Veterinary Dermatology

WAVD World Association for Veterinary Dermatology

Vet Dermatol 2017; **28**: 266–e68 DOI: 10.1111/vde.12440

Diagnosis and treatment of dermatophytosis in dogs and cats.

Clinical Consensus Guidelines of the World Association for Veterinary Dermatology

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Background – Dermatophytosis is a superficial fungal skin disease of cats and dogs. The most common pathogens of small animals belong to the genera *Microsporum* and *Trichophyton*. It is an important skin disease because it is contagious, infectious and can be transmitted to people.

Objectives – The objective of this document is to review the existing literature and provide consensus recommendations for veterinary clinicians and lay people on the diagnosis and treatment of dermatophytosis in cats and dogs.

Methods – The authors served as a Guideline Panel (GP) and reviewed the literature available prior to September 2016. The GP prepared a detailed literature review and made recommendations on selected topics. The World Association of Veterinary Dermatology (WAVD) provided guidance and oversight for this process. A draft of the document was presented at the 8th World Congress of Veterinary Dermatology (May 2016) and was then made available via the World Wide Web to the member organizations of the WAVD for a period of three months. Comments were solicited and posted to the GP electronically. Responses were incorporated by the GP into the final document.

Conclusions – No one diagnostic test was identified as the gold standard. Successful treatment requires concurrent use of systemic oral antifungals and topical disinfection of the hair coat. Wood's lamp and direct examinations have good positive and negative predictability, systemic antifungal drugs have a wide margin of safety and physical cleaning is most important for decontamination of the exposed environments. Finally, serious complications of animal–human transmission are exceedingly rare.

Clinical Consensus Guidelines

Clinical Consensus Guidelines (CCGs) provide the veterinary community with current information on the pathophysiology, diagnosis and treatment of commonly encountered dermatological conditions. The World Association for Veterinary Dermatology (WAVD) oversees selection of relevant topics, identification of panel members possessing the expertise to draft the Clinical Consensus Guidelines, and any other aspects required to assure the integrity of the process. The statements are derived from evidence-based medicine whenever possible, however when such evidence does not exist then expert opinions would be utilized by the members of the panel. A draft is prepared by the panel, followed by a presentation of the guidelines at major national and/or international veterinary meetings. Access to the guidelines will be available on the WAVD web site. Solicitation for input from WAVD member organizations and affiliate and provisional member groups will result in the incorporation of this feedback into the guidelines. The final CCG manuscript will be submitted to the *Veterinary Dermatology* journal, where it is reviewed and edited before publication. The authors are solely responsible for the content of the statements.

Accepted 22 December 2016
Sources of Funding: This study was self-funded.
Conflicts of Interest: Karen Moriello has received honoraria, consulting fees, and/or has collaborated with: 3M Company, Pfizer Limited, Alpharma Co, Novartis Animal Health, Elanco Animal Health, Fort Dodge Laboratories, Delmont Laboratories, Dechra Animal Health, Bayer Animal Health, IDEXX Laboratories, Ogena Solutions, Kinetic Vet, Stanley Steemer and Zoetis Animal Health.
Kimberly Coyner has received honoraria, consulting fees, and/or has collaborated with: Dechra Animal Health and Pfizer/ Zoetis Animal Health.
Sue Paterson has received an honorarium, consulting fees and /or collaboration with Novartis Animal Health, Elanco Animal Health, Dechra Animal Health, Bayer Animal Health, Nationwide Laboratories, Ceva Animal Health, ICF, Zoetis Animal Health, Royal Canin and Merial Animal Health.
Bernard Mignon has received an honorarium, consulting fees, and/or has collaborated with American Cyanamid-Fort Dodge Animal Health, Auriga International, Bayer Animal Health, Dow Corning Europe SA, Eurogentec, Hoescht S.K.W., Janssen Animal Health, MNLpharma Ltd, Oystershell nv, Pfizer, Prodivet sa, Regivet bv, Schering-Plough Animal Health, Vernique Biotech Ltd and Virbac.

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Summary of the Clinical Consensus Guidelines

Diagnosis and treatment of dermatophytosis in dogs and cats

1 Prevalence and risk factors

a Determination of the true prevalence and breed predispositions for dermatophytosis is difficult because this is not a spontaneously occurring disease, it is not reportable and it is not a fatal disease. Infection varies in severity and resolves without treatment in many dogs and cats. All of these factors bias breed and prevalence predilection data.

b Subcutaneous dermatophytic infections have been reported most commonly in Persian cats, and Yorkshire terrier dogs.

c The activities of working and hunting dogs may increase their risk of exposure to dermatophyte spores and hence superficial and, less commonly nodular lesions.

d Seropositive FIV and/or FeLV status in cats alone does not increase the risk of dermatophytosis.

2 Diagnostic testing

a No one test was identified as a "gold standard".

b Dermatophytosis is diagnosed by utilizing a number of complementary diagnostic tests, including Woods lamp and direct examination to document active hair infection, dermatophyte culture by toothbrush technique to diagnose fungal species involved and monitor response to therapy, and biopsy with special fungal stains for nodular or atypical infections.

c Dermoscopy may be a useful clinical tool with or without concurrent use of a Wood's lamp to identify hairs for culture and/or direct examination.

d PCR detection of dermatophyte DNA can be helpful, however a positive PCR does not necessarily indicate active infection, as dead fungal organisms from a successfully treated infection will still be detected on PCR, as will non-infected fomite carriers.

e Contrary to what is believed, Wood's lamp examination is likely to be positive in most cases of *M. canis* dermatophytosis. Fluorescing hairs are most likely to be found in untreated infections; fluorescence may be difficult to find in treated cats. False positive and false negative results are most commonly due to inadequate equipment, lack of magnification, patient compliance, poor technique or lack of training.

f Monitoring of response to therapy includes clinical response, use of Wood's lamp if possible, and fungal culture. The number of colony forming units is helpful in monitoring response to therapy.

g Negative PCR in a treated cat is compatible with cure. Negative fungal culture from a cat with no lesions and a negative Wood's lamp (except for glowing tips) is compatible with cure.

3 Topical antifungal treatments

a Twice weekly application of lime sulfur, enilconazole or a miconazole/chlorhexidine shampoo are currently recommended effective topical therapies in the treatment of generalized dermatophytosis in cats and dogs.

b Accelerated hydrogen peroxide products as well as climbazole and terbinafine shampoos show promise, but cannot be definitively recommended until more in vivo studies documenting efficacy are available.

c Miconazole shampoos are effective in vitro but in vivo are most effective when combined with chlorhexidine.

d Chlorhexidine as monotherapy is poorly effective and is not recommended.

e For localized treatment, clotrimazole, miconazole and enilconazole have some data to document effectiveness. These are recommended as concurrent treatments, but not as sole therapy.

4 Systemic treatment

a Itraconazole (non-compounded) and terbinafine are the most effective and safe treatments for dermatophytosis.

b Griseofulvin is effective but also has more potential side effects compared to itraconazole and terbinafine.

c Ketoconazole and fluconazole are less effective treatment options and ketoconazole has more potential for adverse side effects.

d Lufenuron has no in vitro efficacy against dermatophytes, does not prevent or alter the course of dermatophyte infections, does not enhance the efficacy of systemic antifungal or topical antifungal treatments and has no place in the treatment of dermatophytosis.

e Antifungal vaccines do not protect against challenge exposure but may be a useful adjunct therapy.

5 Environmental disinfection

a Environmental decontamination's primary purpose is to prevent fomite contamination and false positive fungal culture results.

b Infection from the environment alone is rare.

c Minimizing contamination can be accomplished via clipping of affected lesions, topical therapy and routine cleaning.

d Confinement needs to be used with care and for the shortest time possible. Dermatophytosis is a curable disease, but behaviour problems and socialization problems can be life-long if the young or newly adopted animals are not socialized properly. Veterinarians need to consider animal welfare and quality of life when making this recommendation.
e Infective material is easily removed from the environment; if it can be washed, it can be decontaminated.

6 Zoonotic considerations
a Dermatophytosis is a known zoonosis and causes skin lesions which are treatable and curable.
b Dermatophytosis is a common skin disease in people but the true rate of transmission from animals to people is unknown.
c In people, the predominant dermatophyte pathogen is non-animal derived *T. rubrum* and the most common clinical presentation in people is onychomycoses (i.e. "toe nail fungus").
d The most common complication of *M. canis* infections in immunocompromised people is a prolonged treatment time.

1 Introduction

Dermatophytosis in companion animals is a skin disease caused by a superficial fungal infection of keratinized skin structures by zoophilic, geophilic or anthropophilic fungal organisms, most commonly *Microsporum canis*, *M. gypseum* and *Trichophyton mentagrophytes*. Because of the pleomorphic presentation of clinical signs, its infectious and contagious nature, and zoonotic potential, dermatophytosis is an important disease in small animal medicine. In most immunocompetent hosts, dermatophytosis is a self-limiting skin disease within weeks to months. Treatment is recommended with the goal of shortening the course of the disease to prevent spread to other animals and people.

A group was formed [called the Guidelines Panel (GP)] to collect and summarize evidence-based information on the pathogenesis, diagnosis and treatment of dermatophytosis in dogs and cats. Co-chairs of the group, Karen Moriello, Kimberly Coyner and Sue Paterson, and seven other panel members with experience in veterinary dermatology and mycology, from different areas of the world (Australia, Canada, China, France, Japan, Italy, Spain) collected, translated (when appropriate) and reviewed literature from 1900 to the present regarding canine and feline dermatophytosis. Search engines included Micromedex, PubMed, Scopus, UpToDate and Web of Science. Proceedings and abstracts from scientific meetings were searched including the American Academy of Veterinary Dermatology/American College of Veterinary Dermatology Annual Meeting, American Animal Hospital Association, American College of Veterinary Internal Medicine, European Society of Veterinary Dermatology-European College of Veterinary Dermatology, International Society for Human and Animal Mycology, North American Veterinary Dermatology Forum and World Congress of Veterinary Dermatology.

References published in manuscripts and veterinary textbooks related to the topic of small animal dermatophytosis were traced and reviewed. The literature review was used to compose a "Consensus Statement" that was reviewed internally and then presented at the 8th World Congress of Veterinary Dermatology (June 2016). After the oral presentation, it was posted online and submitted to the worldwide veterinary dermatology and mycology communities for feedback and input prior to submission of the final revision to the World Association for Veterinary Dermatology for approval prior to submission to this journal.

The goal of this review was not an exhaustive assessment of all aspects of small animal dermatophytosis, but rather a critical investigation of existing literature from 1900 to 2016, with an emphasis on studies describing diagnostic methods and treatments. This research then led to a series of recommendations on the diagnosis and treatment of dermatophytosis for the benefit of veterinary clinicians and lay people.

2 Disease overview

2.1 Pathogens of importance, new classifications

There are more than 30 species of dermatophytic fungal organisms.[1] This review will concentrate on the diagnosis and treatment of those that commonly affect companion animals: some zoophilic and, to a lesser extent, geophilic species. Zoophilic dermatophyte species are adapted to living on animal hosts. They include *Microsporum canis* (affecting primarily cat and dog), *M. equinum* (horse), *M. persicolor* (voles, as supposed), *M. nanum* (pig), *Trichophyton equinum* (horse), *T. verrucosum* (cattle) and several species of the *Trichophyton mentagrophytes* complex (rodents, rabbits, hedgehogs). Geophilic dermatophyte species are associated primarily with the decomposition of keratin of hair, feathers and horn present in the soil after the keratinized products have been shed from the living hosts. Most of them are non-pathogenic, but some of these organisms can sporadically infect animals and humans after contact with contaminated soil. Species from the *M. gypseum* complex are the most commonly involved.

Dermatophyte species in animals are isolated as asexual forms, called anamorphs, which are identified as belonging to the genus *Microsporum* or *Trichophyton* on the basis of macroscopic and microscopic characteristics of the organism grown in culture.[1] Additionally laboratory mating experiments have produced the sexual or perfect states (teleomorphs) for some dermatophyte species, which allowed them to be classified in the genus *Arthroderma*, phylum Ascomycota. Therefore, several distinct species could be clearly classified in the *M. gypseum* and *T. mentagrophytes* complexes. However, a major

problem identified during the literature review was that a double classification and nomenclature of dermatophyte species exists.

It is not within the scope of this study to review fungal nomenclature in detail. However, it is important to be aware that in 2011 the Amsterdam declaration on Fungal Nomenclature (One Fungus = One Name) was adopted, and that classification of fungi is still evolving (Table 1).[2–6]

Of particular importance is the fact that the traditional name of *T. mentagrophytes* encompasses several different zoophilic and anthropophilic species that have been recently and clearly discriminated based on host preferences, and on morphological, sexual and molecular characteristics (Table 2).[5,7,8] For example, among zoophilic species from the *T. mentagrophytes* complex, *Arthroderma benhamiae* is the teleomorph obtained by mating strains isolated from rodents, including from guinea pigs with dermatophytosis, as well as dogs and cats. The teleomorphic *A. vanbreuseghemii* corresponds to zoophilic strains isolated from mice and chinchillas as well as dogs and cats, and from humans most frequently infected by contact with dogs or cats with dermatophytosis.[9,10] *Trichophyton interdigitale* is a strictly anthropophilic dermatophyte species, distinct from both *A. benhamiae* and *A. vanbreuseghemii,* that belongs also to the *T. mentagrophytes* complex. Likewise, *M. gypseum* is now known to be a complex of three separate teleomorph species with no interspecific sexual reaction, *A. fulvum*, *A. gypseum* and *A. incurvatum*. One should be aware that some zoophilic species, including *M. canis* and *M. equinum,* are phylogenetically closely related to other anthropophilic species, such as *M. ferrugineum* and *M. audouinii*.[11–13]

For the purposes of this review, the traditional names will be used unless otherwise specified. The reader is, however, invited to refer to a review on the subject for additional perspectives and the current nomenclature.[14]

2.2 Prevalence and risk factors

Seventy three papers from 29 countries were reviewed on the incidence and prevalence of small animal dermatophytosis (for references see Supplement 1: Prevalence References). Findings varied greatly depending upon the source of the animals (pets, free roaming, cattery or diagnostic laboratory submissions) and whether or not the animals were asymptomatic or had clinical disease. Because of the wide range in methodologies, studies could not be directly compared, but clear trends were evident. Dermatophytes were more commonly isolated from animals with consistent clinical signs compared to asymptomatic animals, and from animals housed as groups or free-roaming cats. Warm locations (such as Brazil, Chile, India, Italy and southern USA) showed a trend toward an increased prevalence of positive dermatophyte cultures.

Table 1. Major dermatophytes of the domestic animals and their supposed reservoirs

Dermatophyte	Main animal involved and reservoir(s)	Frequency in humans	Geographical distribution
Microsporum canis	Cats, dogs	Common	Worldwide
Trichophyton verrucosum	Cattle	Common	Worldwide
Arthroderma benhamiae	Guinea pigs	Common	Worldwide
Trichophyton erinacei	Hedgehogs	Occasional	Europe, East Asia, New Zealand
Arthroderma vanbreuseghemii	Cats, dogs, rabbits, rodents (mice, chinchillas)	Common	Worldwide
Trichophyton equinum	Horses	Occasional	Worldwide
Trichophyton simii	Monkeys, poultry, dogs	Rare	Rare outside of India
Microsporum equinum	Horses	Rare	Worldwide
Trichophyton gallinae	Chickens	Rare	Worldwide
Microsporum persicolor	Rodents, voles	Rare	Europe, USA
Microsporum nanum	Pigs	Rare	Worldwide
Trichophyton bullosum	Horses, donkeys	Rare	Tunisia, Sudan, Syria, France
Trichophyton quinckeanum	Mice (favus)	Rare	Worldwide
Microsporum gypseum (complex of three different species)	Soil (geophilic species)	Rare (infection from soil, not animals)	Worldwide

Table 2. Species in the *Trichophyton mentagrophytes* complex and taxonomy changes pertinent to veterinary medicine— adapted from Monod *et al.*[5]

Current species classification		
Teleomorph*	Anamorph†	Former species classification
Arthroderma benhamiae	*Trichophyton* sp.‡ (closely related to *Trichophyton erinacei*)	*Trichophyton mentagrophytes* (zoophilic strains)
Arthroderma vanbreuseghemii	*Trichophyton* sp.‡ *Trichophyton interdigitale*	*Trichophyton mentagrophytes* var. *asteroides* (zoophilic strains) *Trichophyton mentagrophytes* var. *interdigitale* (anthropophilic strains)
Arthroderma simii	*Trichophyton mentagrophytes* (*sensu stricto*)	*Arthroderma simii*

*Sexual form of the fungus.
†Asexual or conidial form of the fungus.
‡Anamorph names not formally given for *A. benhamiae* and *A. vanbreuseghemii.*

Studies on the normal fungal flora of healthy pet cats and dogs have shown that *M. canis*, the most common cause of dermatophytosis, is not part of the normal skin microbiome of dogs or cats.[15–20] The "normal" fungal flora of pet cats was diverse and 15 genera were isolated that included 13 saprophytes and two dermatophytes. *Aspergillus*, *Alternaria*, *Penicillium* and *Cladosporium* spp. were the most frequently isolated saprophytes. One colony each of *M. gypseum* and *M. vanbreuseghemii* were isolated from two different cats. Interestingly, *T. rubrum* was isolated from 14 cats. Seven of the cats lived in multi-cat households and seven lived in single cat households. None of the owners reported tinea pedis at the time the study was conducted. In contrast, *T. rubrum* was also isolated from four cats in another study and owners reported historical "athlete's foot fungus" in household members.[17] In dogs, *Cladosporium* and *Alternaria* were the most common isolates. More recent studies on the cutaneous mycobiota of healthy and allergic cats and dogs using Next Generation Sequencing also did not identify dermatophytes as part of the fungal microbiota.[19,20] Based upon these findings, fungi isolated from the hair coat are the result of environmental propagules trapped in the hair coat and not true flora as is the case for bacteria.

Five papers were available that reported on the prevalence of skin diseases diagnosed in dogs and/or cats in small animal practice and found that dermatophytosis is an uncommon diagnosis, even in cats with skin disease. A study from the United States detailing the causes of skin disease in 1407 cats revealed that dermatophytosis was found in only 45 of 1407 (2.4%) of cats, far lower than the more common diagnoses of allergy/atopy (26%), bacterial skin infections (10%), *Otodectes* (6.1%) and fleas (5.2%).[21] In a Canadian study, dermatophytosis was diagnosed in only three of 419 dogs (0.71%) and in four of 111 cats (3.6%) presented for skin disease.[22] In one study from the UK, dermatophytosis was diagnosed in three of 559 dogs (0.53%) and in two of 154 cats (1.3%).[23] In another study conducted in the UK, the medical records of 142,576 cats from 91 practices over a 5 year period were reviewed.[24] Dermatological disorders comprised 10.4% of diseases. Specific diagnoses such as cat bite abscesses and flea infestations were noted, but dermatophytosis was not, suggesting that it was uncommon. Finally, in a study on the causes of pruritus in cats, 11 of 502 cats (2.1%) were diagnosed with a fungal disease.[25]

Review of the prevalence studies (See Supplement 1: Prevalence References) identified trends for at-risk populations, the most common being age (puppies and kittens), lifestyle, free-roaming animals and warm locations.

