Malassezia Dermatitis

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ABSTRACT: Malassezia yeast infections are recognized with increasing frequency in veterinary medicine. These opportunistic yeasts cause secondary ear and skin infections that can be extremely pruritic. Within the past 10 years, the Malassezia genus has been divided into seven species. This article describes the new species of Malassezia and their relevance to companion animals. Additionally, recognition, diagnosis, and treatment of Malassezia infections are discussed.

Yeasts fitting the description of Malassezia have been recognized on human skin since 1846. Their importance as members of the normal cutaneous biota and their role in disease continue to be prominent topics in human and veterinary medical literature. It is now generally accepted that Malassezia yeasts are commensal organisms of mammals and may also be associated with various cutaneous diseases. The predisposing factors and infectious properties of Malassezia are still a focus of research and debate. The following is a review of Malassezia yeasts and their role in cutaneous disease.

CLASSIFICATION
Due to their lipophilic nature, Malassezia species other than Malassezia pachydermatis can be very challenging to culture. This difficulty may account for the initial confusion in classifying the organism (it was identified based on cytologic characteristics alone for over 50 years). These yeasts, previously known as Pityrosporum, are now classified in the genus Malassezia.

The genus Malassezia is taxonomically located in the family Cryptococcaceae. Based on the structure of the yeast cell wall (laminar with distinctive spiraling ridges), positive urea hydrolysis, positive staining with diazinon blue B, and resistance of the cell wall to lysis by β-(1,3)-D-glucanase, Malassezia have been placed into the Basidiomycetes class. Malassezia are globose to ellipsoidal, lipophilic yeasts (Figure 1). Asexual reproduction occurs through monopolar budding from the same site (except for Malassezia sympodialis, which also exhibits sympodial budding). Each bud is separated by a septum. Every separation leaves a scar, or collarette, that can be visualized with light microscopy. Currently, seven species of Malassezia have been identified: M. pachydermatis, M. furfur, M. sympodialis, M. globosa, M. obtusa, M. restricta, and M. slooffiae. The species are defined by morphologic, physiologic, and molecular differences.

M. pachydermatis is usually isolated from animals, particularly carnivores. It is rarely identified on human skin but has been associated with fungal septicemia.
in neonates. M. pachydermatis is unique among the other species of Malassezia because in vitro growth is enhanced but not dependent on lipid supplementation. It is the only species of Malassezia that will readily grow on Sabouraud’s dextrose agar. Two phenotypically different M. pachydermatis colony types (large and small) have been isolated from dogs and cats. The small type is more difficult to subculture on Sabouraud’s dextrose agar after initial isolation on a lipid-rich medium. Recognition of this type of M. pachydermatis is important because it could be mistakenly identified as a lipid-dependent species. This small colony variant may have a transient requirement for lipids or could be exhibiting a period of adjustment to the new culture environment.

Using large subunit rRNA sequencing, M. pachydermatis has been divided into seven rRNA types or sequences (i.e., Ia through Ig). The canine isolates include Ia, Id, and le. Strain Id has the small-colony phenotype (less than 2 mm) and grows poorly on Sabouraud’s dextrose agar. Both Ia and le have large-colony morphology (greater than 2 mm) and grow readily on Sabouraud’s dextrose agar. Guillot and colleagues determined that the seven strains arose from weak mutations that occurred in the course of differentiation and adaptation to various animal species. They believed that the differences were not sufficiently significant to justify the division of M. pachydermatis into different species. This is supported by genetic analysis (RNA sequencing, nuclear DNA reassociation) of the strains.

The lipid-dependent Malassezia species lack the ability to synthesize the long-chain fatty acids necessary for their cell membranes and therefore require an exogenous lipid source (usually fatty acids within the C12 to C24 series, such as those in olive, corn, soybean, or safflower oils). M. furfur was the first lipid-dependent species characterized and has the highest degree of polymorphism. In culture, it is usually impossible to isolate pure colonies of round or oval organisms. When the yeast cells are sequentially subcultured, they change morphologically from round to oval cells (they rarely change from oval to round). The mycelial form is difficult to culture in vitro. The ability to form filaments is a characteristic of M. furfur, M. globosa, and M. obtusa.

