

ASPERGILLOSIS: THE DISEASE AT A GLANCE. REVIEW ARTICLE

Mohammad Salim¹ ✉, **Neha Singh¹,**
Mohammad Shahid Masroor², Shagufta Parween³

¹Sanjay Gandhi Smriti Govt. Autonomous P.G. College Sidhi, A.P.S. Univ., Rewa (M.P.), India

²People's College of Dental Sciences & Research Center, People's Univ. Bhopal (M.P.), India

³All India Institute of Medical Sciences (AIIMS), Bhopal (M.P.), India



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✉ msaleem195195@gamil.com

ABSTRACT

Aspergillosis is mainly a lung infection in human. This is caused by the fungus *Aspergillus*. Though, most of the strains are harmless to humans, only a few of them can cause serious diseases mostly in immunocompromised individuals. The individuals with a medical history of respiratory problems are at high risk of infection. An aspergillosis patient if not treated well within time it may result in invasive aspergillosis developing lung fibrosis, huge hemoptysis and multiple organ failures, CNS and brain infections, endocarditis and death. The present paper deals with their disease causing abilities, diagnosis and treatment in human in the light of recent researches done so far in the field of medical microbiology and pathology.

Keywords: Aspergillosis, *Aspergillus fumigatus*, ABPA, CPA, Invasive aspergillosis, Death

INTRODUCTION

This is quite surprising to learn that we, the people in 21st century still not quite aware and alert about the fungal infections even they are continuously killing us comprehensively. We are least bother about the fungal infections treating it very lightly. These fungal infections are killing more than a million of people with billions of causing new infections every year globally. Further, though these infections are more common in immunodeficient people, the other individuals who are otherwise healthy are also not exempted (Misch and Safdar 2016, Davda *et al.* 2018 and Kanj *et al.* 2018) [1-3].

Of all human fungal infections aspergillosis is one of them. This is caused by the cosmopolitan and most contaminating fungus *Aspergillus* initially described by a Roman clergyman and biologist Pier Antonio Micheli in 1729 (Bennett 1842) [4]. More than 300 species of the genus *Aspergillus* have so far been investigated (Samson *et al.* 2014) [5]. The disease is developed in human when a sufficient number of spores are inhaled. It causes a kind of bronchopulmonary infection in which the lungs are primarily affected. The disease is called as the bronchopulmonary aspergillosis. Of the many species of *Aspergillus*, *A. fumigatus* and *A. flavus* are the two common species to develop pulmonary aspergillosis in human. Aspergillosis is frequently found in HIV/AIDS patients kept under the treatment of corticosteroids, organ transplantation, cancer patients and the patients hospitalized for long as nosocomial opportunistic infections (Denning *et al.* 2013 and Yun *et al.* 2017) [6,7].

Further, different types of aspergillosis have different symptoms. Despite pulmonary aspergillosis, other types of aspergillosis as cutaneous, nail, ear canal, nasal and sinus infections have also been reported in the human body. While some of them are mild, others are very serious (Romett and Newmann 1982, Van Burik

et al. 1998, Mishra and Mehta 2004, Glass and Amedee 2011 and Bongomin *et al.* 2018) [8-12].

The present paper is an attempt to review the status of current researches done so far in the field of aspergillosis.

EPIDEMIOLOGY AND DISSEMINATION OF ASPERGILLOSIS

Aspergillosis has been reported from all over the world. Nearly, 1 to 4 million people are affected from allergic bronchopulmonary aspergillosis (ABPA) globally. It can affect the individuals of any age. According to an estimate about 10% of the individuals suffering from cystic fibrosis or asthma experience to an allergic reaction of *Aspergillus*. Similarly, the individuals undergone organ transplantation with immunocompromization therapies are facing 50% more chances of developing invasive aspergillosis and high mortality rate in future (Stevens *et al.* 2003, Denning *et al.* 2013, Haider and Singh 2018) [6,13,14]. However, the exposure to *Aspergillus* has rarely caused problem for the people with healthy immune systems, this is usually not contagious from person to person (Denning 2010) [15].

TYPES OF ASPERGILLOSIS

Aspergillosis usually affected the lungs with the symptoms associated as fever, night sweats, a cough with sputum, fatigue, malaise and unexplained weight loss. The patients might also coughed up blood in sputum. Depending upon the severity of infections, the disease is broadly categorized as allergic, chronic and invasive aspergillosis grouped as under:

ALLERGIC ASPERGILLOSIS INCLUDING ABPA, SINUS AND EAR CANAL INFECTIONS

(Romett and Newman 1982, Bellini *et al.* 2003, Mishra and Mehta 2004 and Agarwal *et al.* 2013) [8, 10,16,17]

CHRONIC PULMONARY ASPERGILLOSIS (CPA)

(Denning *et al.* 2003 and Lee *et al.* 2004 and Yun *et al.* 2017) [7, 18,19]

INVASIVE ASPERGILLOSIS

(Cornely *et al.* 2018) [20]

CUTANEOUS ASPERGILLOSIS INCLUDING NAIL INFECTIONS

(Van Burik *et al.* 1998, Bongomin *et al.* 2018 and Avkan *et al.* 2020) [9,12,21]

RESISTANT ASPERGILLOSIS

(Shelders *et al.* 2012, Helene *et al.* 2020) [22,23]

CORONAVIRUS COMPLICATING ASPERGILLOSIS

(Kieren *et al.* 2021) [24]

The infection caused by the *Aspergillus* initially developed the inflammation in lungs and sinuses causing ABPA and sinusitis respectively. In fact, both the conditions might be treated as the happenings prior to infection (Glass and Amedee 2011 and Agarwal *et al.* 2013) [11,17]. Similarly, while in chronic pulmonary aspergillosis, the disease is progressed as coughs with blood, the life-threatening invasive aspergillosis took place when these infections are disseminated in other body parts damaging various organs and systems of the body (Mahedano *et al.* 2018)[25].

