

Staphylococcus, Malassezia, and Pseudomonas: Why are they there and what to do about it.

The skin's normal structure and function serve as a very effective defense against infectious agents. Normal skin is designed to keep normal flora in control and prevent opportunistic infections.

Functions of the Skin

Barrier

- (1) Physical (Keeps the good stuff in and the bad out).
 - a. prevention of water, electrolyte & macromolecule loss
 - b. prevention of invasion by external agents: chemical, physical, microbial organisms
- (2) Physiologic (designed to kill or avoid organisms)
 - a. turnover rate - the routine turnover rate is 21 to 30 days for a keratinocyte to progress from basal layer to the surface. Injuries cause an increased mitotic rate resulting in a shorter time for keratinocytes to reach the surface. The skin continuously sloughs to help get rid of nasty bugs.
 - b. sebum and fatty acids are bacteriostatic and fungistatic
 - c. inorganic salts are antimicrobial
- (3) Immunologic - The skin is the largest immunological surveillance organ.
 - a. Langerhans's cells (antigen presenting cells) in the epidermis
 - b. lymphocytes, neutrophils, macrophages
 - c. IgA in sweat
- (4) Bacterial - the normal bacterial flora produces products that inhibit the growth of pathogens

Temperature Regulation

- (1) hair coat
- (2) cutaneous vasculature
- (3) subcutaneous fat
- (4) sweat (species specific)
 - a. horses - apocrine sweat
 - b. dogs & cats - eccrine sweat in footpads only

Secretion

- (1) apocrine glands - pheromones
- (2) sebaceous glands - antimicrobial
- (3) epidermal lipids - wax seal

When the skin is affected by almost any primary disease (allergies, endocrinopathies, parasites, autoimmune skin disease, etc) the normal structure and function of the skin is altered. These changes cause the effective antimicrobial defenses (salts, acidity, turnover, temperature, dehydration, etc) to become dysfunctional. The result is increased colonization, invasion, and secondary infections.

The infections are secondary to the primary/underlying disease. Obviously, aggressive antimicrobial therapies must be used to resolve the infection; however, until the primary skin disease is identified and controlled, the infections will continue to recur due to the changes in the skin defenses.

Changes that occur with skin disease the predispose to secondary skin infections.

Region	Function	Change with dermatitis
Epidermis -	Saran wrap	Transformed into permeable paper
	Dehydrated	Increased moisture allows organism adherence and penetration
	Turnover every 21 days	Turnover rate is changed to prevent normal maturation and exfoliation of cells
	Essential fatty acids and waxes: antimicrobial	Composition is altered decreasing the antimicrobial functionality
	Langerhans cells: search for antigens initiating a defense immune response	Langerhans cells will preferentially stimulate an allergic response which is ineffective against organisms
Dermis	Vessels cool the skin	Vasodilatation increases skin temperature - warm
Glands	Sebum: antimicrobial	Increased and altered composition is less antimicrobial and provided nutrients for yeast
	Sweat: antimicrobial	Increased and altered composition increase skin moisture
	Acidity	Increases in pH are less antimicrobial
	Salts	Diluted salt concentrations decrease the antimicrobial effect
	IgA	Decreases in IgA and switched to IgG secretion decrease antimicrobial effect
General		Pruritus damages the skin and spreads organisms from the mouth to the skin.

Staphylococcal Pyoderma

Pyoderma (bacterial folliculitis) is the most common skin disease in dogs. Secondary pyoderma is a complicating factor in most dermatologic conditions. Approximately 80 percent of allergic dogs will have an active secondary pyoderma at the time of diagnosis. The secondary infection complicates the evaluation and treatment of the patient due to its ability to alter the clinical pattern of disease and response to therapeutics.

Staphylococcus bacteria are Gram-positive cocci that are commonly found on the skin of most mammals. Most of the Staphylococcus organisms are innocuous inhabitants and cause few problems. There are several more aggressive (coagulase positive) species of Staphylococci that are frequently associated with cutaneous disease. In dogs, *Staphylococcus intermediates* is the most common cause of pyoderma; however, *Staphylococcus aureus* and *Staphylococcus schleiferi* have been documented and are emerging as pathogenic species.

