Chapter 1
Fungal Diseases of Bovines

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1.1 Introduction

Yeasts are found ubiquitously in nature, in association with plants, mammals and insects. Accordingly, animals are continually exposed to multiple genera of yeasts via various routes. Depending on the interaction between host mucosal defence mechanisms and fungal virulence factors, yeast colonization may be transient or persistent, with either systemic or local disease.

Bovinae is a subfamily of ruminant mammals of the biological family Bovidae, which includes several important species of farm animals, particularly the species *Bos taurus* cow or zebu, gayal, buffalo and yak, knowing that the family of cattle includes other subfamilies and in particular that of goats with goats and sheep (Table 1.1). Generally there are ten genera in this family includes *Bison, Bos*, *Boselaphus*, *Bubalus*, *Pseudoryx*, *Syncerus*, *Taurotragus*, *Tetracerus*, *Tragelaphus* and *Pseudonovibos* (Wilson and Reeder 2005).

These animals have a great importance for the agricultural sector and economy and provide the mainly basic raw materials for industrial processing such as meat, milk, head, skin, gelatin, wool, cashmere and soil compost. But the latter may be exposed to a range of diseases usually caused by viruses, bacteria, fungi, prions and parasites which cause not only suffering and death but also severe economic implications (Aiello and Mays 2016).

1.2 Fungal Diseases Transmission

Fungi are a group of non-photosynthetic microorganisms which live as saprophytes in the soil and on dead organic matter or as parasites of plants and animals including man. Fungal diseases are often caused by fungi that are common in the environment

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Table 1.1 Summary of the representative species and whether they were considered domesticated (MacEachern et al. 2009)

Subfamily Bovinae			
Tribe	Representative species	Domesticated	Note
Tragelaphini	*Taurotragus oryx* (eland)	No	Undomesticated
Bovini	*Syncerus caffer* (African buffalo)	No	Undomesticated
Bovini	*Bubalus bubalis* (water buffalo)	Yes	Domesticated in India and Asia
Bovini	*Bubalus carabensis* (swamp buffalo)	Yes	Domesticated in East Asia
Bovini	*Bison bison* (bison)	No	Undomesticated
Bovini	*Bos grunniens* (yak)	Yes/no	Domesticated in Asia and some wild species still exist
Bovini	*Bos taurus* (domestic cow)	Yes	Domesticated in Mideast
Bovini	*Bos javanicus* (Bali cattle)	Yes/no	Domesticated in Indonesia and some wild species still exist
Bovini	*Bos gaurus* (gaur)	No	Some history, but in general considered undomesticated
Bovini	*Bos frontalis* (mithun)	Yes	May be a domestic version of *B. gaurus*

and dominant in soil, water, plants, vertebrates and invertebrates (Cockcroft 2015). Various means of transmission of fungal diseases can be through direct or indirect contact including the following:

- Direct contact with other animals (e.g. livestock)
- Transfer infections by grooming, sexual activity and bites
- By vectors (e.g. biting flies, mosquitoes, ticks)
- Through the air and shared water and/or feed
- Waste products (e.g. urine, faeces)
- Watercourses, run-off and dung heaps
- Animal ecosystems
- Environment pollution related to waste water (e.g. crops and insect diseases)
- Environment changes (e.g. climate, heat stress, water availability)

1.3 Principal Bovine Fungal Diseases

1.3.1 Epizootic Lymphangitis

The most common form of this disease is an ulcerative, suppurative, spreading dermatitis and lymphangitis. However, other forms, including pneumonia or ulcerative conjunctivitis, also occur. It is clinically characterized by a spreading suppurative inflammation of cutaneous lymphatic vessels, lymph nodes and adjacent skin.

Epizootic lymphangitis spreads most readily where large numbers of animals are assembled and is a result from infection by a dimorphic fungus, *Histoplasma capsulatum* var. *farciminosum*. This fungus has also been known as *H. farciminosum*, *Cryptococcus farciminosis*, *Zymonema farciminosa* and *Saccharomyces farciminosus*. *H. capsulatum* var. *farciminosum* exists as yeast in animal tissues and a saprophytic mycelium in the environment (Spesivtsevia and Noskov 1959; Radostits et al. 2007).