Immunosuppressive diseases are thought to predispose cats and dogs to the development of dermatophytosis. Three papers evaluated the fungal flora of immunosuppressed cats to determine if this was a risk factor.[26–28] In the first study, the fungal flora of cats seropositive for feline immunodeficiency virus (FIV) (n = 24), feline leukaemia virus (FeLV) (n = 10) or both (n = 1) were compared with the cutaneous fungal flora of seronegative cats with various systemic illnesses (n = 50). The study found that FeLV and FIV seropositive cats had a greater diversity of saprophytic fungal carriage and increased carriage of *Malassezia*, but dermatophyte carriage was rare and there was no difference between seropositive and seronegative but systemically ill cats.[26] In a second study, fungal carriage was compared between FIV seropositive cats (n = 35) and FIV seronegative cats (n = 55).[27] These cats were from homes, shelters or were free roaming. In this study, 26 of 35 (FIV seropositive) and 14 of 55 (FIV seronegative) cats were culture positive for *M. canis* but free of clinical signs of dermatophytosis. Because of the varied sources of cats (shelters, free roaming, pets), it is unclear from this study if FIV infected cats are more susceptible to fomite carriage of *M. canis* or not. However, in another study, no association between FIV infection and fungal carriage was noted.[28] There is one study reporting a cat with cutaneous xanthomas and concurrent demodicosis and dermatophytosis.[29] The development of concurrent dermatophytosis in cats receiving immunosuppressive drugs for the treatment of pemphigus foliaceus was not reported in either of two large studies.[30,31] One cat developed *M. canis* dermatophytosis while receiving ciclosporin for treatment of pseudopelade.[32]

Five papers describe dogs (n = 10 total dogs) with concurrent illnesses and dermatophytosis. Four papers describe concurrent dermatophytosis and hyperadrenocorticism in dogs.[33–36] Another paper describes six Yorkshire terrier dogs with dermatophytosis and concurrent leishmaniosis (n = 4), leishmaniosis and ehrlichiosis (n = 1) and diabetes mellitus (n = 1).[37] Although there is only one paper documenting concurrent dermatophytosis and demodicosis, in the authors' opinion it is considered likely that dual infection is more common than may be realised.[38]

With regard to breed predilections, there is indirect evidence that Persian cats are pre-disposed to dermatophytosis. One study noted that 75% of the cases occurred in Persian cats but the total number of cases diagnosed was only four.[22] In another study, 15 of 61 cases of dermatophytosis were diagnosed in Persian cats.[39] Data from that study showed that Persian cats were over-represented; they accounted for 5% of all feline cases in the hospital but 24.6% of cats with dermatophytosis.[39] Persian cats are commonly over-represented in treatment studies, further supporting the observation that this breed is predisposed to dermatophytosis.[36,40–54] For example, the first reports of the use of griseofulvin were in Persian cats; then in another example, Persian cats comprised a large part of each of the study groups reporting on the pharmacokinetic and pharmacodynamics of the dosing of itraconazole.[43–45] Almost without exception, descriptions of subcutaneous dermatophytic infections are reported in long-haired breeds, in particular, Persian cats.[36,46–54]

Some dog breeds also appear to be predisposed to dermatophytosis. There are several case reports of Yorkshire terrier dogs identified as being predisposed to superficial dermatophytosis and subcutaneous dermatophytic infections, most commonly due to *M. canis*.[36,37,55–58] In one study, 13 of 55 (23.6%) dogs with dermatophytosis were Yorkshire terrier dogs.[55] In another study, 10 of 27 (37%) dogs were Yorkshire terrier dogs.[59] Hunting and working breed dogs (German

short-haired pointers, fox terrier, Labrador retriever, Belgian Groenendael, beagle, pointer, Jack Russell terrier, German shepherd dog and Jagdterrier) also appear to be predisposed to dermatophytosis, specifically *M. persicolor* and *M. gypseum*, possibly due to increased contact with contaminated soil.[60–62]

2.3 Conclusions

1. Determination of the true prevalence and breed predispositions for dermatophytosis is difficult because this is not a spontaneously occurring disease, it is not reportable and it is not a fatal disease. Infection varies in severity and resolves without treatment in many dogs and cats. All of these factors bias breed and prevalence predilection data.
2. Subcutaneous dermatophytic infections have been reported most commonly in Persian cats and Yorkshire terrier dogs.
3. The activities of working and hunting dogs may increase their risk of exposure to dermatophyte spores and, hence, superficial and, less commonly, nodular lesions.
4. Seropositive FIV and/or FeLV status in cats alone does not increase the risk of dermatophytosis.

2.4 Pathogenesis of infection/Immune response

The infective form of dermatophytes is the arthrospore which is formed by fragmentation of fungal hyphae into very small infective spores. These can be transmitted by direct contact between an infected and uninfected animal or by fomite transmission, which can include grooming appliances, bedding, collars, ectoparasites and exposure to a contaminated environment; concurrent microtrauma to the skin is an important factor in development of clinical infection. *Microsporum canis* infections are typically due to contact with an infected animal, mainly cats. Transmission from contaminated environments is not an efficient route of transmission. Most *Trichophyton* infections are suspected to be due to contact with infected rodents or their nests. *Microsporum gypseum* infections are less common and are presumed to be due to contact with contaminated soil as this is a geophilic organism. Increased microtrauma to the skin from pruritus/self-trauma, humidity and ectoparasites all contribute to conditions optimal for dermatophyte infection.[63] Experimental dermatophyte infections required that the skin surface was lightly abraded prior to dermatophyte inoculation and kept moist as the infection developed.[64,65] Additionally, normal grooming is likely a host defence mechanism in cats. Clinical infection was very difficult to establish in laboratory cats experimentally infected with dermatophytes, and Elizabethan collars and prevention of self-grooming were required to allow clinical infection to develop.[64]

The literature describes three stages of the development of a dermatophyte infection. The first involves the adherence of arthroconidia to corneocytes, which is thought to occur within 2–6 h of exposure.[66–68] This process is likely mediated by carbohydrate-specific adhesins expressed on the surface of arthroconidia, as well as dermatophyte-secreted proteases such as subtilisins.[67,69–71] The second stage involves fungal conidial germination in which germ tubes emerge from the arthroconidia and then penetrate the stratum corneum. This infection step was shown to occur within 4–6 h in an *in vitro* corneocyte model of *Trichophyton* infection and by 24 h in a human full-thickness epidermis model.[72,73] The third stage involves dermatophyte invasion of keratinized structures, which occurs as dermatophyte hyphae invade the stratum corneum and grow in multiple directions, including into the follicular unit for most dermatophytes encountered in animals. Within 7 days of incubation, hyphae begin to form arthroconidia, completing the fungal life cycle.[72] The clinical lesion appearance typically occurs one to three weeks after exposure.[64,74,75]

Dermatophytes secrete both endoproteases, such as subtilisins and fungalysins, and exoproteases that digest keratin into usable peptides and amino acids. Keratin degradation is accompanied by the simultaneous reduction/cleavage of keratin cysteine disulphide bonds, via a dermatophyte sulphite efflux pump encoded by the *SSU1* gene.[76] The regulation of sulfite formation from cysteine is another likely important pathogenic mechanism relying on an enzyme called cysteine dioxygenase (Cdo1).[77] The pattern of proteases secreted by dermatophytes is likely species- and host-specific, and may be important in resultant host inflammation and immune responses. Dermatophytes can counter the host immune response in a number of ways, including lymphocyte inhibition by cell wall mannans, macrophage function alteration and altered/slowed keratinocyte turnover.[67,78,79]

Both antibody and cellular immune responses have been shown to occur in dermatophyte-infected animals.[80] However clinical cure and protection against re-infection depends on a strong cell-mediated immune response involving effector cells such as macrophages and neutrophils, and cytokines such as interferon gamma.[67,81] Natural infection of cats with *M. canis* is associated with positive immediate and delayed intradermal test reactions to fungal proteins, elevated antibody titres and alterations in lymphocyte blastogenesis response to fungal antigens.[82] Cats currently or previously infected with *M. canis* had a significantly higher lymphocyte reactivity to dermatophyte antigens compared to uninfected controls. Although lymphocyte reactivity was similar in both culture-positive and infected/recovered cats, antibody titres were significantly higher in the culture-positive group, suggesting that the higher lymphocyte reactivity may represent a cell-mediated Th1 response and that antibodies are more reflective of exposure but are not protective.[82]

2.5 Clinical signs

The clinical signs of dermatophytosis reflect the pathogenesis of the disease: it invades keratinized structures. With that said, there can be any combination of hair loss, papules, scales, crusts, erythema, follicular plugging, hyperpigmentation and changes in nail growth/

appearance. Typically lesions are asymmetrical. Pruritus is variable, but in general is minimal to absent. When pruritus is present, self-trauma can mimic areas of pyotraumatic dermatitis or ulcerative eosinophilic lesions in cats.[64] Experimental co-habitant exposure challenge studies have documented the clinical observation that lesions tend to occur most commonly on the face, ears and muzzle of cats, and then progress to paws and other body areas.[83,84] Dermatophytosis is a differential diagnosis in cats with pododermatitis.[85] It is a differential diagnosis in any cat with widespread exfoliative dermatitis.

Variations in clinical presentation reflect the host's immune response and inflammatory response. Multifocal and diffuse lesions are most commonly seen in animals with concurrent skin or systemic disease and/or physiological stress. Cats from large-scale hoarding environments were found to be at a higher risk of dermatophytosis.[86] The disease is transmitted via direct contact with another infected host or contaminated fomite (e.g. *M. gypseum* and soil); concurrent microtrauma is important to establish true infection versus fomite carriage. Hunting dogs may develop lesions on the muzzle and paws. Nail involvement characterized by onychogryphosis on one or multiple digits may occur. Pustular dermatophytosis has rarely been described in dogs and histologically it can mimic pemphigus foliaceous.[87,88]

Nodular lesions

Both dogs and cats can develop nodular dermatophyte infections diagnosed primarily via biopsy or cytological examination of aspirates, and these include kerion, pseudomycetoma and mycetoma reaction patterns.[36,46–54,56,57,89,90] Clinically, kerions present as single or multiple erythematous, alopecic, dome-shaped, exudative nodules characterized histologically by granuloma or pyogranuloma formation, often with fragments of hair shafts containing fungal spores.[89] Clinically, pseudomycetomas and mycetomas present as nodules that fistulate, ulcerate and drain serous to purulent debris with tissue grains.

The clinical characteristics of 43 cases are summarized in Table S1. The most commonly represented breeds were Persian cats and Yorkshire terrier dogs. Clinically these animals presented with one or more subcutaneous nodules, although one cat had an intraabdominal mass. Persian cats often had a history of prior dermatophytosis, but not always. In Persian cats, Wood's lamp findings were often negative; however, it must be noted that many of these cats had received prior treatment over long periods of time. Dogs with kerion reactions (n = 23) were all negative on Wood's lamp examination and only eight of 23 had positive direct hair examinations.[89] Interestingly, cytology was diagnostic in 21 of 23 cases. The most commonly isolated pathogen was *M. canis* and often this was diagnosed only from tissue and not hair samples, highlighting the importance of submitting tissue for culture at the time of sampling. Prognosis was good for dogs with kerion reactions. In dogs or cats with pseudomycetoma or mycetoma, the treatment of choice was surgical excision and concurrent systemic antifungal treatment, and prognosis was guarded. Short-term remissions and relapses that resulted in euthanasia were common.

3 Diagnostic testing

Because dermatophytosis is an infectious and contagious disease, rapid confirmation of true disease is needed for both treatment and to limit contagion to other susceptible animals and people.

Confirmation of infection within hair follicles or the epidermis is complicated by two factors. The first is the difficulty of detection of lesions within the hair coat of animals. Infected hairs can be small and/or obscured by inflammatory crusts. This problem is compounded by prior treatments that may change the appearance of the lesions and/or by an inability to safely restrain the animal for a thorough examination. The second is that fomite carriage from contact with an infected animal or exposure to a contaminated inanimate object can lead to false positive fungal cultures due to arthrospores trapped within the hair coat.

The question is commonly asked "what is the gold standard" for confirmation of dermatophytosis in small animals? Diagnostic testing for any small animal skin disease is dependent upon the stage of the infection, presence or absence of treatment, sampling technique, site selection, clinician training, quality of the tool (e.g. Wood's lamp) and ability to examine the animal.

For dermatophytosis, the question is not "what is the gold standard", but rather

1. What test(s) confirm the presence of an active infection in order to make an informed decision (i.e. treat or not treat, euthanize, quarantine)?
2. What test or tests confirm the absence of an active infection (i.e. the animal poses no infection risk, the animal cured)?

3.1 Wood' lamp and fluorescence

The Wood's lamp is a point-of-care diagnostic tool, with which a test can be performed in clinic. It is an ultraviolet lamp that was invented in 1903 by Robert W. Wood as a light filter used in communications during World War I. The original glass filter material has been replaced by newer materials (e.g. barium-sodium-silicate glass incorporating 9% nickel oxide) that coat the inside of glass tubes. The Wood's lamp glass is deep violet blue and is opaque to all visible light rays except the longest red and shortest violet wavelengths. It is transparent in the violet/ultraviolet band between 320 and 400 nm with a peak at 365 nm and a broad range of infrared and the longest, least visible red wavelengths.[91] Fluorescence occurs when light of shorter wavelengths initially emitted by the lamp, is absorbed and radiation of longer wavelengths is emitted.[91] Thus, it excludes most of the burning and tanning shorter rays (<320 nm) and the visible rays longer than 400 nm).

A Wood's lamp is often mistakenly referred to as a "black light" but these are distinctly different things. A black light is composed of a clear glass that filters medium- and short-wave ultraviolet light (UV) and emits a large amount of blue visible light along with long-wave UV light. An example of a black light is the black light bulbs in

bug catchers. It is hard to see fluorescence due to the large amount of visible light.

Many microbial organisms produce phosphors as a result of their growth on skin and/or hairs and this can aid in detection and/or confirmation of infection. With the exception of *T. schoenleinii*, dermatophytes that produce fluorescence are members of the *Microsporum* genus. The primary dermatophyte of veterinary importance that produces fluorescence is *M. canis*. Clinical reports of *M. gypseum* or *M. persicolor* dermatophytosis in dogs and cats note a lack of fluorescence on infected hairs.[60–62,92–95]

Microsporum canis fluorescence

The characteristic green fluorescence observed on *M. canis*-infected hair shafts is due to a water-soluble chemical metabolite (pteridine) located within the cortex or medulla of the hair.[96–99] The fluorescence is due to a chemical interaction that occurs as a result of the infection and is not associated with spores or infective material.[98]

Historical note

The earliest report in the English literature of positive fluorescence in a *M. canis*-infected cat was by Davidson in 1933.[100] The Wood's lamp was credited with identification of an infected kitten that otherwise would have gone undetected during an investigation into the source of infection in a child. The authors subsequently identified other infected kittens with a Wood's lamp and experimentally infected 10 other cats and kittens with *M. canis* to confirm that this was a repeatable finding. These authors encouraged the use of this tool in the investigation of skin diseases of animals especially because fungal culture was not widely available as a routine diagnostic test.

True or false? "Fewer than 50% of strains fluoresce"

One anecdotal criticism of the Wood's lamp examination has been the widely cited low percentage of "strains", "isolates" or "cases" that fluoresce under Wood's lamp examination. Molecular testing of isolates with respect to fluorescence has not been reported so the term "strain" is inappropriate. For this discussion "isolates" or "cases" are considered synonymous.

Review of the literature reveals that the ranges of percentages of isolates or cases of *M. canis* fluorescence (30–54%) originated from four laboratory studies.[55,93,101,102] The first report in the English literature regarding the percentage of positive fluorescence of *M. canis* in animals was from a study on the public health implications of animal dermatophytosis by William Kaplan in 1958.[93] Samples submitted to a diagnostic laboratory over an 18 month period were examined by a Wood's lamp for fluorescence, direct examination for spores/hyphae and then, finally, fungal-cultured on a selective isolation medium. Of the 2,183 specimens from dogs and cats, 445 were culture positive for *M. canis* and 30% of infected hairs showed fluorescence. In the second retrospective laboratory report, which spanned 20 years, Wright reported only 32% of culture-positive *M. canis* specimens (n = 300) were found to fluoresce.[102] In the third retrospective laboratory study (n = 1368), hairs were again examined with a Wood's lamp, direct examination and then fungal-cultured. That study found 54% and 38% positive fluorescence in *M. canis* cat and dog hair, respectively.[101] This study found that Wood's lamp examination had a positive predictive value of 90% and negative predictive value of 94%. In the last laboratory study, 424 clinical samples submitted to a laboratory were examined with 77 of 99 culture positive for *M. canis*. Wood's lamp fluorescence was positive in 37 of 77 (48%) of samples.[55] Except for the time span in these studies, no information was provided regarding the training of the technicians, number of technicians involved, examination procedure, or type of Wood's lamp used in any of the four studies.

Interestingly, Kaplan reported on the treatment of 31 cats in two papers and these data were not included in papers on the use of Wood's lamp examinations.[44,45] The first paper reported on 22 cats and the second on 31 cats; however, 22 of 31 cats were from the first paper. Review of these 31 cats as a group revealed that 29 of 31 were Persian cats. A total of seven cats were reported to be Wood's lamp negative. All seven were Persian cats with no or minimal lesions. These cats rapidly became culture negative with just systemic therapy (one to three weeks) and/or after a single antifungal dip, suggesting these cats were not truly infected but merely fomite carriers. If the data had been presented as a single case series of 31 cats, 71% (22 of 31) were Wood's lamp positive. If Kaplan had published the papers as two separate cases series with no duplication of data, percentages of positive fluorescence would have been 68% (15 of 22) and 100% (n = 9 kittens).

Fifty seven studies involving either spontaneous (n = 42) or experimental (n = 15) *M. canis* infections in cats and dogs (n = 2,027) were identified and of these, 30 described Wood's lamp findings.[40–45,64,65,74,75,83,103–147] When data were pooled from studies describing the first examination of animals with spontaneous disease, 72% (378 of 523) of animals were Wood's lamp positive.[40,45,108,109,111,115,117,119,122,129,132,135,137,139,144] In untreated cats, positive fluorescence varied from 91 to 100%, and in animals with previous treatment fluorescence varied from 39 to 53%. When data from cats with experimentally induced disease were examined, 100% (190 of 190) showed positive fluorescence at the time of diagnosis.[64,65,74,75,83,112–114,116,123,124,133,134,136,147] This is not an unexpected finding because the investigators were actively searching for a known infection.

True or false? "Not all strains fluoresce on all cats"

The anecdotal comment "not all strains of *M. canis* will fluoresce on all cats" is not supported by the findings from the experimental studies. Within each experimental study, investigators used the same field isolate to infect kittens/cats and experimental infection resulted in 100% fluorescence in all cats, most of which were unrelated.

True or false? "Topical therapy destroys fluorescence"

Another anecdotal statement is that bathing or topical therapy will "change or destroy fluorescence". Reviews of experimental or field studies using Wood's lamp

examinations to monitor response to therapy did not report loss of fluorescence due to topical shampoo therapy or with the use of lime sulfur or enilconazole rinses.[109,112,117,130,131,136]

True or false? "False fluorescence is a problem"
The problem of false fluorescence has been recognized since the development of the Wood's lamp. Lint, topical medicaments, seborrhoeic material and even soap residue may fluoresce but lack the apple green/emerald green fluorescence of *M. canis*.[74,91,148] The fluorescence of *M. canis* hairs (apple green) is strikingly distinct and in active infections involves the intrafollicular portion of the hair shaft, which can be examined grossly to confirm fluorescence and microscopically to confirm infection.[149] Original descriptions of use of the Wood's lamp stressed the necessity of holding it close to the skin (2–4 cm) to minimize false fluorescence and to concentrate on examination of hair shafts, not scale. In one author's experience (KM), lamps with built-in magnification facilitate examinations.

True or false? "Not all fluorescent hairs are culture positive"
Another confounding factor in the interpretation of Wood's lamp examinations literature is that "not all fluorescent hairs are culture positive", supporting either claims of "false positives" or "false negatives". The published literature does support these claims; however, their validity is dependent upon when hairs are examined in the course of the infection. Naturally occurring or experimental studies using fluorescence to monitor disease development and resolution consistently report similar findings. Fluorescence has been noted to develop as early as days 5–7 and usually by day 10–14 post-infection.[64,74,100,149,150] It is reported to be obscured by crusts making it important to lift crusts to examine infection sites for fluorescence.[64] Very early in the infection the hairs are short and easily overlooked. Within 12 to 14 d post-infection the entire hair shaft is involved, as is the intrafollicular portion, but it is difficult to remove these hairs with the hair bulb intact. In one author's experience (KM), "sticky" tape can be used to epilate these hairs in order to examine the hair bulb.

