

A Review on Candidiasis and Opportunistic Mycosis in Human and Animals

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DOI: 10.7176/JNSR/9-9-01

Publication date: May 31st 2019

INTRODUCTION

CANDIDIOSIS

Candida albicans (*C. albicans*) is part of the normal microbial flora in human beings and domestic animals, and is associated with the mucous surfaces of the oral cavity, gastrointestinal tract and vagina. Immune dysfunction can allow *C. albicans* to switch from a commensal to a pathogenic organism capable of infecting a variety of tissues and causing a possibly fatal systemic disease (Traynor and Huffnagle, 2001). Mucosal infection is the most usual form of the disease but cutaneous lesions are seen on occasion (Lehmann, 1985).

In cattle, as a consequence of the abundant use, and occasional abuse, of antibiotics in the treatment of mastitis, there is a selection of flora, mainly members of the genus *Candida*, that are new etiological agents of these processes, which are initially difficult to diagnose because their presence is not expected. Candidiasis in birds is related to malnutrition and stress, generally produced by the same strains that are found naturally on the food plants of these animals. Arthritis caused by yeasts in horses is relatively frequent as a consequence of contamination of wounds or after surgical treatment. In pigs, candidiasis usually takes the form of digestive alterations in young animals, and is usually related to problems that predispose to the disease, like treatment with antibiotics (Garcia and Blanco, 2000). *C. albicans* is a common causative agent of stomatitis in the dog (Jadhav and Pal, 2006). Although fungi need pre deponent factors to produce the disease, it is known that saprophytic colonization of the mucous membrane by *C. albicans* does not need the host to be immune compromised, since it is detected in immune competent individuals (Garcia and Blanco, 2000).

Etiology

Candidosis is the most common fungal infection of the oral cavity and is caused by an overgrowth of commensal *Candida* species. *Candida albicans* (*C. albicans*) is the most commonly isolated species in both health and disease. Less common species include *C. glabrata*, *C. tropicalis*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, and *C. kefyr*, and more recently, *C. dubliniensis* (Neville *et al.*, 2002).

Host risk factors

Endocrine disorders

Diabetes mellitus (DM) may increase susceptibility to development of candidal infections owing to immune system aberrations such as impaired opsonization and decreased chemotactic activity of neutrophils and monocytes (van Burik & Magee, 2001). *Candida*-associated lesions including denture stomatitis, median rhomboid glossitis, and angular cheilitis have been reported to be more prevalent in patients with DM (Guggenheimer *et al.*, 2000). The individuals with DM are more prone to candidal infections, particularly when host resistance is modified due to local factors such as smoking and denture wearing (Dorocka-Bobkowska *et al.*, 1996). Patients with poorly controlled DM may exhibit reduced salivary flow rates, reduced salivary pH, increased salivary glucose levels - factors known to facilitate oral candida growth and colonization (Bell *et al.*, 1999).

Nutritional factors

Several nutritional deficiencies may result in a diminished host defense and loss of epithelial integrity, which may facilitate subsequent fungal invasion and infection (Sherman *et al.*, 2002).

Iron deficiency anemia has been proposed as an important factor in the etiology of oral candidosis (Paillaud *et al.*, 2004). Decreased lymphocyte response to *Candida* antigens in some iron-deficient subjects was associated with an increased frequency of *C. albicans* in the oral cavity, suggesting that iron deficiency may predispose to oral candidosis by depressing cell-mediated immunity (Sweeney *et al.*, 1994). Deficiencies of vitamin B12 and folic acid may also predispose to oral candidosis (Davenport *et al.*, 2001).

Immune defects, immunosuppression

Oral candidiasis is a common manifestation in a variety of immune deficiencies. Both humoral and cell-mediated immune systems participate in the prevention and elimination of candidosis (Farah *et al.*, 2010). Reduced or defective immune function increases susceptibility to such infections. In HIV infection, the immunodeficiency affecting T-helper lymphocytes makes the infected patients more predisposed to secondary infections, notably opportunistic candidal infections (Farah *et al.*, 2000).

