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Analysis of treatment methods for canine and feline dermatomycosis

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Abstract. Dermatomycosis is a kind of superficial infectious disease of skin, mucous membrane and skin accessory organ, which is caused by fungi. Dermatomycosis is a zoonosis characterized by recurrent, infectious and high morbidity. Nowadays, all studies on the treatment of dermatomycosis in cats and dogs are relatively scattered, so the purpose of this research is to analyze the therapeutic drugs of the dermatomycosis comprehensively by comparing the experimental data and results in other literatures, and point out the cons and pros and the target groups. Terbinafine is a good choice for both topical and systemic use or even as a medicated bath. For topical antibacterial treatment, ketoconazole, which has uncertain hepatotoxicity, is not recommended for young pets or those whose liver function is impaired. For systemic treatment, the itraconazole suspension is a better option, and fluconazole is not recommended to be the first choice if the sick animal is canine due to dogs' poor sensitivity to it. Among the Chinese medicines, simple Chinese gallnut solution, compound prescription composed of Chinese gallnut, smoked plum and other 8 Chinese herbs, and a shampoo called Sanzi Qingbai are both safe and effective treatments, which is less likely to develop drug resistance. People should consider the overall condition of the sick animal and the nature of the drugs when choosing the most suitable treatment, and the combination of Chinese and Western medical treatments is also a new direction.

Keywords: dermatomycosis; antifungal agents; traditional Chinese medicine.

1. Introduction

Dermatomycosis is one of the most common types of skin diseases in humans and animals. The main pathogenic bacterium are dermatophytes. Dermatophytes harm the skin and skin tissues by superficially infecting the skin, mucous membrane and skin accessory organ such as hair and nails. Dermatomycosis is featured by high morbidity, highly infectious and it is easy to relapse. C. immitis (Microsporum gypseums and canine Microsporums) and trichophyton mentagrophytes are the two main dermatophytes which cause canine and feline dermatomycosis. The former accounts for the majority (about 90%), followed by the latter (about 10%) [1]. When the infected hair samples were microscopic-examined directly, typical hyphae were seen to proliferate around the hair [2]. From the Meason-Smith study, it is clear that body site doesn't influent the composition or structure of healthy skin fungal communities [3]. It can be inferred that any epidermal part of the body is able to infect fungus, which predisposes localized infections to develop into systemic infections that ultimately have irreversible effects on the animal's organism. The general clinical signs of dermatomycosis in companion animals vary with the time of infection. Initially, alopecia, erythema, crusting, and dander are visible on the skin surface [4]. In the middle stages of the disease, dogs and cats are pruritic, restless, and be out of appetite. Long-term morbidity causes the decrease in weight of animals due to malnutrition and may be followed by bacterial infections, which may finally result in systemic infectious diseases [5, 6]. Almost all breeds of dogs and cats are susceptible animal, especially some breeds with a high proportion of breeding, as Teddies, field cats and English Shorthair cats and other [7]. Therefore, canine and feline dermatomycosis is one of the most extremely common and susceptible diseases in daily life.

Dermatomycosis is a zoonosis, usually more susceptible to fungal infection when immunity is low, and is limited to the initial site of infection, but the fungus can enter the circulatory system and cause

systemic infection through three ways, which are Trojan horse crossing, across damaged barrier tissues through transcytosis and paracellular crossing, and exit of blood vessels into the viscera by neutrophils and Kupfer cells [8]. Direct contact transmission is the predominant mode of transmission of dermatomycosis. In addition, indirect transmission can result from contact with any object carrying the pathogenic bacterium [9]. Furthermore, with the surge in the proportion of domestic pets and the development of pet medical care, unlike in the past, veterinary clinics may be a place which is susceptible to pathogenic bacteria, so the risk of infection for veterinarians has increased considerably [10]. Therefore, being capable to better protect the health of practitioners in the animal healthcare industry is also the aim of studies on efficient and safe treatments for dermatophytosis.