During treatment or spontaneous recovery, as hairs grow, the proximal (intrafollicular) portion of the hair is nonfluorescent but strong fluorescence remains on the distal hair shaft.[44,123] One characteristic finding in cats under treatment or after cure is the persistent presence of "glowing tips".[108,150] Interestingly, this was noted in detail as an important finding in the first studies reporting on the use of griseofulvin to treat feline dermatophytosis in 1959 and 1960.[45] The pteridine pigment within the medulla or on the cortex remains readily detectable by a Wood's lamp on the tips of the hairs as they grow out, even though the infection may have been eliminated. In addition, fluorescence will remain long after the hair shafts are culture negative.[150] And in one author's laboratory (KM), hairs were observed to still fluoresce after 18 years.

Historically, Wood's lamp examinations were used as the primary method of detecting and monitoring response to treatment of *M. canis* infections, especially in cat colonies.[44,45,65,108,111,137,151] Wood's lamp examinations are still considered to be valuable diagnostic aids in the management of outbreaks in shelters and during the intake screening period.[132,152] In one eight month period, 1,226 cats were surrendered to a shelter and 273 were culture positive.[132] Sixty of the 273 dermatophyte culture-positive cats were lesional, Wood's lamp positive and direct examination positive, and 50 of 60 infected animals were kittens. The remaining 213 cats were found to be fomite carriers. The lay person intake staff were trained in a short course to use a Wood's lamp with built-in magnification.[132,153]

3.2 Dermoscopy

Dermoscopy is a noninvasive point-of-care diagnostic tool that allows for illuminated magnification of the skin. It is widely used in human medicine in the clinical diagnosis of a number of skin diseases, but in particular hair and follicular abnormalities. Description of dermoscopy of normal cat skin has been published and the authors concluded that it is useful for hair follicle examination.[154] In a follow-up study, the same authors described dermoscopic findings in 12 cats with dermatophytosis and 12 cats with noninfectious causes of hair loss.[144] Unique to the cats with dermatophytosis were opaque, slightly curved or broken hairs with a homogenous thickness ("comma hairs") in nine of 12 cats. Affected areas also had variable amounts of brown to yellow crusts (12 of 12 cats). Eight of 12 cats had positive Wood's lamp examinations. Microscopic examination of comma hairs identified via dermoscopy showed hyphae and spores on the shafts in three of the four cats with a negative Wood's lamp examination. Dermoscopy findings in cats with dermatophytosis were distinctly different than in cats with other causes of alopecia.

In another study, 21 of 36 culture-positive cats had comma-like hairs found on dermoscopy.[155] Nineteen of the cats were diagnosed with *M. canis* and two with *M. gypseum*. Comma-like hairs were described as opaque, broken with an homogenous thickness and a slight curve. These hairs were easier to identify in lighter coloured cats than black cats; in black cats the hairs still appeared white or pale. The authors of this study also described nine kittens with dermatophytosis where fungal culture did not identify *M. canis* due to contaminant overgrowth; however, dermoscopy identified comma hairs that were Wood's lamp and direct examination positive, allowing for confirmation of the infection and subsequent successful treatment of the kittens. In that study, the authors noted that patient cooperation was the biggest obstacle in conducting a dermoscopic examination. These preliminary studies seem to show that comma hairs and hairs with a corkscrew or coiled appearance typical of fungal invasion in people, are likely to be similar findings in cats.[156]

3.3 Direct examination of hair and/or scale

Direct examination of hairs and scales is a point-of-care technique used to confirm the presence of a dermatophyte infection. The origins of this technique are unknown; however, Davidson described its use in cats in 1933.[100,157] It involves microscopic examination of hair and scales for hyphae and/or fungal spores and provides

rapid confirmation of infection. Hairs and scales can be mounted in mineral oil, compounded chlorphenolac or potassium hydroxide (KOH) of varying concentrations.[157–159] Potassium hydroxide or mineral oil with or without the addition of stains (lactophenol cotton blue, India Ink) can also be used to aid in visualization of fungal elements.[159–161] Sparkes *et al*. described the use of calcofluor white (a textile brightener) as an alternative to KOH because it binds specifically to the fungal cell wall and fluoresces strongly when viewed under a fluorescence microscope, and found it to be significantly superior to routine microscopy (76% versus 39%), although a human study found no difference in positive predictive value when compared to KOH.[162,163]

There are limited reports of studies correlating fungal culture results with Wood's lamp examinations and/or direct examinations in veterinary medicine. In Wright's study, fungal elements were detected in only 41% of culture-positive samples.[102] In Sparkes 1993 study, the results of Wood's lamp examinations, direct examinations and culture were compared.[101] For *M. canis* infections, when compared to fungal culture, Wood's lamp examination had a positive predictive value of 90% and a negative predictive value of 94%. For direct examination, the positive and negative predictive values were 93%. When data from the experimental infection studies was pooled, there was a high correlation between positive fungal culture, positive Wood's lamp examinations and direct examinations. This is not an unexpected finding because the investigators were actively searching for a known infection. In the spontaneous infection studies where data were reported and pooled, direct examinations were positive in approximately 61.5% of the entire population (210 of 341). Of greater interest was that in three studies, direct examinations of hairs from lesional sites identified infected cats that were Wood's lamp negative.[111,129,144]

The most commonly used sample collection technique for direct examination is to pluck hairs. However, one study compared two methods for collecting samples for microscopic examination of hair shafts for evidence of dermatophytosis.[164] Lesion sites were sampled in 37 dogs and 40 cats but were not examined with a Wood's lamp prior to sampling. Hairs were plucked from the periphery of the lesions and skin scrapings were done on alopecic areas. Mineral oil was used for mounting samples. Hair plucking resulted in positive results in 20 of 37 dogs and 27 of 40 cats. Skin scrapings resulted in positive results in 29 of 40 dogs and 32 of 37 cats. When results of both techniques were combined, positive results were found in 31 of 37 dogs (83.7%) and 35 of 40 cats (87.5%). Most of the negative cases were negative on both tests. The authors speculated that some of the negative results could have been due to the fact that only one site was sampled. In addition, some of the negative direct examinations were in cases which grew *M. gypseum* or *Trichophyton* sp. on fungal culture. One comment of interest was that it was difficult to find spores on darkly coloured hairs.

There are no studies in the veterinary literature comparing mineral oil, chlorphenolac and KOH with fungal culture results for the detection of spores. With that said there are some practical differences to consider. The advantage of chlorphenolac and mineral oil is that both can be examined immediately or at a later time. KOH preparations require 10 to 20 min for digestion and need immediate examination to avoid problems with artefacts. Another problem is that KOH destroys the fluorescence on *M. canis*-infected hairs, making it impossible to use a Wood's lamp to help locate glowing hairs on a slide for microscopic examination[99,153] The major advantages of mineral oil are the ready availability, no risk of injury to animals or people by accidental exposure to the caustic chemical, no permanent damage to microscope lens if the chemical is spilled, and no loss of fluorescence of *M. canis* hairs. Clearing agents such as KOH or chlorphenolac will damage microscope lenses. The lack of digestion and clearing of epidermal scales does not affect visualization of spores and hyphae on the hairs; mineral oil is recommended as the mounting medium.[153]

3.4 Fungal culture

It is often stated that fungal culture is the gold standard of diagnosis, but this diagnostic tool merely detects the presence or absence of fungal spores on the hair coat or hair sample. As with any diagnostic tool, false positives and false negatives test results occur.[101] In one of the early studies evaluating the use of dermatophyte test media in veterinary medicine, the author concluded that positive fungal cultures *may* offer proof of infection but negative cultures are less definitive.[165] Overgrowth of fungal culture plates in both point-of-care and reference laboratories can occur, leading to false negatives or false positives if there is insufficient training of on-site staff to evaluate cultures. Another source of false negative fungal culture results is insufficient sampling technique, particularly when hairs are plucked.[101] False negatives will occur if the reference laboratory is unfamiliar with how to inoculate a toothbrush fungal culture.

Sampling techniques

Three sampling techniques for small animals have been described in the literature: hair coat brushings, hair plucking and sticky tape sampling. The first is the brushing technique or the "Mackenzie" brush technique developed to identify nonfluorescent tinea capitus in people (i.e. *Trichophyton*).[166] However, it was Goldberg in 1965 who first investigated its use in animals using a toothbrush and reported that it was superior to simple plucking of hairs for detection of animal sources of infection.[167] Instead of brushes, small pieces of sterile carpet can also be used and results were found to be similar in one study.[168] The brush technique is the most commonly described procedure in published studies and case reports and is widely used. It is simple, atraumatic, economical and fast. Individually wrapped soft bristle toothbrushes are mycologically sterile; carpet squares must be sterilized before use to prevent overgrowth of contaminants. There is no standard technique and 20 brush strokes, 2–3 min of brushing or brushing until the bristles are full of hair are all sampling end points. It is important to use a soft bristle toothbrush to allow for atraumatic sampling of ears and the face. False negatives occur most commonly if the lesions are not sampled thoroughly

or if the sample is not properly inoculated onto the surface of a fungal culture plate. The latter happens most frequently if diagnostic laboratories are unfamiliar with how to inoculate plates and randomly pluck hairs from the bristles.[169] False positives are very common with this technique because the technique is very sensitive with respect to detecting spores on the hair coat. For example, in 5,644 cats screened at a shelter via toothbrush cultures, 10.4% of the cats were culture positive; however, when all of the clinical data were examined, only 1.67% of cats had true disease, whereas the other 8.8% of cats were exposed and mechanically carrying spores on their hair coat but did not have clinical infection.[153]

The second technique to obtain samples for dermatophyte culture is plucking of suspect hairs and/or crusts from the margins of the lesions. There are no published studies directly comparing this technique with brushings, but Sparkes *et al.* noted 50 instances in which there were false negative fungal cultures in samples obtained via hair pluck but conclusively positive direct examinations.[101]

The third is a rarely described but potentially useful technique. In the sticky tape technique, a 4 cm length of tape is pressed over lesions and then pressed to the surface of a fungal culture plate. Lesions cultured using the brush technique or sticky tape technique had comparable results, although the sticky tape technique appeared to be more sensitive.[136]

Fungal culture medium and incubation condition

Sabouraud's dextrose agar (SDA) and isolated selective media containing cycloheximide, penicillin and streptomycin were used in most diagnostic laboratories until point-of-care fungal culture medium was developed. In the late 1960s Dermatophyte Test Medium (DTM) was developed for field evaluation by paramedical personnel for skin infections in military forces operating in the tropics.[170] Dermatophyte Test Medium is a nutrient growth medium with antibiotics to suppress bacterial and contaminant fungal overgrowth and a colour indicator to aid in the early recognition of possible dermatophyte species. The colour change in the medium from yellow to red is the result of a pH change triggered by fungal growth. The first published article concluded that colour change alone was diagnostic of a dermatophyte, but numerous studies shortly thereafter documented a wide range of contaminants that also cause a red colour change in the medium.[171,172] In 1974, Carroll[165] reported on the evaluation of DTM for the diagnosis of small animal dermatophytosis and also reported >20% of cultures had false positive results. In that study, dermatophytes produced a red colour change within two to 14 days, with a mean of nine days.

Guillot reported on the performance of a proprietary DTM medium and found that when infected hairs were inoculated there was a rapid colour change in the medium (three to five days).[173] In addition, that study did not find that incubation at 37°C enhanced fungal growth. There is one published study comparing six commercially available fungal culture media with respect to first growth, first colour change and first sporulation for *M. canis*, *M. gypseum* and *Trichophyton* sp. at either 25°C or 30°C.[174] Five of six products showed 100% growth at both temperatures. The one product found to be inferior was a flat self-sealing incubation plate. The volume of medium on the plate was most important; a small volume was inferior. Review articles commonly state that plates should be incubated in the dark, but in Moriello's study there was no difference in growth or sporulation with 24 h of light, 24 h of dark, 12 h light/12 h dark, or room lighting.

Kaufmann *et al.*[175] compared the results of point-of-care dermatophyte cultures with those from a diagnostic laboratory. When fungal culture storage and incubation instructions were followed along with use of macro- and microscopic identification characteristics, there was 97% agreement between the two. However, when macro- and microscopic examination was not used, there was a significant (19.4%) chance of an incorrect diagnosis.

Fungal culture and monitoring of infections

For decades, clinical cure and Wood's lamp examinations (*M. canis*) were used to monitor response to treatment. The term "mycological cure" with respect to treatment did not appear in the literature until 1959 when Kaplan and Ajello reported on the use of griseofulvin for the treatment of dermatophytosis in cats. In that study, mycological cure was defined by two negative fungal cultures taken at two weeks apart.[44] The monitoring of colony forming units (cfu) per plate to assess disease severity and recovery was first described in the mid-1900s when guinea pig models of experimental infections were being developed. In 1968, Dawson & Noddle[111] described using the number of cfu per plate to monitor cats receiving treatment. Successful response to antifungal treatment was associated with a rapid decrease in cfu/plate as lesions resolved. Spontaneous and experimental studies most commonly report using two to three negative fungal cultures to define mycological cure, and decreases in cfu/plate as a method of monitoring response to treatment.[42,109,112,116–118,121,123,129,136]

Shelter screening and treatment studies for dermatophytosis have shown that reporting of "positive" or "negative" fungal cultures is not adequate for interpretation of fungal cultures. Some type of quantitative measure of the number of cfu/plate is needed to aid screening and monitoring of infections. For example, a culture plate with one cfu/plate and another with confluent growth would both be reported as "positive", but be interpreted differently with the latter being typical of an animal with true infection and the former a recovery or fomite carriage. The use of two negative consecutive cultures as mycological cure and cfu/plate for screening and monitoring of infections is widely used in shelters.[105,126,130,131]

Box 1 and Box 2 summarize one system for monitoring treatment success or failure using lesions, Wood's lamp examinations and colony forming units.[153,176]

3.5 Polymerase chain reaction

Although there are many published reports on the identification of *Microsporum* and *Trichophyton* spp. via PCR, published studies on use of PCR on clinical specimens from veterinary patients are few.[177] Nardoni *et al.*[178] reported on the use of a PCR protocol on paraffin embedded tissues to aid in the diagnosis of deep dermatophyte infections in cats. There were 100% concordant results

Box 1. Steps for using culture and colony forming units (cfu) to monitor treatments*[176]

Dermatophyte culture

Fungal culture plate Use a fungal culture plate with adequate surface area that allows for toothbrush inoculation of cultures and counting of colony forming units. Standard petri dishes (≥90 mm) or dual compartment plates are recommended

Inoculation Inoculate plates by stabbing bristles onto the surface of the plate in 4–5 areas. A 'stab' pattern should be visible. DO NOT over inoculate plates as this will delay the development of identifying macro and microconidia due to competition for growth. Typically this is characterized by rapid growth and unsporulated hyphae upon microscopic examination.

Incubation Incubate the plates at 25–30°C: store plate medium side up and in an individual plastic bag to prevent dehydration.

DTM Monitoring/interpretation

Monitor daily, record growth once weekly

- c-contaminant growth
- hc: heavy contamination-plate overgrown with growth; consider reculturing
- suspect growth
- *Microsporum* or *Trichophyton* (identified via microscopic examination).

When a pathogen is identified, count the number of colonies on the plate. The semi-quantitative system will reflect the severity of the growth similar to what is done for cytology or bacterial cultures

Pathogen score 1: 1–4 cfu/plate (P1)
Pathogen score 2: 5–9 cfu/plate (P2)
Pathogen score 3: >10 cfu/plate (P3)

Untreated pets with active infections in most cases tend to have a starting score of P3. Early in treatment P3 cultures commonly show confluent growth. As treatment progresses and the infection is eradicated in the hair follicle and the hair coat disinfected, the density of growth will decrease and the number of cfu/plate will decrease to 10 (P3) and then P2, P1. This is a strong and consistent indicator of a positive response to treatment. Cured animals will have no growth, contaminant growth, or P1 scores.

Troubleshooting

- Cultures fluctuating from negative (no growth or contaminant growth) and P1: Thispattern is common in animals exposed to fomite contamination.
- Sudden increase in P score, e.g. P1 or P0 to P3: The common causes of this include:
  - Lack of inadequate disinfection of the hair coat, particularly hairs around the face and ears, this pattern is commonly seen in pets where the face and ears may not have been adequately treated due to concerns about applying topical treatments
  - Development of new lesions, new lesions commonly develop on the face and ears
  - Fomite exposure
- Persistent P2/P3 scores:
  - If clinical cure is apparent, potential causes may be
    - lack of disinfection of the hair coat
    - subclinical infection, most commonly on face and/ears
    - fomite carriage on the hair coat from contact with inadequately cleaned environment
  - If clinical lesions are persistent, potential causes include
    - Too short of a treatment period, continue treatment
    - Concurrent systemic illness
    - Treatment compliance problems

*Adapted from: Moriello KA & DeBoer DJ. Dermatophytosis. *Kirk's Current Veterinary Therapy XV;* St. Louis MO: Elsevier Health Sciences, 2013; 449-451.[176]

between PCR and culture. The use of PCR to diagnose infectious agents in nodular lesions in cats again confirmed the usefulness of PCR, given that this can rarely be done via histological examination alone.[179] There are two published studies evaluating PCR-based methodology for the diagnosis of dermatophytosis from cat or dog hair.[180,181] In the first study, 187 hair samples from dogs and cats suspected of having dermatophytosis were tested via PCR.[180] Infection was confirmed via culture in 59 of 183 (32.2%) samples. Direct microscopic examination with KOH confirmed infection in 22 of 183 samples (12.0%). One-step PCR identified dermatophyte DNA in 49 of 183 (26.8%) and nested PCR was positive in 63 of 183 (34.4%) of specimens. False positive results were attributed to either nonviable DNA on the hair coat or conversely false negative fungal culture results. There was no evidence that PCR was affected by systemic treatment. In a second study, 15 specimens from dogs and cats with confirmed dermatophytosis via both culture and KOH direct examination, were tested. PCR correctly identified *T. mentagrophytes* infection in seven of seven dogs and *M. canis* in eight of eight cats. A positive PCR test can be the result of active infection, fomite carriage or nonviable fungal organisms from a successfully treated infection. A false negative test can occur because sampling techniques have not been optimized or if a global

Box 2. Interpretation of P-score, lesions and Wood's lamp findings in diagnosis and treatment of *M. canis* infections*

P-score	Examination	Wood's lamp examination of hair shafts	Wood's examination of hair tips	Interpretation	Plan	Comments
P3 (>10 cfu/plate)	Lesional/ Nonlesional	Positive/Negative	Positive/Negative	High risk/Not cured	Treat or continue treatment	A single infected hair can produce a P3 culture, examine carefully.
P2 (5–9 cfu/plate)	Lesional	Positive/Negative	Positive/Negative	High risk/Not cured	Treat or continue treatment	
	Nonlesional	Positive	Positive/Negative	High risk/Not cured	Treat or continue treatment	
	Nonlesional	Negative	Positive/Negative	Cured/Low Risk	Re-examine, apply whole body antifungal treatment, then repeat culture when dry	Likely represents a "dust mop" scenario
P1 (1–4 cfu/plate)	Lesional	Positive/Negative	Positive/Negative	High risk/Not cured	Treat or continue treatment	
	Nonlesional	Positive	Positive/Negative	High risk/Not cured	Treat or continue treatment	
	Nonlesional	Negative	Positive/Negative (glowing tips are common in cured animals)	Cured/Low Risk	Re-examine, apply whole body antifungal treatment, then repeat culture when dry	If "dust mop" cat, repeat culture will be negative

Note

cfu, colony forming unit; "dust mop" refers to a cat that is mechanically carrying spores from environmental contamination

*Adapted from the treatment and monitoring procedures used in the Felines In Treatment Program at the Dane County Humane Society, Madison, Wisconsin, USA.

dermatophyte marker is not used as many infections in dogs are due to pathogens other than *M. canis.*

3.6 Biopsy

The histological examination of tissue is rarely reported as a routine diagnostic aid to diagnose small animal dermatophytosis. Review of the literature reveals three clinical presentations where diagnosis via skin biopsy has been reported. The first is the investigation of a nonhealing wound or nodule caused by dermatophytosis (kerion, pseudomycetoma and mycetoma).[46–50,56,57] The second is in the investigation of dogs with facial lesions of a chronic nature and/or for suspected pemphigus.[88,182,183] Histological similarities between dermatophytosis and pemphigus included acantholytic intraepidermal pustules and interface dermatitis. The third is the investigation of animals with unusual skin lesions not easily attributed to other causes.[56,61,90,184] In any of these situations, routine haematoxylin and eosin staining (H&E) may or may not identify dermatophytes and special stains such as periodic acid Schiff (PAS) and Grocott methenamine silver (GMS) are needed. Histological staining cannot identify the dermatophyte species and molecular testing is not widely available. Isolation of the dermatophyte from tissues (via submission of a biopsy sample in a small amount of sterile saline for macerated tissue fungal culture) is ideal but false negative culture may occur.