High-carbohydrate diet

High-carbohydrate intake has been assumed to predispose to oral candidosis. This is supported by in vitro studies showing that the growth of *Candida* in saliva is enhanced by glucose despite the presence of a nutrient competing bacterial salivary flora (Basson, 2000). Furthermore, the adhesive properties of *C. albicans* to oral epithelial cells and to acrylic surfaces are augmented by dietary carbohydrates. In studies investigating the effects of dietary sugars on candidal adhesion and biofilm formation, glucose was shown to be the most effective followed by galactose and sucrose (Jin et al., 2004).

Pathogenesis

Virulence factors

C. albicans has several known virulence factors contributing to its pathogenicity that include adherence to epithelial and endothelial cells, proteinase production (Ross et al., 1990), hypha and pseudohypha formation (Odds et al., 1988), phenotypic switching, phospholipase production (Ibrahim et al., 1995), and antigenic modulation as a result of pseudohypha formation (DeBernardis et al., 1994). If *C. glabrata* is low in virulence, the lack of hypha formation may be a contributing factor. Indeed, hypha formation is a recognized means of increased adherence and tissue invasion by *C. albicans* as well as a means of increasing proteolytic enzyme elaboration and antigen modulation (Odds, 1988).

Adherence is an extremely important virulence factor, although the actual adherence property may be compounded by other virulence properties. For example, cell surface hydrophobicity (CSH), which is affected by environmental factors, can affect specific adherence based upon interaction of adhesin receptors. In a study with limited numbers of *C. glabrata* isolates tested, *C. glabrata* was shown to have comparable CSH to *C. albicans* (Klotz et al., 1988).

Extracellular membrane-damaging phospholipases are considered virulence factors for *C. albicans* (Ibrahim et al., 1995). Although these enzymes have not been studied extensively, phospholipase A and B and lysophospholipase-transacylase are produced by virulent but not avirulent (commensal) strains of *C. albicans*. These phospholipase-producing strains also adhered most strongly to epithelial cells. Furthermore, the production of these phospholipases by clinical isolates correlated with pathogenicity and was predictive of mortality in animal models (Ibrahim et al., 1995). Another virulence factor of *C. albicans* is specific phenotypic instability, which allows strains to switch colony phenotype without affecting the identifiable genotype; this is termed "phenotypic switching" (Soll, 1988 & 1992).

Host defenses

Clinically, this is supported by the fact that neutropenic patients are particularly susceptible to systemic *C. albicans* infections. In addition, it has been shown in an animal model that T cells may be of some significance against systemic *C. albicans* infections. Specifically, studies in mice have shown that a Th1-type response characterized by the cytokines interleukin-2 (IL-2), gamma interferon, and IL-12 is associated with protection against systemic infection whereas Th2-type responses characterized by the cytokines IL-4, IL-5, and IL-10 and antibody production (immunoglobulin A [IgA] and IgE) is associated with susceptibility to systemic infection (Romani et al., 1996). T cells and cell-mediated immunity (CMI), on the other hand, form the predominant host defense mechanism against mucosal *C. albicans* infection. This comes from both clinical observations (a high incidence of mucosal candidiasis in patients with reduced CMI) and clinical and experimental studies showing the critical role of T cells in protection against *C. albicans* mucosal infections (i.e., chronic mucocutaneous candidiasis and gastrointestinal candidiasis) (Bennett, 1990).

Preventive measures

Any nutritional deficiency states (iron, folate and vitamin B12), diabetes mellitus, and any immune deficiencies should be excluded (Farah et al., 2010; Williams et al., 2011; McCollough & Salvage, 2005). Any pharmacologic agents that may contribute should be identified, and if practical, substituted for an alternative drug. Use of corticosteroid inhalers for asthma should be coupled with rinsing the mouth with water after each use (Williams et al., 2011).