Until now, treatments for dermatomycosis are broadly categorized as follows. Firstly, it is important to know that the rate of animal infection will be markedly increased because of the impaired skin barrier or the low immunity, therefore, Martins et al. believe that the barrier function of the skin and mucous membranes can be repaired by regular consumption of specific foods [11]. Secondly, the externally applied agent is the first choice for pets' owners. Commonly used ointments are 1% terbinafine emulsion or 2% ketoconazole emulsion [12]. At the same time, some data have demonstrated that broad-spectrum antifungal agents such as clotrimazole, miconazole, and uniconazole are effective for topical treatment [13]. A more specific kind of topical medications is known as medicated bath. Common medicated bath lotions are Petefen Spray or Vick's Pie-O-Gel [12]. And Parafilm Magic Wash, manufactured and marketed by Parafilm, has a strong ability to inhibit the extracorporeal growth of the dominant causative fungi that cause skin diseases in pets [14]. In addition to the agents listed above, miconazole shampoos are extremely effective in vitro, but are most effective in vivo when combined with chlorhexidine, a fungistatic lotion [13]. If topical medications fail to be effective in a short time, then systemic medications are needed. Systemic medication helps to shorten the time of treatments and reduces the environmental pollution as well as the risk of people being infected. The most traditional systemic therapeutic agent is griseofulvin, which is gradually being replaced by itraconazole, terbinafine, and fluconazole due to its lower safety profile [10]. Among these, itraconazole (non-compounded) and terbinafine are the safest and most effective agents for the treatment of dermatophytosis, whereas ketoconazole and fluconazole are second therapeutically effective, and ketoconazole is more likely to cause side effects [13]. More specifically, herbal medicines that are widely available, less toxic, and less likely to develop drug-resistance have great potential in the animal dermatomycosis treatments [15]. A 10% or 5% solution of Chinese gallnut has been shown to have good efficacy in dermatomycosis [16]. A preparation of traditional Chinese medicine consisting of Chinese gallnut, medicine terminalia fruit and smoked plum is more effective to inhibit canine Microsporum [17]. Sanzi Qinbai lotion is commonly used in medicated baths for Feline tinea, and natural botanical shampoos have been shown to be clinically effective and advantageous [7, 18].

The extant literature for presenting treatments for dermatomycosis is fragmented, which increases the difficulty for scholars to systematically review, and is not conducive to efficiently conducting further research on dermatomycosis. Therefore, the aim of this research is to collect the most universally used treatments for dermatomycosis today and then compare them to point out their advantages, disadvantages and scope of application. After comprehensive analysis, recommendations are given to provide reference for subsequent studies.

2. Overview of canine and feline dermatomycosis

The onset of dermatomycosis is seasonal, usually occurring in the wet and warm seasons, and animals with weak or physiologically defective skin are more susceptible to infection and morbidity [1]. M. canis is more likely to be infected from October to February of the following year, with a low incidence from March to September. While Trichophyton is more susceptible and it is susceptible throughout the whole year, with a peak in November and December. Juvenile companion animals are more susceptible to fungal infections due to their lower immunity, different biochemical properties of the skin and sebaceous secretion status from adults [19]. Skin fungal infections are also influenced

by other factors such as hygienic management of the environment in which the animals live and the animals' outdoor activities [10]. Poor hygienic conditions accelerate morbidity in infected animals, or aggravate symptoms. The more time a companion animal spends outdoors, theoretically, the greater the probability of potential infection and morbidity are. Whether outdoor areas are dry is an important contributing factor. Skin fungi are transmitted either by direct contact or by fomites. In other words, in addition to contact directly with animals who carry pathogenic bacterium, healthy animals are also highly susceptible to infection and morbidity when exposed to such fomites with live pathogenic bacterium or spores of pathogenic bacterium. Dermatophyte spores have an extremely high survival rate, with the ability to survive for up to a year under optimal temperature and humidity conditions, and even are able to resist most disinfectants commonly used in hospitals [4]. Although there is evidence that boosting the body's immunity through the consumption of specific ingredients is beneficial to the treatment and recovery of dermatophytosis, mostly, the main treatment for dermatophytosis is to use antibacterial drugs, which are generally categorized as topical medications, systemic medications, and Chinese herbal remedies [11]. There are many effective measures to prevent dermatophytosis. For example, keeping the animal's living environment clean and tidy, cleaning the animal after outdoor activities, regularly sterilizing the equipment used for companion animals, paying attention to the well-balanced nutrition of cats and dogs to improve their immunity, and regularly checking for pathogens [12].

