Ringworm in Small Exotic Pets

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Dermatophytes are fungi that can use keratin as a nutrient source. These organisms invade keratinized tissue (skin, hair, and nails) and cause dermatophytosis or ringworm. Colonization is usually restricted to the nonliving, cornified layer of the epidermis because of the inability of dermatophytes to penetrate viable tissue of an immunocompetent host. However, infection does elicit a host response ranging from mild to severe that is related to the species and strain of fungus. Zoophilic species are primarily parasitic on animals, and infections are often mild or symptomless in exotic pets. Infection with unusual or geophilic (soil-associated) dermatophytes causes severe inflammatory lesions. Ringworm has long been associated with rodents and rabbits: it is common in rabbits and guinea pigs; uncommon in chinchillas, mice, and rats; rare in golden and dwarf hamsters; and unreported in gerbils. Dermatophytosis is rare in ferrets and unreported in pet African pygmy hedgehogs. In naturally occurring infections, *Trichophyton mentagrophytes* is the fungal species most commonly isolated; *Microsporum sp.* are occasionally reported. Because dermatophytes cause a communicable disease, pets that are symptomless carriers represent a potential zoonotic source to their owners. Current methods of diagnosis and clinical management of dermatophytosis, including a survey of recent trends in therapy are presented.

Key words: Dermatophytosis, ringworm, rabbits, guinea pigs, rats, mice, hamsters, chinchillas, ferrets, hedgehogs, *Trichophyton spp., Microsporum spp.*

Most fungi are saprophytes and do not cause disease in animals or man, even when they gain entrance into the body through inhalation or other ways. The few fungi that do cause disease are usually classified according to their clinical manifestation (Table 1). Within these 5 groups, dermatophytes are by far the most common and important fungi in exotic pets. Of the 4 other groups, only occasional reports of systemic and opportunistic mycoses occur, and rarely subcutaneous mycoses. To date, there have been no reports of superficial mycoses in exotic pets.

Pathophysiology

The only obligate parasites within the fungi are a taxonomically related group known as dermatophytes, which have the ability to use keratin as a nutrient source. Reminding people that fungi are not plants is still often necessary. The 3 main eukaryotic kingdoms are animals, plants, and fungi. Consequently, the correct term is "saprotrophe" rather than "saprophyte." Dermatophytes are classified traditionally into 3 anamorphic (asexual or imperfect) genera, *Epidermophyton, Microsporum,* and *Trichophyton,* which together contain over 40 species. Although these organisms are relatively similar, they can be distinguished by colony morphology, macroscopic appearance, and some biochemical tests. Recent comparison of nuclear ribosomal DNA (rDNA) sequences have led to the discovery of a teleomorphic (sexual or perfect) stage of several dermatophytes.[1,2] Before comparative studies of rDNA sequence were commonplace, a separate classification for asexual species was necessary. As more information based on comparative molecular biology becomes available, the need to classify asexual fungi separately becomes redundant. From our perspective, dermatophytes are now reclassified as the family Arthrodermataceae, which contains the genus *Arthroderma.* Most of the sexual forms of common veterinary dermatophytes are in this genus eg. *Arthroderma gypseum* is the teleomorphic form of the anamorphic *Microsporum canis,* and *Arthroderma benhamiae* is the teleomorphic form of the anamorphic *Trichophyton mentagrophytes.* It is now believed that the speciation of true dermatophytes or anamorphic Arthrodermataceae, resulted most likely from a very recent evolution by adaptation to parasitism. Adaptation to growth on humans and animals by dermatophytes appears to result in diminished loss of sporulation and sexuality.[1]

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Table 1. Classification of Fungi by Their Disease Manifestation

Clinical Manifestation	*Examples of Typical Fungal Infections*
Superficial mycoses	*Malassezia* infections
Cutaneous mycoses	Candidiasis, dermatophytosis
Subcutaneous mycoses	Sporotrichosis, zygomycosis
Systemic mycoses	Blastomycosis, coccidiomycosis, histoplasmosis
Opportunistic mycoses	Aspergillosis, cryptococcosis

NOTE. More common examples of fungi known to infect animals are listed. Superficial, cutaneous, and subcutaneous mycotic infections are referred to as dermatomycoses because the skin is infected. In dermatophytosis, only the keratin layer of the skin is affected.

Dermatophytes live in keratin layers of the skin and cause ringworm. The disease process in dermatophytosis is unique because no living tissue is invaded; the keratinized stratum corneum is simply colonized. However, the presence of the fungus and its metabolic products usually induces an allergic and inflammatory eczematous response in the host. The type and severity of the host response is often related to the species and strain of dermatophyte causing the infection. Dermatophytes do not live as saprophytes, and are the only fungi that have evolved a dependency on human or animal infection for the survival and dissemination of their species.