ASPERGILLOSIS

Aspergillosis is the group of diseases caused by *Aspergillus*. The most common subtype among paranasal sinus infections associated with aspergillosis is *Aspergillus fumigatus* (*A. fumigatus*). In humans, the major forms of disease are; *Allergic bronchus pulmonary aspergillosis*, which affects patients with respiratory diseases such as asthma, cystic fibrosis, and sinusitis, *Acute invasive aspergillosis*, a form that grows into surrounding tissue, more common in those with weakened immune systems such as AIDS or chemotherapy patients, *Disseminated invasive aspergillosis*, an infection spread widely through the body, *Aspergilloma*, a "fungus ball" that can form within cavities such as the lung (Bozkurt et al., 2008).

In humans, the lungs are the most common location of *Aspergillus* infections but in domestic animals, the situation is different and varies between species. For example, in cows, the fore stomachs, especially the omasum, are mostly affected, from which the infection may spread to other organs, including the placenta (Garcia et al.,

2001a). A few cases of pulmonary involvement and later dissemination have been reported in dogs (Clercx *et al.*, 1996). Aspergillosis of the air passages is also frequently reported in birds, and certain species of *Aspergillus* have been known to infect insects (Geiser, 2009).

Etiology

Aspergillus was first described in 1729 and receives its name due to its resemblance to an aspergillum used to sprinkle holy water. A member of the family Trichocomaceae, *Aspergillus* species are closely related to another mold, *Penicillium*. However, identification of the causative organism responsible for most infections is usually not difficult, with four species responsible for the majority of illnesses. *A. fumigatus* is responsible for more than 90% of invasive disease in some reviews, with *Aspergillus flavus* (*A. flavus*), *Aspergillus terreus* (*A. terreus*), and *Aspergillus niger* (*A. niger*) responsible for the majority of remaining invasive aspergillosis cases (Patterson *et al.*, 2000).

Host risk factors

Risk factors for invasive aspergillosis may be associated with the changes in macrophage and neutrophil function, which may explain why infection mainly affects bone marrow and solid organ transplant recipients, Intensive Care Unit (ICU) patients, post-operative patients, those with chronic pulmonary diseases, patients with AIDS and patients on immune modulating drugs (TNF- α inhibitors), neutropenic patients, or those who have received corticosteroid treatment. Other risk group is patients with chronic granulomatous disease, drug user, patients with sarcoidosis, severe burn patients and alcoholics (Ascioglu *et al.*, 2002). *Aspergillus* can also develop when no risk factors are present. Thus, cases have been explained of community-acquired pneumonia due to *Aspergillus* in apparently immune competent patients (Franquet *et al.*, 2001) but it is likely that the patients had some undetected defect in macrophage and neutrophil function that allowed invasive infection to develop.

Malnutrition, vitamin deficiencies (especially vitamin A), long term antibiotic use, age (young or old) also contributes to the presentation of the disease, as well as trauma, dusty environments, lead poisoning and irritants of the airways like smoke of cigarette or ammonia (Washburn *et al.*, 1990).

Pathogenesis

Virulence factors

Aspergilli produce catalase, an enzyme that breaks down hydrogen peroxide (H₂O₂) to water and oxygen. The strong association of aspergillosis with chronic granulomatous disease (CGD) (Cohen *et al.*, 1981) provides indirect evidence that catalase is a virulence factor. *A. fumigatus* produces gliotoxin, a metabolite in the epipolythiodioxopiperazine family with a broad range of immunosuppressive properties. Gliotoxin inhibits macrophage phagocytosis (Eichner *et al.*, 1986), as well as T-cell activation and proliferation. It induces DNA fragmentation and programmed cell death (apoptosis) in macrophages by mechanisms apparently distinct from its antiphagocytic properties (Waring, 1990). It is not known whether clinically significant amounts of gliotoxin are produced in human disease. In a case report, concentrations of gliotoxin approximately 100 times greater than that needed for in vitro effects were found in a bovine udder infected with *A. fumigatus* (Bauer *et al.*, 1989).

In addition to gliotoxin, *A. fumigatus* produces an 18-kDa cytotoxin that acts by cleaving a phosphodiester bond of the 28S rRNA of eukaryotic ribosomes (Smith *et al.*, 1993).