M. sympodialis was the third Malassezia species to be identified and is named for its unique sympodial budding. It is the most common species identified on normal human skin and may be found on cats, horses, and cattle. The four newer Malassezia species are difficult to maintain in culture and may have strict lipid requirements. M. globosa is named for the typical round shape of the yeast cell. It exhibits relatively narrow-based budding and is often found on the skin of cats, cattle, and humans. M. restricta, named for its restricted growth in vitro, is found predominantly on the scalp of humans. M. obtusa is a relatively large yeast that is rarely isolated from healthy or diseased human skin. M. slooffiae is found most often on pigs and occasionally on humans and ruminants.

**Cutaneous and Mucosal Colonization**

M. pachydermatis has been isolated from the skin (chin, interdigital web, axilla, groin), ear canals, lip, buccal mucosa, anal sacs, vagina, and anal mucosa of healthy dogs. The role Malassezia plays as a member of the cutaneous and mucosal microbiota in dogs has been a matter of debate. Investigators have proposed that Malassezia is a resident of the skin, but it is generally isolated in low numbers from the skin and in high numbers from the mucosa of healthy dogs. This has led to speculation that M. pachydermatis is shed onto the skin from mucosal carriage sites. To date, M. pachydermatis is the most common Malassezia species isolated from dogs. It is possible that collection methods used thus far have been primarily directed toward isolation of the non–lipid-dependent species. In the future, it will be interesting to evaluate dogs for the presence of the newly recognized lipid-dependent species.

Malassezia is isolated less frequently from cats than dogs. It has been isolated from the skin, anal sacs, ears, and mucosa of healthy cats. M. pachydermatis, M. sympodialis, and M. globosa have been cultured from healthy cats.

**Virulence Factors**

The virulence factors for Malassezia yeasts have not been well defined. Zymogens from the cell wall of
Malassezia are capable of activating the complement system and liberating C5a anaphylatoxin. Lipases and lipoxygenases produced by Malassezia can alter sebum and may help the yeasts utilize cutaneous lipids as nutrients. Malassezia produces an extracellular glycoprotein that may also contribute to virulence.

Yeasts adherence to the stratum corneum may be an important factor in skin colonization and infection. In humans, there is a positive correlation between Candida species adherence and virulence. To date, this association has not been demonstrated with Malassezia yeasts. At this time, with the use of RNA sequencing, adherence assays, and electrophoretic protein profiles, there is no evidence that one strain of Malassezia is more pathogenic than another. These findings emphasize the opportunistic nature of Malassezia.

PREDISPOSING FACTORS

Due to the opportunistic nature of Malassezia, infection only occurs when there are changes in the cutaneous microenvironment or defense mechanisms. Various systemic disorders, cutaneous diseases, and medications have been reported as underlying causes of Malassezia infection. The relationship between these predisposing factors and yeast overgrowth is still being elucidated.

The cutaneous microclimate plays an important role in controlling Malassezia populations. Increased cutaneous relative humidity (as may be found in skin folds or ear canals) promotes yeast growth. Additionally, changes in skin surface lipids induced by hormonal effects, bacterial lipases, keratinization disorders, or nutritional deficiencies can encourage yeast proliferation. Excessive wax or cerumen in the ear canal has been reported as a predisposing factor of Malassezia otitis. Although human cerumen is reportedly mycostatic (Candida), canine cerumen often supports yeast growth.

