REVIEW ARTICLE

SPECTRUM OF ASPERGILLOSIS: PATHOGENESIS, RISK FACTORS AND MANAGEMENT

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ABSTRACT

This article reviews comprehensively the spectrum of diseases (aspergillosis) caused by *Aspergillus spp*, the commonest pathogenic form being the *A.fumigatus*. *Aspergilus spp* are ubiguitous in the environment and the respiratory tract is the portal of entry in most cases. Aspergillosis is associated with significant mortality and morbidity, the prevalence appears to be on the increase. About 10million people are at risk of aspergillosis, and 50% would die even with treatment. Immunodeficiency, especially neutropenia is central to the pathogenesis of aspergillosis. Diseases caused by *A. fumigatus* include;1) Invasive aspergillosis seen mostly in stem cell and organ transplant recipients, patients with haematological malignancies, cancer patients on chemotherapy and patients with AIDS. Invasive aspergillosis is life threatening, it affects the lungs and sinuses but could disseminate to affect the CNS, eye, skin and kidney. 2) Chronic pulmonary Aspergillosis occurs in the setting of previous cavitatry lung disease, most commonly tuberculous infections. 3) Allergic bronchopulmonary aspergillosis (ABPA) affects people with asthma and cystic fibrosis. *A. fumigatus* is also implicated in the exacerbation of asthma. The clinical symptoms of aspergillosis depend on the type and the systems affected; respiratory symptoms are more common as the respiratory tract is disproportionately affected in aspergillosis. Diagnostic features and treatment also depends on the type of aspergillosis. Diagnostic testing for aspergillosis includes radiologic tests, culture tests, galactomannan testing in body fluids, immunologic tests to detect*Aspergilus* -specific immunoglobulins. Treatment modalities include surgery, use of antifungals and immunomodulatory therapy with cytokines.

SPECTRE DE L'ASPERGILLOSE: PATHOGENESE, LES FACTEURS DE RISQUES ET LA GESTION.

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RÉSUMÉ

Ce document, comprehensivement, fait un compte rendu du spectre des maladies (aspergillose) causées par *Aspergillus spp.*,la plus courante de la forme pathogénique était le *A. fumigatus* . *L'Aspergillus spp*estomniprésent dans l'environnement et dans la plupart des cas, les voies respiratoires sont les portails d'entrée. L'aspergillose est associe à un significatif de mortalités et morbidité, la prévalenceparait d'être en augmentation. A peu près 10 million des personnes sont en danger d'aspergillose et 50% mourrait même avec le traitement, déficience immunologique en particulierneutropénie est centrale àla pathogenèse de l'aspergillose. Les maladies causées par *A. fumigatus*comprennent :

1. L'aspergillose invasive qui est trouvé principalement dans les cellules souches et des receveurs de greffes d'organes, les maladies avec les magnites hématologiques, les patients cancéreux sous chimiothérapie et les patients atteints du SIDA. L'aspergillose invasive est dangereuse pour la vie. Il affecte les poumons et les sinus, mais pourrait diffuser à affecter le système nerveux central, l'œil, la peau et le rein.
2. L'aspergillose pulmonaire chronique se produit dans le cadre de la malade de poumon précédente, fréquemment les infections tuberculeuses.
3. L'aspergillose broncho – pulmonaire allergique (ABPA) affecte les gens atteints d'asthme et mucoviscidose. *L'A.fumigatus* est aussi compris dans l'exacerbation d'asthme.

Le symptôme clinique d'aspergillose dépend du type et les systèmesaffectés ; les symptômes respiratoires sont plus courants la voie respiratoire est affectée de manière disproportionnée dans l'aspergillose. Les caractéristiques diagnostiques et traitement dépendent aussi du type d'aspergillose. L'analyse diagnostique pour l'aspergillose comprend les tests radiologiques, testes culture, le test galactomannan pour fluides organiques, testes immunologique pour détecter

l'Aspergillus – **immunoglobuline spécifique. Les modalités de traitement comprennent la chirurgie, l'usage des antifongiques et la thérapie avec des cytokines immuno modulatrices.**

1. INTRODUCTION

Fungal infections have become very prevalent with associated increase in mortality and morbidity. This is especially so for life-threatening invasive fungal infections as a result of increase in immunodeficiency disorders such acquired immune deficiency syndrome (AIDS), cancer and cancer treatment, and immunosuppressive therapy following transplantation. The result of these is an increased risk of invasive aspergillosis which has a mortality of 30% even with treatment [1,2]. *Aspergillus* also complicates other chronic medical conditions; allergic bronchopulmonary aspergillosis affects people with asthma and cystic fibrosis while chronic pulmonary aspergillosis occurs in the setting of previous tuberculosis infection.