Dermatophytes are generally grouped into 3 categories according to their primary host or environmental source. Anthropophilic species are primarily parasitic on man. They are unable to colonize on other animals and have no other environmental sources. Geophilic species normally inhabit the soil where it is believed they primarily decompose keratinaceous debris. However, some geophilic species may cause infections in animals and man after contact with soil. Zoophilic species are primarily parasitic on animals, and infections may be transmitted to humans after contact with the animal host. Zoophilic infections are often mild or symptomless in exotic pets, but in man usually elicit a strong host response on the skin where contact with the infected animal has occurred (ie, arms, legs, body, or face).

Dermatophyte infection is acquired by contact with infected animals, or with soil or fomites carrying the pathogenic fungi. These fomites are usually hairs or skin flakes derived from infected animals. Under favorable conditions the fomites can remain infectious for 2 or more years. Infection normally involves contact between the dermatophyte arthrospores and keratinocytes or hairs. Adherence to the keratinocyte is followed by germination, after 2 hours or more, and the production of a filament that then invades the stratum corneum or mouth of the hair follicle.[3] In follicular infections, the hyphae proliferate on the surface of the hairs and grow toward the base of the hair, invading the hair shaft by means of keratinases. Penetration stops at the keratogenous zone. As hair growth continues, hyphae invade the keratinised inner root sheath and arthrospores are formed (Fig 1). Continuing invasion occurs only in growing hairs and ceases when the hairs enter telogen phase.[3]

Infection does not occur on healthy, intact skin, and spores reaching the skin may be removed by grooming or cleaning of the fur. Dermatophytosis can assume variable forms that are affected primarily by factors influencing the susceptibility or resistance of the host.[4] For example, only mild damage is required to make the skin susceptible to infection. Clipping, gentle rubbing, and occlusion have been used experi-

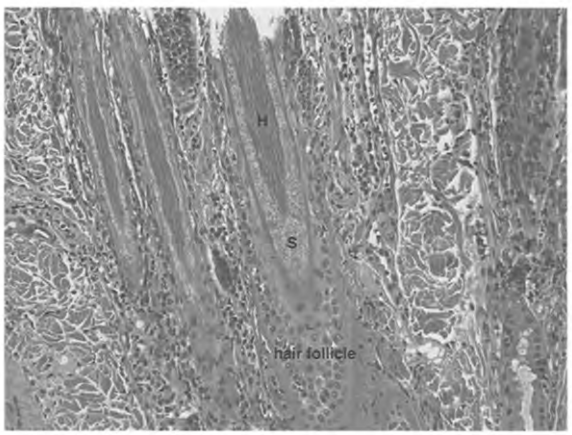

Figure 1. Section of skin with hair follicles that contain numerous fungal hyphae (H) and spores (S). Fungal spores are mostly present in the follicular keratin, whereas hyphae are mostly present within the hair cortex. There is marked multifocal follicular infiltration by neutrophils. Perifollicular dermal infiltrates of mixed lymphocytes, histiocytes, and some eosinophils are also seen. The presence of folliculitis generally indicates secondary bacterial infection. (hematoxylin and eosin [H&E] stain).

mentally.[5] Wetting and surface maceration, overshampooing, ectoparasites, and self trauma in response to pruritus may also promote dermatophyte invasion.[3,6] Immune status is important in determining susceptibility. Very young, old, or immunosuppressed animals are more vulnerable.[5,7,8] Genetic factors also seem significant both in relation to immune status and coat characteristics (eg, there is an increased susceptibility to chronic or inapparent infection in long haired cats).[9]

Infection in healthy animals is normally self resolving, and, unless exposed to a high level challenge, these animals develop long-term immunity to reinfection.[3,10,11] The severity of infection is partly dependent on the species and the strain of dermatophytes involved.[9,12] In both animals and man, infection with unusual or geophilic dermatophytes causes severe inflammatory lesions.[1] Specific antibody production to dermatophyte antigens in cats and guinea-pigs exposed to infection but not developing disease, suggests that active immune responses are involved in fighting off infection.[9,10] Chronic or recurrent infection is indicative of inappropriate immune responses or immunosuppression.[1]

Clinical Disease

Dermatophytosis has long been associated with rodents and rabbits. It is more common as a disease of rabbits and guinea-pigs. It is uncommon in chinchillas, mice, and rats; rare in hamsters (golden and dwarf hamsters); and unreported in gerbils. Dermatophytosis is rare in ferrets and unreported in pet African pygmy hedgehogs.