Several key features make the coagulase positive Staphylococci particularly virulent pathogens. These bacteria are able to produce and secrete numerous cell products that cause severe tissue damage.

- Hyaluronidase - Degrades hyaluronic of connective tissue
- Coagulase - Converts fibrinogen to fibrin which causes clotting
- Kinases - Converts plasminogen to plasmin which digests fibrin
- Leukocidin - Disrupts neutrophil membranes and causes discharge of lysosomes
- Staphylokinase - Activates plasmin-like proteolytic activity that dissolves clots
- Streptolysin - Repels phagocytes and disrupts phagocyte membrane and causes discharge of lysosomal granules
- Hemolysins - Phospholipases or lecithinases that destroy cells by lysis
- Protein A - binds IgG in a non-functional orientation to avoid phagocytosis
- Exfoliative toxin - Alter keratinocyte function causing blistering
- Exotoxins - Induce local tissue damage and inflammation
- Toxin Shock Syndrome Toxins - Induce a severe systemic inflammatory reaction that can be fatal
- Super Antigen - Staph can cause a non-specific “super” immune response that induces systemic inflammatory changes

Staphylococci are also particularly adept at avoiding the effects of antibiotics. In particular, methicillin-resistant Staphylococci have emerged as a serious medical problem. These Staphylococci are able to develop and transfer resistance to numerous antibiotics by means of several divergent mechanisms. This flexibility allows them to rapidly adapt to new therapeutic strategies. Unique strains of *Staphylococcus aureus* have been identified that are resistant to all known antibiotics. Until recently, these extremely resistant Staphylococci were limited to the species *Staphylococcus aureus* and remained primarily a human dilemma. Recent reports have identified *Staphylococcus aureus* infections in dogs that are multidrug resistant and potentially zoonotic. *Staphylococcus schleiferi* has recently emerged as a common cause of canine pyoderma. *Staphylococcus schleiferi* has the ability to develop multidrug resistance (using similar mechanisms as *Staphylococcus aureus*) and is known to be zoonotic.

Treatment:

The three essential components of successful treatment of secondary bacterial pyoderma in dogs include the proper selection of antibiotic, treatment with appropriate dose and duration of antibiotic therapy, and the identification and control of all underlying dermatoses (allergies, endocrinopathies, autoimmune diseases, keratinization defects). Bacterial pyoderma is a common cause of pruritus. For this reason, it is important to determine the cause of a patient's pruritus (pyoderma, yeast dermatitis, allergies) rather than treating the itch with steroids. Topical therapy is also of great benefit to help mechanically remove organisms as well as providing a nonantibiotic method of killing the organisms. Shampoos containing chlorhexidine or benzoyl peroxide are highly effective at reducing the superficial colonization of *Staphylococcus*.

Treating first time pyodermas:

The overwhelming majority of first time bacterial pyodermas in dogs are caused by *Staphylococcus intermedius*. This organism has demonstrated consistent sensitivity patterns making empiric antibiotic selection possible. Amoxicillin with clavulanic acid and cephalexin are commonly used antibiotics that demonstrate good efficacy. Clindamycin, potentiated sulfur drugs, and erythromycin also demonstrate consistently good efficacy. The antibiotic selected should be used for a minimum of 21 days to eliminate the infection and allow the normal antimicrobial function of the skin to return to a more normal and effective function. If inappropriately low doses of antibiotic are used or if the duration of therapy is too short, the populations of *Staphylococci* are altered so that antibacterial resistance strains are selected leading to chronic/recurrent infections.

Treating chronic/recurrent pyodermas:

Dogs with chronic/recurrent *Staphylococcus* pyoderma almost always have an identifiable underlying disease. This primary disease alters the normal structure and function of the skin and predisposes the animal to secondary bacterial infections. Until the underlying disease is identified and controlled, the secondary bacterial pyoderma will recur. The cycle of recurrent infection is further complicated by the frequent use of low-dose antibiotic therapy for inappropriately short durations. The result is a multidrug resistant *Staphylococcus* species that requires more aggressive diagnostic assessment through culture and antibiotic sensitivity profiles so the appropriate antibiotic can be selected.

