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Review on Prevention and Treatment of Fungal Diseases of Veterinary Importance

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Abstract

Fungal diseases can be localized to a single body surface or they can spread throughout the body. Systemic fungal disease, also called systemic mycosis, is defined as the entry of a fungal organism into an animal and the subsequent spread of that organism's toxins to various organs of the body. Similarly, mycotoxicoses are fungal diseases caused by toxins produced by various fungi or molds growing on cereals, hay, straw, pastures, or any other type of fodder. Treatment and prevention are required to control mycosis, but prevention is preferable to cure. Here is a brief overview of the main methods for preventing and treating fungal diseases of veterinary importance.

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Introduction

The infection of humans, animals, birds, and plants caused by various pathogenic fungi is referred to as “mycosis” (mykes = mushroom). Mycotoxicosis is an additional term used to characterize the illness caused by ingesting mycotoxins (intoxication) found in feed. Similar to this, “mycetism” refers to the pathogenesis that the fungi create as a result of their in vivo toxin synthesis once they have entered the host (Samanta, 2015).

Despite the fact that hosts are continuously exposed to infectious propagules, fungi are very uncommon causes of disease in immunocompetent and healthy humans and nonhuman vertebrates (Ko *et al*., 2015; Mccraw & Gurr, 2013). Nevertheless, throughout the years, a growing variety of stubborn fungal infections in animals have emerged, with the cause being opportunistic and pathogenic fungi (Mccraw & Gurr, 2013).

Infections known as mycotic zoonoses can spontaneously spread from vertebrate animals to humans. Since zoonotic infections have been known about for many centuries, they are mostly responsible for the emergence and reemergence of infectious illnesses on a global scale (Seyedmousavi *et al.,* 2018).

The global issue of mycotoxin contamination of food and animal feed is also present. According to studies, the combination of unfavorable agricultural conditions, poor harvesting practices, and poor storage causes mycotoxins to arise more commonly in tropical climates (Kabak, 2010).

Thus, through consumption, become a source of infection. Similar to this, the pulmonary tract is typically the route of entrance for many mycoses, yet direct skin contact inoculation is not unheard of Bennett *et al.,* (2003).

Several strategies have been developed to prevent mycoses, the growth of mycotoxigenic fungi as well as to decontaminate and/or detoxify mycotoxin contaminated foods and animal feeds (Mehta and Visenuo, 2015; Kabak, 2010). The antifungal agents have been also developed to treat mycoses in animals as well as in humans.

So, the focus of this paper is to brief the possible prevention strategies and available treatment options of fungal diseases of veterinary importance.

Brief on Fungal Diseases of Veterinary Importance

Mycoses

The diseases known as mycoses are caused by fungi growing haphazardly on animal hosts (Bennett *et al.,* 2003). Based on the type of infected tissue in the host, they can be classified into five groups: superficial, cutaneous, subcutaneous, systemic, and opportunistic mycoses.

Superficial Mycoses

The fungi responsible are limited to the outer surface of hair and skin and hence are called superficial (Prescott & Klein, 2002). Dermatophytosis caused by *Microsporum* species and *Trichophyton* species is the principal example (Cannole, 1990).

Cutaneous Mycoses

Cutaneous mycoses, which penetrate deeper into the epidermis and are also referred to as dermatomycoses, ringworms, or tineas, are found all over the globe (Prescott & Klein, 2002). They are caused by the imperfect (anamorphs) of the three genera *Epidermophyton*, *Microsporum* and *Trichophyton* (Cannole, 1990).

Subcutaneous Mycoses

The dermatophytes that cause subcutaneous mycoses are normal saprophytic inhabitants of soil and decaying vegetation. Because they are unable to penetrate the skin, they must be introduced into the subcutaneous tissue by a puncture wound that has been contaminated with soil containing the fungi (Prescott & Klein, 2002). Phaehyphomycosis and Sporotichosis are the two examples (Cannole, 1990).

