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Candidiasis and opportunistic mycosis in human

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Abstract

Pathogenic fungi cause serious diseases in humans, plants and animals. These include mainly, *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Fusarium* spp., and *Pneumocytis* spp. *Candida* species cause infections in individuals with deficient immune systems, and Th1-type cell-mediated immunity (CMI) is required for clearance of this fungal infection. *Candida albicans* is an opportunistic pathogen of humans and has a parasexual cycle that appears to be stimulated by environmental stresses. *Aspergilli* represent the most common pathogenic species especially for *Aspergillus flavus* and *A. fumigatus*. *A. flavus* produces aflatoxins which act both as toxins and carcinogens, and can potentially contaminate foods. *A. clavatus* causes allergic disease of human; its symptoms include; fever, cough chest pain or breathlessness. *Cryptococcus neoformans* is one of the most effective human pathogens; it causes severe form of meningitis and meningo-encephalitis in patients with HIV infection and AIDS. *C. gattii* was endemic to tropical parts of Africa and Australia; cause disease in immunocompromised people. *Fusarium* spp. are important pathogenic mold fungi; second only to *Aspergillus* spp. *Fusaria* also produce toxins that could cause poisoning through consumption of toxin-contaminated foods. The aims of this review were to highlight the etiology, risk factors, pathogenesis, human defence and preventive measures of some of the most common fungal human pathogens, to avoid infections and their subsequent cause of fatal diseases.

Keywords: *Candida albicans*; *Cryptococcus gattii*; *Aspergillus* spp.; *Fusarium* spp.; *Pneumocytis* spp; human diseases

1. Introduction

Mycoses are conditions, where fungi pass the resistance barriers of humans and establish infections, thus cause a group of diseases with varied clinical manifestations (Blanco and Garci, 2008). Fungal infections (mycoses) lead to significant rates of morbidity and mortality worldwide, through causing mild to invasive diseases in humans (Beardsley *et al*., 2015). Velayuthan *et al*., (2018) pointed out that individuals with a dysfunctional immune system such as; immunecompromised patients with underlying HIV or AIDS infections, very young children, and elderly people were prone

to fatal fungal infections. In the current review we discussed a number of human diseases caused by potent pathogenic fungi.

2. Candidosis

Candida albicans (*C. albicans*) is a part of the normal microbial flora in human beings that is associated with the mucous surfaces of the oral cavity, gastrointestinal tract and vagina. An infection caused by *Candida* was termed Candidiasis or Candidosis. *Candida* infections were among the most common human mycoses (Edwards *et al*., 2015). *C. albicans* is a commensal yeast of humans; but was frequently the source of mucosal infections, and can in severe cases cause life-threatening systemic infections (Vylkova and Lorenz, 2014). Although fungi need pre-disposing factors to cause disease, it was known that saprophytic colonization of the mucous membrane by *C. albicans* did not need the host to be immune compromised, since it was detected in immune competent individuals (Okada *et al*., 2013).

2.1. Etiology

Candidosis was the most common fungal infection of the oral cavity, caused by an overgrowth of commensal *Candida* species. Although several studies have reported the epidemiology of Candida infections in China; they focused mainly on adults invasive *Candida* infections, or were conducted among special groups (Li *et al*., 2015). *C. albicans* was the most commonly isolated species in both healthy and diseased people. The emergence of *C. albicans* raised several serious concerns for public health. First, many isolates were multidrug-resistant, with some strains had elevated minimum inhibitory concentrations (MIC) to drugs in all three major classes of antifungal medications (Lockhart *et al*., 2016).

2.2. Host risk factors

2.2.1. Endocrine disorders

Diabetes mellitus (DM) might 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 and 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 (Kelly *et al*., 2015). Individuals with DM were more prone to *Candida* infections, particularly when host resistance was modified due to local factors such as; smoking and denture wearing (Rai *et al*., 2015). Many previous investigations confirmed that use of broad-spectrum antibiotics and prolonged antibiotic therapeutic duration, were the most common risk factors associated with neonatal Candidemia (Kelly *et al*., 2015).