3.7 Conclusions

1. No one test was identified as a "gold standard".
2. Dermatophytosis is diagnosed by utilizing a number of complementary diagnostic tests, including Wood's lamp and direct examination to document active hair infection, dermatophyte culture by toothbrush technique to diagnose fungal species involved and monitor response to therapy, and biopsy with special fungal stains for nodular or atypical infections.
3. Dermoscopy may be a useful clinical tool with or without concurrent use of a Wood's lamp to identify hairs for culture and/or direct examination.
4. PCR detection of dermatophyte DNA can be helpful; however, a positive PCR does not necessarily indicate active infection, because dead fungal organisms from a successfully treated infection will still be detected on PCR, as will noninfected fomite carriers.
5. Contrary to what is believed, Wood's lamp examination is likely to be positive in most cases of *M. canis* dermatophytosis. Fluorescing hairs are most likely to be found in untreated infections; fluorescence may be difficult to find in treated cats. False positive and false negative results are most commonly due to inadequate equipment, lack of magnification, patient compliance, poor technique or lack of training.
6. Monitoring of response to therapy includes clinical response, use of Wood's lamp if possible, and fungal culture. The number of colony forming units is helpful in monitoring response to therapy.
7. Negative PCR in a treated cat is compatible with cure. Negative fungal culture from a cat with no lesions and a negative Wood's lamp (except for glowing tips) is compatible with cure.

4 Topical antifungal treatments

Transmission of dermatophytosis occurs via direct contact with infective material originating from the skin and hair coat of infected animals. Thus, the purpose of topical therapy is to decrease the infectious, contagious and zoonotic risks associated with this disease by disinfecting the hair coat and minimizing contamination of the environment. The usefulness of topical therapy in preventing "in-contact cats" from acquiring infection or becoming culture positive was shown in a shelter study.[130] The shelter protocol was to not separate litters of kittens being admitted for treatment of dermatophytosis. Twice weekly lime sulfur was used as the topical therapy of choice. Cage-mate kittens or juvenile cats ($n = 32$) never developed lesions or became culture positive as a result of being housed in direct contact with an infected cat(s).[130] Topical therapy is also an important component of strategies to minimize shedding and spread of infective material in the environment. For example, in a study evaluating the use of adjuvant topical therapy for the treatment of dermatophytosis in a cattery of Persian cats ($n = 14$ cats), dermatophytes were not cultured from the environment housing the cats treated with topical therapy.[42] In a more recent study, cats received oral itraconazole on a week on/week off cycle and one of two topical antifungal shampoos. Within one week of starting treatment, topical therapy combined with cleaning instructions resulted in clearance of infective material from the environment. The environment stayed culture negative throughout the remainder of the study.[129]

4.1 Whole body treatments (See Supporting Information Table S2 for summary)

4.1.1 Lime sulfur (calcium polysulfide)-leave on rinse

Sulfur is one of the oldest topical medicaments dating back to the time of Hippocrates. When it was combined with calcium or copper it became widely used in agriculture and vineyards to treat and/or prevent fungal infections on plants.[185] One of the best known sulfur-based fungicides is the Bordeaux mixture.[185] Lime sulfur's characteristic "rotten egg smell" is due to hydrogen sulfide. The exact mode of action is unknown. It is fungicidal on contact due to the formation of hydrogen sulphide. It is keratolytic.[186,187] In plants, the antifungal efficacy of sulfur is believed to be due to its conversion to pentathionic acid which is toxic to fungi.[187]

The first *in vitro* documentation of lime sulfur's antifungal effects against *M. canis* was by White-Weithers *et al.*[188] Using isolated infected whole hairs, test samples were treated twice weekly with 5 min applications (30 to 60 mL/L) and cultured once weekly. After two lime sulfur treatments, samples were culture negative. Further documentation of its antifungal efficacy against *M. canis* was shown in several *in vitro* studies using isolated infective spores which demonstrated 100% sporicidal efficacy with dilutions as low as 1:528 (manufacturer recommended dilution 1:33) and treatment times as short as 5 min.[189,190] In a study evaluating different commercial preparations ($n = 9$), isolated infective *M. canis* spores were incubated for 5 min with three different dilutions (1/2 recommended strength, labelled strength, and 2×labelled recommendation). All veterinary preparations showed 100% sporicidal efficacy. One colony on one plate grew at half the recommended dilution of a commercial garden lime sulfur product.[191]

There are three field studies on the use of lime sulfur to treat feline dermatophytosis.[126,130,131] In one study ($n = 58$ cats), shelter cats were treated with oral itraconazole and twice weekly lime sulfur (8 oz/gal or 30 mL/L). The mean number of days to cure was 18 and all cats were cured by day 49 after starting treatment.[130] In the second study, 90 shelter cats were treated with oral itraconazole and an original formulation of lime sulfur ($n = 31$), a less odorous formulation ($n = 27$) and a miconazole/chlorhexidine dip ($n = 32$).[131] The original formulation of lime sulfur was found to be associated with shorter treatment times compared to the other two topical products. The median number of days to cure for the original formulation was 30 (range 10–69).[131] In a study of 85 shelter cats treated with twice weekly lime sulfur and a three week course of oral terbinafine, the mean time to mycological cure was 22.7 days.[126] In this study, when lime sulfur rinses were decreased to once a weekly there was an increase in the number of cfu/plate; cats did not cure until twice weekly applications were used. Lime sulfur can be used at a concentration of 4 or 8 oz/gallon (15 or 30 mL/L); however, in shelters the clinical impression is that the higher concentration was more efficacious as determined by shorter treatment times.[192]

Documented cutaneous adverse effects of lime sulfur were drying of the footpads, loss of hair on the ears, drying of the hair coat and, with repeated application, yellow discolouration of the hair coat of white cats.[126,130–132] Oral ulceration associated with an irritant reaction from contact with lime sulfur on the hair coat has not been documented in any of the shelter studies where it was used at a dilution of 8 oz/gal or 30 mL/L.[126,130–132] Reports of oral ulcerations in cats under treatment in shelters occurred concurrently with fever and development of upper respiratory infections and did not have an irritant pattern. There are two likely explanations for these reports. The first is confusion with ulcers associated with upper respiratory infections. The second explanation is dilution error resulting in a solution that is 3–4× as concentrated. Most veterinary commercial formulations of concentrated lime sulfur typically list 97.8% saturated lime sulfur. In some countries, it is labelled as 23% calcium polysulfide or 23% sulfur sulfide. This is equivalent to 79.9% lime sulfur solution but the same dilution (1:16) is required to make a 5% dilution.

4.1.2 Enilconazole leave on rinse

Enilconazole is a broad spectrum antimycotic belonging to the imidazole group that is widely used in agriculture and approved for use in the treatment of dermatophytosis in cats (France only), dogs, cattle and horses. It is available as a 10% concentrated solution in Canada and

Europe and it is currently not available or licensed for use in the United States.

Several of the same independent *in vitro* studies documenting the antifungal efficacy of lime sulfur against *M. canis* also tested enilconazole. Isolated infected hairs were culture negative after two applications of enilconazole.[188] Isolated infective spore studies showed that it was equally effective as lime sulfur against *M. canis* and *Trichophyton* spp.[189,193] Two studies tested a 1:100 enilconazole dilution against unfiltered dermatophyte-infected macerated hair solutions at increasing concentrations of 1:10, 1:5 and 1:1 disinfectant to infective material, and enilconazole was 100% sporocidal at all concentrations.[193,194] When toothbrushes containing infective hairs were immersed in a 1:100 dilution of enilconazole for 3 min or 10 min, post-treatment cultures were positive in 0 of 10 samples with 3 min contact time and in one of 12 samples with 10 min contact time (1 colony/plate).[194]

There are four peer-reviewed studies reporting on the use of enilconazole as a sole or adjuvant topical treatment for feline dermatophytosis and all showed some degree of efficacy as a topical therapy.[40,105,109,115] The first study focused on tolerability and not clinical cure. In that study involving 14 Persian cats, 10 of 14 were treated twice weekly with 0.2% enilconazole emulsion for eight weeks. All 10 cats were culture negative at weeks five and eight, whereas only one of four controls was culture negative. All cats were culture negative at week 10; however, when cats were euthanized at weeks 10 or 12, all had focal lesions and evidence of dermatophyte infection was found in the skin of three cats on histological examination. In a second study involving the treatment of endemic dermatophytosis in a Persian cattery, 22 cats were treated twice weekly for eight treatments and monitored for 180 days.[115] No systemic antifungal therapy was used. By day 28, all cats had negative fungal cultures and clinical lesions appeared to have resolved; however, lesions started to recur at day 60, and by day 180 all cats were culture positive for *M. canis* and several were lesional. Owner noncompliance with regard to adhering to treatment recommendations, limiting new additions to the cattery and suspending breeding was noted in the study. In a third study, 100 cattery cats from two catteries received once weekly 0.2% enilconazole dips for four weeks in combination with either griseofulvin for five weeks or two doses of lufenuron administered on days 0 and 30. All cats initially had partial clinical improvement and reduced fungal colony numbers on dermatophyte cultures after two to four weeks of treatment; however, no cat was culture negative and colony counts increased a month after treatment was finished.[109] A more recent shelter study describing the eradication of dermatophytosis from a shelter showed good success when stringent environmental decontamination and animal location stratification according to lesional and culture status was used in combination with oral itraconazole and twice weekly 0.2% enilconazole dips; 24 clinically affected cats and 22 lesion-free carrier cats were cured and culture negative after between 30 and 56 days of treatment.[105]

Three of four studies involving a total of 132 cats specifically mentioned adverse effects.[40,109,115] All studies noted that topical therapy was well tolerated. No eye, mucous membrane or skin abnormalities were reported. There was a slight discolouration to the hair coat. Several cats experienced drooling for several minutes to 1 h post-treatment. Drying of the hair coat post-application eliminated this adverse effect. One cat developed hind limb muscle weakness after four treatments but this resolved even with continued topical treatments.[115] When laboratory monitoring of complete blood counts and serum biochemical tests were compared between treated and untreated cats, there were no consistent abnormalities.[40] One study reported that six of 22 cats developed mild elevations of serum alkaline phosphatase, but all cats remained clinically normal.[115] In three studies, pregnant queens were treated and no abnormalities were noted in their kittens.[109,115] In one study, two of 10 kittens were still-born and two failed to thrive and died after several days, but the breeder reported that this was typical for this cattery.[115]

4.1.3 Miconazole/chlorhexidine formulations

After a clinical report showed efficacy of a combination miconazole/chlorhexidine shampoo in the treatment of dermatophytosis, two *in vitro* studies investigated the antifungal efficacy of stock solutions of miconazole, chlorhexidine, or a 1:1 combination of both against *Microsporum* spp. and *Trichophyton* spp.[42,195,196] In the first study, an agar dilution technique was used to assess the minimum inhibitory concentrations (MIC) of miconazole, chlorhexidine and a 1:1 combination of both agents for 10 isolates of *M. canis*.[195] The MIC of chlorhexidine, miconazole and chlorhexidine/miconazole ranged from 12.5 to 25 μL/mL, 0.29 to 1.17 μL/mL, and 0.14 to 0.39 μL/mL, respectively. For nine of 10 of the isolates, the miconazole/chlorhexidine combination was more effective than either agent alone; there was either a synergistic (n = 5 isolates) or additive (n = 4 isolates) effect. This study protocol was repeated but this time evaluated these agents against *T. mentagrophytes* (n = 9), *T. erinacei* (n = 9) and *M. persicolor* (n = 5). The MIC of chlorhexidine, miconazole and miconazole/chlorhexidine ranged from 12.5 to 50 μL/mL, 0.24 to 1.56 μL/mL, and 0.11 to 1.66 μL/mL, respectively. The mean MICs did not vary significantly between the three dermatophyte species tested, but the MICs of miconazole alone and in combination with chlorhexidine for *T. erinacei* were significantly greater than for *T. mentagrophytes* and *M. persicolor*. A synergistic or additive effect was seen in 15 of 23 isolates tested.[196]

There are two *in vitro* studies reporting on the efficacy of commercial products containing miconazole/chlorhexidine.[190,194] The antifungal efficacy of a commercial rinse formulation of 5.2% miconazole and 5.9% chlorhexidine gluconate was compared to lime sulphur using isolated infective spores at a dilution of 1:1 spores to test solution. Test solution dilutions ranged from 1:2 to 1:28 for both products. Lime sulfur was 100% sporocidal at all test dilutions at both 5 min and 4 h. The miconazole/chlorhexidine gluconate was 100% sporocidal at all but the 1:128 dilution after 5 min of incubation and 100% sporocidal when incubated with spores for 4 h.[190] More recently, the antifungal efficacy of two different commercial miconazole/chlorhexidine shampoos against *M. canis* and *T. mentagrophytes* was tested using two different

challenge models.[194] In the first, a 1:10 dilution of shampoo was tested against an increasing spore challenge (1:10, 1:5 and 1:1). Both products were 100% sporicidal when used for a 10 min contact time. In an infected cat hair challenge model, *M. canis* culture-positive toothbrushes containing large amounts of hair were soaked in a 1:10 dilution of shampoo solutions for 3 or 10 min. Post-treatment cultures were positive in seven of 20 test at a 3 min contact time (1–10 cfu/plate) and in 0 of 24 samples with 10 min contact time.[194]

There are five *in vivo* studies evaluating miconazole/chlorhexidine shampoo or rinse and comparing it with other topical therapies (lime sulfur, miconazole or chlorhexidine).[42,129,131,136,140] It is important to note that only one was a controlled study, two involved the treatment of Persian cats, one was conducted in an animal shelter and the last was an open field study. The first field study compared the efficacy of oral griseofulvin alone to oral griseofulvin with adjunct shampoo treatment in 22 Persian cats.[42] In the second study (n = 21 cats), experimentally infected cats were treated with oral griseofulvin alone, oral griseofulvin with adjunct topical therapy, and or no treatment.[136] Both studies showed that twice weekly bathing resulted in faster resolution of clinical signs and cure faster than using griseofulvin alone. In the third study, an unreported number of Persian cats in a cattery with naturally occurring dermatophytosis were treated with oral griseofulvin and water (placebo), 2% miconazole shampoo, 2% chlorhexidine shampoo, or with a combination of 2% chlorhexidine and 2% miconazole shampoo. Cats treated with the combination shampoo showed negative cultures as early as two weeks post-treatment. The combination shampoo was found to be superior to miconazole alone and chlorhexidene shampoo alone was no better than placebo.[140] In the shelter study, a miconazole/chlorhexidine rinse was compared to two formulations of lime sulfur in a group of 90 naturally infected cats.[131] All of the cats were treated with itraconazole and topical therapy. Thirty two cats were treated with the miconazole/chlorhexidine rinse and 13 of 32 cats required repeat treatment with lime sulfur due to persistent culture-positive status and development of new lesions. The median number of days of treatment for the 19 cats that cured with miconazole/chlorhexidine rinse was 48 (range 14–93 days), compared to 30 and 34 (range 10–80 days) in the two groups of cats treated with different formulations of lime sulfur.[131] In the open field study, 14 infected cats were treated with itraconazole and one of two topical therapies including 2% chlorhexidine and 2% miconazole shampoo. The median time to clinical cure was six weeks and the median time to mycological cure was six weeks (range 7–21 weeks).[129]

4.1.4 Chlorhexidine formulations

Chlorhexidine is a biguanide compound. Low concentrations affect the cell membrane integrity and higher concentrations result in congealing of cytoplasm.[197] Four studies report on the use of chlorhexidine against the naturally infective state of *M. canis*.[112,140,188,189] In the first study using isolated infective hairs, infected hairs were culture negative after four treatments with a 2% chlorhexidine solution 25–50 mL/L.[188] In a second *in vitro* study using isolated infective spores in which a 1:1 dilution of spores to solution was exposed to different concentrations of chlorhexidine solution, it was found that 2% chlorhexidine 1:25 to 1:3,200 was ineffective at all concentrations tested.[189] In the first *in vivo* study, there was no difference in cure between controls and cats treated with twice weekly 0.5% chlorhexidine shampoo followed by a rinse with 0.06% chlorhexidine solution. In this study, no concurrent systemic antifungal medication was administered.[112] In the second *in vivo* study, Persian cats with spontaneous disease were treated with griseofulvin and twice weekly shampoos. The chlorhexidine/miconazole group were culture negative at week two and the chlorhexidine- and placebo-treated groups were culture negative at week four.[140]

4.1.5 Miconazole formulations

Miconazole as a sole shampoo formulation has been evaluated in two studies. In one study it was used as adjunct topical therapy for the treatment of *M. canis* dermatophytosis in Persian cats. When used as a 2% shampoo, it was superior to chlorhexidine and placebo; miconazole performed best when used in combination with chlorhexidine.[140] When tested using two *in vitro* models using unfiltered natural infective spore suspensions of *M. canis* and *Trichophyton* sp., a 1:10 shampoo dilution was 100% sporicidal with a 10 min contact at challenges of 1:10, 1:5 and 1:1 shampoo to spore suspension. When toothbrushes with infective hairs were soaked for 3 or 10 min, post-treatment cultures were positive in one of 12 test samples with a 10 min contact time (1 cfu/plate) and in seven of 10 with a 3 min contact time (1–20 cfu/plate).[194]

4.1.6 Terbinafine formulations

The antifungal efficacy of systemic terbinafine is well established. There is only one published study on the use of this compound for topical therapy. In one small study, four of eight dogs with naturally occurring *M. canis* dermatophytosis were washed twice weekly in a shampoo containing 1% terbinafine and 2% chlorhexidine and the other four dogs were washed with a control shampoo. After three baths, two of four dogs were culture negative and none of the control dogs were culture negative.[128]

4.1.7 Ketoconazole formulations

There are no *in vivo* reports of the use of ketoconazole shampoo alone or in combination as topical therapy for dermatophytosis. In one study, isolated infected whole hairs were culture negative after eight treatments with a ketoconazole shampoo.[188] In a second *in vitro* study, 1% ketoconazole/2–2.3% chlorhexidine gluconate combination shampoos were 100% sporocidal against naturally infective spore suspensions of *M. canis* and *Trichophyton* sp., with a 10 min contact time at increasing challenges of 1:10, 1:5 and 1:1 shampoo to spore suspension. In the same study, when toothbrushes full of infected hairs were immersed in a 1:10 shampoo dilution, 12 of 30 samples were culture positive after a 3 min contact time and four of 36 were culture positive after a 10 min contact time.[194]

4.1.8 Climbazole formulations

There are no *in vivo* studies reporting on the use of climbazole formulations for treatment of dermatophytosis. There is only one *in vitro* study evaluating it in two different test models. A 1:10 dilution of a 0.5% climbazole/3% chlorhexidine shampoo was 100% sporicidal against natural unfiltered infective spore suspensions of *M. canis* and *Trichophyton* sp., with a 10 min contact time at increasing challenges of 1:10, 1:5 and 1:1 shampoo to spore suspension. In the same study, when toothbrushes full of infected hairs were immersed in a 1:10 shampoo dilution, five of 10 and four of 12 samples were culture positive after a three and 10 min contact time, respectively.[194]

4.1.9 Accelerated hydrogen peroxide

There are no *in vivo* studies on the use of accelerated hydrogen peroxide (AHP) for topical therapy of dermatophytosis. In one *in vitro* study, a 1:20 dilution of 7% topical shampoo/rinse was 100% sporicidal against natural infective spore suspensions of *M. canis* and *Trichophyton* sp., with a 10 min contact time at increasing challenges of 1:10, 1:5 and 1:1 AHP dilution to spore suspension. In the same study, when toothbrushes full of infected hairs were immersed in a 1:10 AHP solution, two of 10 and one of 12 and samples were culture positive after a three and 10 min contact time respectively.[194] In a follow-up experiment in that study, when a 1:20 dilution of a 7% formulation was used as a leave on rinse post-shampoo therapy with chlorhexidine / miconazole, ketoconazole, miconazole or climbazole shampoos, all post-treatment test samples were culture negative. Of note, the product is currently supplied as a 3.5% concentration to be diluted 1:40.