Host defense

Antigen release evokes production of IgE, IgG and IgA antibody against the *A. fumigatus* and intense production of nonspecific total IgE. IgE mediated mast cell degranulation in the bronchi release mediators that would cause bronchospasm as well as permeability changes in the epithelium. Eosinophilic chemotactic factors cause pulmonary and peripheral blood eosinophilia IgG-*A. fumigatus*, IgA-*A. fumigatus* also causes activation of complement in the bronchi. It has been demonstrated that there occurs hyper releasability of histamine from basophils of ABPA patients (Ricketti *et al.*, 1983).

Preventive Measures

In developed countries, where regulations allow higher aflatoxin concentrations in animals, the agricultural industries have developed alternative approaches chemoprotection and enterosorption to limit biologically effective exposure without the high cost of preventing contamination. Chemoprotection is based on manipulating the biochemical processing of aflatoxin to ensure detoxification rather than preventing biological exposure. Enterosorption is based on the approach of adding a binding agent to food to prevent the absorption of the toxin while the food is in the digestive tract; the combined toxin-sorbent is then excreted in the feces. This approach has been used extensively and with great success in the animal feeding industry. (Williams *et al.*, 2004).

It has been shown that HEPA filtration can reduce or even eliminate *Aspergillus* spores from the air (Comet *et al.*, 1999). Caring for high-risk patients in rooms supplied with HEPA-filtered air has helped to prevent the acquisition of this infection within the hospital (Oren *et al.*, 2001), provided certain technical requirements are met. Components of a protected hospital environment should include a well-sealed room, HEPA filtration of incoming air, directed (or laminar) airflow within the room, positive room air pressure relative to the corridor, and high rates of room air exchange (Center for Disease Control and Prevention, 1997)

CRYPTOCOCCOSIS

Cryptococcosis is a rare fungal infection produced by inhalation of encapsulated yeast called *Cryptococcus neoformans*. *C. neoformans* can be found worldwide in soil, pigeon/bird, cat, dog, fox, monkey, cattle, horse, goat, and many other mammals' feces (www.doctorfungus.org, 2008). Recently, a differentiation has been made between two species, *Cryptococcus gattii* (*C.gattii*) and *C. neoformans*. This differentiation was made on the basis of genetic variation and a lack of evidence for genetic recombination between both gene types (Duncan *et al.*, 2006a, b). These genetic differences are consistent with differences in habitat, geographical distribution and, most importantly, in pathogenicity and the effectiveness of the response of the host immune system. *C.neoformans* infects predominantly immune compromised hosts, while *C. gattii* has not been associated with a suppressed immune system (Duncan *et al.*,2006a,b) and is mostly found on eucalyptus trees and in the soil (Traynor and Huffnagle, 2001; Duncan *et al.*,2006a).

The primary route of entry for *Cryptococcus* is via the lungs, where the fungus may establish a primary infection. If the initial pulmonary infection is not controlled, the fungus can disseminate to other organs and the central nervous system, resulting in fatal cryptococcal meningoencephalitis (Traynor and Huffnagle, 2001; Aguirre *et al.*, 2004; Chen *et al.*, 2007).

Human disseminated cryptococcosis has two unusual features that distinguish it from other disseminated fungal infections. First, patients have cryptococcal polysaccharide antigen in their body fluids, and detection of this is useful in diagnosis of the disease. Second, there is a limited inflammatory response in tissues harbouring *C. neoformans*. One could interpret these findings to mean that individuals with the highest levels of cryptococcal polysaccharide in their body fluids simply had higher number of organisms in their tissues and therefore were the most likely not to respond to antifungal therapy. Another interpretation could be that the cryptococcal polysaccharide had an adverse effect on host defence mechanisms, thus allowing a progressive disease, concluding that cryptococcal polysaccharide in the bloodstream exacerbates disease (Clemons *et al.*, 2000).