Aspergilli are saprophytic fungi found worldwide in soil and decomposing vegetable materials. There are over 350 accepted species of Aspergillus, and the commonest disease-causing species is *A.fumigatus*, followed by the *A. flavus*. Other disease-causing species include *A. amstelodani,A. terreus,A. niger,A. avenaceus*, and *A.nidulans* [3]. *A. fumigatus* is fast growing and sporulates abundantly, and the spores or conidia are released into the environment. The conidia is small(about 2-3um in diameter) , and can withstand extreme atmospheric condition because of their outer protein coat being hydrophobic. The fungus is thermophilic; it can grow at temperatures of up to 77^0C, but grows best at ~ 37^0C.

The respiratory system is disproportionately affected by deep-seated fungal infections. *A. fumigatus* is the most prevalent airborne fungal pathogen[4]. *Aspergillus* spp. cause a wide spectrum of pulmonary infections including acute invasive, chronic and allergic, as well as implantation disease such as fungal keratitis. This review highlightsthe pathogenesis, risk factors, clinical features, diagnosis and treatment of diseases caused by *A. fumigatus* as reported in literature.

2. VIRULENCE FACTORS OF A.FUMIGATUS

The ability of fungi to cause disease and their virulence factors are borne out of strategies to overcome and survive in the harsh environment of the host. Primary pathogens cause disease in immunocompetent hosts; A. *fumigatus* is an opportunistic pathogenand cause disease in immunocompromised persons. This distinction however, is not clear cut, as primary pathogens such as *C. immitis* may cause virulent disease in immunocompromised persons and opportunistic fungi such as*C. neoformans* may occasionally cause disease in immunocompetent persons.

*A .fumigatus*is able to cause disease by a number of virulence factors. These factors include structures (adhesins) that enable them to adhere to tissues so as to avoid being cleared or swept away by ciliary movement or mucous. Conidia of *A.fumigatus* are covered with hydrophobic proteins known as rodlets. These rodlet proteins are encoded for by RODA and RODB genes and, mediate adhesion of the conidia to albumin and collagen. Receptors on the surface of hyphae include galactomannan and chitin of *A. fumigatus* which mediate adhesion to complement, fibrinogen, immunoglobulin, and surfactant A and D[4]. Ability to grow at elevated temperature is another virulence factor. Fungi that cause systemic infections are able to grow at body temperature and even at febrile temperatures of 38-42^0C. *A. fumigatus* is particularly thermophilic, and can grow at temperatures of up to 55-77^0C[5]. HSP 70 is thought to be required by fungi to adapt to high temperatures [6].

A.fumigatus secretes proteases (serine and aspartic protease, metalloprotease) and phospholipases which degrade elastin present in lung tissue. The serine proteases degrade collagen, fibrin and fibrinogen [7]. Production and release of degradative enzymes enable them to establish disease and disseminate, and also protects from the effects of oxidation. *A. fumigatus* produces three catalases; Cat- A associated with conidia, and Cat 1p and Cat 2p associated with hyphae [4] as well as superoxide dismutases (containing Mn, Cu and Zn) that protect it from oxidative damage [8].Melanin is also synthesised by *A. fumigatus* from acetate using a 6 genes pathway [4].Melanin protects against harsh conditions and ROS [8].The ability to obtain Fe from the storage or transport forms in the host is another virulence factor.*A. fumigatus* uses three mechanisms of Fe uptake; reductase Fe uptake, siderophore-mediated Fe uptake and ferrous Fe uptake mechanisms [9]. *A. fumigatus* secretes a number of toxins such as aflatoxin and gliotoxin. Aflatoxin does not have any bearing on virulence of *A. fumigatus*, it is hepatotoxic and carcinogenic. Gliotoxin is immunosuppressive and inhibits phagocytosis by macrophages and T-cell activation [7]. It also slows ciliary movement thus making it difficult for the fungal cells to be swept away, and causes damage to the epithelia [10]. Calcineurin acts as a sensor for*A. fumigatus*, it is said to influence the expression of several virulence factors [11].