The lipids and cells of the stratum corneum protect the skin against invasion by microorganisms. When this epidermal barrier is disrupted, secondary yeast and bacterial infections can occur. There are a variety of primary cutaneous and systemic diseases that decrease the cutaneous barrier function of the skin. One example is allergies, which cause inflammation, pruritus, and self-trauma. Parasitic, environmental, and dietary hypersensitivity disorders are common predisposing causes of Malassezia dermatitis and otitis. Endocrinopathies (e.g., hypothyroidism or hyperadrenocorticism) also predispose to Malassezia infections by causing alterations in skin surface lipids and the immune system. Other underlying diseases associated with disruptions in barrier function include metabolic disorders (e.g., necrolytic migratory erythema, zinc deficiency, cutaneous or internal neoplasia) Normal bassett hounds have increased cutaneous and mucosal carriage of M. pachydermatitis when compared with other breeds of dogs. Plant and colleagues also identified the dachshund as a breed that tends to have elevated cutaneous levels of Malassezia. This high carriage may be related to breed differences in cutaneous physiology (e.g., lipid composition, pH). Although the significance of these findings is not clear, bassett hounds and dachshunds are both predisposed to Malassezia yeast infections. Other breeds of dogs predisposed to Malassezia dermatitis and otitis include the American and English cocker spaniel, boxer, German shepherd, bloodhound, Lhasa apso, shih tzu, Maltese, miniature poodle, Shetland sheepdog, weimaraner, beagle, Chihuahua, collie, miniature schnauzer, cavalier King Charles spaniel, English setter, and terriers (i.e., West Highland white, Australian, Jack Russell, silky, cairn, Scottish, Wheaton, wire fox). Breed prevalence may suggest an inherited predisposition for Malassezia dermatitis or may be a reflection of a hereditary predisposition for underlying disorders (e.g., hypersensitivity).

Epidermal dysplasia of West Highland white terriers was previously reported as an inherited disorder characterized by a dysplastic epidermis that predisposes this breed to Malassezia infection. Recently, Nett and colleagues suggested that epidermal dysplasia of West Highland white terriers is an epidermal reaction to the presence of Malassezia yeasts, not a congenital keratinization disorder. In their report, resolution of the yeast infection resulted in the elimination of both inflammation and epidermal dysplasia.

Another proposed predisposing cause of Malassezia dermatitis is an altered immune system. Cutaneous populations of Malassezia are probably controlled by T-cell responses, chemotaxis of inflammatory cells, and activation of the alternative complement cascade. Bond and colleagues found no association between IgA deficiency and Malassezia dermatitis. In fact, dogs with Malassezia dermatitis had higher IgG and IgA levels than normal dogs. This evidence suggests that humoral immunity is not protective against Malassezia infection, a finding consistent with the reports of immunity to other fungal organisms (e.g., dermatophytes). The association between the cell-mediated immune system and Malassezia dermatitis is not as clear.

Antibiotic use has been proposed as a cause of M. pachydermatitis overgrowth and subsequent infection. Although this association between antibiotic use and fungal overgrowth has been documented in humans with Candida, it is not well substantiated in dogs with Malassezia. The likelihood that antibiotic therapy predisposes animals to infection with Malassezia is low. In fact, there is only one documented
case of *Malassezia* infection (stomatitis, pharyngitis, tonsillitis) that occurred 5 days after oral antibiotics were given to a dog for recurrent bacterial pharyngitis.\(^3\)

Little is known regarding the predisposing factors for feline *Malassezia* dermatitis and otitis, but they are probably similar to those discussed for dogs. *Malassezia* infections are not as common in cats, possibly reflecting the lower incidence of underlying causes in this species. Cats with feline leukemia virus and feline immunodeficiency virus were found to have increased populations of *Malassezia* in the external ear canal and on the coat compared with normal cats.\(^4\)

**MALASSEZIA-ASSOCIATED DISEASES**

In dogs, *Malassezia* yeast infections cause intense pruritus associated with erythema, yellow scales, and crusts. Most affected dogs have greasy, malodorous skin, with hyperpigmentation and lichenification (Figure 2). The skin regions that are usually affected include the face, paws, ventral neck, and abdomen. Additionally, infections may be localized to the interdigital areas, nail beds, lip, muzzle, and skin folds (Figure 3). *Malassezia* is also a common perpetuating factor of canine otitis externa and is characterized by pruritus and inflammation of the external ear canal and a yellow-brown waxy exudate.