Clinical cryptococcosis has been reported worldwide in many animal species. It is the most common systemic fungal infection in cats and is often described in dogs (Duncan *et al.*, 2006b). In cats, *C. neoformans* is most commonly isolated from immunosuppressed individuals, whereas *C. gattii* is considered as primary pathogen because it infects immune competent hosts, even in areas where the organism is endemic (Duncan *et al.*, 2006a). In other animal species, cryptococcosis can appear to be related to immune depression, although not always. Then, have been described outbreaks of ovine and caprine cryptococcosis with respiratory signs, and without immune depression situation detected in those animals (Garcia and Blanco, 2000). In these cases, respiratory symptoms associated with cachexia were the predominant clinical picture; liver and brain involvement was also documented (Baro *et al.*, 1998).

Cryptococcosis may occur in horses as a disseminated cryptococcal infection with osteomyelitis of both the axial and appendicular skeleton produced by *C.gattii*. The administration of corticoids led to clinical deterioration due to immune modulating effects. Administration of systemic corticoids occurred after lesions had appeared; however, the horse deteriorated significantly after corticosteroid treatment (Lenard *et al.*, 2007).

Etiology

Cryptococcus spp. are fungi in the Division Basidiomycota. Although there are more than 30 species of *Cryptococcus*, only two organisms – *C. neoformans* and *C. gattii* (previously *C. neoformans* var. *gattii*) - commonly affect humans and animals. Other species including *C. laurentii*, *C. albidus*, *C. uzbekistanensis*, *C. adeliensis*, *C. curvatus*, *C. magnus*, *C. humicolus*, *C. luteolus*, *C. macerans*, *C. flavescens* and *C. uniguttulatus* have been found in clinical cases; however, this is rare. Of the latter group of organisms, *C. laurentii* and *C. albidus* have been described most often in people (The Center for Food Security and Public Health, 2013).

Host risk factors

C. neoformans also an opportunistic pathogen, which can cause cryptococcosis in patients with HIV infection and HIV-negative patients with immunological conditions predisposing to this fungal infection, such as a history of systemic corticosteroid therapy, immunosuppressive treatments, organ transplant, chronic organ failure (liver, lung, and kidney), malignancy, rheumatic diseases, systemic lupus erythematosus and diabetes mellitus (Casadevall *et al.*, 2008).

Pathogenesis

Virulence Factors

C. gattii and *C. neoformans* share many attributes that increase their ability to invade and survive in a host organism (Ellerbroek *et al.*, 2004). The main virulence factors identified in *C. gattii* to date include an outer polysaccharide capsule, melanin, mannitol, extracellular proteinase, products of the laccase pathway, superoxide dismutase, phospholipases, urease, and the STE12 transcription factor (a homologue of *Saccharomyces cerevisiae* STE12) that is present only in the mating type (Chang *et al.*, 2000). Other properties of *C. gattii* contribute to its infectivity such as its ability to grow at physiological temperature (Sorrel, 2001) its tolerance of low pH and elevated salt levels (Kidd *et al.*, 2007), and its ability to switch capsular phenotype (Jian *et al.*, 2006).

Host defenses

Clearance of *Cryptococcus* infection requires the development of a Th1-type CMI and the subsequent pulmonary recruitment and activation of leukocytes. The leukocytic infiltrate in response to *cryptococcal* infection includes a mix of myeloid and lymphoid cells, all of which are capable of inhibiting the growth of, or killing, the organism in vitro (Romani, 2004).

Neutrophils and macrophages are the two phagocytic cells in the natural host defence that are most likely to be responsible for clearing the *cryptococcal* cells from the tissues. There was very little inflammatory response, i.e. influx of neutrophils, lymphocytes and macrophages, into infected host tissues (Clemons *et al.*, 2000).

In this Th1-CMI, IFN-g, TNF-a, IL-2, IL-12, IL-15, IL-18, monocyte chemotactic protein-1, macrophage inflammatory protein-1a and nitric oxide have been shown to have important roles in murine models. GM-CSF plays a complex role in the development of anticryptococcal immunity in the lungs: it is required for early recruitment of leukocytes into the lung, movement of recruited leukocytes into the alveolar space and the formation of inflammatory foci in the lungs (Chen *et al.*, 2007).