2.3. Nutritional factors

Several nutritional deficiencies may result in a diminished host defense and loss of epithelial integrity, which may thus facilitate subsequent fungal invasion and infection (García-elorriaga and Rey-pineda, 2013). According to Tizard, (2013), iron deficiency anemia has been proposed as an important factor in the etiology of oral Candidosis. Later, Rai *et al*., (2015) added that decreased lymphocyte response to *Candida* antigens in some iron-deficient people, was associated with an increased frequency of *C. albicans* in the oral cavity, suggesting that iron deficiency might predispose to oral Candidosis by depressing human cell-mediated immunity. Earlier, Davenport *et al*., (2001) reported that deficiencies of vitamin B12 and folic acid might also predispose to oral Candidosis.

2.4. Immune defects and immunosuppression

Oral candidiasis was a common manifestation of a variety of immune deficiencies. Tsai *et al*., (2013)

stated that both humoral and cell-mediated immune systems participate in the prevention and elimination of Candidosis. Reduced or defective immune function increased susceptibility to such infections. In HIV infection, immunodeficiency affecting T-helper lymphocytes made the infected patients more predisposed to secondary infections, notably opportunistic Candidal infections (Kwamin *et al*., 2013).

2.5. High-carbohydrate diet

High-carbohydrate intake has been assumed to predispose to oral Candidosis. This was supported by in vitro studies which showed that the growth of Candida in the saliva was enhanced by glucose, despite the presence of a nutrient competing bacterial salivary flora (Ermert *et al*., 2013). Furthermore, the adhesive properties of C. albicans to oral epithelial cells, and to acrylic surfaces were augmented by dietary carbohydrates. In studies of Kelly *et al*., (2015) 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.

2.6. Pathogenesis

2.6.1. Virulence factors

Mycoses caused by several fungi such as Candida showed a wide spectrum of clinical presentations and can be classified as superficial; as with cutaneous and mucosal infections, to deep, widespread and of high severity, as was the case with invasive Candidiasis (Hirakawa *et al*., 2015). Candidiasis might be associated with hypha and pseudohypha formation (Ermert *et al*., 2013), phenotypic switching and phospholipase production (Sardi *et al*., 2013), and antigenic modulation as a result of pseudohypha formation (Ermert *et al*., 2013). Indeed, hypha formation was a recognized means of increased adherence and tissue invasion by *C. albicans*, as well as means of increased proteolytic enzyme elaboration and antigen modulation (Ermert *et al*., 2013).

In the multivariate logistic regression models, Kelly *et al*., (2015) found that mechanical ventilation affected the risk of Candidemia infection with non *C. albicans* isolates. Mechanical ventilation would play an important role in the pathogenesis of invasive Candidiasis because of abrading the respiratory mucosa, providing Candida species with a portal of entry into the bloodstream.

Extracellular membrane damaging phopholipases were considered virulence factors for *C. albicans* (Pinhati *et al*., 2016). Although these enzymes have not been studied extensively, phospholipase A and B and lysophospholipase-transacylase were produced by virulent but not avirulent (commensal) strains of *C. albicans*. These phospholipase-producing strains also adhered most strongly to the epithelial cells. Furthermore, productions of these phospholipases by clinical isolates were correlated with their pathogenicity. Another virulence factor of *C. albicans* was specific phenotypic instability, which allowed strains to switch colony phenotype without affecting the identifiable genotype; this was termed as "phenotypic switching" as reported by Ermert *et al*., (2013).