TABLE I: VIRULENCE FACTORS OF PATHOGENIC ASPERGILUS SPP.

VIRULENCE FACTOR	ROLE IN PATHOGENICITY	REFERENCE
Galactomannan, Chitin , Rodlet	Adhesion	4
Proteases and Phospholipases	Degradation of elastin in lung tissue and tissue damage	7
Catalases and SOD	Protection from oxidative damage	4,8
Melanin	Protection from oxidative damage and harsh conditions	4,8
Fe-siderophores (Sid-A genes)	Fe uptake and growth.	9
Gliotoxin	Immunosuppression	7,10
Calcineurin CNAA-gene	Growth of fungi and tissue invasion	11
Ability to grow at 37-42^{0}C	Survival in host tissue, ability to cause systemic infection	5,6

3. DISEASES CAUSED BY *ASPERGILLUSSPECIES* (ASPERGILLOSIS)

The portal of entry in most cases is the respiratory tract. Humans inhale conidia in the environment which can get to the lung alveoli because of their small size and hydrophobic coat (aerodynamics) [12]. However, most immunocompetent persons are able to eliminate the spores by innate immune mechanisms. Those who are at great risk of developing disease are people with immune defects such as patients with neutropenia, and people with neutrophil and macrophage dysfunction. Other susceptible hosts are patients on chemotherapy and long term corticosteroid therapy, patients with haematological malignancies such as leukaemia, bone marrow transplant recipients, solid organ transplant recipients and AIDS patients. Apart from immunosuppression, steroids have been shown to accelerate the growth rate and doubling time of *A. fumigatus* [3]. The diseases caused by *A. fumigatus* are invasive aspergillosis, chronic pulmonary Aspergillosis (including aspergilloma), and allergic bronchopulmonary aspergillosis (ABPA). *A. fumigatus* is also implicated in the exacerbation of asthma [13].

3.1CHRONIC PULMONARY ASPERGILLOSIS (CPA)

CPAis also known as pulmonary aspergillosis with cavities. CPA occurs in immunocompetent people who have had previous cavitatry lung diseases, with tuberculosis being the underlying disease in most cases[14, 15]. About 30-44% of patients with CPA had underlying TB [15, 16]. Other predisposing diseases are sarcoidosis [17], bronchiectasis, pulmonary infarcts, lung abscesses, bronchial cysts [18], ABPA, emphysema, prior treated lung CA [16] and cavities formed by other fungal infections [19, 20]. CPA occurs in different forms; *chronic cavitatry pulmonary aspergillosis* (CCPA), *chronic fibrotic pulmonary aspergillosis* (CFPA), and *pulmonary aspergilloma*. *Chronic necrotising pulmonary aspergillosis* (CNPA) involves hyphal invasion of tissues and is thus considered as a sub-acute form of IPA, it occurs in people with mild impairment of immunity such as defects in mannose binding lectin (MBL), diabetes mellitus (DM) and corticosteroid use[21, 22]. Patients with CCPA have multiple cavities which increase over time by expansion or formation of new cavities. Pulmonary aspergilloma occurs as fungal balls in CCPA. CFPA is the end result of CNPA or more commonly untreated CCPA, there is marked fibrotic reaction within the cavities [21].

In pulmonary aspergilloma, *A. fumigatus* over grows on the surface of these cavities forming a spheroidal mass of hyphae with inflammatory cells, fibrin, mucous and tissue debris. These appear as intracavitatry spherical structures with a surrounding area of translucency on radiographs [18]. Complex pulmonary aspergilloma may be synonymous with CCPA, though not all CCPA contain fungal balls [21]. Simple pulmonary aspergilloma occur as isolated thin-walled cysts in persons who do not have any underlying lung disease, this makes up about 18% of pulmonary aspergilloma cases [14]. *A. fumigatus* colonising the bronchial tree is said to secrete digestive enzymes which creates space for the fungal ball to grow [23].