Figure 1. Chronic dermatitis in allergic dogs caused by excessive fungi growth [11]

3. Analysis of various antifungal drugs

3.1. Nutritional foods

Foods containing certain nutrients help to improve the immunity of companion animals. The skin barrier is the body's first barrier against external microorganisms. It can prevent the loss of water and electrolytes from the body, prevent from the damage of the external environment, especially the pathogenic microorganisms, and help maintain homeostasis within the body. Animals with broken skin barrier are more likely to be infected by dermatophytes, while supplementation with nutrients (pantothenic acid, inositol, niacinamide, choline and histidine) is beneficial for skin barrier. Vitamin B also has a strengthening effect on immunity [5]. It has been shown that the above nutrients increase the synthesis of skin ceramides and reduce epidermal water loss, as a means of increasing the

resistance of the skin barrier to Trichophyton mentagrophytes and canine Microsporum [11], as shown in Fig. 1. For healthy animals, these nutrients have a preventive effect against dermatomycosis. At the same time, for sick animals, they can also be used as adjunctive medications to shorten the duration of treatment and reduce the toxicity of antimicrobials to the body.

3.2. Topical therapeutic drugs

Topical treatments are intended to reduce the risk of infection and transmission of dermatophytes and their associated diseases by disinfecting the coats of cats and dogs which are suspected of being infected or have already diseased [13]. The necessary step before taking medication is to shave off the infected area on a large scale, with gentle movements to avoid damaging the skin barrier which can accelerate the fungal infection. Terbinafine is an allylamine antifungal agent. Its mechanism of action is inhibiting squalene epoxidase during the synthesis of ergosterol in fungal cells and causing squalene to accumulate in the cells to act as a fungicide. Clinically, 1% terbinafine emulsion is commonly used and it should be applied once or twice a day until healing [12]. Ketoconazole is an imidazole broad-spectrum antifungal agent with uncertain hepatotoxicity, and overdose may cause irreversible damage to the liver. It is not recommended for use in cats and dogs whose liver function is impaired. In addition, for topical therapy, there are some data that demonstrate the effectiveness of clotrimazole, miconazole, and uniconazole [13]. They are all broad-spectrum antifungal agents, and the mechanism of action of the first two drugs is to inhibit fungal growth by affecting the formation of fungal cell membranes. Some data suggest that a combination of miconazole and chlorhexidine is more effective than either agent alone. When used externally, creams containing miconazole are effective in inhibiting fungal growth, but when used internally (capsules, injections, or suppositories), they are most effective when combined with chlorhexidine. Because the safety of these products awaits additional studies, these medications are recommended as a treatment for comorbidities or as a topical enhancement of treatment. People should take care that the smear range is applied to a slightly larger area than the infected area to achieve better treatment results.

Topical medications, except applicator preparations, the medicated bath is a common treatment for dermatomycosis in companion animal today. The drugs which are mentioned above are suitable for smaller areas of epidermal damage, whereas terbinafine shampoos have shown good results for larger areas of damage. Petefen Spray, a kind of medicated bath preparation, contains terbinafine hydrochloride and often abbreviated as terbinafine [14]. The theoretical advantage of it is that the metronidazole contained has a significant antimicrobial effect on all anaerobic infections complicated by dermatophytosis. That is to say, Petefen Spray does good for limiting the infection to the local area. Besides, Vicopa OJ contains 3% chlorhexidine gluconate and metronidazole, which has some bactericidal effect. However, data from studies have shown that chlorhexidine alone is not therapeutically effective and therefore is not recommended for use alone. Then, Parafilm Magic Wash containing 2% chlorhexidine and 1% ketoconazole is more advantageous in comparison. It has been shown to have a targeted and strong effect in vitro inhibitory on the predominant causative fungi of dermatomycosis in cats and dogs [14]. The advantages of Parafilm Magic are even more obvious: it has great detergency and is well tolerated by the skin of cats and dogs. In other words, for cats and dogs with a relatively fragile laminated layer compared to humans, this wash does not cause damage to the animal's skin. In cases where a medicated bath is required, it is recommended that Parafilm Magic Wash or the Terbinafine shampoo should be preferred.