However, the disease is more common in tropical and subtropical regions than in temperate zones, and sporadic cases have been reported from other parts of the world. Currently, *H. capsulatum* var. *farciminosum* is endemic in some countries in the Mediterranean region and in parts of Africa and Asia including India, Pakistan and Japan. *H. capsulatum* var. *farciminosum* is a thermally dimorphic fungal soil saprophyte. The mycelial form is present in soil, while the yeast form is usually found in lesions. This fungus is highly resisted to the effects of physical and chemical agents. It may survive for up to 10 weeks in non-sterile water at 26 °C (Spesivtsevia and Noskov 1959; Radostits et al. 2007).

The mode of disease transmission includes transmission by direct or indirect contact of fungi with traumatized skin, by biting flies, by ticks or by inhalation of fungi spores. Direct contact with infective materials through injured skin or through cutaneous abrasions is the most common mode of infection. Spread of infection can also occur by indirect contact through feeds and water (Abdisa 2017).

Surgical excision of lesions combined with antifungal drugs (amphotericin B) could be used. Intravenous dosing of iodide may be used, particularly in endemic areas. The intravenous injection of 100 ml of sodium iodide of a 10% solution, repeated weekly for 4 weeks is recommended (Gabal 1984; Rochette et al. 2003).

1.3.2 Ringworm (Dermatomycosis)

Bovine dermatophytosis caused by *Trichophyton verrucosum* is a disease that affects many species, livestock in tropical and subtropical areas such as African countries. This skin disease is present worldwide and is responsible for high economic losses in cattle farming. The disease is caused by a group of keratinophilic filamentous fungi called dermatophytes (club lamb fungus) in the genera *Trichophyton*, *Microsporum* and *Epidermophyton*. *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* have been the major agents encountered (Table 1.2) (Papini et al. 2009; Nweze 2011).

Ringworm infections acquired from animals usually involve direct contact with infected dogs or cats or contact with contaminated material. The infected animals may not show obvious signs of infection. Close confinement, host factors (age, immunocompetence, the type of breed, host grooming behaviour), dietary factor deficiencies, condition of exposed skin in prolonged wetting are thought to be important predisposing factors. In addition, affected animals initially develop characteristically discrete, scaling patches of hair loss with grey-white crust that later become a thickly suppurated crust whose location is highly variable.

Table 1.2 Antifungal drugs in use[a] in cattle with dermatomycosis (Rochette et al. 2003)

Antifungal (trade name)	Formulations	Indications	Treatment schedule
Enilconazole (Imaverol)	Emulsifiable solution	*Trichophyton, Microsporum*	Wash or spray with diluted emulsion (2000 p.p.m.) four times at 3–4-day intervals
Clinafarm	Antimycotic disinfectant	*Trichophyton*	For disinfecting of environment with spray or smoke generator
Griseofulvin (Fulcin, Grisovin)	7.5% powder feed additive	*Trichophyton, Microsporum*	10 mg/kg body weight for 7 days in mild infections; in severe cases 2–3 weeks
Natamycin (Mycophyt)	Suspension	*Trichophyton, Microsporum*	Spray suspension two times with interval of 4–5 days; retreat remaining lesions after 14 days
Thiadiazine (Defungit)	Powder for dilution	*Trichophyton, Microsporum*	0.5% dilution repeat two to three times with interval of 2–4 days; if no bensuldazin cure, repeat schedule after 14 days
Thiabendazole (in 90% DMSO)	4% solution, ointment	*Trichophyton, Microsporum*	Washing with solution

DMSO dimethyl sulphoxide

[a]Drugs in bold are officially licensed as veterinary products for cattle in most of the EEC countries

Cattle ringworm is rapidly spreading in the herd via infected propagules (hyphae and specialized fungal spores named arthrospores). The disease is responsible for great economic losses due to skin injuries and many casualties in animal products (wool, meat, etc.) (Mignon and Monod 2011; Swai and Sanka 2012).

1.3.3 Aspergillosis

Aspergillus species are saprophytic filamentous fungi, class *Eurotiomycetes*, *Trichocomaceae* family; they are commonly found in soil, where they thrive as saprophytes, with an occasional potential to infect living hosts including plants, insects, birds and mammals. *Aspergillus fumigatus* is the main species responsible for aspergillosis, mycotic pneumonia, gastroenteritis, mastitis, placentitis and abortions in ruminants, domestic animals and especially cows worldwide with several economic losses, chiefly in areas of intensive rearing, whereas *A. flavus*, *A. nidulans* and *A. niger* are secondary. *A. fumigatus* is a ubiquitous saprophytic fungus and an opportunist pathogen and survives in a wide range of environmental conditions (Seyedmousavi et al. 2015).