The commonly affected site is the upper lobe, and some patients may be asymptomatic with the disease picked up during routine chest radiograph. It frequently affects middle-aged people with a predominance of males [14, 21]. However, symptomatic persons present frequently with haemoptysis, with bleeding from the bronchial arteries that is usually self-limiting [24]. Local invasion of these blood vessels or the release of endotoxin or trypsin-like proteolytic enzymes is said to cause haemoptysis [18]. Recurrent large volume haemoptysis is associated with poor outcome. Other symptoms are cough, dyspnoea, chest pain, malaise, shortness of breath, and weight loss [21]. Diagnostic features include radiologic demonstration of 1 or more cavities and/or fungal balls, precipitating antibodies to *A. fumigatus*, and positive culture tests.

The outcome of patients with CPA depends on the presence and severity of underlying lung condition, the fungal balls do not respond to antifungals. Amphotericin B and itraconazole show some benefits and IFN-γ is used as an adjunct [21]. Increasing *Aspergillus*-specific IgG titre, size and number of lesions are associated with poor outcome [18]. Treatment is thus surgical involving lobectomy or resection [15]; however, there could be recurrence [14] and associated post-operative complications such as pleural aspergillosis, fistula, respiratory failure or disseminated disease [15, 25-27]. The annual mortality rate of CPA is 15% (range 5-25%) and patients usually die from respiratory failure or pneumonia [18]. Factors which have been associated with poor prognosis include severe underlying lung disease and recurrent haemoptysis [14].
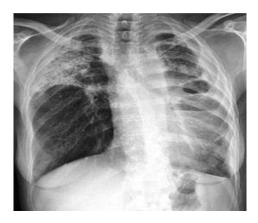

FIGURE I CHRONIC PULMONARY ASPERGILLOSIS Severe bilateral chronic pulmonary aspergillosis with the left upper lobe replaced by one large and several smaller cavities and a fluid level (which on aspiration grew a pure growth of Aspergillusfumigatus). There is also extensive disease of the right upper lobe with a more consolidation-type appearance, but containing multiple small cavities.© LIFE @http://life-worldwide.org

3.2ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

ABPA is a severe allergic pulmonary disease seen commonly in patients with cystic fibrosis and asthma, with an incidence estimated to be about 2.5% in adults with asthma from five referral cohorts[28, 29]. It is a hypersensitivity reaction to *Aspergillus* antigens, about 28% of asthmatic are shown to be sensitised to the antigens from studies done[30,31]. Sensitisation to *Aspergillus* antigen apart from increasing the risk for ABPA increases the severity of asthma in this group of people. Among patients with cystic fibrosis the presence of atopy predisposes to the development of ABPA [32]. ABPA has also been described in people with

allergic fungal sinusitis [28], chronic granulomatous disease and hyper IgE syndrome [34].

Central to the pathogenesis of ABPA is an IgE-mediated hypersensitivity reaction and specific IgG-mediated type III hypersensitivity reaction[35]. Impaired mucociliary action in CF, and inflammation in the airways in asthma makes the inhaled *Aspergillus* allergens to persist. *Aspergillus* attaches and grows on the bronchial epithelial cells, producing allergens including several proteases and these proteases detach the epithelial cells and elicit release of pro-inflammatory mediators [36]. These mediators cause damage to the airways over years resulting in bronchiectasis, and recruitment of inflammatory cells [37]. There is also a specific Th-2 CD4+ response seen in people with ABPA [38]. There seem to be some genetic predisposition to ABPA as familial clustering has been shown amongst asthmatics and cystic fibrosis patient, about 5% of ABPA patients showed familial clustering in one study [39,40]. The cystic fibrosis Trans membrane regulator (CFTR) gene is also thought to have an etiologic role in ABPA in cystic fibrosis patients[41,42].