3.3. Systemic therapeutic drugs

If topical medication is not valid, the systemic antimicrobials is the best choice. If topical medications are not effective in inhibiting the growth of the fungus, then the lesions on the bodies of the infected animals will slowly spread and their fur will continue to transmit infectious fungal spores, becoming a potential source of infection for other animals and people. Topical antifungal medications focus on eliminating the fungus from the epidermis of the skin and the surface of the fur, while systemic treatments focus on eliminating the systemic infection that spreads from the local infection. In the

past, griseofulvin was one of the most prominent systemic therapeutic agents for the treatment of dermatomycosis. However, it was classified as the 2B carcinogen by the International Agency for Cancer Research of World Health Organization in 2017, which means that it may cause cancer in animals, and there haven't been any more in-depth clinical studies to confirm its toxic effect. Veterinarians have become more cautious about its use. Today, the most commonly used systemic antifungal drugs for canine and feline dermatomycosis are itraconazole, terbinafine, fluconazole, and ketoconazole. Itraconazole is a kind of potent broad-spectrum triazole antifungal agent, and its mechanism of action is to inhibit the synthesis of ergosterol, an important component of fungal cell membranes, by binding to fungal cytochrome P450 isoenzymes. Its suspension is better absorbed and more bioavailable than the capsule form, so it is suggested that itraconazole should be mixed with food before being fed to pets. It has also been documented to be able to modulate immune function and resist inflammation [10]. Overall, itraconazole is the most effective and safest antimicrobial drug. Also, a conclusion in the study of Moriello et al. mentioned that terbinafine was the same safe and active as itraconazole [13]. Combined with the discussion of terbinafine in this article on topical therapeutic agents, it can be concluded that terbinafine is a therapeutic option that lies at the top of the list for both topical and systemic therapy. In contrast, ketoconazole and fluconazole are less active. It has been proved that side effects will happen in about 20% of the cats treated with ketoconazole as the main therapeutic agent, whereas the probability and the impact of side effects on animals are lower when treated with itraconazole [10]. The latter, fluconazole, is a kind of imidazole antifungal agent with a broader antimicrobial spectrum and has the same mechanism of action as itraconazole. However, it has been experimentally found that the M.canis isolated from infected dogs were less susceptible to fluconazole [20]. Therefore, fluconazole is not advised to be preferred if the diseased animal is canine.

3.4. Chinese herbal medicine

At present, the international clinical treatment of canine and feline dermatomycosis is mostly based on chemical synthetic drugs. Due to certain factors, there are more and more cases and mutant strains of cutaneous fungal diseases, and there are irregularities in the application of clinical medication, and the drug resistance of sick animals and the toxicity and side effects of overdose of drugs have become increasingly serious, which has led to a certain degree of rejection of this type of drugs by some dog and cat owners who need to use them for a long period of time [16]. Then, the development of antifungal herbs or natural drugs has become a new direction.

3.4.1. Natural plant antifungal shampoos

Numerous studies have shown that many compounds in the composition of plants have the ability to resist fungi [21]. Natural plant antifungal shampoo, which consists of officinal magnolia bark extract, perilla leaf extract, and the cell-penetrating peptide, is a shampoo developed for dermatomycosis in animals. Officinal magnolia bark is anti-inflammatory, antifungal, and antitumor, especially against M.canises and trichophyton mentagrophytes [7]. The application of traditional Chinese medicine adds the options of medicinal bath products for owners of sick animals, and natural plant antifungal shampoos can also be effective in preventing disease.