4.1.10 Essential oils

An essential oil (EO) is the volatile oil derived from some part of a plant, for example a leaf, stem or flower and usually carries the odour or flavour of the plant. Essential oils are usually lipophilic compounds and therefore are not miscible in water. Some EO are pure compounds (e.g. oil of wintergreen), but most are mixtures of many chemicals. There is increased interest in EO as alternatives to synthetic drugs because of concerns regarding drug resistance. In addition, there is interest in exploring the application of EO in skin products to order to treat or avoid skin infections. The reader is referred to reviews for summaries of research on the antimicrobial and antifungal properties of EO.[198–200] Essential oils result in fungal cell wall damage by slowing growth and/or destruction of intracellular organelles.

There are two *in vivo* studies on the use of EO for topical therapy.[127,129] In the first study, 14 cats were divided into two groups.[127] The first group received oral itraconazole 5 mg/kg on a week on/week off basis repeated three times. The second group was treated with a topical solution twice daily for 30 days comprising *Thymus serpillum*, *Origanum vulgare* and *Rosmarinus officinalis* in sweet almond oil. At the end of 30 days, six of seven and four of seven cats treated with itraconazole and EO, respectively, were cured. There were no reported adverse effects. The three EO were selected from a screening panel of 11 compounds and had the lowest MIC against *M. canis.* In the second study, 14 cats with confirmed *M. canis* dermatophytosis were treated with oral itraconazole 5 mg/kg orally on a week on / week off basis repeated three times and washed twice weekly with either miconazole/chlorhexidine or a neutral shampoo with added EO (*Thymus serpillum*, *Origanum vulgare* and *Rosmarinus officinalis*).[129] Both groups of cats were clinically normal by six weeks and the mean time to mycological cure was 13 weeks (miconazole/chlorhexidine) and 15 weeks (EO shampoo). Owners were given cleaning instructions and environmental cultures were negative and stayed negative after one week post-treatment.

The observed *in vivo* efficacy of EO against dermatophytes has been confirmed with *in vitro* testing with veterinary isolates and studies testing compounds against veterinary isolates.[201,202] When 20 EOs were assayed against clinical animal isolates of *M. canis, T. mentagrophytes, T. erinacei, T. terrestre* and *M. gypseum*, the three most effective EOs identified were *Thymus serpyllum, Origanum vulgare* and *Litsea cubeba*. When a herbal mixture composed of chemically defined EOs of *Litsea* cubeba, *Illicium verum*, *Foeniculum vulgare* and *Pelargonium graveolens* was sprayed on naturally *M. canis* infected hairs, fungal growth was inhibited after four daily applications.[202]

4.1.11 Pythium oligandrum

There is one study describing the *in vitro* efficacy of *Pythium oligandrum* against *M. canis*, *M. gypseum* and *T. mentagrophytes*.[203] *Pythium oligandrum* is a soil micromycete with mycoparasitic properties and has been used in agriculture to control fungal infection in plants. The organism obtains necessary growth nutrients by consuming target fungi. In this study, pathogen fungal colonies in contact with *P. oligandrum* showed rapid loss of hyphae on dermatophyte-infected hairs. Currently there are two commercial formulations of this biological agent available in the Czech Republic.

4.1.12 Focal treatment products

There is one *in vivo* study evaluating the efficacy of miconazole and clotrimazole in the treatment of experimentally induced *T. mentagrophytes* ($n = 13$) and *M. canis* ($n = 9$) infections in dogs.[120] After the infection was established dogs were randomly assigned to either a treatment group or an untreated control group. Lesions were treated once daily for 28 days and lesions were evaluated by daily scoring of lesion severity and by semi-weekly culturing throughout the treatment period. Compared with untreated controls, the clinical and mycological response to clotrimazole was significantly better from day 11 until the end of the study. The response to clotrimazole equalled or occasionally exceeded that of miconazole. In an experimental infection model, 176 guinea pigs were infected with either *T. mentagrophytes* ($n = 88$) or *M. canis* ($n = 88$) and divided into one of four treatment groups: vehicle treatment, bifonazole topically, oral itraconazole or itraconazole solvent.[204] Animals were treated once daily for 14 days and evaluated at postmortem examination on day 14 or at day 21 ($n = 10$/group). Within 24 to 48 h after starting oral itraconazole, light and electron microscopy

showed that azole induced changes in fungal organisms with the hair shafts (i.e. accumulation of vesicles in the cell wall, enlargement of the vacuolar system and presence of lipid globules in the cytoplasm). Topical treatment alone affected organisms in the stratum corneum but did not prevent invasion of fungi into the hair shafts. One study showed that the topical application either terbinafine or econazole was noninflammatory on the skin of cats or dogs.[205]

One study described successful treatment of five dogs and four cats with focal application of enilconazole. The hair around the lesions was clipped and the lesions were treated every three days for four weeks. Eight of nine animals were culture negative after four weeks of treatment. One cat was clinically cured but culture positive.[143]

4.2 Conclusions

1. Twice weekly application of lime sulfur, enilconazole or a miconazole/chlorhexidine shampoo are currently recommended effective topical therapies in the treatment of generalized dermatophytosis in cats and dogs.
2. Accelerated hydrogen peroxide products as well as climbazole and terbinafine shampoos show promise, but cannot be definitively recommended until more *in vivo* studies documenting efficacy are available.
3. Miconazole shampoos are effective *in vitro* but *in vivo* are most effective when combined with chlorhexidine.
4. Chlorhexidine as monotherapy is poorly effective and is not recommended.
5. For localized treatment, clotrimazole, miconazole and enilconazole have some data to document effectiveness. These are recommended as concurrent treatments, but not as sole therapy.

5 Systemic treatment

Systemic antifungal therapy targets the active site of fungal infection and proliferation on the infected animal. Until the infection is eliminated in this site, the infected animal is at risk for further spread of lesions on its body, continued seeding of the hair coat with infective spores, and being a source of infection for other animals and people. The most commonly used systemic antifungal drugs for dermatophytosis in veterinary medicine are itraconazole, ketoconazole, terbinafine and griseofulvin.

5.1 Itraconazole (See Supporting Information Table S3 for summary)

Itraconazole is a first generation triazole. At low doses it is fungistatic and at high doses it is fungicidal. Itraconazole works by inhibiting fungal cytochrome P450 enzyme 14α demethylase to prevent the conversion of lanosterol to ergosterol. Ergosterol is best suited for maintaining cell wall integrity and activity.[206]

Itraconazole is insoluble and requires specific formulations to be absorbed in the gastrointestinal tract because it is highly lipophilic and a weak basic compound. The bioavailability is pH dependent with absorption being greater in an acidic environment. Capsules are recommended to be administered with food to decrease gastrointestinal adverse effects and to decrease gastric pH and enhance absorption.[207] Due to its highly lipophilic character, itraconazole accumulates in adipose tissue and sebaceous glands.[208] Distribution to these tissues is extensive and tissue concentrations are many times higher than plasma concentrations. Levels in the stratum corneum of skin areas with a high density of sebaceous glands were up to 10 times higher than plasma levels. In people, the drug has been shown to persist in the epidermis for up to four weeks after discontinuation of treatment.[208] Concentrations of itraconazole in cat hairs were measured after domestic short hair cats received 5 mg/kg or 10 mg/kg once daily for 14 days.[43] The drug was rapidly detected in all hairs, but lower concentrations were found in areas with fewer sebaceous glands or slower hair growth. Concentrations were also dose dependent.[43] In pivotal drug studies for the licensing of itraconazole for cats using a pulse treatment schedule (5 mg/kg on a week on/ week off basis) the median concentration of itraconazole in hairs was 0.168 μg/g at 24 h after the first dose (5 mg/kg). After one week, the median itraconazole hair concentration increased to 1.17 μg/g and then 2.0 μg/g and 2.99 μg/g at the end of the second and third treatment periods, respectively. During nontreatment weeks median values decreased to 0.8–1.5 μg/g. Two weeks after the last dose, the mean hair itraconazole concentrations were still 1.5 μg/g, which exceeds the MIC for itraconazole of 0.25 μg/mL to 1.0 μg/mL.

Pharmacokinetic studies in dogs have found that itraconazole is rapidly absorbed and the mean half-life is 28 h.[209] A study in dogs looking at the bioequivalence of orally administered generic, innovator and compounded formulations of itraconazole in healthy dogs found that generic and compound formulations were not bioequivalent to the parent compound; however, pharmacokinetics data for the generic formulation was similar enough to the parent compound that therapeutic serum levels could be achieved.[210] Less than 6% of the compounded formulation was absorbed.

In a manufacturer's toxicology study, dogs received placebo, 2.5, 10 or 40 mg of itraconazole/kg of body weight daily for 90 days and there were no observed effects on behaviour, appearance, food consumption, body weight, laboratory tests or gross pathology. At 40 mg/kg there were slight histopathological changes in the thymus and adrenals, whereas the liver was not affected. Doses of 10 mg/kg were not teratogenic but embryotoxicity and teratogenicity were seen at >40 mg/kg.[211] The drug is not recommended for use in pregnant or nursing dogs.

Information on adverse effects is extrapolated from studies reporting on its use in the treatment of intermediate or deep mycoses. In dogs, the drug is well tolerated with the most common adverse being anorexia.[212] Elevations of liver enzymes are not uncommon. Cutaneous vasculitis or "skin ulcerations" have been reported in association with the administration of itraconazole, but review of those reports reveals that dogs were being

treated for subcutaneous, opportunistic or deep mycoses, not dermatophytosis. This adverse effect appears to more common in dogs receiving doses ≥10 mg/kg for deep mycoses.[212–215] This is a rare adverse effect and may be associated with the underlying disease as it has not been reported in drug safety tests. No published cases of cutaneous vasculitis in dogs treated for dermatophytosis were identified.

Three independent studies evaluated the pharmacokinetics of itraconazole in healthy cats, although none used the currently licensed formulation for cats.[216–218] Oral formulations of 5 mg/kg were rapidly absorbed, the half-life was approximately 15.6 h and bioavailablity was low (52%).[217] It was reported that the oral human paediatric formulation was better absorbed than a capsule formulation. In addition, it took 14 to 21 days to reach steady-state concentrations in some cats.[218] Another study evaluated an alternate day dosing schedule intended for treatment of cats with systemic fungal infections. The rationale for this study was that the current 100 mg itraconazole capsules are hard to reformulate, compounded formulations have poor bioavailability in dogs, and/or liquid formulations may be cost prohibitive or poorly tolerated. Ten healthy pet cats were given 100 mg of itraconazole /cat (12–26 mg/kg) every 48 h for eight weeks.[216] Therapeutic trough concentrations (>0.5 μg/mL) were achieved in eight of 10 cats within three weeks.

The original target animal safety studies for cats were not readily available for review; however, there is a summary of findings.[43] Cats were given 0.5, 5, 15 and 25 mg/kg once daily of oral itraconazole for six weeks and evaluated for an additional two weeks. The target dose of 5 mg/kg was reported to be safe on all of the monitored parameters. At 15 mg/kg there was a slight increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Upon postmortem examination the liver was pale; histopathological changes were not reported.[43] At 25 mg/kg these elevations were more pronounced and decreased appetite, food consumption and body weight were noted; however, all clinical and biochemical changes were reversible during the two week recovery period. A dose of 5 mg/kg orally once daily was used to assess its safety in kittens. Ten-day-old kittens were treated once daily for four weeks and no treatment-related adverse effects were observed.[43]

Two of three independent pharmacokinetic studies made note of adverse effects and/or did a tolerability study. In one study, 12 healthy cats received 10 mg/kg itraconazole twice daily for six weeks and showed no physical or biochemical abnormalities.[218] In the other study, in which cats received 100 mg itraconazole/cat every other day, eight of 10 cats showed no clinical abnormalities or had laboratory evidence of hepatopathy.[216] Evidence of hepatopathy based on clinical laboratory tests was noted in two cats at weeks three and five (12.5 mg/kg and 26 mg/kg, respectively). One cat developed clinical signs (icterus, inappetence). Both cats recovered after discontinuation of the drug and supportive care. At doses used to treat feline dermatophytosis, studies report the drug is well tolerated and if adverse effects are observed they are mild and include decreased food consumption, depression and increased serum ALT concentration.[125] Itraconazole is commonly used to treat feline sporotrichosis and hyporexia, vomiting and/or diarrhoea were the most common adverse effects reported in 54 of 175 cats; no deaths were attributed to itraconazole.[219] Review of the literature did not reveal any documented cases of fatal liver toxicity in cats receiving therapeutic doses for dermatophytosis. Fatal liver toxicity has been reported in one cat being treated for cryptococcosis with itraconazole. In that study, cats were treated with large doses (median 13.8 mg/kg, range 10.9–26.3 mg/kg) for 8.5 months (range, 4–16 months) and adverse effects occurred in nine of 21 cats.[220] Adverse effects resolved and ALT concentrations decreased in eight of nine cats two weeks after stopping the drug. In only one cat being treated with 100 mg/day (27.8 mg/kg) of itraconazole were adverse effects serious, leading to icterus and death.[220]

In a study reporting on the fungicidal efficacy of itraconazole against *M. canis* and *T. mentagrophytes*,[221,222] MICs for both pathogens ranged from 0.01 to 0.1 μg/mL for *M. canis* (n = 43) and 0.001 to 1.01 μg/mL for *T. mentagrophytes* (n = 46). Efficacy against *M. canis* isolates (n = 38) from animals was further verified by another study (MIC 0.1 μg/mL).[223] Using testing methodologies recommended by the National Committee for Clinical Laboratory Standards (NCCLS), the MIC range for itraconazole is 0.25 μg/mL to 1 μg/mL.[224]

Twelve studies have described the treatment of 316 cats with *M. canis* dermatophytosis using itraconazole alone or in combination with topical therapy.[41,90,105,114,121,123,125,127,129–131,225] See Supporting Information Table S3 for a summary. The studies span a treatment time from 1998 to 2016, during which period a wide range of treatment schedules were used: low dose pulse therapy (1.5 to 3.0 mg/kg every 15 days on/15 days off), daily therapy combined with pulse therapy (10 mg/kg for 28 days then week on/week off), daily therapy until cured (8–10 mg/kg), daily (5–10 mg/kg) therapy for 21 days followed by just topical therapy until cured, 5 mg/kg once daily for 28 days, and two studies using the licensed treatment protocol of 5 mg/kg week on/week off. Concurrent topical therapies with enilconazole, lime sulfur, miconazole/chlorhexidine rinse or shampoo, or an herbal antifungal shampoo were used in five of 10 studies.[90,105,129–131] A clinical response was noted in all treated cats and mycological cure was reported in 271 cats. In one study, seven of 15 cats did not reach mycological cure but itraconazole was used at 1.5 to 3.0 mg/kg.[121] Four of seven cats were clinically normal and had one or few cfu/plate isolated. The number of days to mycological cure, when reported, ranged from 36 to 112. Three studies reported Persian cats in the population and one of these studies had three cats that did not achieve mycological cure, and all had greater numbers of days to mycological cure. Four studies involved shelter cats and it was reported that occasionally some cats did not eat well for the first few days of hospitalization in the treatment ward.[105,125,130,131] Whether or not this was due to the physiological stress or drug is unknown. No treatment study reported stopping the drug due to adverse effects and no deaths were reported. Discontinuation of the drug

due to vomiting and/or decreased appetite has been reported in individual case reports.

5.2 Ketoconazole (See Supporting Information Table S4 for summary)

Ketoconazole was the first oral azole released in the 1980s. It works by inhibition of lanosterol 14α demethylase leading to ergosterol depletion and accumulation of aberrant and potentially toxic sterols in the cell membrane.[226] Mammalian cells can use exogenous cholesterol from the diet and can compensate for the temporary effects of ketoconazole on cholesterol.

The drug is highly lipophilic and this leads to high concentrations in fatty tissues. Its absorption may be enhanced by administration with a small amount of food. The drug is dissolved by gastric acidity and any other drugs that decrease gastric secretions will decrease bioavailabilty.[227] In dogs, an oral dose of 10 mg/kg leads to a peak plasma concentration of 8.9 μg/mg with a half-life of 2.7 h.[228]

In dogs, ketoconazole has been shown to interfere with endogenous steroid synthesis, which is reversible.[229] In cats receiving 30 mg/kg ketoconazole once daily for 30 days plasma cortisol, cholesterol, testosterone and progesterone did not change.[230] There were significant increases in albumin, calcium and serum alkaline phosphatase which did not preclude its continued use. Obvious signs of depression or inappetence were not observed, but cats had a decrease in body weight and the hair coats of some cats became slightly dry and rough.[230] The weight loss and hair coat abnormalities are likely to have been best explained by anorexia because previously reported anorexia and weight loss was seen in cats treated with ketoconazole (10 mg/kg/day for 90 days) that were experimentally infected with cryptococcosis.[231] Large studies on the use of ketoconazole in cats for the treatment of dermatophytosis are not available for review; however, 252 of 598 of cats receiving ketoconazole for treatment of sporotrichosis had signs of anorexia, vomiting and diarrhoea.[219] Ketoconazole has been shown to be teratogenic in rat models and to be excreted in the milk of bitches, and therefore is not recommended for use in pregnant or lactating animals.[227,232] A more limiting factor is the wide range of ketoconazole–drug interactions. Ketoconazole administration leads to increased plasma concentrations of ivermectin and midazolam in dogs and ciclosporin in dogs and cats. It should be avoided in breeding animals because it can decrease production of testosterone.[233]

Ketoconazole has a good of spectrum activity against dermatophytes yet there are relatively few peer-reviewed reports describing its use in the treatment of small animal dermatophytosis. There are two likely explanations: first, at the time of its release, griseofulvin was still widely available and relatively inexpensive compared to ketoconazole; second, literature searches for descriptions of its use in animals reveals that the primary interest in ketoconazole was for the treatment of intermediate and deep mycoses.

There are five peer-reviewed publications describing its use in dogs and cats for dermatophytosis and one case report.[38,107,122,138,139,143] In one study, 40 cats were treated with 10 mg/kg ketoconazole orally once daily for 14 days which was found to be inadequate; cats were cured after the addition of application of enilconazole every 3–5 days and environmental treatment.[138] In another study by the drug's manufacturer, 60 cats and 53 dogs were treated with 10 mg/kg ketoconazole orally once daily for 10 days and 35 cats and 71 dogs were treated once daily for 20 days.[139] No additional topical therapy or environmental cleaning was used. The authors reported a better response with a 20 day treatment period and an overall *clinical cure* in 96.8% of cats and 90.5% of dogs. The data in this study are difficult to interpret because it is unclear if all of the treated animals were truly infected. There were 219 treated animals in this multi-centre study, but pre-treatment fungal cultures were only obtained in 153 animals; cultures were positive in 151 of 153 cases (*M. canis* or *T. mentagrophytes*). Wood's lamp examinations were positive in 49 of 50 examinations but it is not stated if fungal cultures were also performed in the same animals. The authors reported no adverse effects in any of the 95 treated cats, but that two puppies vomited immediately after ingestion of the drug.