Systemic Mycoses

Except for *Cryptococcus neoformans,* which has only a yeast form, the fungi that cause the systemic or deep mycoses are dimorphic; that is, they exhibit parasitic yeast like phase (Y) and a saprophytic mold or mycelial phase (M). Most systemic mycoses are acquired by the inhalation of spores from soil in which the mold-phase of the fungus resides (Prescott & Klein, 2002). Cryptococcosis, Candidiasis and Histoplasmosis are the examples (Cannole, 1990).

Opportunistic Mycoses

In a healthy setting, an opportunistic fungus is usually not dangerous, but in a damaged host, it turns pathogenic. The condition has numerous causes, some of them are as follows: malnourishment; alcoholism; leukemia, cancer, diabetes, or another infectious condition; trauma from an injury or surgery; a changed microbiota as a result of long-term antibiotic usage (Prescott & Klein, 2002). These include: Aspergillosis, Mucormycosis, Cryptococcosis, Coccidioidomycosis, Histoplasmosis, Blastomycosis, etc (Seyedmousavi *et al*., 2018).

Mycotoxins and Mycotoxicoses

Mycotoxins are defined as the chemicals of fungal origin being toxic for (warm-blooded) vertebrates (Seyedmousavi *et al.,* 2018). Mycotoxins are categorized by fungal species, structure, and (or) mode of action. A single species of fungi may produce one or several mycotoxins and individual mycotoxins may be produced by different fungal species (Table 1) (Hussein S. Hussein, 2001). The mycotoxins cause intoxications in both animals and humans, resulting in severe diseases called acute or chronic mycotoxicoses, depending on species and susceptibility of the host (Bennett *et al.,* 2003).

Prevention of Fungal Diseases

Prevention Strategies of Mycoses

Preventing infections in animals entails keeping areas clean and getting rid of things that make them more susceptible. During therapy, keeping the animal in a clean room helps prevent environmental contamination. Large animals with cutaneous infections should have the crusts removed and the underlying areas treated with topical solutions of povidone-iodine, copper sulfate, or copper naphthenate (Bond, 2010).

Live, attenuated but virulent strains of *T. verrucosum* that produce abundant microconidia have been used in extraordinarily successful mass vaccination campaigns in cattle herds in Norway (Lund and Deboer, 2008).

Veterinary technicians and veterinarians may be exposed to mycoses such as dermatophytosis and blastomycosis at work. Therefore, when handling animals or tissues that have been confirmed or suspected to have blastomycosis, care should be taken to reduce the risk of exposure (Seyedmousavi *et al.,* 2018; Mehta and Viscenuo, 2015; Bond, 2010).

Prevention Strategies of Mycotoxicoses

Prevention and control methods have been prescribed for mitigating mycotoxin contamination of feeds (Hussein and Brasel, 2001). Grain mill operators and feed handlers must use these measures to store grain at less than 14% moisture content and maintain clean grain bins. Ingredients of feed must be devoid of oxygen, dry, fermented, or mold growth inhibitor-treated.

To lower the risk of mycotoxin contamination in silage crops, it is crucial to harvest them at the proper moisture content and to load and seal the silo (to keep out oxygen and promote the desired anaerobic fermentation) (Magan and Aldred, 2007).

Chemical treatment and processing are anthropogenic factors that may decrease mycotoxin contamination of foods or feeds. Wet and dry milling processes as well as heat in the cooking process have been shown to reduce *Aspergellus flavus* in foods. Heating and roasting have been shown to significantly decrease *Aspergellus flavus* content in corn reviewed in (Hussein and Brasel, 2001).Antimycotic feed additives may also be used but may not deal with toxins already formed. Certain minerals additives, however, have been shown to bind mycotoxins and reduce their effects (Magan and Aldred, 2007).

Treatment of Fungal Diseases

Animals with fungal infections are treated with many of the same antifungal medications that are used on humans. These can be polyenes (like nystatin and amphotericin B), azoles (like imidazoles and triazoles), allylamines (like terbinafine), and echinocandins.