3.4.2. Traditional Chinese medicine (TCM) and their formulas

Chinese medicines are characterized by wide sources, strong safety, low toxicity, low side effects and low drug-resistance, and they are capable of anti-bacterial inflammation, insect prevention and skin repairment [17]. Research has been conducted on the antifungal mechanism of Chinese medicines, and with the deepening of study and the advancement of pharmaceutical technology, Chinese medicines are increasingly used in canine and feline dermatomycosis [15]. Chinese veterinary medicine has its own unique theoretical system, which is called treatment based on syndrome differentiation. This theory suggests that canine and feline dermatomycosis is caused by the exogenous pathogenic wind that leads to an impact on the skin microcirculation and a subsequent decrease in the body's detoxification efficiency, and finally resulting in skin metabolic disorders [18].

Chinese gallnut is a kind of antifungal traditional Chinese medicine. Some studies have shown that 5% or 10% concentration of simple Chinese gallnut solution has a helpful alleviating effect on the infections by canine Microsporium and Trichophyton mentagrophytes. Its vitro fungicidal rate can even reach 100%, and Chinese gallnut solution will not have adverse effects on the cats and dogs. In addition to Chinese gallnut, medicine terminalia fruit, smoked plum, honeysuckle bud and flower, turmeric, etc. are demonstrated by the results of some vitro experiments that they are the most effective Chinese medicine inhibiting canine Microsporium. As a result, some researchers conducted further studies based on these findings, and developed a compound herbal preparation consisting of smoked plum, golden thread, golden larch bark, blackberry lily, amur cork-tree, Cynanchum atratum, Chinese gallnut, and medicine terminalia fruit, with a ratio of 1:1:1:1:1:1:1:1:2:2, and a concentration ranging from 1.56 to 100 mg/ml [17]. However, this compound preparation has not yet entered the clinical research stage, and the clinical effects have yet to be studied. The representative of the Chinese herbal lotion that has been put into use nowadays is San Zi Baicalin Bai Lotion, which contains 14 herbs that play the role of mutual assistance and promotion. Sick dogs and cats are washed for 40 min each time, so that the effect of the medicine is fully realized, and then rinsed clean. Sick animals should be rinsed twice a week, and can be cured in 2 weeks [18]. Based on the safety of traditional Chinese medicine for animals and human being, we propose an alternative treatment method, namely, combining the use of traditional Chinese medicine with the chemical synthetic drugs, which may shorten the course of treatment, reduce the toxicity and side effects of drugs on the sick animals and slow down the resistance of the chemical synthetic drugs.

4. Comparative analysis of drug therapy

For canine and feline dermatomycosis, a disease that is easily infected and easily relapsing, the treatment plan is changing with the depth of research. There are various reasons for these changes. The first one is that the clinical data of commonly used drugs in the past shows that drugs' toxicity and side effects are greater, and the adverse effects on the sick dogs and cats are more serious, such as hepatotoxicity and carcinogenicity, so the frequency of the use of some medications has been reduced (griseofulvin). Next one is the changes in dosage form. In terms of those drugs with better clinical data, more in-depth and comprehensive research has brought about innovative advances. For instance, a study has shown that the syrup solution of itraconazole is more easily absorbed by the body and has better efficacy than the more common capsule form, but of course, it may be more difficult for the owners to medicating their sick pets [4].

Nutritional balance in daily life and special nutritional supplementation is particularly important, which mainly plays a role in the immunity of susceptible cats and dogs. Nutrients such as vitamin B, pantothenic acid, inositol, niacinamide, choline and histidine are beneficial in increasing the resistance of the skin barrier against canine Microsporum and Trichophyton mentagrophytes. For healthy animals, the main role of nutrients is to prevent dermatophytosis; for diseased animals, it is an adjunct to systemic or topical therapy. Different drugs should be used according to the severity of the disease and the drug resistance of the animal body. When the infection is localized, terbinafine emulsion is preferred, and ketoconazole should be used with caution due to its unknown hepatotoxicity. Clotrimazole, miconazole, and uniconazole are also effective ointments, and it is worth noting that a combination of miconazole and chlorhexidine is more effective than either agent alone, especially for use in vivo. In addition to terbinafine emulsion, terbinafine shampoo is a good choice if a medicated bath is needed to treat a larger range of localized infection. Parafilm Magic Wash containing 2% chlorhexidine and 1% ketoconazole, which is more specific to canine Microsporum and Trichophyton mentagrophytes, is also extraordinarily effective. When topical medications are not effective or in cases of extremely severe infections, it is necessary to switch to systemic medications in addition to keeping the environment clean and the food nutritionally balanced. Itraconazole is the most effective and safest systemic antimicrobial drug, as evidenced by the study of Moriello et al. [13]. At the same time, terbinafine can be used internally as a systemic drug. Terbinafine is an all-purpose drug that can be used both topically and systemically. This article also