There is one case report describing a 10-year-old dog treated with 11 mg/kg ketoconazole once daily for 90 days.[38] At the time of presentation, *Demodex* mites were found on skin scraping and a concurrent *T. mentagrophytes* infection was diagnosed. Mycological cure was not documented but the dog was reported to be normal after 90 days of treatment. The owner reported intermittent constipation during drug administration. In another study, seven dogs and three cats with dermatophytosis were treated with 10 mg/kg ketoconazole once daily for 6 weeks.[143] Clinical cure was noted by the end of five weeks in seven of 10 animals. One cat did not achieve clinical cure. Two dogs were reported to show signs of depression, diarrhoea and vomiting. After two weeks oral ketoconazole treatment was stopped and the dogs were treated topically with enilconazole for four weeks. Mycological cure was not documented in this study. Another study described the treatment of six dogs with dermatophytosis treated with 10 mg/kg ketoconazole once daily until cured but only clinical cure was described.[107]

In the final study, 12 cats with confirmed *M. canis* dermatophytosis (11 of 12 were Wood's lamp positive) were treated with ketoconazole 10 mg/kg orally once daily.[122] Cats were treated until there was resolution of clinical signs or adverse effects necessitated discontinuation of ketoconazole. Complete resolution of clinical signs was noted in eight of 12 cats after 2 to 10 weeks of treatment (median 6 weeks). Treatment was stopped in three of 12 cats due to gastrointestinal adverse effects. It was stopped in one cat after two weeks of treatment due to diarrhoea. In another cat, treatment was stopped after 10 weeks due to anorexia, vomiting and weight loss. In the third cat, ketoconazole was stopped due to diarrhoea that developed after an increase in dose due to lack of response to treatment. Nine of 12 cats had a documented mycological cure. No topical therapy or environmental cleaning was reported and follow-up fungal cultures in

nine cats remained consistently culture negative after their first negative fungal culture.

5.3 Fluconazole

Fluconazole is a first generation triazole that was first released in 1990. Its mechanism of action is similar to that of other azoles. It is water soluble and minimally protein bound. Absorption is not affected by concurrent use of antacids and does not require food for optimal absorption.[234] In dogs the mean oral and intravenous half-life is 12 to 14 h and in cats the oral and intravenous half-life is 12 to14 h.[235,236] Vomiting, diarrhoea and dose-dependent elevated serum ALT were the most common adverse effects. The drug is used primarily for the treatment of systemic mycoses. Fluconazole has poor antifungal efficacy against dermatophytes; it has the highest MIC compared to itraconazole, terbinafine, ketoconazole and griseofulvin for both *Microsporum* spp. and *Trichophyton* spp.[224,237–239] This was further verified in veterinary isolates.[240] Reports of the use of fluconazole for the treatment of dermatophytosis are rare. One study reported mycological cure in 56 to 70 days in kittens ($n = 6$) with *M. canis* dermatophytosis when treated with 10 mg/kg fluconazole once daily.[176] There is one case report of two Persian cats with *Chrysosporium* dermatophyte infections successfully treated with fluconazole 5 mg/kg for six weeks and no adverse effects were reported.[241] Another study described the treatment of six dogs with dermatophytosis (pathogen not specified) with fluconazole 5 mg/kg orally once daily until clinical cure at four weeks.[107]

5.4 Terbinafine (See Supporting Information Table S5 for summary)

Terbinafine is a synthetic allylamine which was developed by chemical modification of naftitine.[242] Terbinafine exerts is antifungal effects by inhibiting fungal sterol biosynthesis to a greater extent than mammalian sterol biosynthesis. It reversibly inhibits the membrane-bound enzyme squalene epoxidase in a concentration-dependent manner which prevents conversion of lanosterol to cholesterol and/or ergosterol.[243] Its mode of action does not affect mammalian cytochrome P450.

Compared to itraconazole, fluconazole, ketoconazole and griseofulvin, terbinafine has the lowest MIC for *Microsporum* sp. and *Trichophyton* spp.[238] This was verified in several studies using veterinary isolates ($n = 24$ *M. canis* isolates and $n = 19$ *Trichophyton* spp.) and in a larger study ($n = 300$ isolates).[240,244] Data from a guinea pig model of experimental dermatophytosis reported that *M. canis* infections required a higher oral dose of terbinafine than infections with *T. mentagrophyes*.[245] Review of that study revealed that for both pathogens the MIC of terbinafine was 0.006 μg/mL. Ten of 10 guinea pigs infected with either *T. mentagrophytes* or *M. canis* were cured with a terbinafine dose of 6 mg/kg and 20 mg/kg, respectively; however, it is important to note that animals were treated only for nine days. In the study with 300 veterinary isolates, terbinafine MICs ranged from 0.002 to 0.25 μg/mL, but MIC values were within a range of 0.008–0.03 μg/mL in over 90% of fungal isolates. In addition pre- and post-MIC from 37 animals treated for one to 39 weeks revealed no increase in MIC or minimum inhibitory fungal concentration (MFC) of terbinafine post-treatment.[244] These authors concluded that *M. canis* was not significantly less susceptible to terbinafine compared to other dermatophytes.

There are four studies evaluating the pharmacokinetics of terbinafine in dogs that are pertinent to its use in the treatment of dermatophytosis.[246–249] Manufacturer's data reports that the drug is well absorbed >46% after oral administration.[249] In greyhound dogs receiving 30 mg/kg terbinafine, the drug was rapidly absorbed reaching the highest plasma concentrations at 2 h post-administration with a half-life of 8.6 h.[247] At 24 h post-administration, the mean plasma terbinafine concentration was 0.092 μg/mL. In a third study, using a dose of 30 to 35 mg/kg the maximal terbinafine plasma concentration was at 3.6 h (range 2–6 h).[246] The time above MIC calculated for fungi, including dermatophytes, was 17 to 18 h after a single oral dose. In the last study, dogs received 30 mg/kg orally once daily for 21 days and drug concentrations were measured in the serum, sebum and stratum corneum.[248] In this study, terbinafine did not accumulate or persist in the canine stratum corneum or sebum compared to serum concentrations. The mean terbinafine concentrations in paw stratum corneum, skin on the thorax and sebum did not reach the MIC_{90} of 0.25 μg/mL for *Malassezia,* but within 1 day after starting therapy skin terbinafine concentrations were >0.01 μg/mL and within seven days were ≥ or greater than 0.100 μg/mL which would be deemed effective for dermatophytosis.[248]

There are four pertinent studies evaluating the pharmacokinetics of terbinafine in cats.[116,250–252] It is important to remember that the drug is stored in body fat and differences between studies may be due to age of the cats, body condition score and number of hairs in anagen (i.e. kittens versus adult cats). In one study, the absolute bioavailability after oral administration (30 mg/kg) was found to be 31 ± 10.85%.[250] Peak serum terbinafine concentrations were reached in less than 2 h post-administration, with a half-life of 8 ± 3.36 h.[250] Three studies have reported on the concentration of terbinafine in cat hair all showing that the drug is highly concentrated in cat hair.[116,251,252] In a methodology paper, concentrations in cat hair after a 10 to 40 mg/kg dose of terbinafine ranged from 0.47 to 9.6 μg/g.[251] In another study comparing low (10 to 20 mg/kg) and high (30 to 40 mg/kg) dose terbinafine treatments, the median hair terbinafine concentration after nine days of oral treatment with low or high dose was 0.96 μg/g and 1.86 μg/g, respectively.[116] In the same study, after 60 days of continuous treatment the median hair terbinafine concentration was 1.24 μg/g and 4.91 μg/g, for low- and high-dose treatments respectively.[116] In another study, the concentration of terbinafine in cat hair was 2.30 ng/mg (2.3 μg/g) after 14 days of continuous dosing at 35 to 45 mg/kg terbinafine once daily.[252] Eight weeks after the last dose of terbinafine, eight of 10 cats had hair concentrations above the MIC_{90} of 0.03 μg/mL for the common dermatophytes.

Given that this drug is not licensed for use in small animals, there are no published target animal safety studies for review. Published reports of its use either as

treatment for dermatophytosis or pharmacokinetic studies were reviewed for mention of adverse effects.[103,106,110,114,116,118,126,132,141,246–248,250,252–259] Because of the low number of dogs treated with terbinafine described in the literature, two studies involving the use of terbinafine for the treatment of *Malassezia* were included.[258,259] Studies reported that the drug was well tolerated, adverse effects were uncommon and mild, and no study reported any deaths associated with the administration of the drug. Vomiting post-administration of the drug was usually ameliorated by feeding the animal immediately after medication and decreases in appetite were transient. One study reported that treatment was stopped for one of 12 cats due to three episodes of vomiting.[118] Intermittent soft stools and diarrhoea were reported in dogs and cats; however, in one placebo-controlled study this occurred with equal frequency in dogs receiving the placebo.[258] When haematological parameters were monitored in dogs or cats, mild elevations in serum ALT or SAP were noted. A safety and tolerability study in cats receiving either 10 to 20 mg/kg or 30 to 40 mg/kg terbinafine orally revealed no changes outside normal laboratory ranges for serum biochemistry parameters or complete blood counts.[254] In a pharmacokinetic study, two cats were reported to develop systemic clinical signs including lethargy, anorexia and weight loss 1 week after the 14 day drug trial.[252] In addition, these two cats developed intense facial pruritus and a macular to papular skin reaction seven to 14 days *after* discontinuation of the drug. Histological findings were suggestive of an allergic reaction.[252] The cats in this study were privately owned and lived in a semitropical region, and it is unknown if the cats were from the same household. Interestingly, in another pharmacokinetic study two dogs developed periocular swelling, chemosis and conjunctival erythema 8 h post-terbinafine administration, but were unassociated with any ocular discomfort or pruritus and resolved spontaneously.[246] Using an *in vitro* whole embryo culture system, ketoconazole and griseofulvin had relatively high teratogenic potential and terbinafine had none.[232] In a Chinese study, four groups of cats ($n = 7$ each) received oral terbinafine once daily at 0, 10, 20 or 40 mg/kg for up to 35 days. Translated review of the entire original paper reported that postmortem examination of cats did not reveal renal or liver changes; the abstract does not reflect the content of the translated study (Chen C, 2016 personal communication).[256]

There are 10 studies describing the use of terbinafine to treat small animal dermatophytosis.[103,106,110,114,116,118,126,132,133,141,254] The studies are summarized in Table S5 and span a time frame from 1998 to 2014, during which a wide range of doses from 5 mg/kg to 40 mg/kg were used once daily. Time to cure ranged from 21 days to 158 days; however, it is important to note that except for two shelter studies, concurrent topical therapy was not used and environmental cleaning was noted in only four studies (Table S5). Although a pharmacokinetic study showed that after 14 days of therapy therapeutic concentrations of terbinafine remained in the hair follicle for >8 weeks, this short-term therapy failed in a field trial; cats were cured when 21 days of continuous therapy were used.[126,252] There are two studies reporting on histological changes associated with the use of terbinafine as sole therapy in cats. In the first, skin biopsy specimens were examined for the presence of fungi in cats treated with either 10 to 20 mg/kg or 30 to 40 mg/kg terbinafine orally once daily.[253] After 43 days of treatment, dermatophytes were detected in eight of nine and two of nine cats in the low- and high-dose groups, respectively. Fungi were no longer detectable after 73 day and 103 days of treatment in the high- and low-dose groups, respectively.

5.5 Griseofulvin (See Supporting Information Table S6 for summary)

Griseofulvin was first isolated from the homogenized mycelium of *Penicillium griseofulvin* in 1939 and it was first successfully used to treat dermatophytosis in people in 1958.[260,261] Griseofulvin inhibits nucleic acid synthesis and cell mitosis by arresting division in metaphase.[262–264] The drug also interferes with the function of spindle microtubules. It causes morphological changes in fungal cells and may antagonize chitin synthesis in the fungal cell wall.

The drug is weakly water soluble and is poorly absorbed from the gastrointestinal tract. Absorption is affected by dietary fat, drug formulation, and particle size and dissolution rate.[265] Nonmicrosized particles are better absorbed with a high fat meal.[266] Micronanization improves absorption. Absorption in dogs improved when polyethylene glycol (PEG) was used as a dispersal carrier in the ultramicrosized formulations.[267] In a study conducted in two dogs, 50 mg/kg intravenously of griseofulvin PEG showed a half-life of 4 and 47 min.[262] Griseofulvin is carried in the extracellular fluid to the stratum corneum by diffusion, sweating and transepidermal water loss.[268]

Griseofulvin's spectrum of antifungal activity is limited to that of the dermatophytes.[269] In one study with 100 veterinary isolates and another with 300 veterinary isolates, griseofulvin was more effective than fluconazole and less effective than itraconazole or terbinafine when MICs or MFCs were compared.[237,244] With respect to griseofulvin and ketoconazole, comparative efficacies vary with the pathogen. In one study, the mean MIC against 100 isolates was 1.43 μg/mL (range 0.125–>8 μg/mL) and 1.21 μg/mL (range 0.25–>16 μg/mL) for griseofulvin and ketoconazole, respectively.[237] The MIC_{50} and MIC_{90} for both were identical, 2 μg/mL and 8 μg/mL respectively. In the same study, the mean MIC for griseofulvin was 0.75 μg/mL for *Microsporum* and 2.06 μg/mL for *Trichophyton* spp. The MIC of ketoconazole for *Microsporum* was 1.36 μg/mL and 1.30 μg/mL for *Trichophyton*, respectively.[237] Another study evaluated 275 dermatophyte isolates and reported a mean MIC for *M. canis* of 1.5 μg/mL (0.5–>16) and for *T. mentagrophytes* ($n = 18$) of 4.5 μg/mL (0.5–>16).[238] In a retrospective study of canine and feline dermatophytosis due to *M. gypseum,* the reported MIC of griseofulvin was 150 μg/mL.[95]

Fifteen prospective studies described the treatment of 242 cats and dogs treated with griseofulvin (Table S6).[42,44,45,65,103,107–109,111,117,123,134,136,137,259] In

four studies, concurrent topical therapy was used on all or part of the study group animals and in one study cats were pre-treated with lufenuron.[42,81,109,117,137] In addition, five of 14 of the studies were conducted in catteries, many of which had a high number of Persian cats.[42,44,45,109,137] One additional study describes the use of griseofulvin and four different topical therapies in a colony of Persian cats. Detailed information is not presented in the abstract except that the combination of griseofulvin and miconazole/chlorhexidine was superior to other treatments.[140]

In 1959 the first description of the use of griseofulvin to treat small animal dermatophytosis involved the treatment of 22 cats, 20 of which were Persian cats.[44] They reported a rapid resolution of clinical signs using 60 mg/kg griseofulvin once daily orally and cats were monitored with Wood's lamp examinations and fungal culture. They noted a rapid clinical response to griseofulvin therapy but systemic therapy alone cured only eight of 22 cats after 12 weeks of treatment. The investigators hypothesized that the persistent culture-positive status may have been due to unresolved disease or environmental contamination. Negative mycological status was finally accomplished after the use of topical therapy (captan dip or napthlane soap). In 1960, the same authors published a study describing the use and response to griseofulvin treatment in 31 cats; however, 22 cats were from the original paper.[45] This paper is of historical significance because it is the first mention of mycological cure being defined as two negative cultures.[45] The nine new cats achieved mycological cure without topical therapy or environmental treatment in 63 to 112 days. Three papers describe the use of griseofulvin, clipping of infected hairs, topical therapy and environmental cleaning as recommended protocols to treat feline dermatophytosis in catteries.[108,111,137] In two of three catteries, clinical cure was the criterion used for the end-point of treatment.[108,137] In the third cattery, cats were culture negative within 56 days.[111] These studies established the treatment protocols for catteries that are still relevant today.

Three experimental studies describe the use of griseofulvin alone or in conjunction with clipping of the hair coat and/or topical therapy.[123,134,136] O'Sullivan reported resolution of clinical signs (*not mycological cure*) in treated and untreated cats by days 11–14 and 70, respectively.[134] Similar resolution of clinical signs with treatment was noted in the other two studies.[123,136] In two studies, cats were treated with concurrent topical therapy and clipping of lesions and mycological cure occurred between days 42 and 55.[134,136] All three studies contained a griseofulvin treatment only group and mycological cure occurred in all cats between days 70 and 118. In one study, untreated control cats cured between days 70 and 91 while in the other two studies control cats were still culture positive at the end of the study period (100 to 127 days).[136] These experimental studies established that systemic treatment with or without concurrent topical therapy shortened the course of infection. Clipping of Wood's lamp positive hairs, topical therapy and systemic therapy resulted in the fastest time to mycological cure.

Potential adverse drug reactions to griseofulvin have been studied since its release. The first toxicity study on griseofulvin was published in 1960.[270] In that small study, cats were administered one of two doses (50 mg/cat $n = 3$ cats) or 250 mg/cat ($n = 1$ cat) for 30 days. There were no detectable changes in cat growth or abnormalities on postmortem examination. Griseofulvin is a known teratogen in experimental rat studies.[232,271] Teratogenesis has been documented in cats both in the field and in an experimental study.[272] Abnormalities affected the brain, skeleton, eyes, gastrointestinal tract, ears, soft palate and heart.[272] In one study the toxicity of high doses of griseofulvin in cats was tested.[273] Ten cats received griseofulvin 110 to 145 mg/kg orally once daily or placebo for 11 weeks. There were no changes in pre- and post-treatment haemograms, liver enzymes, bone marrow aspirates or ACTH stimulation tests. Studies in dogs are limited; therapeutic doses of griseofulvin had no effect on semen quality.[274]

In the 14 studies describing the use of griseofulvin to treat clinical dermatophytosis, no deaths were reported. Adverse reactions were noted in four cats. Pruritus was the only adverse effect noted in one cat.[44] In another study, three white cats developed clinical signs of malaise, with or without anorexia, pruritus, walking with a straddled gait, and a thick scruffy coat with brown scales and marked erythema.[137] Clinical signs resolved after withdrawal of griseofulvin. However, in five papers serious adverse reactions have been reported in animals receiving griseofulvin. In one report, seven cats developed lethargy, pyrexia, anorexia, depression, ataxia, upper respiratory infections, and in five of seven cases leukopenia or pancytopenia.[275] In another study a kitten developed ataxia and pancytopenia and bone marrow hypoplasia that led to euthanasia.[276,277] There is evidence that the bone marrow suppression is an idiosyncratic drug reaction.[278] Six of seven FIV positive cats being treated with griseofulvin at a dose of 500 mg/cat once daily (80 to 147 mg/kg) developed fever, depression, anorexia, diarrhoea and/or petechial haemorrhages. Four of seven cats developed severe neutropenia and one of these died. Once the drug was withdrawn, neutrophil counts returned to normal within 15 days. The neutropenia recurred in two FIV positive cats upon rechallenge with griseofulvin. Four clinically normal FIV negative cats were treated with equivalent doses for 14 days without any adverse effects.[278] This idiosyncratic reaction may be unique to cats as there is only one putative drug-associated pancytopenia in a dog attributed to griseofulvin.[279]

5.6 Lufenuron (See Supporting Information Table S7 for summary)

Lufenuron is a benzoylphenylurea drug that disrupts chitin synthesis. Chitin is a critical component of the exoskeleton of arthropods, and is also an important component of the outer cell wall of fungi. Interest in lufenuron as a possible antifungal treatment was triggered by a retrospective computer review of medical records which found that animals receiving lufenuron as a flea preventative were not treated for dermatophytosis.[280]

In an initial study, the authors used lufenuron to treat a total of 14 dogs (54.2–68.3 mg/kg orally at monthly intervals) and 23 cats (51.2–266 mg/kg orally at monthly

intervals) diagnosed with dermatophytosis. Results suggested that gross lesions on the dogs resolved in 21 days and on the cats in 12 days with a mean time to negative fungal cultures of 14.5 days (dogs) and 8.3 days (cats). The authors also reported that microscopic examination of fungal cultures revealed damaged and distorted macroconidia, missing septa and distorted fungal cell walls.[280] In subsequent studies the authors suggested a dose rate of 80 to 100 mg/kg orally once every two weeks until mycological cure.[281,282]