The Th2 cytokines IL-4 and IL-5 were not secreted at significantly higher levels in *Cryptococcus*-infected brains of immune mice compared to control mice (Uicker *et al.*, 2005). CD4⁺ T-cells are critical for the control of *Cryptococcus*. An antigen-specific CD4⁺ T cell response occurs when the T cell receptor recognizes processed antigen fragments presented by MHC Class II. Then CD4⁺ T cells secrete cytokines and proliferate (Kwon-Chung *et al.*, 2000). Nevertheless, in the lung, both CD4⁺ and CD8⁺ T cells are required to clear the *cryptococcal* infection. If yeasts escape and colonize the brain, rapid proliferation leads to serious central nervous system disease. Work with severe T cell and B cell-deficient combined immune deficient mice and wild-type controls has demonstrated a CD4⁺ T cell-mediated resistance to *cryptococcal* organisms that colonize the brain. Depletion of CD8⁺ T cells had no detectable effect on T cell-mediated resistance in brain in vivo. In contrast, CD8⁺ T cells play a well-defined and important role in containment of pulmonary infection (Aguirre *et al.*, 2004).

Preventive measures

There is no vaccine available for cryptococcosis; thus, prevention through environmental condition control is vital. Reduction of aerosolization of the *C. neoformans* is key and should be done wetting or chemically disinfecting a region, then removing large accumulations of bird/animal droppings. Corticosteroid medications usage should be minimized to prevent cryptococcosis due to their tendency of exacerbating compromised patients conditions (<http://www.aidsmap.com/en/news>; McCarthy, 2006).

FUSARIOSIS

Fusarium spp. are important infectious filamentous fungi, second only to *Aspergillus* spp. These fungi are ubiquitous in the environment and are found in the soil and air. Interestingly, *Fusarium* spp. are primarily known as plant pathogens but can also infect humans and animals, causing superficial, locally invasive, and disseminated disease. (Nucci and Anaissie, 2007). Infection is mainly through inhalation of airborne conidia or via breaks in the skin due to trauma and/or burns. *Fusarium* spp. also produces toxins that can cause food poisoning through the consumption of toxin-contaminated food (Dignani & Anaissie, 2004).

In humans, *Fusarium* species cause a broad spectrum of infections, including superficial (such as keratitis and onychomycosis), locally invasive, or disseminated infections, with the last occurring almost exclusively in severely immunocompromised patients (Nucci & Anaissie, 2002). *Fusarium* species may also cause allergic diseases (sinusitis) in immunocompetent individuals (Wickern, 1993) and mycotoxicosis in humans and animals following ingestion of food contaminated by toxin-producing *Fusarium* spp. (Nelson *et al.*, 1994)

Etiology

More than 100 species of *Fusarium* have been identified, but only a few cause infections in humans (Alastruey *et al.*, 2008). *Fusarium solani* (*F. solani*) is the most frequent cause of invasive disease (in approximately half of all cases), followed by *F. oxysporum*, *F. moniliforme* (previously *F. verticillioides*), and *F. proliferatum* (Torres *et al.*, 2011). Other species that rarely cause infections in humans include *F. dimerum*, *F. chlamidosporum*, *F. sacchari*, *F. antophilum* and others. Fusarial keratitis is most commonly caused by *F. solani* (Doczi *et al.*, 2004), whereas fusarial onychomycosis is most commonly caused by *F. oxysporum* (Brilhante *et al.*, 2005; Godoy *et al.*, 2004; Ninet *et al.*, 2005).

Host risk factors

Neutropenia is one of the most important risk factors for acquiring fusariosis. Patients undergoing Hematopoietic Stem Cell Transplantation (HSCT) or solid organ transplantation, those with hematological malignancies or acquired immune deficiency syndrome (AIDS) and those taking pharmacological immunosuppressant therapies are at high risk for fusariosis. (Nucci *et al.*, 2004 & Enoch *et al.*, 2006).

Pathogenesis

Virulence Factors

Fusarium species possess several virulence factors, including the ability to produce mycotoxins, including trichothecenes, which suppress humoral and cellular immunity and may also cause tissue breakdown. In addition,

Fusarium species have the ability to adhere to prosthetic material and to produce proteases and collagenases (Nelson, 1994).