The major cause of dermatophytosis in rodents, rabbits, and other small exotic pets is confined to a single anamorphic fungal species, *Trichophyton mentagrophytes*. This species is one of the most polymorphic of the dermatophytes, and failure to recognize its range of forms in the past has led to confusion in the taxonomy and literature. Mycologists recognize 5 major forms of this organism:

1. *T. mentagrophytes* var. mentagrophytes, a zoophilic form of *T. mentagrophytes* with a worldwide distribution and a wide range of animal hosts including rodents, rabbits, kangaroos, cats, horses, and sheep.
2. *T. mentagrophytes* var. quinckeanum, a zoophilic form of *T. mentagrophytes*. On wild mice it causes a mouse favus. The geographical distribution of this dermatophyte is difficult to establish, but is probably worldwide. It is often associated with mice plagues in the Australian Wheat Belt.[13]
3. *T. mentagrophytes* var. interdigitale, an anthropophilic fungus that is a common cause of tinea pedis and tinea corporis in man. Distribution is worldwide.
4. *T. mentagrophytes* var. nodulare, an anthrophilic fungus that is an unusual cause of tinea pedis in man. It has a worldwide distribution.
5. *T. mentagrophytes* var. erinacei, a zoophilic fungus associated with the European hedgehog (*Erinaceus europeaeus*). The distribution of this fungus is New Zealand and Europe.

Mouse

Dermatophytosis is uncommon in pet mice and is caused by *T. mentagrophytes* var. mentagrophytes. Lesions, when present, are most common on the face, head, neck, and tail. The lesions have a scurfy appearance with irregular, patchy areas of alopecia, broken hairs, scales, and variable degrees of erythema and crusting. Pruritus is usually minimal to absent.[14,15] A more severe form of dermatophytosis, known as mouse favus, is seen on wild mice and is caused by *T. mentagrophytes* var. quinckeanum. The primary lesion is characterized by the development of thick, yellow, saucer-shaped crusted lesions up to 1 cm in diameter called scutula that consist of large quantities of dermatophyte mycelium and neutrophils.[16] *Microsporum spp.* infections of mice are rare. Difonzo et al[17] reported an outbreak of dermatomycosis due to *M. canis* in inbred C57/BL laboratory mice, and Feuerman et al[18] isolated *M. gypseum* from 3 out of 58 mice without disease in Israel.

From a clinical perspective, mice are important as symptomless carriers of *T. mentagrophytes* and represent an important zoonosis, especially for children with pet mice. Mackenzie[19] examined over 800 pet-shop and laboratory mice for *T. mentagrophytes*. There was a high incidence of the organism among laboratory animals (49 of 160 breeders and 104 of 149 nonbreeders), but lesions were only seen in 2 of the 104 nonbreeder positive carriers. Twelve of 20 pet shop

mice were infected. Fischman et al[20] studied *T. mentagrophytes* infection in a breeding colony of 42 white mice and observed symptoms in only 3 out of the 12 animals shown to carry the dermatophyte on their coats. Similar surveys in laboratory mouse colonies have shown similar asymptomatic carrier rates.[21]

Rat

Dermatophytosis is rare in rats and is associated with *T. mentagrophytes* var. mentagrophytes. It is very rarely reported in laboratory rats—the most recent report was in 1986.[22] The authors observed cutaneous lesions such as alopecia and hyperkeratosis due to the fungus in 10% of adult females and 44% of adult males. No infection was seen in infant rats, even in those fostered by infected females. *T. mentagrophytes* was isolated from 107 (90.7%) of 118 rats clinically diagnosed with dermatophytosis. Cutaneous lesions are most common on the neck and the back, and besides alopecia have variable degrees of erythema and crusting. Pruritus is minimal to absent.

T. mentagrophytes can be isolated from the haircoat of clinically normal rats and represents a potential zoonosis.[18,23,24] However, because of its rarity in laboratory rats compared with mice and guinea-pigs, it most likely poses a lesser potential zoonotic threat. Feuerman et al[18] isolated *M. gypseum* from 1 out of 47 rats without disease in Israel.