Subsequent to these reports, a number of field studies reported on the efficacy of lufenuron with conflicting findings. A French study compared two groups of cats with *M. canis* dermatophytosis over a 90 day period.[109] Both groups were treated weekly with enilconazole rinses (0.2%) for four weeks. One group was treated with micronized griseofulvin (25 mg/kg orally twice daily for five weeks) the other with lufenuron (60 mg/kg orally at days 0 and 30). Mycological cure was not achieved in either group at 90 days. In one Persian cattery study from the UK, 31 cats and 32 kittens were treated every two weeks with 100 mg/kg of lufenuron and topical enilconazole for 112 days. Lesions resolved but all of the cats were still culture positive; routine environmental decontamination was carried out.[104] In a study from Brazil, 46 Persian and mixed breed cats were treated with 120 mg/kg lufenuron orally every 21 days for 84 days. Except for two cats, all were culture negative at the end of treatment.[135] In a second study from Brazil, 49 dogs and cats were divided into four treatment groups each receiving a different dose of lufenron.[142] Clinical and mycological cure occurred in 22 to 60% of animals, with the highest efficacy in the group receiving 120 mg/kg lufenuron intravenously every three weeks. The drug was reported to be more effective in dogs than cats. Persian cats and Yorkshire terrier dogs had the highest rate of treatment failure. A German study involving 39 cats receiving either oral or injectable lufenuron found that clinical cure occurred in treated cats but not mycological cure.[283] This was also observed in an open uncontrolled Italian field study which investigated the time to mycological cure of *M. canis*-infected cats pre-treated with lufenuron.[117] There were three lufenuron treatment groups, all receiving 100 mg/kg every 15 days for 60 days before: no further treatment (n = 13), 40 days of griseofulvin 50 mg/kg (n = 14) or 28 days of once weekly enilconazole rinses (n = 11). These three groups were compared to two groups receiving either 40 days of once daily griseofulvin 50 mg/kg (n = 7) or 28 days of once weekly enilconazole (n = 5). The results of this study are difficult to interpret because of the five different treatment groups, but lufenuron was found to be ineffective as a sole treatment with six of 13 cats still culture positive at day 150. The authors proposed that lufenuron may speed clinical cure as 32 of 38 cats were clinically cured after 60 days of lufenuron only treatment;[117]a similar trend was reported in a separate study.[113]

The ability of lufenuron to enhance the effects of terbinafine, enilconazole or griseofulvin has also been investigated.[114,117] In the first study five groups of cats were treated with one of five different protocols:[114] lufenuron suspension (133 mg orally every two weeks); terbinafine 15–30 mg/kg orally daily; lufenuron plus terbinafine at the same dose rates; itraconazole 8 mg/kg orally once daily; or untreated controls. The results demonstrated that both itraconazole and terbinafine performed equally well with regard to time to cure. However the results showed no evidence for a synergistic effect of lufenuron when used with terbinafine, and the time to cure for lufenuron-only-treated cats was not significantly different from the untreated controls. The second study also failed to show that pre-treatment with lufenuron enhanced either griseofulvin or enilconazole treatment with respect to time to cure.[117]

There are three controlled studies evaluating the efficacy of lufenuron on the course of *M. canis* infection. In a standard animal testing model (experimental guinea pig infection), infected animals received up to five doses of oral lufenuron 80 mg/kg and were compared to itraconazole and vehicle controlled groups.[284] All lufenuron-treated animals failed to show any change in clinical signs. There are two blinded controlled studies on the efficacy of lufenuron to prevent or alter the course of experimental infection with *M. canis* in cats.[113,124] In the first trial, three groups of kittens were treated with two oral monthly treatments with lufenuron (30 or 133 mg/kg) or placebo.[124] On day 60, treated cats were challenged using *M. canis* spores applied to the skin under occlusion. All cats became infected and the infection progressed and regressed in a similar manner in all three groups. This was a robust challenge and the investigators next performed a co-habitant challenge trial to mimic natural exposure.[113] Twenty four healthy juvenile cats (n = 8 cats/group) were given lufenuron orally (133 mg/cat/month), lufenuron by subcutaneous injection (40 mg every 6 months) or no treatment. After 4 months, each group of cats was challenged by the introduction of one experimentally infected cat with infection limited to Wood's lamp positive hairs. The lufenuron-treated cats were shown to have significantly lower infection scores during the first few weeks of infection, but pre-treatment with lufenuron did not prevent establishment of dermatophytosis or speed resolution of infection.[113]

The *in vitro* effects of lufenuron on 20 different clinical isolates (*M. canis* n = 10, *M. gypseum* n = 5 and *T. mentagrophytes* n = 5) was assessed using three different testing methods.[285] In the first method, 0.1 mL of a commercial preparation of 3.5 mg of lufenuron was applied directly onto SDA plates. In the second, 0.05 mL of serum from a dog treated with 80 mg/kg of lufenuron was applied to SDA culture plates. This was done to examine the possibility that the efficacy of lufenuron occurs only after it has passed metabolic changes. In the third, skin and adipose tissue from a dog having received 80 mg/kg of lufenuron was placed onto SDA culture plates. This was done because lufenuron is reported to concentrate in skin and subcutaneous tissue. There was no evidence of inhibition of growth of pathogens by any of these *in vitro* testing methods.

5.7 Fungal vaccines (see Supporting Information Table S8 for summary)

There are ten published reports on the safety, immunology and/or use of live or inactivated vaccines for

treatment and/or prevention of dermatophytosis in dogs or cats. Three studies described protective efficacy against experimental dermatophyte infections in dogs.[143,286,287] In the first study, dogs were vaccinated with either a live *T. verrucosum* or *M. canis* vaccine twice and 36 days post-vaccination challenged by direct application of the infectious agent to the skin.[286] Dogs vaccinated against *M. canis* did not develop overt disease but, rather, mild scaling at the challenge site. This was in contrast to dogs vaccinated against *T. verrucosum* that developed overt disease. In the second study, farmed foxes were vaccinated at four and six weeks of age and five weeks later challenged via direct application of *M. canis*.[287] Control animals developed clinical disease and vaccinated animals developed superficial scaling seven to 14 days post-challenge. Investigators from both studies concluded that vaccination against *M. canis* had a prophylactic effect against experimental infection. In the last study, there was no clinical response to a commercial vaccine used as a sole therapy.[143]

There are seven studies describing various aspects of the use of fungal vaccines in cats.[75,83,145,147,288–290] Three studies evaluated the prophylactic effect of vaccination against *M. canis* infection in cats. In the first, vaccination of *M. canis* naïve kittens with an experimental killed cell wall *M. canis* vaccine revealed development of IgG and IgM antibodies against *M. canis* in vaccinated cats compared to controls; however, it offered no protection against infection using a direct application challenge infection.[147] In another study, an adjuvanted killed vaccine also failed to protect vaccinated kittens from infection in a natural exposure challenge model.[83] In the third study, evaluating an experimental combined live inactivated dermatophytosis vaccine and a commercial inactivated dermatophytosis vaccine, showed that neither vaccine provided prophylactic immunity against topical challenge exposure with *M. canis;* neither product provided a more rapid cure of an established infection.[75]

There is one study from Poland that reported vaccination with a commercial vaccine to be protective against infection in a direct challenge model and natural exposure model in cats over 1 month of age receiving 3 mL.[288] Two field studies and one case report describe the use of commercial vaccines for the treatment of feline dermatophytosis.[145,289,290] In the first field study ($n = 38$ long-haired cats), 27 cats were treated with an inactivated *M. canis* vaccine twice at 15 day intervals. The authors reported clinical remission occurred within 15 days of vaccination and cats were culture negative at day 28 and remained culture negative. Untreated cats remained lesional and culture positive.[145] In the second field study ($n = 50$ cats), a pentavalent vaccine incorporating microconidia of *T. mentagrophytes, M. canis, M. canis vars distortum, M. canis vars obesum* and *M. gypseum* was administered every other week for three treatments, and cats were assessed on days 0, 14, 28 and 42. The primary end-point for the study was a reduction in the lesions at day 42. This end-point was not met for the group as a whole but vaccinated cats with severe lesions showed a slightly faster recovery compared to placebo-treated cats over the study period. When ages were evaluated, the primary end-point was met for vaccinated cats under 1 year of age and cats that had not been treated previously (i.e. first time infection).[290] In another report, an 8-year-old cat was treated with a commercial vaccine only at days 0, 14 and 28; it reached clinical and mycological cure at day 28.[289]

5.8 Conclusions

1. Itraconazole (noncompounded) and terbinafine are the most effective and safe treatments for dermatophytosis.
2. Griseofulvin is effective but also has more potential adverse effects compared to itraconazole and terbinafine.
3. Ketoconazole and fluconazole are less effective treatment options and ketoconazole has more potential for adverse effects.
4. Lufenuron has no *in vitro* efficacy against dermatophytes, does not prevent or alter the course of dermatophyte infections, does not enhance the efficacy of systemic antifungal or topical antifungal treatments and has no place in the treatment of dermatophytosis.
5. Antifungal vaccines do not protect against challenge exposure but may be a useful adjunct therapy.

6 Environmental disinfection

The two most commonly cited reasons for environmental disinfection are

1. to minimize the risk of disease transmission to people and other animals
2. to minimize fomite carriage on the hair coat of animals that can complicate monitoring of disease.

From a clinical perspective, the primary aim is to shorten the course of treatment by preventing/minimizing false positive fungal culture or PCR results due to fomite carriage of spores on the hair coat. False positive fungal culture results lead to prolonged systemic and/or topical therapy and excessive confinement of pets.

Our literature searches showed that contact with a contaminated environment alone *in the absence of concurrent microtrauma* is an exceedingly rare source of infection in both people and animals. One publication was found documenting a child with no history of any animal contact contracting *M. canis* from a contaminated environment (car upholstery).[291] In another study, infected owners were found only in households containing cats and owner infection seemed most commonly associated with direct contact with the cat (kittens) rather than through the environment; in 23 contaminated homes no owner infection was noted even though animals were in the home.[119] *In vivo* data exist that support the primary mode of dermatophyte transmission is animal–animal contact even in the presence of a contaminated environment. In one study, 24 specific pathogen-free kittens were exposed to an experimentally infected cat with a strongly fluorescent strain of *M. canis*.[113] Environmental and cat cultures were monitored weekly along with development of lesions. The

environment became readily contaminated as did the hair coat of cats, but lesions in cats were slow to develop and lacked a clear pattern. The most social cats developed lesions first and the shy cats were the last to develop lesions. The first place that lesions developed was on cat to cat contact sites. If casual exposure to spores in the environment is a high risk factor for contracting the disease, it is reasonable to assume that infection should have developed in all of the 24 cats within the same time period.[113] One report describes two rooms of cats in a shelter that were fungal culture positive.[132] Examination revealed one lesional, Wood's lamp positive cat in each room with confirmed infection via direct examination and fungal culture. Each cat had *one* infected hair on its chin; all cats and the environment had cfu/plate scores that were too numerous to count. After removal of these cats and decontamination of the room, fungal cultures from all cats were negative. In other studies, persistent exposure to spores in the environment did not result in reinfection in cats that were cured of infection.[75,112,114,123]

6.1 Fungal spores in the environment

The infective propagule of dermatophyte fungi is called an arthroconidium and it forms as a result of segmentation and fragmentation of existing hyphae.[72,292] Shed arthroconidia and fragmented/shed hairs are the source of environmental contamination. Environmental contamination is common in environments where there are dermatophyte-infected people or animals. In one study, 30 households with infected cats (n = 21) or dogs (n = 9) were sampled for environmental contamination prior to treatment or cleaning.[119] Contamination was found in 25 of 30 homes and was heaviest in homes where kittens lived. Contamination was found on soft surfaces (carpets, quilts) and hard surfaces (furniture and floors). Air samples collected 1 m above the floor detected spores in all but three of 21 homes housing infected cats, but none from homes housing infected dogs. In most cases, positive air samples correlated with positive surface samples and were most likely the result of natural air currents in the home. The most heavily contaminated homes harboured kittens (n = 9). It is helpful to explain to owners that in people, dermatophytes have been isolated from environments frequented by people where transmission is believed to be a risk factor due to high levels of exposure, moisture and/or microtrauma: swimming pools, floors in athletic clubs, beaches, airports, podiatrists' offices, nail salons, places of worship, wrestling mats, hairdressing tools, shared shoes or slippers.[293–300]

There are two common misconceptions in the lay literature regarding environmental dermatophyte contamination. The first has to do with fungal spores being isolated from air currents and the fear of contracting 'dermatophyte lung'. Dermatophytosis is a skin infection and does not cause fungal respiratory disease. Fungal respiratory infections are caused by the deep mycoses or organisms or moulds commonly found in the environment, such as *Aspergillus*, *Cladosporium*, *Mucor* and *Rhizopus*, which are commonly found in home environments.[301] Infections with these organisms are often associated with natural disasters such as flooding.[302] It is critical to explain this distinction to pet owners given the widespread media coverage of long-term health risks associated with water damage. The second misconception has to do with dermatophytes "living" and "multiplying" in the house. Dermatophytes have evolved to survive on human and animal hosts and require keratin as a source of nutrients.[303] Dermatophytes do not "live in" or "invade" a structure as black mould (*Stachybotrys chartarum*) or mildew can.

6.2 Veterinary clinics

There are two studies evaluating the presence of dermatophytosis in the environment.[304,305] In one study, the floors of 50 private veterinary clinics were sampled randomly throughout the day.[304] Four hundred samples were collected. Dermatophytes were isolated from the floors in 15 of 50 clinics. The most commonly isolated dermatophyte was *M. canis* (n = 46 of 400 plates). In the second study, the floors of one veterinary medical teaching hospital were monitored for 1 year.[305] A total of 1604 fungal culture plates from 401 samples found 23 of 401 sites to be culture positive. Positive samples were most commonly isolated from the dermatology examination room (10 of 23). During this time period there were no reports of outbreaks. There were no changes in cleaning routines. In wards, examination rooms and client-pet waiting areas, there was continual removal of hair and debris and wet mopping to remove bodily fluids. In the evening floors were swept, mopped and disinfected with a quaternary ammonium-based product.

6.3 Viability and infectivity of environmental spores

There are many published studies in both the human and veterinary literature on the dormancy of dermatophyte spores. The ability to remain dormant and then sporulate under appropriate circumstances is a property of both human and animal pathogens. *Trichophyton shoenlenii* from epilated hairs stored at room temperature showed that 840 samples were still viable after 18 months of storage; however, over time specimens died and after 4.5 years only six specimens were still viable.[306] *Trichophyton verrucosum* and *T. equinum* have been reported to remain viable for up to 4.5 years under laboratory conditions, but again it is important to note that only some, but not all specimens were viable.[307,308]

One of the earliest English language reports on the long-term viability of spores was published in 1960 by Keep.[150] In that study, selected hairs from three kittens with a strongly fluorescing *M. canis* isolate were cultured once weekly until there were six negative consecutive fungal cultures. The first negative fungal cultures were noted at six to nine months and the last positive fungal cultures were noted at 10 to 14 months. The remaining hairs were unable to infect susceptible kittens in an experimental infection model. In another widely referenced study, a total of 25 specimens were cultured periodically during a 36 month period of time. During the first 0–12 months, eight of eight specimens were culture positive. Between 13 and 24 months, only three of six specimens were culture positive. After 24 months, all 11 remaining specimens were culture negative.[309] In one of the authors' laboratories (KAM), 30% of stored samples (n = 150) were culture negative within five months of collection and another 10% of samples grew less than

10 cfu/plate.[310] The number of days from inoculation to positive culture was longer than 21 days and laboratory manipulations (hydration and growth on enriched medium) were needed to reach culture-positive status. Dermatophyte colonies from stored samples may have abnormal gross and microscopic characteristics and be poorly sporulating. The hairs in these studies were stored under laboratory conditions and protected against changes in temperature, humidity and cleaning/disinfectants. Although viable when nurtured under laboratory conditions for several weeks, their infectivity to a healthy host under natural infection conditions is likely to be doubtful.

6.4 Antifungal disinfectants

In addition to having good antifungal efficacy, a product should be nontoxic with a low irritancy to the animals and users. In addition, it should be affordable, easy to apply, preferably ready to use out of the container to minimize dilution errors, and compatible with surfaces it is to be used upon.

1. Sodium hypochlorite (household bleach) has been consistently shown to be an effective disinfectant when used at concentrations ranging from 1:10 to 1:100 even with short contact times.[189,193,311–313] It is important to note that there are different concentrations of household bleach sold over the counter, and that it can fail if it is out of date. One study showed that if a 5.25% solution of household bleach was diluted 1:100 and not stored in a brown opaque container it retained only 40–50% of chlorine after 30 days.[314] If household bleach is used it should be prepared at least once weekly and stored in a dark opaque container. There are many reasons not to use bleach and these include: lack of detergency which is a critical factor for disinfection, potential to react with other chemicals to create toxic gases, unpleasant odour, damage to hard surfaces, discolouration of fibres and coloured surfaces, damage to floor finishes, rapid loss of efficacy once diluted and human health concerns. The product is an irritant to both animals and people.
2. Enilconazole is a well-established antifungal product and is available as both a spray and environmental fogger. It is very effective at a concentration of 20 μL/L. Its use is limited by its relatively high cost and lack of availability in some countries.[188,189,193,315]
3. Accelerated hydrogen peroxide (AHP) is a proprietary compound. It differs from hydrogen peroxide in that it contains surfactants (wetting agents) and chelating agents that help to reduce metal content and/or hardness of water. It is one of the newer broad spectrum disinfectants that have gained widespread use in many medical and veterinary environments. The Materials and Data Safety Sheet (US) states that it should not be mixed with a concentrated sodium hypochlorite product. It is currently available in concentrates, ready-to-use formulations and over-the-counter products available to clients. Its antifungal efficacy against *M. canis* and *Trichophyton* sp. have been shown in several studies.[193,311]
4. Potassium peroxymonosulfate was initially found to have poor antifungal activity; however, the product was tested against a robust spore challenge with less than the recommended 10 min contact time.[189] Recently a 1% solution was found to be effective as a pre-treatment disinfectant for carpets and a 2% solution was consistently antifungal against robust spore challenges.[193,316]
5. Over-the-counter bathroom or general disinfectants with labels claiming fungicidal action against *Trichophyton mentagrophytes* were found to be effective, again when used liberally and with a 10 min contact time.[317]
6. Essential oils are gaining popularity as ingredients in products formulated for use as disinfectants. There is preliminary data supporting their use as environmental disinfectants (limonene, geranial, neral).[202] A spray containing these products inhibited fungal growth in vitro.

Disinfection of nonporous surfaces

Disinfection of nonporous surfaces involves three steps. The first is the mechanical removal of all debris via vacuuming or sweeping. Disinfectants will not work in the presence of organic debris. The second is the washing of the target surface with a detergent until the area is visibly clean. The use of a detergent is important because it will lift debris from surfaces. Detergents must be rinsed from the target surface because some may inactivate disinfectants. These two steps are the most important and in many cases alone will decontaminate a surface as has been shown in shelter situations.[310] The final step is the application of a disinfectant to kill any residual spores.

Disinfection of laundry

In one study, cotton, terry cloth and denim fabrics were contaminated with infective spores and hairs and then washed in 30°C or 60°C with or without a sodium hypochlorite additive, and with and without mechanical drying.[318] This study found that washable textiles could be decontaminated via mechanical washing in any water temperature and that sodium hypochlorite was not helpful. Two washings on the longest wash cycle were effective. It was important not to overload the machine to allow for maximum agitation. The washing machine and the dryer were minimally contaminated and this was easily eliminated by spraying the surface with accelerated hydrogen peroxide.

Disinfection of carpets

A study investigated methods to decontaminate carpets exposed to infective *M. canis* hairs and spores.[316] Vacuuming alone did not decontaminate the surfaces but was recommended to remove gross debris including infective hairs. The vacuum was disinfected using AHP spray and/or wipes. Exposed carpeting could be decontaminated by washing twice with a carpet shampooer with detergent or via hot water extraction. Hot water extraction was associated with the fastest drying time and no discolouration. Heavily contaminated carpets were best decontaminated by pre-treatment with

a disinfectant and then washed with a beater brush carpet shampooer. Disinfectants were found to discolour carpets. Household cleaners with label efficacy against *Trichophyton* spp. were effective as well as 1% potassium peroxymonosulfate.