Furthermore, aspergillosis fungal diseases affected bovines in all age groups and often occur in the last third of gestation. Mycotic placentitis is a major worldwide cause of abortion in cattle, generally occurring in the third trimester of pregnancy. Also, placentitis and abortion are common features associated with bovine

aspergillosis and can account for up to 20% of bovine abortions. *A. nidulans* and *A. fumigatus* have also been described as causal agents of bovine mastitis (Puntenney et al. 2003; Bakr et al. 2015).

However, the main portal entry of fungi is the respiratory and gastrointestinal tracts. In addition, *A. pneumonia* caused a fatal disease bronchopulmonary aspergillosis with a hard sign that includes pyrexia; rapid, shallow and stertorous respiration; nasal discharge; a moist cough and appearances of multiple discrete granulomas in the lungs, and the disease grossly resembles tuberculosis. Primary pulmonary infections are mainly established subsequent to exposure to heavy loads of spores from mouldy feed stuffs in damp buildings (closed farm) that have a mouldy smell or obvious mould growth. Also tuberculosis and aspergillosis have been reported in cattle with underlying mycotic lymphadenitis (Zmeili and Soubani 2007).

In cows, the gastrointestinal tract (omasum) is the primary site of mycotic lesions caused by *A. fumigates* which produces mycotoxicosis such as gliotoxin and tremorgens that are toxic to cattle and cause deterioration, protein deficiency, malnutrition, diarrhoea, irritability, abnormal behaviour and occasionally death (Tresallet et al. 2010).

Moreover, a neurological syndrome in dairy cattle associated with consumption of contaminated foodstuffs by strains of *A. clavatus* has been described. *A. clavatus* is known to produce several tremorgenic metabolites such as patulin and clavatol that are selectively neurotoxic to animals. Enilconazole antifungal is recommended for use in animals against aspergillosis by wash lesions with 0.2% solution 4 times at 3 to 4 days intervals (Seyedmousavi et al. 2013; Finnie et al. 2011).

1.3.4 Mycotic Mastitis

Bovine mastitis is a disease caused by a wide variety of microorganisms such as *A. fumigatus, Candida albicans*, *C. kefyr*, *Cryptococcus neoformans*, *Trichosporon*, *Toluropsis, Prototheca zopfii*, *Trichosporon mucoides* and *Saccharomyces* species, but mastitis due to filamentous fungi mostly *A. fumigatus* has been reported occurring as sporadic cases affecting a small percentage of cows or as outbreaks affecting the majority of animals. However, the disease causes large economical loses and damages to the dairy industry (Pachauri et al. 2013; Adebiyi and Oluwayelu 2018).

Antibiotic therapy, micronutrient inadequacy especially vitamin A and zinc, contamination of teat dips, intramammary infusions, mouldy surroundings, feed and fodder algal contamination by *Prototheca zopfii*, pollution of drinking water and livestock grazing polluting regions with sludge are the most common factors of disease prevalence. In addition, *Candida* spp. were included in mycotic cases of bovine mastitis especially *C. glabrata* and *C. kruse* (Pachauri et al. 2013; Adebiyi and Oluwayelu 2018).

On the other hand, samples from the subclinical mastitis group showed a diversity of *Candida* species, including *C. zeylanoides*, *C. norvegica*, *C. viswanathii*, *C. guilliermondii*, *C. crusei* and *C. tropicals* (Elad et al. 1995; Malinowski et al. 2001; Dudko et al. 2010). Mastitis symptoms include abnormalities such as a watery appearance of milk, flakes, clots or pus in milk.

Also, the disease can be identified by external symptoms such as swelling, heat, redness, hardness or pain of the udder. Nystatin, sulfadiazine and prednisolone are the main antifungal drugs for mycotic mastitis; it is taken two times daily, for a single period of seven consecutive days. In addition, mastitis control and prevention requires an effort in improving the milking system, cattle feeding and hygiene, housing conditions and breeding policy (Geraldo et al. 2012; Kuria and Gathogo 2013).