Guinea-pig

Dermatophytosis is common in guinea-pigs and natural infection is always associated with *T. mentagrophytes* var. mentagrophytes.[25-30] Lesions typically begin as broken hairs and circular, scaley alopecia initially occurring at the tip of the nose, which spread to the periocular, forehead, and pinnal areas. In severe cases, the dorsal sacrolumbral area is also affected, but the limbs and ventrum are usually spared. Pruritus is usually minimal or absent. Some animals have more inflammatory lesions characterized by erythema, follicular papules, pustules, crusts, pruritus, and occasional scarring. High temperature and humidity may contribute to a more severe infection.[28] *T. mentagrophytes* can be isolated from the skin and haircoat in up to 15% of clinically normal guinea-pigs and represents an important potential zoonosis.[15,31] Historically guinea-pigs have been an important cause of ringworm in humans.[32] In 40 patients diagnosed with ringworm contracted from experimental animals in Roumania, the animal source in 22 patients was guinea-pigs.[33]

There is some confusion in the literature regarding the potential for other dermatophytes to cause disease in guinea-pigs. Experimental infections with *M. canis, M. gypseum, T. verrucosum, T. equinum,* and *Epidermophyton spp.* have been described.[10,12,34-39] However, these infections are not naturally occurring and only result after inoculation with high-infective doses, selected pathogenic strains, or both on dermal-abraded skin. Unfortunately, several textbooks on guinea-pigs and small animal dermatology have failed to make this differentiation. Isolation of other dermatophytes is rare, the animals are without clinical signs, and the reports are 20- to 40-years-old. Koch and Reith[42] isolated *T. rubrum* from a colony of guinea-pigs in Germany; Feuerman et al[18] isolated *M. gypseum* from 3 out of 63 guinea-pigs in Israel; and 2 reports describe isolation of *M. audouinii.*[40,41] In a survey that included 22 patients who contracted ringworm from guinea-pigs, *T. mentagrophytes* was isolated in 20 patients, *T. rubrum* in 1 patient, and *M. audouinii* in 1 patient.[33]

Hamsters

Spontaneously occurring dermatophytosis is extremely rare in the Syrian or Golden hamster (*Mesocricetus auratus*). The only description is from Sebesteny who included *T. mentagrophytes* and *Microsporum spp.* as causes of skin lesions in Syrian hamsters.[43] He described infections with these dermatophytes causing dry, scaly lesions, encrustations with broken hair or no clinical signs. However, Sebesteny did not describe individual cases or present the incidence of infection. Alteras[33] reported a case of *T. mentagrophytes* infection that occurred on the arm of an elderly patient who came in contact with laboratory maintained Syrian hamsters in Roumania. However, cultures from suspected carrier hamsters were not performed.

In contrast to Syrian hamsters, infection due to *T. mentagrophytes* has been described in a laboratory colony of Djungarian hamsters (*Phodopus sungorus*) and a pet Djungarian ham-

ster.[44,45] There have been no reports of ringworm in humans handling Djungarian hamsters. Fungal infection has not been described in Roborovsky's hamster (*Phodopus roborovskii*), the other dwarf hamster that is being seen increasingly as a pet.

Gerbil

There have been no reports of naturally occurring or experimental dermatophytosis in the Mongolian gerbil (*Meriones unguiculatus*).

Chinchilla

Dermatophytosis is uncommon in chinchillas. Although *M. canis* and *M. gypseum* have been incriminated in outbreaks of spontaneously occurring dermatophytosis, *T. mentagrophytes* is the dermatophyte most commonly isolated.[46-49] Small scaly patches of alopecia on the nose, behind the ears, or on the forefeet are seen in infected chinchillas.[47] Lesions may appear on any part of the body, and in advanced cases a large circumscribed area of inflammation with scab formation is not unusual. Although most mycological studies of chinchillas are based on animals with clinical signs, *T. mentagrophytes* has been cultured in 5% of fur-ranched chinchillas with normal skins and 30% with fur damage.[47,48,50]

A popular theory in chinchilla fur-trade periodicals attributes a yet-to-be-discovered fur breakage fungus as the cause of fur chewing in chinchillas.[51] Consequently, some fur ranchers still regularly add fungicide to dust bath material to prevent fur chewing, despite the scant experimental investigation.[52] As part of a doctoral dissertation, Eidmann[53] cultured skin and fur of 39 fur chewers and 19 healthy chinchillas for bacteria and fungi. She concluded that an infectious etiology of fur chewing was unlikely and suggested that affected animals suffer from malnutrition and chew their fur for dietary requirements.