ABPA presents clinically as worse asthma with wheezing, pleuritic chest pain, fever, and expectoration of brown mucus plugs [43]. Diagnostic criteria of ABPA in asthmatics are increased levels of allergen specific IgE and total serum IgE (>417kIU/L), pulmonary infiltrates on chest radiograph, and proximal bronchiectasis. This group of ABPA patients are known as ABPA – central bronchiectasis. Most ABPA patients also have a positive skin reactivity test to *Aspergillus* antigens, increased serum specific IgG antibodies and eosinophilia [43, 44]. A second diagnostic group of ABPA patients has all features except central bronchiectasis; this group is known as ABPA-seropositive. The diagnostic criteria for ABPA in cystic fibrosis is slightly different, a worsening of clinical condition is one of them, central bronchiectasis is not a criterion and the total serum IgE concentration should be > 1000kIU/L [44].

There are five stages described for ABPA based on radiographic infiltrates and total serum IgE; stage I is the acute stage with infiltrates in the upper or lower lobe involvement and a markedly elevated IgE. Stage II is a remission stage without infiltrates and a normal or elevated IgE, while stage III is an exacerbation stage with features same as the acute phase. Patients with infiltrates could also be in stage IV when they have corticosteroid –dependent asthma, and stage V is the end stage with fibrotic or cavitatry lesions [45]. Both oral and inhaled steroids are used to reduce the inflammation in ABPA[44]. Antifungals such as itraconazole are given concomitantly to eradicate fungal growth in the

lung and minimise the production of allergens, reducing inflammation, and risk of invasive aspergillosis [46,47].

3.3 SEVERE ASTHMA AND *A. FUMIGATUS*

Some patients with asthma tend to have more severe symptoms than others, this is characterised by prolonged hospital stay and increased use of bronchodilators. Fungal sensitisation has been linked to severe asthma, although many fungal allergens may cause this, *Aspergillus* allergens are important in the exacerbation of asthma [13,48]. *A. fumigatus* is a major indoor aeroallergen [49], with proteases which are implicated in the hypersensitivity reactions in the lung [50]. This *Aspergillus* protease has also been shown to cause damage to the airway epithelium, and release of inflammatory cytokines-IL6 and IL8 [51]. *Aspergillus* specific Serum IgG antibody level which is a diagnostic feature for aspergillosis was found to be associated with severe asthma [52].

3.4 INVASIVE ASPERGILLOSIS

Invasive aspergillosis (IA) commonly affects people with neutropenia with the risk for IA more after the third week of the neutropenia. It is seen in immunosuppressed people such as those on chemotherapy and/or long-term steroids, recipients of bone marrow transplant or solid organ transplant, with those who receive heart and lung transplant at an increased risk, and patients with hematologic malignancies such as leukaemia. IA is also common in persons with congenital immunodeficiency disorders such as CGD and acquired immunodeficiency disorders [53-55]. It is rare in immunocompetent hosts. Invasive aspergillosis is responsible for 30% of fungal infections seen in cancer patients [56]. Despite treatment, the mortality rate of IA was 75-90% in leukaemia patients in the 1980s and 1990's but has now fallen to ~30% [1,2] and up to 25% of leukaemia patients develop IA [57-59]. This makes it a major cause of death in leukaemia patients, and also in bone marrow or organ transplant recipients.

There are four groups of IA; acute or sub-acute invasive pulmonary aspergillosis, tracheobronchitis and obstructive bronchial disease, invasive Aspergillus sinusitis, and disseminated disease. These occur almost exclusively in immunocompromised patients, with the portal of entry being the respiratory tract. Invasive aspergillosis can also occur by direct invasion of wounds and burns on skin, the cornea (keratitis) or by association with in-dwelling catheters [3, 54]