Dogs with recurrent chronic *Staphylococcus* pyoderma are more likely to develop multidrug resistant staphylococci species due to the long history of antibiotic treatment. It is usually best to perform a bacterial culture with antibiotic sensitivity profile to select an appropriate antibiotic for treatment. In these patients it is even more crucial to use high dose antibiotic therapy with long durations of treatment.

Treating resistant pyodermas:

If the patient is on seemingly appropriate doses of antibiotic for an appropriate duration (minimum of 21 days) without clinical improvement in the papular crusting alopecia lesions, a resistant *Staphylococcus* infection should be suspected. Other dermatoses that can mimic pyoderma include Demodicosis, dermatophytosis, scabies, and pemphigus. Once these differentials have been eliminated, the skin lesions should be cultured and antibiotic sensitivity profile performed to

help guide antimicrobial selection. It is especially important in these patients to use the highest possible antibiotic dose for sufficient duration to completely resolve the infection. The antibiotics should be continued for two to three weeks past complete clinical resolution to assure that the organisms have been eliminated. If antibiotic therapy is discontinued prematurely, the resistant *Staphylococcus* populations will be allowed to expand making additional treatment even more difficult.

In these cases high dose long-term treatment with fluoroquinolones seems to be an effective therapeutic option; however, resistance may develop especially with inappropriately low dose or short duration. Resistance to fluoroquinolones seems to be mediated by repeated exposure to suboptimal doses of the antibiotics rather than a single mutation event. This suggests that as long as high doses are used for prolonged durations, fluoroquinolone resistance is unlikely to develop. It is essential that if the case fails to respond or seems to reach a state of stasis (never proceeding to complete resolution), the patient should be culture and antibiotic sensitivity panel be performed to appropriately modify the antibiotic treatment protocol.

In patients with multidrug resistant *Staphylococcus* infections, it becomes paramount to find and control the underlying dermatoses. Aggressive diagnostic workups should be used to explore the endocrine status and identify any allergic disease. Cutaneous biopsies are often useful to determine if the patient has cutaneous changes typical of allergy, endocrine disease, autoimmune skin disease, or a keratinization defect.

Preferred antibiotics and doses:

Amoxicillin-clavulanate	22 mg per kilogram every 12 hours
Cephalexin	22 mg per kilogram every eight hours
	30 mg per kilogram every 12 hours
Clindamycin	10 mg per kilogram every 12 hours
Ormetoprim sulfadimethoxine	27.5 mg per kilogram every 24 hours (on the first day give two doses q12 hours)
Trimethoprim sulfa	15-30 mg per kilogram every 12 hours
Enrofloxacin	10-20 mg per kilogram every 24 hours
Marbofloxacin	5 mg per kilogram every 24 hours
Orbifloxacin	7.5 mg per kilogram every 24 hours

Malassezia Dermatitis

Yeast Dermatitis

Etiology

- Malassezia pachydermatis
- Secondary colonizer/invader
- Many primary conditions may predispose
 - atopy/food allergy/flea allergy
 - endocrinopathies

Clinical Presentation

- Intense pruritus
 - Not responsive to symptomatic therapies - they itch like crazy until you kill the yeast - even if you blast them with Depo (which you would never do :))
- Lichenification and hyperpigmentation
 - Ventral neck and/or axilla
 - Inguinal area

Before treatment



After treatment



Variable

- greasy seborrhea - terriers, hounds
- mucocutaneous
- Interdigital dermatitis - with brown nail discoloration

Diagnosis

- Clinical signs (treat if classic pattern is present)
- Cytology - generally most useful but sometimes hard to find
 - smears, scrapings, or scotch tape
 - new methylene blue or Diff Quick
 - heat fix - improves recovery
 - find budding yeast often associated with squamous cells on 100X (oil immersion)
- Culture
- Biopsy
 - may or may not see in stratum corneum or in follicles
 - Usually report states acanthosis (a non-specific change)

Therapy

Topical Shampoos (use as often as everyday - weekly for maintenance)

Antifungal shampoos

Ketoconazole shampoo

Miconazole shampoo/conditioner/spray

Chlorhexidine containing shampoos (4% works better)

Selenium sulfide shampoos

not as effective but cheap

1.0% selenium in Selsun Blue or veterinary selenium shampoos

best to increase contact time

may be contact sensitizer

Systemic

Treatment of choice for severe cases (like the Westie above)