It has been proposed that *M. pachydermatis* acts as an allergen in some dogs.\(^40,41\) Morris and colleagues demonstrated that atopic dogs with cytologic evidence of *Malassezia* dermatitis had stronger wheal and flare reactions to *Malassezia* antigen than atopic dogs without evidence of *Malassezia* dermatitis.\(^40\) A hypersensitivity reaction may explain why some dogs have such severe pruritus associated with *Malassezia* infections. *Malassezia* dermatitis is rare in cats.\(^42\) Excessive greasiness, exfoliative dermatitis, and pruritus are consistent features. *Malassezia* can be a perpetuating factor in feline otitis externa and may be associated with excessive cerumen accumulation, inflammation of the ear canal, and pruritus. *Malassezia* yeasts have also been isolated from lesions of feline chin acne, which may be related to the presence of relatively large sebaceous glands in this location.

**DIAGNOSIS**

Cytologic preparations are the most common technique used to detect *Malassezia* yeasts. There are several ways to collect cytologic samples, including a superficial skin scraping, a cotton swab, acetate tape impression of the skin, and direct impression of the skin with a glass slide. The wooden end of a cotton swab should be used to sample waxy debris from the nail beds. Although all of these methods are effective for moist lesions, acetate tape impressions or skin scrapings may be more effective for drier areas. Additionally, acetate tape is useful for areas that are difficult to access (e.g., the interdigital areas). The tape is pressed onto the lesion, then applied to a glass slide sticky side down. With the exception of tape...
preparations, the slides are heat-fixed and stained (Diff-Quik®, Giemsa, Gram’s, methylene blue). The tape preparation should not be heat-fixed; it should be stained with methylene blue or dipped into the purple solution of Diff-Quik® Solution II stain. The tape then acts as a coverslip through which to view the sample. Microscopic examination with 1000× magnification reveals round to oval yeasts (M. pachydermatis: 2.0 to 3.5 × 2.5 to 5.0 µm) with monopolar budding (Figure 1).

Since Malassezia is a member of the normal cutaneous biota, a small number may be found in cytologic preparations taken from a normal animal. The amount of yeast that is considered pathogenic is difficult to define. Some patients have large numbers of yeasts, whereas it may be difficult to isolate in others (a finding that led to the suspicion of a hypersensitivity response to the yeast cells). The best way to diagnose Malassezia infections is by combining the index of suspicion for infection, based on the historical and clinical findings, with cytologic evidence of Malassezia. Additionally, an animal with Malassezia infection should show a beneficial response to antifungal therapy.

Many techniques can be used to culture Malassezia from the skin but are not usually necessary because the yeasts are frequently found on cytology. Cotton swab, acetate tape, contact plate, and detergent-scrub methods have been described. Because most normal animals will have some yeast growth on a culture, interpretation should be based on history and clinical signs. A skin biopsy can be performed to identify yeasts and underlying causes of the Malassezia infection. Malassezia organisms are usually located in the stratum corneum in dogs and are occasionally seen in the follicular infundibulum. In humans, Malassezia yeasts can also be found in sebaceous glands and ducts. Due to the loss of some of the stratum corneum during processing, a biopsy is not typically considered a very sensitive diagnostic tool for Malassezia infections. There are many histopathologic changes associated with Malassezia infections. In dogs, prominent orthokeratotic hyperkeratosis, focal parakeratosis, crusts, irregular epidermal hyperplasia, epidermal spongiosis, lymphocyte exocytosis, and epidermal neutrophil infiltration are common along with budding yeasts in the crusts and orthokeratotic areas (Figure 4). The dermis may have superficial perivascular to interstitial inflammation. Subepidermal alignment of mast cells may be an important histopathologic indicator of Malassezia dermatitis in dogs.