Rabbit

Dermatophytosis is common in the rabbit. *T. mentagrophytes* is the most common dermatophyte isolated from rabbits.[47,54-57] Infection with *M. canis* is occasionally reported and individual cases of *M. gypseum*, although rare, are infrequently described.[55,58-63] Infection with 3 other species, *M. audouinii, T. verrucosum,* and *T. schoenleinii* are extremely rare, and previous reports of these infections in rabbits were most likely due to misidentification.[41,64-67]

Young rabbits are most susceptible to infection. Lesions usually arise on or about the head, and are characterized by patchy alopecia, broken hairs, erythema, and yellowish crusting.[15] The lesions are pruritic and may spread secondarily to the paws, especially the toenail beds, and to other areas of the body.[67] Rabbits can be asymptomatic carriers of *T. mentagrophytes*. Franklin et al[56] found 5 out of 8 rabbits that cultured positive for *T. mentagrophytes* had no histological evidence of infection, and Balsari et al[68] isolated *T. mentagrophytes* from the haircoat and skin of up to 36% of clinically normal rabbits. These rabbits represent an important zoonotic source. Dermatophytosis in rabbits is usually self-limiting, although factors such as reduction of stress and improved environmental conditions are important considerations in lesion regression.[56]

Ferret

Dermatophytosis is extremely rare in the ferret. Despite constant descriptions of dermatophytosis in reviews of ferret disease, references citing specific cases or outbreaks are not provided.[69-72] Hagen and Gorham[47] also made this observation and Marini et al[73] described ringworm as a "potential" zoonotic disease of the ferret. To date there are still no specific reports of dermatophytosis in the ferret. However, there is one description by Hagen and Gorham[47] to an outbreak of *M. canis* over 3 successive years in the authors' ferret colony. In the first year, kits in 2 of 50 litters showed clinical signs of ringworm, but in subsequent years the ratio increased to 5 and then to 10 of 50 litters. No adults were involved in this outbreak.

Lesions appeared as large circumscribed areas of alopecia and inflammation on all parts of the kits' body. Skin was thickened, red, and covered with scaling crusts. As the kits became older, the lesions regressed and clinical signs of ringworm were no longer apparent when the kits were fully grown. The authors noted that some kits weakened and died when they were 2 to 3 weeks old. After the third year, ringworm did not appear again in the colony. The source of the outbreak

was unknown, but cats had access to the bedding used for ferrets.

Hedgehogs

The two most familiar hedgehog species are the European hedgehog (*Erinaceus europaeus*) and the Central African hedgehog (*Ateletrix albiventris*) that is native to subSaharan central and eastern Africa. The European hedgehog is indigenous to Western Europe, including the British Isles, is frequently kept as a pet in this part of the world, and is an introduced pest in New Zealand. In the United States, the Central African hedgehog is rapidly becoming a popular exotic pet and is commonly known as the African pygmy hedgehog. The European hedgehog is not kept as a pet in North America and the African pygmy hedgehog is not kept as a pet in Europe. Unfortunately, failure to differentiate between these two species has led to the misconception that ringworm is a common finding in the African pygmy hedgehog.

European hedgehogs in the wild are commonly infected with *T. mentagrophytes* var. erinacei.[74] However, many hedgehogs carry the fungus without developing any lesions.[75] Clinical signs are generally mild to minimal, with most lesions occurring on the face. A few animals will have extensive host reactions.[76,77] In these severe cases, owners initially notice a dandruff-like scaling of the skin that develops into patches of dry, crusty skin with bald patches where the spines have fallen out. Soft hair from the face, limbs, and abdomen is also lost. Small scabs may develop around the nose and lower face. Morris and English[76] suggested that prolonged and repeated exposure may be necessary for infection to be acquired, because animals under 1 year of age rarely develop ringworm.[78] This observation is in contrast to other forms of ringworm (eg, *M. canis* infection is more widespread in kittens than in adult cats).

European hedgehogs are believed to acquire ringworm by fighting or from contact with the linings of hedgehog winter nests. Male hedgehogs in the wild are infected more frequently than females, and this has been linked to their aggressive behavior during the breeding season.[76,78] A survey in southern England showed that the linings of approximately 25% (14 out of 60) of hedgehog winter nests contain *T. mentagrophytes* var. erinacei.[79] Fungus from infected nest material can survive for at least 1 year in dry nest debris, and is the most common source of indirect cross-infection among hedgehogs and man.