Ketoconazole 10 mg/kg/day x 30 days

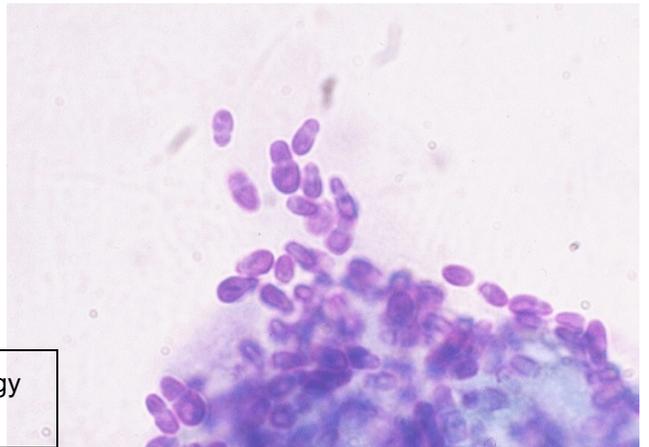
Itraconazole 5 mg/kg/day x 30 days

Most important - identify and treat underlying cause

Malassezia is ALWAYS secondary (allergies or endocrine)

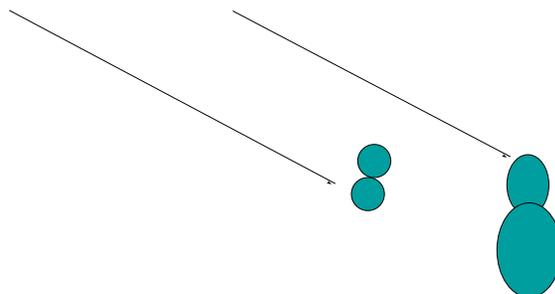


Malassezia
pododermatitis
note nail discoloration



Malassezia cytology

Size comparison between Staph and Malassezia:



Pseudomonas aeruginosa

Pseudomonas is an opportunistic pathogen of both human and veterinary species. This bacteria almost never affects healthy tissue but prefers damaged or diseased regions of the skin. Pseudomonas has a special affinity for areas of increased moisture suggesting that hyperhidrosis is a fundamental components of Pseudomonas infections.

Pseudomonas is commonly found in soil and water and is one of the most modal aquatic bacteria in ponds and lakes and can even be found growing in distilled water and hot tubs . Many cases of swimmer's ear are associated with opportunistic Pseudomonas infections. Approximately 3 to 5 percent of humans have Pseudomonas on their non-diseased skin at any given time. Pseudomonas is one of the main causes of nosocomial infections in United States.

Pseudomonas produces numerous products which increase its pathogenicity: protease, elastase, cytotoxin, hemolysin, leukocidin, pyocyanin, pyoverdin, and exotoxins. Pseudomonas produces a capsular slime layer that plays a role in adherence and invasion of the tissue as well as effectively protects the bacteria from the host's immunologic attack.

In dogs, Pseudomonas otitis is the principal disease process caused by this organism. Almost all cases of resistance Pseudomonas are associated with chronic and recurrent otitis induced by a primary/underlying disease (atopy, food allergy, hypothyroidism, Cushing's, and conformational abnormalities of the ear). It is likely that the chronic alterations in the otic microenvironment associated with persistent inflammation, sets up a state of hyperhidrosis which is preferred by Pseudomonas. The unique pathogenicity of Pseudomonas allows it to take advantage of the diseased tissue and develop resistance to antibiotics.

The single most important component for the successful treatment of chronic/recurrent otitis is control of the underlying disease process that has caused the alteration in otic microenvironment. Both allergies (atopy and food allergy) and endocrine diseases (hypothyroidism and Cushing's disease) are common causes of otitis . The infection will not be successfully managed and the recurrent otitis will not stop until the predisposing/underlying disease is identified and controlled. Bacterial culture's and antibiotic sensitivity profiles should be used to determine which organisms are present and for the selection of appropriate antibiotic therapy. During the course of treatment, cultures and antibiotic sensitivity panels should be repeated to monitor changes in the bacterial population and antibiotic resistance.