When Malassezia yeasts are found, predisposing factors or underlying diseases must be identified. Additionally, many dogs with increased Malassezia yeast populations also have elevated cutaneous populations of Staphylococcus intermedius. These two organisms are probably mutually beneficial through utilization of products made by bacterial and yeast lipases. Therefore, patients with Malassezia dermatitis should be evaluated for a concurrent bacterial pyoderma.

**TREATMENT**

Animals with Malassezia infections usually respond well to antifungal therapies. To prevent recurrent Malassezia dermatitis and otitis, it is necessary to diagnose and address the underlying causes or predisposing factors of the Malassezia infection. In many patients, systemic antifungal medication is necessary to eliminate the infection. Topical medications are usually not very effective alone but are frequently used in conjunction...
with systemic therapies to speed relief and resolution of the disease and to help prevent recurrence.

The systemic agents used most commonly are the azoles (i.e., ketoconazole, itraconazole, fluconazole). These medications should be given with food. The most common adverse effects of the azole medications include anorexia, diarrhea, and vomiting. These side effects are usually dose related and may be eliminated by reducing the dose or dividing the dose into twice-daily treatments. Elevated serum liver enzyme activity, icterus, and hepatotoxicosis can also occur. Doses commonly used for Malassezia dermatitis include ketoconazole (5 to 10 mg/kg/day PO) or itraconazole (5 mg/kg/day PO) for 21 to 30 days. If the underlying cause of the infection cannot be easily controlled, the animal may require a longer duration of therapy or retreatment in the future. Controversy exists as to whether ketoconazole or itraconazole is more effective (fluconazole has not been extensively studied). In humans, ketoconazole and itraconazole are delivered to the stratum corneum through the sebaceous glands and can remain there for at least 10 to 12 days. This quality makes pulse-dosing iraconazole and ketoconazole for the treatment of fungal dermatitis an attractive option. The distribution of these medications in domestic animals has not been well established, but Pincheback and colleagues reported successful treatment of canine Malassezia dermatitis by giving iraconazole 5 mg/kg PO on 2 consecutive days per week for 3 weeks. In our experience, this pulse-dose therapy is effective, but it takes longer to see clinical improvement in some dogs. Griseofulvin is not effective against Malassezia.

Topical agents that are useful for Malassezia infections include ketoconazole, miconazole, selenium sulfide, enilconazole, zinc pyrithione, propylene glycol (50%), chlorhexidine (greater than 1%), nystatin, clotrimazole, coal tar, and lime sulfur. In vitro studies using Malassezia pachydermatis demonstrated that the antifungal activity of ketoconazole was superior to that of clotrimazole, miconazole, nystatin, and pimaricin. Topical antifungal products come in a variety of forms, including sprays, shampoos, and conditioners. Additionally, Malaseb™ Pledgets (2% chlorhexidine, 2% miconazole; DVM Pharmaceuticals, Miami, FL) are a convenient option for owners.

Otic preparations designed for otitis externa in dogs usually contain several ingredients. Some of the more common antifungal agents include clotrimazole, thiabendazole, nystatin, and miconazole. Ear cleaning products are often used in conjunction with topical medications to help decrease exudate accumulation and to acidify the ear canal. Dilutions of acetic acid (1:2 or 1:1), as well as products containing chlorhexidine, salicylic acid, lactic acid, boric acid, and surfactants, have been used for this purpose. Lloyd and colleagues evaluated the effects of an ear cleaning product (2.5% lactic acid, 0.1% salicylic acid [Epi-Otic®, Virbac, Ft. Worth, TX]) on bacteria and Malassezia yeast both in vitro and in vivo. In comparison with controls, the number of microorganisms decreased significantly both in vitro and in vivo after addition of the ear cleaning solution. Malassezia otitis is often a recurrent problem in dogs, and these cleaners may be useful adjuncts in controlling canine otitis externa.