Well-documented cases of human ringworm associated with the European hedgehog have come from Smith et al[80] who recorded 103 patients with hedgehog ringworm in New Zealand, and English et al[81] who recorded about 20 cases in Great Britain. These authors concluded that most infections result from indirect contact with hedgehogs via infected disused nests or dogs that have fought hedgehogs. The few reports of ringworm associated with direct hedgehog contact are described in hedgehog rescuers.[77,82]

Gregory and English[83] described ringworm caused by *Arthroderma benhamiae* (see the beginning of article) in Central African hedgehogs caught near Nairobi, Kenya. Of the 45 animals examined, 10 were positive on culture, including a litter of 4 young. Six infected animals were without lesions, and 2 littermates showed scaly areas similar to those described in the European hedgehog caused by *T. mentagrophytes* var. erinacei.[84] However, ringworm-like lesions were found that were repeatedly negative on culture. The same authors have also obtained isolates of the conidial state of *A. benhamiae* from dry, scaly lesions on the ears of three hedgehogs in the Ivory Coast.[85] A human ringworm infection caused by *A. benhamiae* was associated with the hedgehogs caught in Kenya.

It is highly unlikely that ringworm caused by *A. benhamiae* will be seen in the US in pet African pygmy hedgehogs because the US Department of Agriculture forbids the importation of hedgehogs from Africa. All hedgehogs available in the American pet trade are captive born. Ringworm caused by *T. mentagrophytes* var. erinacei has not been described in African pygmy hedgehogs.

Diagnosis

Diagnosis of dermatophytosis is aimed at the identification of hyphae or arthrospores. A Wood's light, microscopic examination of hair and skin samples, and dermatophyte cultures are the basic tools. The Wood's light produces an ultraviolet light that results in a bright, yellow-green fluorescence on infected hair shafts.

Wood's light causes fluorescence in about 50% of *M. canis* infections and some strains of *M. audouiini, M. gypseum, T. equinum,* and *T. verrucosum.*[61,86] The other dermatophytes do not fluoresce. Consequently, dermatophyte infections of rabbits, rodents, and hedgehogs will not be detected by Wood's light.

For microscopic examination of keratinized structures, hair samples and skin scrapings should be collected from the margins of nonmedicated lesions, alopecic and adjacent areas. Infected hairs are most likely to appear stubbed, broken, or misshapen. To achieve good microscopic preparations, hair and scrapings should be suspended on a slide in a mixture of chlorphenolac, 10% potassium hydroxide (KOH)/dimethyl sulfoxide (DMSO) (1:1) and 20% KOH 1.2% Indian ink (2:1); alternative mixtures are 25% KOH with 5% glycerol, or a chlorphenolac cotton blue solution.[1,87] These solutions break down or "clear" tissue and cellular debris to provide greater visibility of fungal elements which contain chitin. Infected hairs are most likely to appear stubbed, broken, or misshapen. Fungal hyphae appear as branching and septate within the hair shaft and arthroconidia vary from bead-like to sparse chains. Although this technique is described in virtually every textbook or review on dermatophytosis, in my experience I find it is used infrequently. The technique is time-consuming, artifacts develop after preparation time, and experience is required to avoid misinterpretation if saprophytic fungal spores are present in the specimen. Because dermatophytosis is not a life-threatening disease, the preferred procedures for diagnosis of dermatophytosis are fungal culture and histopathology.

A fungal culture is required for a definitive diagnosis and is the only way to trace carriers of dermatophyte infections. For collection of the sample, a new toothbrush or surgical scrub brush is vigorously combed over all parts of the hair coat for 2 to 3 minutes. The bristles are then impressed onto the dermatophyte test medium (DTM) in several sites. For single lesions, hairs are collected and inoculated onto DTM after the lesion is clipped of excess hair, disinfected locally with 70% alcohol-impregnated gauze, and allowed to air dry. DTM is a selective medium that contains broad-spectrum antibacterial and antimycotic agents for the suppression of nonpathogenic bacteria and fungi, and indicators that change color as the pH of the medium alters with fungal growth (Fig 2). DTM offers the advantage that culture can be performed as an in-house procedure. For incubation, DTM containers should be loosely capped at room temperature and protected from ultraviolet light and dessication. DTM must be evaluated daily for 20 days; white mycelial growth and a color change to red within 10 days after inoculation is conclusive for the presence of dermatophytes. After 10 days saprophytic fungi can also induce a color change to red, so then further microscopic examination of the culture is necessary. The presence and morphology of macroconidia and microconidia finally determine the species involved.

Stained histological sections from biopsy may provide a diagnosis of ringworm. Routine hematoxylin and eosin (H&E) stain shows hyphae and arthrospores in hair shafts. Other stains, such as periodic acid-Schiff or Gomori's methenamine silver, selectively stain fungal elements, which makes identification easier. Histology does not detect carriers of dermatophytes and the identification of the genus and species of fungus always requires culture. However, histology offers the advantage of a rapid interpretation compared with fungal culture.