Table 2 highlights the applications of several antifungals that have been effective in different animal species (Seyedmousavi *et al.,* 2018).

Table.1 Common mycototins of some fungal species and related toxicity

Fungal species	Mycotoxins	Toxicity
Aspergillus flavus, A. parasiticus, A. nomius, A. argenticus, etc.	Aflatoxin	Genotoxic, Hematotoxic, Hepatotoxic, Immunotoxic
Penicillium verrucosum, P. nordicum, A. ochraceus, A. carbonarius, A. niger, A. sclerotioniger	Ochratoxin	Genotoxic, Hematotoxic, Hepatotoxic, Immunotoxic, Nephrotoxic
Fusarium graminearum, F. culmorum, F. sporotrichioides, F. poae, F. tricinctum	Deoxydevalenol	Alimentary hemorrhage and vomiting; Dermatotoxic
F. sporotrichioides, F. poae	T-2 toxin	Alimentary hemorrhage and vomiting; Dermatotoxic
F. graminearum, F. semitectum, F. tricinctum, F. oxysporum, etc	Diacetoxyscripenol	Alimentary hemorrhage and vomiting; Dermatotoxic
Fusarium nivale, F. poae	Nivalenol	Alimentary hemorrhage and vomiting; Dermatotoxic
Fusarium graminearum, F. culmorum	Zearalenone	Dermatotoxic, Estrogenic, Genotoxic, Hematotoxic,
Fusarium proliferatum, F. verticillioides (syn. *F. moniliforme), A. niger, A. carbonarius*	Fumonisin B1	Neurotoxic, Hepatotoxic and Carcinogenic
Acremonium species and *C. purpurea*	Ergot alkaloids	Dermatotoxic, Neurotoxic

Source: (Seyedmousavi *et al.,* 2018 and Bennett *et al.,* 2003)

Table.2 Recommended indications of antifungals in veterinary practice

Group	Antifungal agent	Animal species	Indications
Systemic	Amphtericin B	Birds, Cats, Dogs, Horses	Aspergillosis, Candidiasis, Cryptococcosis, Blastomycosis, Histoplasmosis, Coccidioidomycosis, Mucormycosis
	Nystatin	Birds	Candidiasis of the gastrointestinal tract
	Terbinafine	Dogs, Cats	Cryptococcosis, Sporotrichosis, Dermatophytosis and *Malassezia* dermatitis
	Ketoconazole	Birds, Dogs, Cats	Blastomycosis, Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Sporotrichosis, *Malassezia* dermatitis and Dermatophytosis
	Parconazole	Birds	Candidiasis (trush)
	Itraconazole	Birds, Dogs, Cats, Horses, Rodents, Rabbits	Aspergillosis, Blastomycosis, Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Sporotrichosis, Dermatophytosis and *Malassezia* dermatitis
	Fluconazole	Birds, Dogs, Cats	Aspergillosis (CNS infection), Cryptococcosis, Blastomycosis, Coccidioidomycosis
	Voriconazole	Birds, Dogs, Cats, Horses	Aspergillosis, Scedosporiosis
	Posaconazole	Dogs, Cats	Aspergillosis, Mucormycosis
	Flucytocine	Cats	Cryptococcosis
	Gruseofulvin	Birds, Dogs, Cats, Horses, Ruminants, Rodents, Rabbits	Dermatophytosis, Sporotrichosis
Topical	Chlotrimazole	Birds, Dogs, Cats, Horses, Rodents, Rabbits	Aspergillosis, Dermatophytosis and *Malassezia* dermatitis
	Miconazole	Birds, Dogs, Cats, Horses, Rodents, Rabbits	Dermatophytosis, *Malassezia* dermatitis
	Enilconazole	Birds, Dogs, Cats, Horses, Ruminants, Rodents, Rabbits	Dermatophytosis, *Malassezia* dermatitis, Disinfection
	Natamycin	Horses, Ruminants	Dermatophytosis
	Thiabendazole	Birds, Horses, Ruminants, Rodents, Rabbits	Dermatophytosis, Disinfection