Invasive pulmonary aspergillosis (IPA) is the most common type of IA (80-90%) [3], the acute type being more common than the sub-acute type. There are two pathologic entities of IPA; angio-invasive or non-angio-invasive. The angio-invasive is seen in neutropenic patients and manifests as vascular invasion by hyphal elements with coagulative necrosis and haemorrhage. While in non-angio-invasive IPA seen in non-neutropenic patients, there is a pyogranulomatous inflammation and necrosis without evidence of vascular invasion [60]. IPA has been increasing in incidence, with a prevalence of about 56% of all invasive mycoses found on autopsy[57, 61]. Neutropenia is a strong risk factor, the degree and duration contributing greatly to the risk of developing IPA [53]. Patients with leukaemia have neutropenia, while those with CGD have dysfunctional neutrophils. Neutropenia, immunosuppression and prolonged hospital stay make bone marrow transplant recipients at great risk; about 5% of bone marrow recipients develop IPA and this risk is higher with allogeneic stem cell transplantation[59, 62, 63]. Solid organ transplantation especially, that of heart and lung carries a high risk for IPA, with an incidence of 19-26% [59, 63].

Sub-acute IPA occurs in people with AIDS, CGD [64], and in apparently immunocompetent persons especially those with chronic obstructive pulmonary disease (COPD) [65]. Low CD4 count (<50 cells/mm3), co-existing neutropenia and steroid therapy are associated risk factors for AIDS patients [66, 67]. COPD patients are susceptible because of long term therapy with steroids and other factors resulting from their treatment and hospital stay [68]. Steroids impair the phagocytic functions of neutrophils and macrophages [3]. Co-morbidities such as DM, alcoholism, malnutrition and asthma also predispose COPD patients to sub-acute IPA [69].

The symptoms of IPA depend on the immune status of the host; immunocompetent individuals have more prominent symptoms which may last over weeks or months, while immunocompromised persons tend to have less symptoms but rapid progression of disease. Symptoms are non-specific; cough dyspnoea, pleuritic chest pain, haemoptysis and fever that do not subside with antibiotics use. Fever is however absent in patients on corticosteroid therapy, and patients with chronic IPA also have malaise and weight loss [51]. AIDS patients with IPA have an increased incidence of tracheobronchial involvement in addition to the symptoms described [67,70].

Early diagnosis and prompt use of antifungal agents such as amphotericin B or voriconazole could reduce mortality rate. However, rapid diagnosis is difficult and there are treatment limitations with amphotericin B and voriconazole due to toxicities [71, 72]. Chest radiograph in the early stages of the disease is usually non-specific;

the hallmark of diagnosis is histological examination of lung tissue [73]. Detection of *Aspergillus* antigens such as galactomannan in body fluids can diagnose the disease even before the appearance of clinical signs and symptoms [74]. Bronchoscopy and bronchoaveolar lavage (BAL) is done to obtain fluids for culture and detection of Aspergillus antigens and PCR[60,75], especially in patients with diffuse lung involvement [69]. Prognosis of IPA also depends on removal of the underlying defects, for example, restoration of neutrophil counts and function. Immunomodulatory therapy such as colony-stimulating factors and interferon-γ could be used as adjuvant therapy; IFN-γ was shown to accelerate cure without clinical toxicity in renal transplant recipients with IPA [76, 77].

Aspergillus tracheobronchitis is isolated to the tracheobronchial tree. The risk factors are same as IPA, but tracheobronchitis is more common in AIDS patients [67, 70] and lung transplant recipients [78]. In about a quarter of patients, no apparent immunosuppression is observed [70].There are three forms of the disease; an obstructive type with limited inflammation but with production of thick mucus plugs full of *Aspergillus*, the ulcerative type which affects a limited area of the tracheobronchial tree and is common in recipients of lung transplant, and the pseudomembranous type with extensive inflammation of the membranes [79] .Most patients present with symptoms of cough, fever, chest pain, dyspnoea and haemoptysis[3, 69].

Mortality is high (78%) especially in the pseudomembranous and obstructive types, patients die from respiratory failure[3, 80]. Dissemination or tracheal perforation may complicate the disease [3][6]. Diagnosis is based on characteristic findings on bronchoscopy and microscopic demonstration of the fungus from respiratory specimens. Outcome is good with antifungal therapy, especially with the ulcerative type [69].