Host Defenses

The innate immunity plays a major role in the defense against mold infections (Shoham & Levitz, 2005). Macrophages and neutrophils damage fusarial hyphae, and their effect is primed by gamma interferon, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) (Gaviria *et al.*, 1999), and interleukin-15 (Winn *et al.*, 2005). The importance of T-cell defenses against *Fusarium* is illustrated by the occurrence of disseminated fusariosis in non-neutropenic HSCT recipients (Nucci *et al.*, 2004). These patients have severe T-cell immunodeficiency caused by multiple therapies for their underlying disease and for graft-versus-host disease (GvHD). Further supporting the importance of T-cell immunity and phagocytes is the major impact of corticosteroid therapy on the outcome of fusariosis, as shown by the much higher death rate among recipients of such therapy than among patients who were not receiving corticosteroids (Nucci *et al.*, 2003).

Preventive measures

General preventive measures that should be employed in patients at significant risk of invasive fusariosis, such as patients with hematologic malignancies undergoing induction chemotherapy or hematopoietic cell transplantation, include: Avoidance of activities associated with skin breakdown, avoidance of contact of areas of skin breakdown with tap water., Careful examination for and treatment of onychomycosis and paronychia and surgical debridement of infected wounds prior to commencing anti-cancer therapies, delaying severely immunosuppressive therapies until areas of skin breakdown are healed, when possible. (Nucci & Anaissie, 2007; Nucci & Anaissie, 2002).

Following appropriate air and water precautions during periods at risk. These include use of a high efficiency particulate air filter and positive pressure isolation rooms, avoiding contact with reservoirs of *Fusarium* spp, such as tap water, and having showers cleaned thoroughly prior to use by high-risk patients (Anaissie *et al.*, 2001; Anaissie *et al.*, 2002).

PNEUMOCYTIS

Pneumocystis carinii (*P. carinii*) is an opportunistic and widespread fungus found in the lungs of humans and other mammals. It can be the cause of severe pneumonia, especially in humans suffering from AIDS (Cailliez *et al.*, 1991). In the veterinary literature *P. carinii* pneumonia (PCP) has been reported in foals (Tanaka *et al.*, 1994) (especially Arabian foals with inherited severe combined immunodeficiency, in pigs (Kondo *et al.*, 1993) and in domestic goats. Only a few cases of *P. carinii* pneumonia have been reported in dogs, and most commonly among young animals (Furuta *et al.*, 1994). *P. carinii* was considered as a group of heterogeneous populations, genetically isolated from each other, that have undergone a prolonged process of genetic and functional adaptation to each mammalian species (Dei-Cas, 2000).

Further genetic analysis has shown that *Pneumocystis* isolated from different species has significant differences in gene sequence and chromosomes. This has prompted nomenclature changes and *P. carinii* is now reserved for the rat pathogen, *P. carinii* f.sp. *muris* for the murine pathogen, and *P. jiroveci* for the human pathogen (Steele *et al.*, 2005). It may be that this situation will be repeated in different animal species, like the description of the genetically different *P. canis* in dog (English *et al.*, 2001). *Pneumocystis* pneumonia is a well-recognized major opportunistic infection in HIV-positive individuals, and is growing in importance in HIV-negative patients undergoing immunosuppressive treatment for malignancy, connective tissue disease or organ transplantation.

In the veterinary field, *Pneumocystis* has been described as producing pneumonia in dogs, causing serious pulmonary alterations. *Pneumocystis* is important in horses, where treatment with immunosuppressive drugs, like corticoids, is a relatively frequent practice in animals.