1.3.5 Sporotrichosis

Sporotrichosis is a subacute or chronic infection caused by the saprophytic thermodimorphic fungus *Sporothrix schenckii* and *Sporothrix chilensis* that are found worldwide in high-humidity and high-temperature regions and river valleys. The disease is caused by members of the fungal genus *Sporothrix* of *Ophiostomataceae* family and order *Ophiostomatales*.

However, *S. schenckii* is now known to contain several individual species including *S. schenckii* sensu stricto, *S. brasiliensis*, *S. globosa*, *S. luriei*, *S. mexicana*, *S. pallida*, *S. albicans*, *S. nivea*, *S. stylites*, *S. humicola*, *S. chilensis*, *S. splendens*, *S. narcissi* and *S. inflata* complex (Aiello and Moses 2016; Rodrigues et al. 2016a).

These species were normally growing as saprophytes in the environment and may be present on vegetation and inorganic debris and soil. When fungal spores are accidentally inoculated into the skin (most often via sharp pieces of vegetation), some species of *Sporothrix* transform from filamentous moulds into yeasts and proliferate. In most cases, these organisms remain confined to the skin and lymphatic, causing relatively superficial lesions such as erythematous nodules, ulcers and plaques (Téllez et al. 2014; Rodrigues et al. 2016b).

Without treatment, these lesions may persist for months or years, or even indefinitely. Uncommonly, the organisms invade deeper tissues, including bone, joints and various internal organs, or disseminate widely in the skin. Disseminated infections, including rare instances of pulmonary sporotrichosis from inhaled organisms, can be life-threatening (Zhou et al. 2014; Zhang et al. 2015).

However, various antifungal drugs, such as itraconazole, ketoconazole, amphotericin B and fluconazole, have been used to treat sporotrichosis in animals at least one month. In addition, potassium or sodium iodide can also be employed in the cutaneous or lymphocutaneous forms. Other treatments that have been used in cutaneous sporotrichosis, either alone or in conjunction with antifungal drugs, include surgical removal, cryotherapy and thermotherapy (Rodrigues et al. 2014; Borba-Santos et al. 2015).

1.3.6 *Paracoccidioidomycosis*

Geographically, the disease occurs most commonly in Latin America, Brazil, Colombia, Venezuela and Argentina and around humid forests (subtropical or tropical). Among domestic animals, positivity rates have been reported to be higher in equines (64%) than sheep (41%) and cattle (40%) (Costa et al. 1995; Mendes et al. 2017a).

Paracoccidioidomycosis disease is an acute to chronic systemic infection caused by a thermally dimorphic fungus *Paracoccidioides brasiliensis* and *Blastomyces dermatitidis* (Elad et al. 1995). The natural habitat of *P. brasiliensis*, its environmental niche and life cycle in nature remain unknown, but it is presumed that the fungus is able to survive and proliferate in the soil, from where it has previously been isolated. However, many factors such as human migration, expansion of agricultural frontiers, climate and environmental changes as well as modifications in agricultural and social practices are beginning to influence the occurrence of infection and disease induced by *Paracoccidioides* spp. (Bagagli et al. 2006; Mendes et al. 2017b).

The disease has been shown to occur in several species of domestic and wild animals and is transmitted in an airborne manner, in animals, by inhalation of infective conidia present in the environment or through injuries of the skin and mucous membranes. This systemic granulomatous disease can affect any organ in the body, predominantly the lungs, organs rich in mononuclear phagocyte system cells, the mucous membrane of the upper aerodigestive tract and the skin and adrenal glands. Sulfonamides, ketoconazole, amphotericin B and itraconazole are the most common antifungal drugs indicated in the treatment of paracoccidioidomycosis (Travassos et al. 2008; Martinez 2015).

1.3.7 *Fungal Abortions*

The disease is a widespread disease in many regions of the world, causing significant economic losses. At that, mycotic abortion or mycotic placentitis is caused by many fungi and yeast and is a cosmopolitan, sporadic infection of the genital tract of animals, particularly the cows. Among the fungi, *Aspergillus fumigatus* and *Mortierella wolfii* are identified as the cause of bovine abortion in over 60% of the cases; they have a distinct seasonal pattern and occurring especially in the summer (Al Humam 2014; Pal 2015).