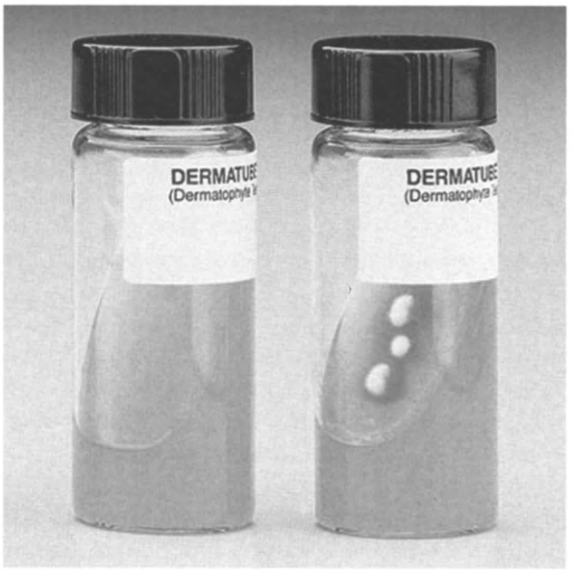

Figure 2. Dermatophyte test medium. There are two REMEL DermaTubes: one is uninoculated and the other is inoculated with a dermatophyte. Mycelial growth with color change of the surrounding media is seen in the inoculated tube. (Photograph courtesy of Remel Labs, Lenexa, KS.)

Clinical Management

Although spontaneous recovery has been reported, the unpredictable course of infection and the potential public health risk warrants treatment of all cases of ringworm. Management of dermatophyte infections should be directed at eradication of infectious material from the affected animals, in-contact animals, and the environment. In addition, treating animals cannot be limited only to local application with topical drugs; a combination with systemic treatment is mandatory. Consequently, the following recommendations are suggested: (1) isolate affected and nonaffected animals; (2) sanitize both the animal and owner's living environment; (3) trace carriers and in-contact animals; (4) gently clip affected animals to discard and loosen infectious hair and scale (even small trauma from the clipper blade may help to spread infection); (5) topically treat affected animals; and (6) systemically administer fungicidal or fungistatic drugs.

For topical therapy 2% chlorhexidine/2% miconazole shampoo, 0.2% enilconazole rinse, or lime-sulfur dips (4 to 8 oz per gal) are currently recommended as most likely to be effective.[87,88] Unpredictable toxicity of enilconazole has been reported in cats, although a study of 14 Persian cats using a 0.2% whole-body rinse produced no adverse reactions.[89,90] Consequently, if using enilconazole in rabbits and ferrets, I recommend caution and advise clients of the concerns. Local or spot treatment with imidazole containing preparations (eg, clotrimazole, ketoconazole, or miconazole) is not recommended because creams, lotions, and ointments are not formulated to penetrate infected hair shafts and follicles.

Topical treatment removes spores from hair shafts, and systemic treatment acts at hair follicles. Dosages recommended for dogs and cats are not based on modern pharmacological studies, but are extrapolated from human recommendations. Clinicians have found that the most effective doses are higher than the manufacturer's recommendations. This has resulted in unpredictable and significant toxicities. The dosages in small exotic mammals are extrapolated from cat and dog doses, so caution should always be used and clinicians must be on guard for idiosyncratic and toxic reactions. Drug interactions with systemic antifungals that may result in complications are listed in Table 2. Systemic drugs that can be used are griseofulvin (microsized form: 50 to 100 mg/kg daily in 2 to 3 divided doses), ketoconazole (10 to 15 mg/kg daily), itraconazole (5 to 10 mg/kg daily), and terbinafine (8 to 20 mg/kg daily).

Griseofulvin (Fulvicin; Schering, Kenilworth, NJ) is an antifungal antibiotic derived from *Penicillium griseofulvum.* It binds to keratin and inhibits fungal growth by disrupting mitosis. Ketoconazole and itraconazole are azole (imidazole) derivatives. Their principal mechanism of action is inhibition of hepatic cytochrome P-450 enzymes. The main enzyme inhibited in fungi is 14 α-demethylase, which is responsible for the conversion of lanosterol to ergosterol.[91] The azoles also interfere, to some extent, with the

Table 2. Drug Interactions With Systemic Antifungals That May Result in Complications

