data (such as Cmax, AUC) and pharmacodynamic
data (such as MIC). The CLSI has provided these values for pets for the 4 approved FQs but NOT for ciprofloxacin. Therefore, labs use interpretive criteria for humans to report S, I, or R. We can all agree that bacterial pharmacodynamics & drug pharmacokinetics are not necessarily similar in dogs & humans nor in cats & humans. Additionally, ciprofloxacin bioavailability studies show the following: 70% in humans, 33-40% in dogs, 0-20% in cats. As summarized by Dr. Boothe in this 2006 publication: "As such, extrapolation of human interpretive criteria as a basis for an "S" versus "R" designation for cipro and canine pathogens is questionable" Dr. Boothe makes 4 additional conclusions that the author feels are very important to share with practicing veterinarians

- An isolate designated as R to one FQ is likely to be resistant to all
- Emphasized using high dose FQ
- With FQ use in companion animals increasingly being scrutinized by regulatory agencies and the public, continued use of cipro despite availability of 4 veterinary FQ's might not be prudent
- Use of generic human products markedly undermines incentives to pursue new animal drug approvals

Other investigators, including the CDC in 2006, have also published studies that warn against the use of FQs as a first line antibiotic and emphasize that the FQ's should only be used when directed by C/S test results.

To summarize, employ antimicrobial practices that

- resolve the infection rapidly & completely
- utilize a protocol with high probability of success from the start
- Once you decide to use antibiotics, go with the best in class antibiotic at optimal dose

One final point that is incredibly important to make after all this discussion of infection and resistance is to remember that the infections are secondary to something else. The infections will continue to relapse until you identify and address the underlying cause.

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