Source: (Seyedmousavi *et al.,* 2018)

Systemic Antifungal agents

Amphotericin B

Amphotericin B is a polyene antifungal that, along with amphotericin A, is produced by the soil actinomycete *Streptomyces nodosus*. Amphotericin B is relatively insoluble in water and derives its name from its amphoteric property to form methanol soluble salts under both basic and acidic conditions (Lyman and Walsh, 1992). It is available as an intravenous preparation formulated by combination with sodium deoxycholate (Anaissie *et al*., 2009).

Mechanisms of Action: The primary antifungal activity of amphotericin B is mediated by its preferential binding to ergosterol in the fungal cell membrane. This interaction results in the formation of pores consisting of eight amphotericin B molecules in the membrane, allowing leakage of potassium and other cellular components that ultimately leads to cell death (Anaissie *et al*., 2009).

Nystatin

Nystatin is a tetraene diene macrolide polyene with the molecular formula of C47H75NO17 and a molecular weight of 926.13. It behaves as a heptaene, like amphotericin B, nystatin is sometimes referred to as a degenerate heptaene (Anaissie *et al*., 2009).

Mechanism of action: The structural similarities of amphotericin B and nystatin suggest that a similar

mechanism of activity should exist for the 2 drugs (Zhang *et al.,* 2002).

Flucytocine

Flucytosine (5-fluorocytosine; 5-flucytosine; 5-FC) is one of the oldest antifungal agents in use (Anaissie *etal*., 2009).

Mechanism of action: Flucytosine is taken up by fungal cells by a unique fungal-specific cytosine permease. Two important and independent pathways for fungal cell injury occur: one leading to protein synthesis inhibition, and the other resulting in DNA synthesis inhibition (Lyman and Walsh, 1992). Both intravenous and oral formulations of flucytosine have been developed and are in clinical use.

Azole antifungal drugs

The commercially available ketoconazole, fluconazole, itraconazole, and voriconazole, posaconazole and ravuconazole azole drugs are shown in table 2. The antifungal azoles are classified chemically as imidazoles or triazoles based on the number of nitrogen atoms (two or three, respectively) in the azole ring (Anaissie *et al*., 2009).

Mechanism of action: The primary antifungal effect of the azoles occurs via inhibition of a fungal cytochrome P-450 enzyme involved in the synthesis of ergosterol, the major sterol in the fungal cell membrane. On a molecular level, binding of the free azole nitrogen with the heme moiety of fungal C-14demethylase inhibits demethylation of lanosterol, thereby depriving the cell of ergosterol and allowing accumulation of various 14 methylsterols. The net result is a disruption of normal structure and function of the cell membrane and ultimately, the inhibition of cell growth and morphogenesis (Anaissie *et al*., 2009).

Topical antifungal agents

Several drugs are used to treat superficial mycoses. Three drugs containing imidazoles: miconazole, ketoconazole, and clotrimazole are broad-spectrum agents available as creams and solutions for the treatment of dermatophyte infections such as athlete's foot, and oral and vaginal candidiasis. Almost all of topical drugs are thought to disrupt fungal membrane permeability and inhibit sterol synthesis (Prescott and Klein, 2002).

Conclusion

Mycoses and mycotoxicoses are significant problems of animals and humans worldwide. Generally, treatment of most fungal diseases is considered as difficult aspect because of the multicellular nature of the organism. Despite, there have been various prevention strategies and treatment options developed through time depending on the type of infectious agents as well as type of infections. Prevention is by far important than treatment especially in the case of mycotoxicoses. Achievements through vaccination are also reported for dermatophylosis of cattle in countries like Norway; suggestive for further researches on other fungal agents in different species of animals.

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