Disinfection of wood floors

There are no safe surface disinfectants for wood floors; however, one author (KAM) has successfully decontaminated wood floors via daily removal of hair and dust using commercial disposable cleaning clothes designed for dry mopping floors (Moriello 2016, unpublished data). Floors were then washed twice weekly with a wood oil soap.

6.5 Strategies to minimize shedding and spread of infective material

Arthrospores are shed into the environment from the hair coat. Client-orientated strategies to prevent or limit this are discussed below.

Clipping of the hair coat

No studies were identified that specifically addressed the question of whether or not to clip the hair coat. In the 57 reviewed treatment studies, clipping of the hair coat was mentioned in nine of 57 studies. In three studies, clipping of the hair coat resulted in spread of the infection to other uninfected sites on the body and overall worsening of the severity of the infection.[64,112,123] Worsening of lesions and spread to other parts of the body was markedly lower in cats treated with systemic antifungals than without.[123] In the other six studies, clipping of the hair coat was deemed helpful for a number of reasons.[44,45,111,115,129,134] In long-haired cats it facilitated application of topical antifungal solutions. In many of the older studies it was noted that clipping of the glowing hair tips or plucking of infected hairs was necessary to reach mycological cure. This is the experience in one author's (KAM) shelter experience and in collaborative studies.[105,126,130–132] Clipping of the entire hair coat is stressful to the animal, requires sedation, puts the kitten at risk for microtrauma to the skin and further worsening of lesions and/or thermal injury from over used clippers. In multi-cat situations it can actually lead to an increase in disease spread if precautions are not taken to prevent mechanical spread.[153]

Use of topical therapy

The major owner actions that can minimize confinement and decrease risk of infection to susceptible people are compliance with oral antifungal therapy and use of topical therapy twice weekly. Two studies showed that topical therapy with twice weekly shampooing with chlorhexidine/miconazole prevented contamination of the home.[42,129]

Confinement to an easily cleaned area

A recent literature review on the welfare implications of socialization has provided guidelines for socialization of puppies and kittens. Socialization should begin at three to four weeks for kittens and three to five weeks of age for puppies. Owners should provide deliberate social and environmental exposure for all puppies and kittens. Kittens do best when this occurs by nine weeks of age and puppies by 12 to 14 weeks of age, but earlier is better.[319,320]

Confinement of infected animals is an important part of disease containment in outbreaks of dermatophytosis. It allows more effective decontamination of the environment and also reduces the risk of transmission of dermatophytosis to other animals and people, especially children. The ages of cats that are most susceptible to developing dermatophytosis are the ones that are the most difficult to confine. This includes kittens that usually contract the disease at a time when socialization is important and older immunosuppressed cats that may have concurrent disease and need additional medical therapy. Although it is important that cats continue to be handled, examined and socialized, staff in a cattery/shelter should be educated about the risk of fomite transmission and the proper handling. When cats are in a home environment especially where there are other pets, family members, especially children, need to be advised about handling and the risk of infection. Items in the confinement area should be limited to those that can be washed daily (e.g. towel, blanket) and all toys should be plastic.

Frequency of cleaning

Based upon shelter studies and studies in the homes where cats were treated, twice weekly cleaning/disinfection is recommended.[130,131,310] This would include mechanical removal of hair, washing and disinfection of target areas. Daily removal of pet hair from the room/area where the pet is being confined is recommended. This can be done with any number of mechanical means (dust clothes, flat mops, sweeping etc.). Use of a daily one-step cleaner can be used on days between more thorough cleaning. In one field study, environmental culturing (n = 20) once weekly for eight weeks in a treatment ward housing 16 to 30 cats, showed zero to two sites of contamination in six of eight weekly samples and four sites of contamination in two of eight weekly samples. This ward was thoroughly cleaned and disinfected twice weekly with routine cleaning on other days.[310]

Environmental sampling

Environmental sampling is not recommended unless there is concern about false positive fungal cultures confounding determination of mycological cure.[152] Based upon environmental culturing of homes where infected animals are living, environmental contamination is an expected finding.[119,321]

6.6 Conclusions

1. Environmental decontamination's primary purpose is to prevent fomite contamination and false positive fungal culture results.
2. Infection from the environment alone is rare.
3. Minimizing contamination can be accomplished via clipping of affected lesions, topical therapy and routine cleaning.
4. Confinement needs to be used with care and for the shortest time possible. Dermatophytosis is a

curable disease, but behaviour problems and socialization problems can be life-long if the young or newly adopted animals are not socialized properly. Veterinarians need to consider animal welfare and quality of life when making this recommendation.

5 Infective material is easily removed from the environment; if it can be washed, it can be decontaminated.

7 Zoonotic considerations

Pet-associated illnesses can occur in any individual, but people at the extremes of age (<5 years of age; ≥65 year), pregnant women or people with immunocompromised conditions are at greater risk.[322] Immunocompromised individuals include, but are not limited to: congenital immunodeficiency, transplant recipients (bone marrow and solid organs), infectious diseases (e.g. HIV), metabolic diseases (e.g. diabetes mellitus, chronic kidney failure), splenectomy, cancers, and treatments with immunosuppressive drugs or chemotherapeutics.[322] Table 3 lists zoonotic diseases frequently listed as greatest concern for high-risk clients.[322,323] Despite increased risk, there are few studies that have investigated precisely what proportion of disease is attributable to pets. The greatest public health concern associated with pet ownership is an animal bite. In one survey study, 27% of respondents reported one or more dog- or cat-derived bite or scratch in the previous 12 months.[324]

Small animal dermatophytosis is a pet-associated zoonosis. The disease is primarily transmitted from contact with the hair coat or skin lesions of an infected animal. Contact with accumulated scales and hair in the environment are possible sources. There is only one well-documented case of a child with no known animal contact contracting dermatophytosis from the inside of a car.[291] No studies were found that prospectively studied disease transmission from an infected pet to disease free owners. In a widely quoted Letter to the Editor, it was reported that of 92 people (23 households) in contact with infected cats, 46 of 92 (50%) developed skin lesions.[325] Another study reported 11 owners with lesions in seven households; in six of seven cases kittens were in the home.[119] One study reported on the isolation of *M. canis* from the hair coat of skin lesion-free dogs and cats belonging to owners with medically documented *M. canis* dermatophytosis.[326] Dermatophytes were isolated from 25% (98 of 384) pets. In the 78 owners with confirmed lesions, 38 had a culture-positive pet in the home (n = 8 dogs, n = 30 cats). *Microsporum canis* was not isolated from the hair coat of dogs whose owners did not have dermatophyte lesions. In cats, *M. canis* was isolated from 28 of 192 (14.6%) of cats living with owners without lesions. In looking at the data from another perspective, *M. canis* was not isolated from the hair coat of 14 of 22 and 26 of 56 dogs and cats, respectively. This study showed that the pet may or may not be the source of a human infection.

Dermatophytosis is a common skin disease in immunocompromised people; however, literature review found that the primary pathogen of concern was *Trichophyton rubrum*, not *M. canis*. Reports of *M. canis* infection were limited to single case reports of tinea capitis, pseudomycetoma or mycetoma and were summarized in three reviews[327–329] Two studies were reviews of patients with *M. canis;* of the 21 cases, animal contact was confirmed in 7 of 21.[327,328] None of the patients died from the dermatophyte infection and the disease was treatable with the most common complication being prolonged treatment. In another extensive review of the literature on severe dermatophytosis and acquired or innate immunodeficiency in 84 patients, occurrence was rare, and the most common pathogen was *T. rubrum* and only a few infections were due to *M. canis*. The most common underlying conditions associated with severe dermatophytosis were solid organ transplant (n = 28), CARD9 deficiency (n-19) and HIV (n = 9).[329]

7.1 Conclusions

1 Dermatophytosis is a known zoonosis and causes skin lesions which are treatable and curable.

2 Dermatophytosis is a common skin disease in people but the true rate of transmission from animals to people is unknown.

3 In people, the predominant dermatophyte pathogen is non-animal-derived *T. rubrum* and the most common clinical presentation in people is onychomycoses (i.e. "toe nail fungus").

4 The most common complication of *M. canis* infections in immunocompromised people is a prolonged treatment time.

Table 3. Zoonotic disease frequently listed as of greatest concern for high-risk clients

Bartonella
Campylobacter jejuni
Campylobacter canimorsus
Cryptosporidium
Dermatophytosis (Microsporum canis, Trichophyton mentagrophytes)
Giardia
Salmonella spp.
Pasteurella multocida
Toxoplasma gondii

Acknowledgements

We would like to thank and acknowledge the following individuals on the Guidelines Panel for their contributions to this paper via searching the literature and/or providing translations: Rui Kano, Department of Pathobiology, Nihon University, School of Veterinary Medicine, Japan; Charles Chen, Asian Specialist Referral Center, Taipei,Taiwan; Silvia Colombo, Servizi Dermavet, Torino and Legnano, Italy; Laura Ordeix, Hospital Ars Veterinaria and Autonomous University of Barcelona, Department of

Animal Medicine and Surgery, Barcelona, Spain; Michael Shipstone, Dermatology for Animals, Stafford Heights, Brisbane, Queensland 4053, Australia; Susan Little, Bytown Cat Hospital, Ottawa, Canada; and Christoph Klinger, Abteilung für Dermatologie und Allergologie Medizinische Kleintierklinik der LMU München, Germany.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Clinical characteristics of nodular dermatophyte infections.
Table S2. Summary of topical therapy treatment studies.
Table S3. Summary of itraconazole treatment studies.
Table S4. Summary of ketoconazole treatment studies.
Table S5. Summary of terbinafine treatment studies.
Table S6. Summary of griseofulvin treatment studies.
Table S7. Summary of lufenuron treatment studies.
Table S8. Summary of fungal vaccine treatment studies.
Supporting Information S1. References on the incidence and prevalence of small animal dermatophytosis.

Résumé

Contexte – La dermatophytose est une dermatose fongique superficielle du chat et du chien. Les pathogènes les plus fréquents des petits animaux appartiennent aux genres *Microsporum* et *Trichophyton*. C'est une maladie importante en raison de sa contagion, de son infection et de sa transmission possible à l'homme.

Objectifs – L'objectif de cet article est de passer en revue la littérature existante et de définir un consensus sur les recommandations pour les vétérinaires cliniciens et de permettre un diagnostic et un traitement de la dermatophytose du chat et du chien.

Méthodes – Les auteurs ont formé un groupe d'experts (GP) et ont revu la littérature disponible avant septembre 2016. Le GP a préparé une revue détaillée de la littérature et a fait des recommandations sur les sujets sélectionnés. La WAVD (World Association of Veterinary Dermatology) a fourni une orientation et a supervisé le processus. Un projet de document a ensuite été présenté au 8ieme congrès mondial de dermatologie vétérinaire (Mai 2016) et a été rendu disponible aux membres de l'organisation de la WAVD par le World Wide Web pour une période de 3 mois. Les commentaires ont été sollicités et postés au GP par voie électronique. Les réponses ont été incorporées par le GP dans le document final.

Conclusions – Aucun test diagnostic n'a été identifié comme test de référence. L'efficacité d'un traitement nécessite l'utilisation concomitante d'antifongiques oraux systémiques et d'une désinfection topique du pelage. Un examen à la lampe de Wood et un examen direct ont une bonne prévisibilité positive et négative, les traitements antifongiques systémiques ont une large marge de sécurité et le nettoyage physique est plus important pour la décontamination des environnements exposés. Finalement, des complications sérieuses de transmission animal-homme sont extrêmement rares.

Resumen

Introducción – La dermatofitosis es una enfermedad cutánea superficial de hongos de gatos y perros. Los patógenos más comunes en pequeños animales domésticos pertenecen a los géneros *Microsporum* y *Trichophyton*. Es una enfermedad importante de la piel porque es contagiosa, infecciosa y puede transmitirse a las personas.

Objetivos – El objetivo de este documento es revisar la literatura existente y proporcionar recomendaciones de consenso para los médicos veterinarios y gente no profesional sobre el diagnóstico y tratamiento de la dermatofitosis en gatos y perros.

Métodos – Los autores actuaron como Panel de Orientación (GP) y revisaron la literatura disponible antes de septiembre de 2016. El GP preparó una revisión bibliográfica detallada y formuló recomendaciones sobre algunos temas seleccionados. La Asociación Mundial de Dermatología Veterinaria (WAVD) proporcionó orientación y supervisión para este proceso. El borrador del documento fue presentado en el VIII Congreso Mundial de Dermatología Veterinaria (mayo de 2016) y fue puesto a disposición de las organizaciones miembros de la WAVD a través de la World Wide Web durante un período de 3 meses. Se solicitaron comentarios que fueron enviados al GP electrónicamente. Las respuestas fueron incorporadas por el GP en el documento final.

Conclusiones – Ninguna prueba diagnóstica fue identificada como el estándar principal. El éxito en el tratamiento requiere el uso simultáneo de antifúngicos orales y sistémicos y la desinfección tópica del pelo. La lámpara de Wood y los exámenes directos tienen una buena previsibilidad positiva y negativa, los antifúngicos sistémicos tienen un amplio margen de seguridad y la limpieza física es muy importante para la

descontaminación de los ambientes expuestos a los hongos. Finalmente, complicaciones serias por la transmisión animal-humana son extremadamente raras.

Zusammenfassung

Hintergrund – Die Dermatophytose ist eine oberflächliche Hauterkrankung von Katzen und Hunden. Die häufigsten Pathogene der Kleinsäuger zählen zu den Gattungen *Microsporum* und *Trichophyton*. Es handelt sich dabei um eine wichtige Hauterkrankung, da sie ansteckend und infektiös ist und außerdem auch auf Menschen übertragen werden kann.

Ziele – Das Ziel dieses Dokuments ist es, eine Review der bestehenden Literatur durchzuführen und Consensus Empfehlungen für tierärztliche KlinikerInnen und Laien in Bezug auf die Diagnose und die Behandlung einer Dermatophytose bei Katzen und Hunden zu liefern.

Methoden – Die Autoren fungierten als Kommission für Richtlinien (GP) und durchforsteten die Literatur, die vor September 2016 zur Verfügung stand. Die GP bereitete eine detaillierte Literaturrückschau vor und sprach Empfehlungen in Bezug auf einzelne ausgewählte Inhalte aus. Die World Association of Veterinary Dermatology (WAVD) unterstützte diesen Prozess durch Anleitungen und Supervision. Es wurde beim 8. Weltkongress für Veterinärdermatologie ein Entwurf des Dokuments präsentiert (Mai 2016) und im Anschluss daran über das World Wide Web den Mitgliedsorganisationen des WAVD für eine Zeitspanne von 3 Monaten zugänglich gemacht. Es wurden Kommentare erbeten, die elektronisch an die GP weitergeleitet wurden. Die Antworten wurden durch die GP im Abschlussdokument eingebaut.

Schlussfolgerungen – Es wurde kein einzelner Test als Goldstandard identifiziert. Für eine erfolgreiche Behandlung ist eine gleichzeitige Behandlung mit systemischen Antimykotika *per os* sowie eine topische Desinfektion des Haarkleides nötig. Die Untersuchung mittels Wood Lampe und die direkte Untersuchung haben eine gute positive und negative Vorhersagekraft, die Antimykotika haben einen großen Sicherheitsfaktor und die physische Reinigung ist zur Dekontaminierung der exponierten Umwelt von größter Bedeutung. Letztendlich sind ernsthafte Komplikationen bei einer Übertragung vom Tier auf den Menschen äußerst rar.

要約

背景 – 皮膚糸状菌症は、猫および犬の表在性の真菌性皮膚疾患である。小動物で最も一般的な病原体は、*Microsporum*および*Trichophyton*に属する。これらは伝染性があり、人に伝播することがあるため、重要な皮膚疾患である.

目的 – 本文書の目的は、既存の文献を再検討し、猫と犬の皮膚糸状菌症の診断と治療に関するコンセンサスを臨床獣医師に提供することである.

方法 – 我々はガイドラインパネル(GP)として、2016年9月以前に入手可能な文献を再検討した。GPは文献の詳細な再検討を行い、選択されたトピックについての提言を作成した。この過程の指針および監視は世界獣医学学会(WAVD)によって行われた。文書の草案は第8回世界獣医学会(2016年5月)で発表され、3か月間ワールドワイドウェブを介してWAVDの構成組織に提供された。コメントが要請され、電子的にGPに掲示された。回答はGPによって最終文書に組み込まれた.

結論 – ゴールドスタンダードとされた単一の診断検査はなかった。治療に成功するためには、全身的経口抗真菌剤および被毛への局所消毒の併用が必要である。ウッド灯と直接顕微鏡検査は、陽性あるいは陰性の予測判断に有効であった。全身的抗真菌薬は広域な安全性マージンを持ち、環境を物理的に掃除することは暴露された環境の消毒に最も重要である。動物-ヒト伝播による重大な合併症は非常にまれであった.

摘要

背景 — 皮肤癣菌病是一种犬猫的浅表真菌性皮肤病。小动物最常见的病原体是犬小孢子菌和毛癣菌。这是一种重要的皮肤病,因其具有传染性,可以感染人类.

目的 — 本文旨在对现有文章进行综述,为兽医临床医生和宠主提供有关犬猫皮肤癣菌病在诊断和治疗上的统一建议.

方法 — 作者们成立指导小组(GP),查阅2016年9月之前所有可获得的文献资料,撰写出一份详尽的文献综述,同时就选定的主题提出相应建议。世界兽医皮肤病学会(WAVD)给予全程指导与监督。本文的草案在第八届世界兽医皮肤病大会(2016年5月)上正式发布,随后,通过万维网向WAVD的成员组织提供为期3个月的免费查阅,广泛征求意见,并以电子方式反馈给指导小组,指导小组将所有答复整合纳入最终文献.

结论 — 目前尚无诊断方法的金标准。成功的治疗需要全身口服抗真菌药,与被毛外部杀菌相结合。伍德氏灯和直接镜检能很好地判定阳性与阴性,全身抗真菌药物具有宽泛的安全边际,对所处环境进行物理清洁最为重要。此外,动物传染人类,出现严重并发症极其罕见.

Resumo

Contexto – A dermatofitose é uma dermatopatia fúngica superficial de cães e gatos. Os patógenos mais comuns em pequenos animais pertencem aos gêneros *Microsporum* e *Trichophyton*. É uma doença importante por seu caráter contagioso, infeccioso e seu potencial zoonótico.

Objetivos – O objetivo deste trabalho é revisar a literatura existente e fornecer um consenso de recomendações para clínicos veterinários e pessoas leigas a respeito do diagnóstico e tratamento da dermatofitose em cães e gatos.
Métodos – Os autores compuseram um Comitê de Diretrizes (CD) e revisaram toda a literatura disponível até setembro de 2016. O CD preparou uma revisão de literatura detalhada e fez recomendações em tópicos selecionados. A *World Association of Veterinary Dermatology* (WAVD) forneceu orientação e supervisão durante todo o processo. Um resumo do documento foi apresentado no *8th World Congress of Veterinary Dermatology* (Maio/2016) e depois foi disponibilizado no portal *World Wide Web* para as organizações que são filiadas à WAVD por um período de três meses. Comentários foram solicitados e postados ao CD eletronicamente e as respostas foram incorporadas pelo CD no documento final.
Conclusões – Nenhum teste diagnóstico foi considerado padrão ouro. O tratamento bem sucedido requer o uso concomitante de antifúngicos por via oral e desinfecção da pelagem por via tópica. A lâmpada de Wood e o exame direto possuem bom valor preditivo negativo e positivo. Antifúngicos sistêmicos tem um amplo espectro de segurança e a desinfecção física é a mais importante para a descontaminação dos ambientes expostos. Finalmente, complicações sérias relacionadas à transmissão da dermatofitose de animais para humanos são extremamente raras.