Recent information suggests that systemic antibiotics may not be appropriate as the sole treatment of resistance Pseudomonas infections. Currently, fluoroquinolone antibiotics have the most consistent efficacy against Pseudomonas; however, these antibiotics do not achieve ideal tissue concentrations even at maximum dosage protocols. Due to the extremely high MIC of Pseudomonas and the limited distribution of fluoroquinolone antibiotics into the skin, the optimal

antibiotic concentration of 5 to 10 times the MIC is not achieved. High concentration topical antibiotic solutions can be used successfully even in partially resistant infections. The extremely high concentrations of antibiotic in the topical solution can be administered directly to the infected tissue. Recently, there has been a trend to move away from systemic antibiotic treatment as the sole therapy for resistance *Pseudomonas* infections. Instead, high concentration topicals are used alone or in combination with systemic antibiotics to achieve optimal drug levels at the site of infection.

Therapy for Refractory *Pseudomonas* Infections

Recent studies suggest that systemic antibiotic therapy does not reach high enough tissue drug levels. This results in selection pressure that eliminated the normal flora and sensitive *pseudomonas* organisms leaving the resistant strains to populate the tissue. Even at the highest antibiotic doses (enrofloxacin 20mg/kg, marbofloxacin 5 mg/kg, etc) the drug levels in the tissue are not ideal and resistant *pseudomonas* infections develop.

Topical solutions can be formulated that have relatively high (extremely high) concentrations of antibiotic. This “super” solution provides a tool to effectively place ideal levels of drugs at the site of the infection, thus providing better results.

Dispense otic topical in dropper bottle with ear dropper so that owner can draw up exact amount of medication desired and directly instill it into the vertical ear canal with ease. Veterinary products that come in squeeze bottles or tubes can be easily repackaged in dropper bottles before dispensing to clients

Topical agents that may be effective include:

- Otomax; Schering (gentamycin, betamethasone, clotrimazole)
- Cortisporin Otic Suspension; Burroughs Wellcome (polymixin B, neomycin, hydrocortisone)
- Coly-Mycin S Otic; Parke-Davis (polymixin E, neomycin, hydrocortisone)
- Tobrex ophthalmic solution; Alcon Labs (tobramycin)
- Amikacin sulfate (Amiglyde-V Injection; Fort Dodge) use undiluted 50 mg/ml and instill 5 to 6 drops BID
- Silver sulfadiazine (Silvadene; Marion) diluted 1:1 in water and instilled BID
- Xenodyne solution (Solvay) dilute 1:5 in water and instill BID

Tris EDTA Solution

T8 Solution (DVM Pharmaceuticals) can be compounded with a variety of injectable antibiotics and used for therapy.

Can add enrofloxacin (100mg/ml injectable) to make a final concentration of 5-10mg/ml or gentamycin sulfate to yield a final concentration of 3 mg/ml or amikacin sulfate to yield a final concentration of 9 mg/ml.

Baytril injectable 100mg/ml solution mixed in T8 Solution (DVM) or Synotic

Long-Term Management in Allergic Otitis

Clean ears routinely 1 to 2 times a week

Resolve secondary bacterial and/or yeast infections

THEN USE

Long-term maintenance therapy with topical glucocorticoid instilled in ears as infrequently as possible to control inflammation. Products that often control allergic otitis include:

If ear infections recur in spite of topical steroids then long-term control may be achieved using a combination steroid/antibacterial/antifungal topical. The ears are treated twice a day until the infection has completely resolved and then the topical treatment is continued every 2 to 7 days as infrequently as possible for long-term maintenance.

Ototoxicity

Ototoxicity is extremely rare in veterinary medicine. What we are told about ototoxicity is mostly based on anecdotal reports, studies performed in species other than the dog and cat, or on reports where drug concentrations are much higher than what is found in proprietary medications.

For instance, in one study when 0.2% chlorhexidine was placed in the external ear canal of dogs with ruptured tympanic membranes, no signs of ototoxicity occurred.

In another study, when 0.3% gentamycin was placed twice a day for 21 days in the external ear canals of dogs with experimentally ruptured tympanic membranes, no signs of ototoxicity developed. However, cats may be more sensitive to aminoglycosides.

References available upon request.