2.7. Host defenses

Clinically, importance of host defence was supported by the fact that neutropenic patients were particularly susceptible to systemic *C. albicans* infections. Fluconazole has been recommended as the best alternative antifungal drug for treatment of prophylaxis and patients with Candidemia, due to its efficacy and safety (Pinhati *et al*., 2016). T cells and cell-mediated immunity (CMI) on the other hand, formed the predominant host defense mechanism against mucosal *C. albicans* infection. This came from both of clinical observations (high incidence of mucosal candidiasis in patients with reduced CMI), and experimental studies which showed the critical role of T cells in protection against *C. albicans* mucosal infections (Rai *et al*., 2015).

2.8. Preventive measures

Nutritional deficiency states (i.e. iron, folate and vitamin B12), diabetes mellitus, and any other immune deficiencies should be excluded. Any pharmacologic agents that might be used should be identified. Moreover, use of corticosteroid inhalers for asthma should be coupled with rinsing the mouth with water after each use (Williams *et al*., 2011).

3. Aspergillosis

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

3.1. Etiology

Aspergillus was first described in 1729 and received its name due to its resemblance to an aspergillum used to sprinkle holy water. It is a member of the family Trichocomaceae. *Aspergillus* species were closely related to another mold, *Penicillium*, however, identification of the causative organism responsible for most infections was usually not difficult. Four *Aspergillus* species were responsible for the majority of illnesses; *A. fumigatus* was responsible for more than 90% of invasive diseases, *Aspergillus flavus* (*A. flavus*), *Aspergillus terreus* (*A. terreus*), and *Aspergillus niger* (*A. niger*) were responsible for the majority of remaining invasive cases of Aspergillosis (Rosbjerg *et al*., 2016).

3.2. Host risk factors

Risk factors for invasive Aspergillosis may be associated with changes in macrophage and neutrophil functions. This might explain why infections mainly affects bone marrow and organ transplant recipients, Intensive care unit (ICU) patients, post-operative patients, those with chronic pulmonary diseases, patients with AIDS, patients using immune modulating drugs (TNF-α inhibitors), neutropenic patients, or those who received corticosteroid treatments. Other groups under risk were; patients with chronic granulomatous disease, drug user, patients with sarcoidosis, severe burn patients and alcoholics (Ascioglu *et al*., 2002).

Aspergillosis can also develop when no risk factors were present. Thus, cases have been encountered with community-acquired pneumonia due to *Aspergillus* in apparently immune competent patients (Franquet *et al*., 2001). However, it was likely that these patients had some undetected defects in macrophage and neutrophil function that allowed invasive infection to develop.

Contou *et al*., (2016) added that, malnutrition, vitamin deficiencies (especially vitamin A), long term antibiotic use, age (young or old), trauma, dusty environments, lead poisoning, and irritants of the lungs such as smoke of cigarette or ammonia, also contributed to the presentation of the disease.

3.3. Pathogenesis

3.3.1. Virulence factors

Aspergilli produce catalase, an enzyme that breaks down hydrogen peroxide (H_2O_2) to water and oxygen. The strong association of Aspergillosis with chronic granulomatous disease (CGD) (Cohen *et al*., 1981), provided indirect evidence that catalase was a virulence factor. Epipolythiodioxopiperazines (ETPs) were toxic secondary metabolites made only by fungi. The best-known ETP was gliotoxin produced by *A. fumigatus*, which appeared to be a virulence factor associated with invasive

Aspergillosis of immunocompromised patients. Gliotoxin inhibits macrophage phagocytosis, as well as T-cell activation and proliferation (Eichner *et al*., 1986). It induced DNA fragmentation and programmed cell death (apoptosis) in macrophages, by mechanisms apparently distinct from its anti-phagocytic properties. It was unknown whether clinically significant amounts of gliotoxin were produced in human diseases. In addition to gliotoxin, *A. fumigatus* produced an 18-kDa cytotoxin that acted by cleaving a phosphor-diester bond of the 28S rRNA of eukaryotic ribosomes (Smith *et al*., 1993).