Animals with Malassezia dermatitis or otitis usually begin to improve within 7 to 14 days of receiving antifungal treatment. Reevaluations, including a dermatologic examination and cytologic evaluation, should be done within 21 days to determine the animal’s progress. If clinical signs and cytologic evidence of Malassezia are still present, the animal may require an extended course of antifungal therapy. When iraconazole or ketoconazole is given systemically, a biochemical panel evaluating liver parameters should be done prior to therapy; parameters should then be monitored every 4 to 6 weeks. Concurrently, the predisposing cause of the Malassezia infection should be managed. Additional management in animals that continue to be pruritic after resolution of the Malassezia infection may include trial therapy for parasites, complete flea control, an elimination diet trial, or environmental allergy testing. Animals that are no longer pruritic should be evaluated for metabolic diseases or endocrinopathies.

**CONCLUSION**

Malassezia yeasts are opportunistic pathogens that can cause an intensely pruritic dermatosis in animals. Although different species of Malassezia exist, there is currently no evidence that one is more pathogenic than another. It is important to recognize the role that Malassezia yeasts play as a complicating factor in many dermatologic diseases. With increasing awareness of Malassezia and associated underlying causes of Malassezia infections, we should be able to increase the comfort of our pruritic patients.

**REFERENCES**

1. What is the most common species of Malassezia identified on dogs?
   a. M. sympodialis  
   b. M. canis  
   c. M. furfur  
   d. M. pachydermatis

2. What breed of dog has a relatively high carriage of Malassezia on normal skin compared with other breeds?
   a. shar-pei  
   b. English bulldog

3. Which of the following clinical sign(s) is consistent with Malassezia yeast infections?
   a. intense pruritus  
   b. yellow-brown waxy exudate in the external ear canal  
   c. greasy, malodorous skin  
   d. erythema, yellow scales, hyperpigmentation, and lichenification  
   e. all of the above

4. Which of the following medications has poor antifungal activity against Malassezia?
   a. griseofulvin  
   b. miconazole  
   c. clotrimazole  
   d. enilconazole  
   e. lime sulfur

5. The best way to interpret cytologic preparations stained to identify Malassezia is based on the
   a. number of yeast  
   b. concurrent presence of neutrophils  
   c. presence of budding, indicative of active proliferation  
   d. index of suspicion according to historical and clinical findings  
   e. concurrent presence of mast cells

6. Which species of Malassezia is not lipid-dependent?
   a. M. restricta  
   b. M. obtusa  
   c. M. globosa  
   d. M. sympodialis  
   e. M. pachydermatis

7. Which statement regarding Malassezia infections is false?
   a. Griseofulvin is not an effective treatment.  
   b. Malassezia yeasts are highly pathogenic and cause cutaneous disease in any animal exposed to them.  
   c. Malassezia may be involved in some cases of feline chin acne.  
   d. Concurrent infections with S. intermedius and Malassezia yeasts are common.  
   e. Malassezia infections may be localized to the interdigital areas, nail beds, lip, muzzle, or skin folds.

8. Which of the following statements regarding the genus of Malassezia is false?
   a. It contains seven species that can be differentiated based on morphologic, physiologic, and molecular differences.  
   b. It was previously classified as Pityrosporum.  
   c. It can produce lipases and lipoxygenases, which can alter sebum.  
   d. Of all the species, M. pachydermatis is the most common cause of infection in animals and humans.  
   e. All of the above
e. Asexual reproduction occurs through monopolar budding from the same site (except in *M. sympodialis*).

9. Which of the following is not a predisposing factor for *Malassezia* dermatitis?
   a. terrier breed
   b. female gender
   c. hypothyroidism
   d. hypersensitivity disorders
   e. neoplasia

10. Treatment of *Malassezia* dermatitis includes
   a. administering systemic ketoconazole or itraconazole and monitoring hepatic enzymes.
   b. reevaluation within 21 days, including examining the skin and collecting cytologic samples.
   c. shampoo therapy with miconazole, ketoconazole, or chlorhexidine.
   d. identification and treatment of an underlying cause or concurrent bacterial pyoderma.
   e. all of the above