Invasive Aspergillus sinusitis may manifest as acute rhinosinusitis, chronic sinusitis or as a paranasal Aspergillus granuloma[3]. It is very uncommon in patients who receive solid organ transplants, but the *acute rhinosinusitis* is common in bone marrow transplant recipients, and patients with neutropenia [81,82]. *A. flavus* is implicated more often in invasive Aspergillus sinusitis [83]. Common sites affected are the maxillary, ethmoid and mastoid sinuses. Patients present with fever, local pain, nasal discharge, epistaxis and headaches. It can occur alone or with pulmonary aspergillosis, but CNS involvement is quite common [3,84] .The disease can spread to surrounding structures such as the palate, orbit or brain, and this is usually fatal[85, 86]. Diagnosis is by demonstration of fluid opacities in the sinuses on CT-scan and a positive

culture. Patients are usually managed with amphotericin B and voriconazole [3], surgery is also important [87].

Chronic Aspergillus sinusitis occurs in immunocompetent persons or those with mild suppression in immunity such as diabetics, alcoholics and people living with HIV [62, 87-89]. The mucosa and other tissues are invaded by the *Aspergillus* hyphae, and the bone may be destroyed. Symptoms include diplopia and visual impairment, headaches, and nasal stuffiness; fever is absent[3, 69]. *Aspergillus* sinusitis may be complicated by osteomyelitis [90], and brain abscess or stroke if the sphenoid sinus is involved [91]. Radiological features (similar to that seen with acute form) and positive culture are diagnostic. Treatment involves antifungal therapy and surgical debridement, the disease usually runs a chronic course and may relapse [3].

Disseminated aspergillosis involves the central nervous system in most cases but also affects organs such as the eye, kidney, skin and heart[92, 93]. About 10-40% of bone marrow transplant recipients are affected, and at autopsy 6-15% of patients who died from haematological malignancies had CNS aspergillosis. CNS aspergillosis is also common in HIV patients ; and neutropenia and steroid use are additional risk factors [93].The disease progresses rapidly with a fatal outcome, and early diagnosis is difficult.

FIGURE II: ASPERGILLUSENDOPHTHALMITISAspergillusinfection of the retina of the eye following dissemination from the lung.© LIFE @http://life-worldwide.org

Cutaneous aspergillosis may occur with disseminated invasive aspergillosis, but it can also occur directly at intravenous catheter sites in neutropenic patients [3]. Cutaneous aspergillosis can also arise from an adjacent affected tissue such as the sinus. A. flavus is most often associated with

primary cutaneous aspergillosis [94]. It has been reported in diabetic patients and apparently immunocompetent persons [95].The lesions are usually distributed over areas of terminal circulation such as the limbs [96].Aspergillus can also cause dermatitis in premature new-borns [97]; it also invades burns and surgical wounds [3].

4. CONCLUSION
The global burden of aspergillosis

Aspergillosis as described are important causes of morbidity and mortality worldwide, affecting mostly the immunosuppressed. The incidences and associated mortalities of invasive aspergillosis have increased as a result of advancement in treatments, and cancers. Prolong hospital stay, frequent hospital visits, prolong duration of treatment and high costs of antifungals are all factors that make aspergillosis to exert a huge financial burden on the economy. Aspergillosis complicating other chronic medical conditions increases the morbidity and mortality from these conditions. Coupled to these is the difficulty with diagnosis especially in developing nations.

About 10million people are at risk of aspergillosis, and 50% would die even with treatment. Most invasive diseases are in stem cell and organ transplant recipients, greater than 75,000 people receive these transplants annually with about 10% at risk of developing invasive disease [98] As discussed, ABPA affects asthmatics and people with cystic fibrosis. About 4 million out of the 193 million with asthma are affected, while 15% of people with cystic fibrosis develop ABPA. Chronic pulmonary aspergillosis has a worldwide prevalence of about 3million, about a third of these cases occur in the setting of previous tuberculosis infection [16]. This is of importance as the rate of tuberculosis seems to be on the increase with AIDS especially in sub-Saharan Africa. Allergic fungal sinusitis and rhinitis may not be associated with mortality, but they affect the quality of life with significant loss of work or school days and reduced performance. They affect 12 million people at any time [99]. Fungal eye infections affect 1million people worldwide, causing about 10% of avoidable blindness [100].

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