3.3.2. Host defence

Antigen release evoked production of IgE, IgG and IgA antibodies against *A. fumigatus*, and intense production of nonspecific total IgE. IgE caused mast cell degranulation in the bronchi, with released mediators that would cause bronchospasm as well as permeability changes in the epithelium. Eosinophilic chemotactic factors caused pulmonary and peripheral blood eosinophilia. IgG-*A. fumigatus*, IgA-*A. fumigatus* also caused activation of complement in the bronchi (Schmidt *et al*., 2014).

3.4. Preventive measures

In developing countries, where regulations allow higher aflatoxin concentrations in animals feed, the agricultural industries have developed alternative approaches to decrease levels of aflatoxins with low cost such as; chemoprotection and enterosorption. Chemoprotection was based on manipulating the biochemical processing of aflatoxins, to ensure detoxification rather than preventing biological exposure. Whereas, enterosorption was based on adding a binding agent to food to prevent the absorption of this toxin, while the food was still in the digestive tract; the combined toxin-sorbent was 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 high-efficiency particulate air (HEPA) filtration can reduce or even eliminate *Aspergillus* spores from the air (Comet *et al*., 1999). Oren *et al*., (2001) added that caring for high-risk patients in rooms supplied with HEPA-filtered air had helped to prevent the acquisition of this infection within the hospital, provided that certain technical requirements were met. Components of a protected hospital environment should include; a well-sealed room, HEPA filtration of incoming air, directed airflow within the room, and high rates of room air exchange (CDCP. 1997).

4. Cryptococcosis

Cryptococcosis was a rare fungal infection produced by inhalation of encapsulated yeast called *Cryptococcus neoformans*. *C. neoformans* can be found worldwide in soil, pigeon/bird, cat, and many other mammals' feces. Recently, a differentiation has been made between two species, *C. gattii* and *C. neoformans*. This differentiation was made on the basis of genetic variation, and lack of evidence for genetic recombination between both gene types (Cadieux *et al*., 2013). These genetic variations were consistent with differences in; habitat, geographical distribution, and most importantly in pathogenicity and effectiveness of the response of the host immune system. *C. neoformans* infected predominantly immune compromised hosts. *C. gattii* has not been associated with a suppressed immune system (Duncan *et al*., 2006a, b), however, was mostly found on eucalyptus trees and in the soil (Cadieux *et al*., 2013).

Traynor and Huffnagle, (2001); Chen *et al*., (2007) reported that the primary route of entry for Cryptococcus was via the lungs, where the fungus might established a primary infection. If this initial pulmonary infection has not been controlled, the fungus could be disseminated to other organs and to the central nervous system, resulting in fatal cryptococcal meningoencephalitis.

Human disseminated Cryptococcosis had two unusual features that distinguish it from other disseminated fungal infections. First, patients had Cryptococcal polysaccharide antigen in their body fluids, and detection of this antigen was useful in diagnosis of the disease. Second, there was a limited inflammatory response in tissues harboring *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 this microorganism 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 the host defence mechanisms, thus its presence in the bloodstream exacerbates disease (Clemons *et al*., 2000).

4.1. Etiology

Cryptococcus spp. are fungi in the Division Basidiomycota. Although there were more than 30 species of *Cryptococcus,* only two of them including; *C. neoformans* and *C. gattii* commonly affected human 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* had been recorded in clinical cases; however, this was rare (The Center for Food Security and Public Health. 2013).

4.2. Host risk factors

C. neoformans was 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; systemic corticosteroid therapy, immunosuppressive treatments, organ transplant, chronic organ failure, malignancy, rheumatic diseases, and diabetes mellitus (Casadevall *et al*., 2008).