mentions that ketoconazole has a higher incidence of side effects for systemic therapy, while fluconazole is less effective in inhibiting canine Microsporum on dogs. Both two are not recommended. For sick animals with recurring infections that are progressively more resistant to drugs, Chinese herbs and herbal formulas are good choices when the dose of drugs is gradually increased to the point where the side effects are too excessive or even when the drugs have no therapeutic effect. And natural botanical antifungal shampoos are more than just antimicrobial, they are also disease-preventive [21]. Chinese gallnut solution or a compound Chinese medicine preparation composed of Chinese gallnut, smoked plum, medicine terminalia fruit and other 5 kinds of herbs in proportion is not easy to develop drug resistance but also has a better fungicidal effect, meanwhile, San Zi Baicalin Bark Lotion is a stable compound Chinese medicine lotion that has been put into clinical use on a large scale. Combining the characteristics and efficacy of chemical systematic drugs and traditional Chinese medicine, it is recommended to combine TCM and Western medicine to treat canine and feline dermatomycosis, which has the advantage of slowing down the resistance of chemical systematic drugs and reducing the adverse effects of their toxicity and side effects on the diseased animals.

5. Conclusion

The morbidity of dermatomycosis occurs throughout the ownership of cats and dogs and seriously affects the health of both pets and their owners. The process of microbial infection is usually a confrontation between the virulence of pathogenic bacterium and the resistance of the infected person. Therefore, increasing the immunity of sick animals can be used as an adjuvant treatment, and also has a preventive effect on healthy animals. For example, foods containing nutrients such as vitamin B, pantothenic acid, inositol and niacinamide can help to improve immunity. Nowadays, the treatment of dermatomycosis in cats and dogs is mainly focused on the use of chemically synthesized drugs, such as terbinafine, itraconazole, ketoconazole, fluconazole, etc. The mechanism of these drugs is to destroy the cell membrane of the fungus, so as to achieve the effect of bacterial inhibition. Overall, terbinafine is safe and effective for both topical and systemic treatment, which is commonly available as tablets, capsules, creams, sprays, etc., being convenient for the owner to use. As for topical treatment, ketoconazole should be used more cautiously than in the past; miconazole is recommended to be used in combination with chlorhexidine, especially in vivo; and for cases that require a medicated bath, Parafilm Magic Wash is preferred, followed by Vic Pellegrino. The safest and most effective of the systemic treatments is itraconazole; whereas ketoconazole has slightly stronger side effects in cats and fluconazole is not recommended for use with canines due to their poor sensitivity to it. There is a unique medical system called Traditional Chinese Medicine (TCM) in China. So are the herbal remedies. In recent years, a variety of Chinese medicines have been found to be antifungal, such as 10% or 5% simple Chinese gallnut solution or compounded Chinese medicinal preparations consisting of Chinese gallnut, smoked plum, and medicine terminalia fruit in proportions, as well as the Sanzi Qinbai shampoo, which has already been clinically put into use on a large scale. In addition, natural botanical antifungal shampoos are an all-natural medicated bath cleanser which can also be effective in preventing dermatomycosis.

The discussion in this paper fills the gap of the current lack of systematic comparisons of the advantages and disadvantages of various therapeutic drugs for dermatomycosis, especially the international knowledge of Chinese medicine is not considered sufficient. And this article provides a reference for veterinarians to select the appropriate drugs and treatments according to the characteristics of the cases and the properties of the drugs. This paper mainly focuses on the of therapeutic drugs, but lacks research on the specific resistance of each drug, and does not summarize the characteristics of the cases to further explore the outcomes and drawbacks of using each drug from the perspective of different types of cases. Afterwards, the comprehensive analysis of drug selection based on the generalized characteristics of cases and the study of drug resistance should be added.

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