However, zygomycetes including *Absida*, *Mortierella*, *Rhizomucor* and *Rhizopus* accounted for about 20% of cases, and the remaining 20% were caused by a wide range of opportunistic filamentous fungi and yeasts, but the exact mode of transmission of infection is not known. The fungus can be isolated from foetal stomach contents and foetal internal organs on mycological media. *Mortierella* abortion is usually associated with feeding of silage with a higher than optimal pH and eating mouldy hay, grass, straw, etc. (Al Humam 2014; Pal 2015).

Table 1.3 Dual mycotic infections of bovine abortion causative fungi demonstrated in placental tissues (Pal 2015)

Aspergillus flavus	+ *Absidia corymbifera*
Aspergillus fumigatus	+ *Absidia corymbifera*
Aspergillus fumigatus	+ *Rhizomucor pusillus*
Aspergillus fumigates	+ *Rhizopus arrhizus*
Candida albicans	+ *Mucor*
Emericella nidulan	+ *Absidia corymbifera*

Aborting cattle may subsequently develop a fatal mycotic pneumonia after haematogenous spread from the placenta or uterus. In addition, the common environmental *Mucor*/*Absidia* fungi are sporadic cases of abortion, in cattle. Also, they are reported to be among the secondary invaders in cases of mycotic rumenitis and enteritis in cattle, though they are rarely cultured (Mangiaterra et al. 1999; Gaastra et al. 2010).

Despite the seriousness of the disease, no antifungal chemotherapeutic agent is recommended for the treatment of mycotic abortion in bovine. However, the treatment of hay with fungicides during haymaking is essential to prevent the growth of fungi, and the animals should be kept in clean, well-ventilated, hygienic and dry sheds/byres/pens as humidity favour the development of many fungal pathogens (Mangiaterra et al. 1999; Gaastra et al. 2010) (Table 1.3).

1.3.8 Cutaneous Pythiosis

The disease has been reported in several regions of tropical, subtropical and temperate climate, more particularly in swamps or flooded areas, and it has also been reported in Southern USA, Mexico, Venezuela, Brazil, Africa, Asia, Australia and New Zealand. This disease occurs in sporadic and epidemic form in several domestic animal species, such as canine, bovine, cats, sheep, dogs and tropical animals.

Pythiosis insidiosi is an emerging tropical disease silently killing, caused by the oomycete *Pythium insidiosum* which is a fungus-like organism that, in contrary to other species of *Pythium*, shows pathogenicity to several animal classes (Ono et al. 2001; Pal and Mahendra 2014). Infection source is exogenous through aquatic environments where the organisms live as a saprobe. Hence, pythiosis can be considered as a waterborne parafungal disease. This disease is characterized by granulomatous ulcerative lesions, mainly in cutaneous and subcutaneous tissues, and it may be life-threatening in some cases (Pal and Mahendra 2014).

In animals such as cats, dogs, horses and cattle, pythiosis is an osseous, subcutaneous or pulmonary infection. Equine pythiosis is marked by chronic ulcerated lesions with numerous yellow coral-like bodies (“kunkers”) on the limbs, chest and abdomen. In addition, dogs and horses may also present with intestinal obstruction due to *Pythium granuloma* in the duodenum or jejunum.

Thus, the common sites of infection in animals are cutaneous/ subcutaneous tissues and the gastrointestinal tract. In addition, this filamentous organism initially affects the skin, and subcutaneous tissues, but can involve adjacent tissues like tendons, ligaments, and bone and invade the gastrointestinal tract or other tissues, and organs, resulting in multisystemic disease (Martins et al. 2012; Granta et al. 2016).

The incubation period of pythiosis is not clearly defined, but the disease is more likely to develop weeks to months after exposure with a contaminated environment. The conventional treatment of the cutaneous form is aggressive surgery and limb amputation, but it cannot be indicated to all anatomical sites, due to the requirement of a large margin resection. The difficulty in detecting the hyphae infection in the tissue results in high recurrence rates.

Antifungal drugs are ineffective for the treatment of pythiosis, because *Pythium* species may lack the drug-target ergosterol. Recently, a new group of antifungal drugs such as caspofungin, micafungin or anidulafungin is applied. The immunotherapeutic vaccine is another treatment option because the favourable outcomes were observed in some patients and animals. However, the vaccine efficacy is usually limited (Pires et al. 2014).