Antifungal Drug (Generic)	*Combination Drug (Generic)*	*Possible Adverse Effect*
Griseofulvin	Barbiturates	Decreased barbiturate effect
	Aspirin (NSAIDs)	Decreased aspirin effect
Ketoconazole and itraconazole	Warfarin	Increased anticoagulant effect
	H1-blocker antihistamines (terfenadine or astemizole)	Syncope and cardiac arrhythmia
	H2-blocker antihistamines (cimetidine or ranitidine)	Decreased antifungal effect (decreased absorption)
	Benzodiazepines (diazepam or midazolam)	Benzodiazepine toxicity (decreased benzodiazepine metabolism)
	Cisapride	Ventricular arrhythmia
	Cyclosporine	Renal toxicity
Terbinafine	H2-blocker antihistamines (cimetidine or ranitidine)	Decreased antifungal effect (decreased absorption)

Reports of adverse interactions are taken from Rizack[93] and are described in humans.

mammalian enzyme that converts lanosterol to ergosterol, and, therefore, toxicity can be a problem. Griseofulvin and the azole antifungals are generally considered fungistatic rather than fungicidal. Therefore, clearance of the organism from the host is dependent on immunocompetent host defenses.

Griseofulvin (Fulvicin, Schering) should be administered with food to avoid vomiting and the food should have a high fat content to enhance absorption. Particle size or micronization enhances oral absorption and bioavailability (ultramicrosized form: 5 to 10 mg/kg daily). This drug should not be given during pregnancy because of its teratogenicity. At higher doses than recommended, bone marrow depression with resultant panelukopenia may be observed. Consequently, hematological checkups every 2 to 3 weeks are indicated. Griseofulvin is effective against dermatophytes only, acts by damaging microtubuli in fungal cells, and is secreted into the skin through sweat glands.[87,92] In addition, griseofulvin (50 mg/kg daily for 14 days) can be used for prophylaxis.

Ketoconazole (Nizoral; Janssen Pharmaceutica, Titusville, NJ) should also be administered with a meal. The principal side effects include gastric irritation, hepatotoxicity, and anorexia.[92] Ketoconazole is not routinely recommended to treat ringworm and is contraindicated for male and female breeding animals because it inhibits Steroidogenesis. Ketoconazole inhibits the ergosterol synthesis of fungal cells.[87] To obtain proper absorption, an acid environment is essential; therefore, this drug should be given a few hours before feeding.[88] Ketoconazole should be reserved for cases in which intolerance of griseofulvin is a problem.

Itraconazole (Sporanox, Janssen Pharmaceutica) has a similar action to ketoconazole, is secreted through both sweat and sebaceous glands, and has a strong affinity to keratinocytes.[87] Incorporation of itraconazole into the keratinocyte basal membrane results in a continuous release to the skin surface until 3 to 4 weeks after finishing treatment. Most dog and cat patients tolerate the drug well at recommended doses, and itraconazole can be administered to young animals and pregnant animals with very low risk. Reported side effects are gastric irritation and elevated plasma liver enzymes.[92] A liquid suspension, with a higher bioavailability than capsules, is available.

One of the newer drugs is terbinafine (Lamisil, Basel, Switzerland), an antifungal allylamine derivative. This drug inhibits ergosterol synthesis independent of cytochrome P-450. It also affects fungal cells by inhibition of squalene epoxidase, resulting in increased amounts of squalene in fungal cells and subsequent cell membrane damage.[87] Terbinafine binds to plasma proteins, is keratophilic and lipophilic. In humans, it has been extremely effective for treating chronic dermatophytosis of the nails. Terbinafine concentrations are present in the corneal layers of the skin up to 3 weeks after the last administration in patients. Potential reported side effects include skin rash, gastrointestinal irritation, and elevated liver enzymes.[87]

Overall it must be realized that the use of trendy antifungal systemic agents does not routinely give better results. The use of drugs, of which there is hardly any experience in pet rabbits, rodents, and ferrets, should not be promoted. Environmental control should be performed every 14 days with enilconazole (0.2%), concentrated chlorine laundry bleach (1:10) solutions, or a detergent peroxide-based product; foggers with enilconazole or formaldehyde are also effective.[87] In contrast, steam cleaning for carpets is not recommended because the steam cools down to 40°C at the carpet surface. This temperature is insufficient for killing infectious spores. Special attention must be given to the bedding and clothing of people in contact with infected or carrier animals. For the latter, professional steam cleaning may be recommended. Contagious material may persist in the owner's clothing and bedding, and is a common reason for a pet's relapse after an initial response. In colony situations, euthanasia of one or more animals with proven responsibility for recurrences within a group (eg, rabbitery, guinea-pig colony, ferret farm) may be considered. Antifungal therapy must be continued until fungal cultures are negative twice, with a 4-week interval between cultures. Usually dermatophyte infections of the skin require a minimum of 3 to 4 months of therapy.

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