4.3. Pathogenesis

4.3.1. Virulence factors

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

4.3.2. Host defences

Clearance of *Cryptococcus* infection requires the development of a T Helper Cell Type 1 cell-mediated immunity (Th1-type CMI), and the subsequent pulmonary recruitment and activation of leukocytes. The leukocytic infiltrate in response to Cryptococcal infection included a mixture of myeloid and lymphoid cells, all of which were capable of inhibiting the growth of/ or killing the microorganism *in vitro* (Leongson et al., 2013). Neutrophils and macrophages were the two phagocytic cells involved in the natural host defence; that most likely were responsible for clearing the Cryptococcal cells from the tissues. There was very little inflammatory response, i.e. influx of neutrophils, lymphocytes, and macrophages into the infected host tissues (Clemons *et al*., 2000).

In this T Helper Cell Type 1 cell-mediated immunity (Th1-CMI), interferon (IFN-g), tumor necrosis factor (TNF-a), interleukin (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. According to Chen *et al*., (2007), Granulocyte-macrophage colony-stimulating factor

(GM-CSF) played a complex role in the development of anti-Cryptococcal immunity in the lungs. It was required for early recruitment of leukocytes into the lung, movement of recruited leukocytes into the alveolar space, and for the formation of inflammatory foci in the lungs.

4.3. Preventive measures

There was no vaccine available for Cryptococcosis, thus prevention through control of environmental condition was vital. Reduction of aerosolization of *C. neoformans* was a vital key; which should be done through wetting or chemically disinfecting a region, and 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 (McCarthy, 2006).

5. Fusariosis

Fusarium spp. were important infectious mold fungi, second only to *Aspergillus* spp. These fungi were ubiquitous in the environment, and were found also in the soil and air. Interestingly, *Fusarium* spp. were primarily known as plant pathogens; but they can also infect humans and animals causing superficial, locally invasive, and disseminated diseases (Nucci and Anaissie, 2007). Infection take place mainly through inhalation of airborne conidia, or via breaks in the skin due to trauma and/or burns. Earlier, Dignani and Anaissie, (2004) pointed out that *Fusarium* spp. also produced toxins that could cause food poisoning through consumption of toxin-contaminated food.

In humans, *Fusarium* sp. caused broad spectrum of infections including; superficial (i.e. keratitis and onychomycosis), locally invasive or disseminated infections, with the last occurring almost exclusively in severely immunocompromised patients (Nucci and Anaissie, 2002). In addition, *Fusarium* sp. may also cause allergic diseases (sinusitis) in immunocompetent individuals (Wickern, 1993), and mycotoxicosis in humans and animals following ingestion of food contaminated with *Fusarium* spp. mycotoxin (Nelson *et al*., 1994).

5.1. Etiology

More than 100 species of Fusaria have been identified, but only few can cause infections in humans (Alastruey-Izquierdo *et al*., 2008). *F. solani* was the most frequent cause of invasive disease, followed by *F. oxysporum*, *F. moniliforme* (previously *F. verticillioides*), and *F. proliferatum* (Torres and Kontoyiannis, 2011). Other species that rarely caused infections in humans include; *F. dimerum*, *F. chlamidosporum*, *F. sacchari* and *F. antophilum*. Fusarial keratitis was most commonly caused by F. solani (Doczi *et al*., 2004), whereas Fusarial onychomycosis was caused by *F. oxysporum* (Brilhante *et al*., 2005; Ninet *et al*., 2005).

5.2. Host risk factors

Neutropenia was one of the most important risk factors for acquiring Fusariosis. Patients undergoing Heamtopoetic stem cell transplantation (HSCT), solid organ transplantation, those with hematological malignancies or acquired immune deficiency syndrome (AIDS), and those taking pharmacological immunosuppressant therapies were at high risk for Fusariosis (Nucci *et al*., 2004; Enoch *et al*., 2006).

5.3. Pathogenesis

5.3.1. Virulence factors

Fusarium species possessed several virulence factors including the ability to produce mycotoxins such as trichothecenes, which suppressed human oral and cellular immunity, and might also cause tissue breakdown. In addition, *Fusarium* species have the ability to adhere to prosthetic material, and to produce proteases and collagenases (Nelson *et al*., 1994).