Dedicated to sport, originating a pneumonic process with bronchopneumonic diffuse image. In pigs, this fungus gives rise to pneumonic processes, affecting animals 7–11 weeks old, with lung damage that includes a decrease of the size of the pulmonary septa with infiltration of mononuclear cells and appearance of exudates in the alveoli. This focal pneumonia evolves toward a diffuse pneumonia, very similar to what happens with this disease in children (Cavallini *et al.*, 2007). *Pneumocystis* infects hosts by a respiratory route, and animal-to-animal airborne transmission has been clearly established (Dumoulin *et al.*, 2000). In humans, the persistence of *Pneumocystis* in the lung is a limited-time phenomenon inversely related to immunological improvement. A normal immune response completely eradicates *Pneumocystis* from the host. However, immunocompetent hosts can be parasitized transiently by *Pneumocystis*: increased titres of *Pneumocystis* antibodies were detected in hospital staff in close contact with *Pneumocystis* pneumonia patients, and immunocompetent experimental hosts were parasitized transiently by *Pneumocystis* after close contact with hosts developing pneumonia by this fungus (Dei-Cas, 2000).

Etiology

Pneumocystis organisms were first reported and named *P. carinii* in the beginning of last century after recognition that pneumocystis organisms in different mammals are different, in 1994 an interim trinomial name change was adopted with the name *P. carinii* f.sp. *hominis* for pneumocystis infecting humans and *P. carinii* f.sp. *carinii* for

one of the two species infecting rats (The Pneumocystis Workshop, 1994). Finally, in 2002, by the recognition of its genetic and functional distinctness, human pneumocystis organism was renamed *Pneumocystis jiroveci*, in honour of Otto Jirovec, who is credited for describing the microbe in humans (Frenkel, 1999; Stringer *et al.*, 2002).

Host risk factors

Although not fully characterized, the known risk factors for *P.jirovecii* infection include impaired immunity because of HIV infection, hematologic malignancies, and connective tissue disorders (Roblot *et al.*, 2002).

Pathogenesis

Host defense

A host defense against Pneumocystis is indistinguishable from that observed for other medically important fungal pathogens of the lung (Steele *et al.*, 2005). As with fungal pathogens such as *A. fumigatus*, *C.neoformans* and *Histoplasma capsulatum*(*H. capsulatum*), alveolar macrophages are an essential component of the immune response against Pneumocystis and are ultimately responsible for clearing this fungus from the lungs (He *et al.*,2003; Steele *et al.*, 2005). CD4+ T cells are absolutely critical for resolution of Pneumocystis, having an essential role in the recruitment and activation of effector cells against the organism. CD8+ T cells by themselves do not aid clearance of Pneumocystis from the lungs (Dei-Cas, 2000; Traynor & Huffnagle, 2001)

IFN- γ is not absolutely required for clearing Pneumocystis from the lungs but is required for modulating the inflammation (Dei-Cas, 2000). B cells and/or Pneumocystis-specific antibody are important for clearance of Pneumocystis from the lungs. Antibodies against Pneumocystis are reported to be readily detectable in the early years of life, at ages similar to that reported for other pathogenic fungi such as *C. albicans* and *C. neoformans* (Goldman *et al.*, 2001; Steele *et al.*, 2005), and most data suggest that the organism is widely encountered in nature and that antibody production is part of the natural host response, predominantly of the IgG class, but also IgM. In this sense, many ELISA-based assays have been developed and employ a wide variety of Pneumocystis preparations and antigens to detect the presence of Pneumocystis-specific antibodies (Steele *et al.*, 2005).

Preventive Measures

Adults and adolescents who have HIV infection (including pregnant women and those on HAART) should receive Chemoprophylaxis against PCP if they have a CD4+ T-lymphocyte count of less than 200/ μ L or a history of or pharyngeal candidiasis (Phair *et al.*, 1990). Persons who have a CD4+ T-lymphocyte percentage of less than 14% or history of an acquired immunodeficiency syndrome (AIDS)-defining illness but do not otherwise qualify should be considered for prophylaxis (Kaplan *et al.*, 1998). When monitoring the CD4+ T-lymphocyte count at least every 3 months is not possible, initiation of chemoprophylaxis at a CD4+ T-lymphocyte count of greater than 200 but less than 250 cells/ μ L also should be considered (CDC, 1989).

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

The authors are thankful to library and ICT office of Madda Walabu University for providing the facilities to prepare this review paper.

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