1.3.9 Pithomycotoxicosis

The disease has appeared in many parts of the world such as New Zealand, Australia, South Africa, France, Spain, Uruguay, Argentina and Brazil, especially in temperate zones. It is called facial eczema or facial dermatitis, caused by the ingestion of high quantity of *Pithomyces chartarum* spores during grazing, which contain a potent hepatotoxin named sporidesmin that was absorbed into the portal bloodstream and taken to the liver where it generates oxygen free radicals which damage cell membranes, causing inflammation and destruction of animal tissues (Di Menna et al. 2009).

Animal deaths, condemnations of jaundiced carcasses, loss of body weight and reduced fertility in sheep and lower milk yields in dairy cattle are the economic losses of this disease. The saprophytic fungus *P. chartarum* grows on dead vegetable matter at the base of the pasture and proliferate in warm, humid weather and light rain (in late summer and autumn), where hepatotoxin production causes pericholangitis and the occlusion of bile ducts, resulting in a reduction in the excretion of phylloerythrin, a photodynamic metabolite produced by the microbial degradation of chlorophyll in the rumen (Pinto et al. 2005; Di Menna et al. 2009).

Sporidesmin is released from ingested spores in the upper digestive tract, absorbed into the portal bloodstream and taken to the liver, where it generates oxygen free radicals which damage cell membranes. Thus, gastrointestinal disorders are the first signs of intoxication in affected animals, where the second sign is characterized by high plasma levels of phylloerythrin and the animal becomes sensitive to sunlight (photosensitization) especially on more exposed and non-pigmented areas of skin (Parkinson et al. 2010; Little et al. 2011).

In addition, cholangiohepatitis, ductal hyperplasia and fibrosis are also seen histologically. Control method of facial eczema was by avoiding toxic pasture, detected by *P. chartarum* spore counts on herbage; later by reducing fungus pasture populations by spray application of substituted thiabendazole fungicides and later still by protecting animals with oral doses of zinc at close to toxic levels. In addition, animals can be protected against ingested sporidesmin by zinc salts (zinc oxide or zinc sulphate) (Toth et al. 2007; Read et al. 2016).

1.3.10 Zygomycosis (Mucormycosis)

Zygomycosis is deep, progressive and rapidly invasive subcutaneous mycosis caused by fungi that belong to the class *Zygomycetes* (including *Entomophthorales* and *Mucorales*). Geographically, zygomycosis occurs mostly in tropical and subtropical areas (Americas, Australia, Asia and Africa) (Jensen et al. 1994; Richardson 2009).

The disease is caused by moulds belonging to the order *Mucorales*, *Mucoraceae* family, which subdivides into the genera *Lichtheimia*, *Absidia*, *Mucor*, *Rhizomucor* and *Rhizopus*. In addition, only a few cases of infection have been reported by the other groups of *Mucorales* such as *Cunninghamellaceae* (*Cunninghamella bertholletiae* spp.) and the *Saksenaceae* (*Saksenaea vasiformis*), *Mortierellaceae* (*Mortierella* spp.) and *Syncephalastraceae* (*Syncephalastrum racemosum*) (Jensen et al. 1994; Richardson 2009).

Mucorales are thermo-tolerant moulds that are ubiquitous in nature and are widely found on organic substrates, including bread, decaying fruits, vegetable matter and crop debris, normal soils between growing seasons, compost piles and animal excreta. However, zygomycosis is predominantly transmitted by inhalation, ingestion or traumatic inoculation of spores, whereas the highest levels of fungal spores were found in the autumn and summer, and the lowest in the winter and spring (Pal 2000, 2007).

Thereby, inhalation of spores into the nasal cavity from the dusty environment produces disease in the susceptible host. Infection occurs through contact of traumatized or abraded skin or wound with fungi that contaminated objects, and cutaneous zygomycosis results from inoculation of fungal spores into the dermis (Pal 2000, 2007; Katharine et al. 2016). In addition, mucormycosis or phycomyces manifestations include abortion, mastitis, gastrointestinal infections, pneumonia, cutaneous lesions and disseminated diseases. The treatment of this disease involves surgical debridement and elimination of infected and necrotic tissues and the use of liposomal amphotericin B and posaconazole antifungal drugs (Jensen et al. 1996; Greenberg et al. 2004; Pal 2015; Pal et al. 2015).

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