5.3.2. Host defences

The innate immunity played a major role in the human defence against mold infections (Shoham and Levitz, 2005). Macrophages and neutrophils damaged Fusarial hyphae, and their effect was primed by gamma interferon, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-15 (Winn et al., 2005). The importance of T-cell defences against *Fusarium* was illustrated by the occurrence of disseminated Fusariosis in non-neutropenic hematopoietic stem cell transplantation (HSCT) recipients (Nucci *et al*., 2004). These patients had severe T-cell immunodeficiency caused by multiple therapies for their underlying disease, and for graft-versus-host disease (GvHD). Further evidence supporting the importance of T-cell immunity and phagocytes was 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).

5.4. Preventive measures

General preventive measures that should be employed in patients at significant risk of invasive Fusariosis 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 prior to commencing anti-cancer therapies, delaying severely immunosuppressive therapies until areas of skin breakdown were healed (Nucci and Anaissie, 2002; 2007). In addition to following appropriate air and water precautions during periods of high risk including; use of a high efficiency air filters, avoiding contact with reservoirs of *Fusarium* spp. such as tap water, and having showers cleaned prior to use by high-risk patients (Anaissie *et al*., 2001; 2002).

6. Pneumocytis

Pneumocystis carinii (*P. carinii*) was an opportunistic and widespread fungus found in the lungs of humans. It might be the cause of severe pneumonia, especially in humans suffering from AIDS (Cailliez *et al*., 1991). Pneumocystis pneumonia was a well-recognized major opportunistic infection in HIV-positive individuals, and was growing in importance in HIV-negative patients undergoing immunosuppressive treatments. *P. carinii* was considered as a group of heterogeneous populations, genetically distinct from each other's (Dei-Cas, 2000).

The persistence of *Pneumocystis* in the human lung was 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 after close contact with hosts infected by this fungus (Dei-Cas, 2000).

6.1. Etiology

Pneumocystis were first reported and named *P. carinii* at the beginning of last century, after recognition that these microorganisms were different in various mammals. In 2002, by the recognition of their genetic and functional distinctness, human pneumocystis microorganism was re-named as Pneumocystis jiroveci as reported by Frenkel, (1999); Stringer *et al*., (2002).

6.2. Host risk factors

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

6.3. Pathogenesis

6.3.1. Host defence

A host defence against Pneumocystis was indistinguishable from that observed for other medically important fungal pathogens of the lung (Steele *et al*., 2005). As with other fungal pathogens such as; *A. fumigatus*, *C. neoformans* and *Histoplasma capsulatum* (*H. capsulatum*), alveolar macrophages were essential components of the immune response against Pneumocystis infection, and were also responsible for clearing this fungus from the lungs (He *et al*., 2003; Steele *et al*., 2005).

Antibodies against *Pneumocystis* were reported by Goldman *et al*., (2001); Steele *et al*., (2005) to be readily detectable in the early years of human life, at ages similar to that reported for other fungal pathogens such as *C. albicans* and *C. neoformans*. Most data suggested that this microorganism was widely encountered in nature, and that antibody production was part of the natural host response, predominantly through the IgG and IgM classes. In this sense, many ELISA-based assays have been developed and employed a wide variety of Pneumocystis preparations and antigens, to detect the presence of Pneumocystis-specific antibodies (Steele *et al*., 2005).

6.4. Preventive measures

Adults and adolescents who have HIV infections should receive chemoprophylaxis against *P. carinii*, if they have a CD4+ T-lymphocyte count less than 200/µl, or had a history of or pharyngeal candidiasis (Phair *et al*., 1990). If monitoring the CD4+ T-lymphocyte count at least every 3 months was not possible, initiation of chemoprophylaxis at a CD4+ T-lymphocyte count greater than 200 but less than 250 cells/µl should be considered (CDC, 1989).

Conflict of interests

The authors declare that they have no conflict of interests.

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