The pulmonary aspergillosis infection is caused mainly by the *Aspergillus fumigatus* and sinuses and ear canal infections are caused by the *A. flavus* and *A. niger* respectively. Moreover, nearly 75% cases of otomycosis is caused by the *A. niger* (Denning *et al.* 2003, Lee *et al.* 2004 Glass and Amedee 2011, Agarwal *et al.* 2013 and Yun *et al.* 2017)[7,11,17-19]. Cutaneous aspergillosis occurs through a break in the skin via postsurgical infections and trauma as wound infection. This is generally caused by a variety of *Aspergillus* species including *A. flavus*, *A. fumigatus*, *A. niger* and *A. terreus* (Van Burik *et al.* 1998 and Avkan *et al.* 2020)[9,21]. Approximately, 35% of all cases of onychomycosis are due to the infection of *Aspergillus*. *A. flavus*, *A. niger* and *A. terreus* have been the most common etiological agents reported for onychomycosis in human (Bongomin *et al.* 2018) [12].

Further, the use of azole fungicides for the plant protection and the use of triazole antifungal drugs in human has developed the azole – resistant *A. fumigatus* infections. Individuals are continuously being infected with the azole – resistant strains of *A. fumigatus* developing resistant invasive aspergillosis in human. In fact, these patients are more likely to die with azole – resistant *A. fumigatus* infections (Shelders

*et al.*2012 and Helene *et al.*2021) [22,23].

There are very limited data available about the incidence of aspergillosis in patients suffering from cancer. However, an increasing trend of aspergillosis has been observed in cancer patients (Chien *et al.* 2022) [26]. Sometimes, the invasive pulmonary aspergillosis (IPA) is found mimicking as the metastatic lung cancer (Michiel *et al.* 2018) [27]. Lastly, the patients suffering from respiratory infections like COVID-19, influenza or pneumonia are more prone to develop lung aspergillosis (Amir *et al.* 2020, Bongomin *et al.* 2020, Frederike *et al.* 2020, Koehler *et al.* 2020 and Florian *et al.*2021) [28-32].

CLINICAL SYMPTOMS OF ASPERGILLOSIS

As the tiny spores of this fungus are unavoidable, normally found in outdoor and indoor environments they cause initially an allergic bronchopulmonary infection (ABPA) in human giving rise to the symptoms as headache, fever, chills, rhinitis, wheezing and coughs accompanied by the stuffy nose following drainage that may contain blood. However, this is yet to understand exactly that why the allergic reactions occur. Similarly, the mucus produced in the lung airways also provided a food environment for the mold to grow. Recurrent allergies may cause bronchiectasis characterized by the scarring of the lung tissues and widening of central airways. If not treated timely, the ABPA may show more severe symptoms with the chronic inflammations of the respiratory tract as bronchitis, asthma, shortness of breath, chest and Joint pain and rashes on body. Similarly, chronic pulmonary aspergillosis (CPA) patients, in addition to the symptoms mentioned above may also reveal the symptoms as cystic fibrosis, hemoptysis with permanent breathing problems. Finally, quite worsening the disease progression, invasive aspergillosis may occur where the infection reaches to other parts of the body as well. Most specifically it occurs in blood vessels. Despite all efforts the absolute mortality rate of invasive aspergillosis patients are achieved (Kosmidis and Denning 2015 and Mahedano *et al* 2018) [25,33].

DIAGNOSIS OF ASPERGILLOSIS

The disease is diagnosed with the help of skin, blood and sputum tests and the culture and biopsy. Chest X-ray and CT/CAT scans are also carried on to visualize symptoms of the disease. Often the patients suffering from chronic pulmonary aspergillosis are seen with cavitation fungal balls or aspergilloma and nodules in their lungs (Horvath and Dummer 1996 and Misch and Safdar 2016) [1,34]. Further, the level of galactomannan is measured as a marker for aspergillosis. Galactomannan enzyme-linked immunosorbent assay (ELISA) is performed. Similarly, serum assays for D-glucan is also done. *Aspergillus* polymerase chain reaction (PCR) is also carried out for the diagnosis of aspergillosis in human (Stubbins and Warnock 1982, Horvath and Dummer 1996, Marty and Koo 2009, White *et al.* 2013&2015, Leeflang *et al.* 2015 and Misch and Safdar 2016) [1,34-39].

DEVELOPMENTAL FEATURES OF ASPERGILLOSIS

Aspergillus fumigatus accounts for almost 90% of the infections in humans. It has been the most common to cause pulmonary aspergillosis. (Marisa 2019)[40]. The main route of the entry of the same fungus in the human body is by the inhalation of spores to cause allergic bronchopulmonary aspergillosis (ABPA) developing severe asthma with fungal sensitization (SAFS).The incubation period varies depending on the dose of *Aspergillus* and the host immune responses. The peoples already suffering from chronic lung problems such as asthma, bronchitis, cystic fibrosis and immunocompromisation or certain pulmonary conditions like tuberculosis, emphysema or sarcoidosis are more prone to have the disease (Stevens *et al.* 2003, Agarwal *et al.* 2013, Denning *et al.* 2013 and Jack and Bajaj 2022)[6,13,17,41].If ABPA is not cured the chronic pulmonary aspergillosis (CPA) is developed. This is characterized by the hemoptysis and coughing with blood, chest pain, fever, shortness of breath and fatigue. And this is all due to the formation of fungus balls, aspergilloma or mycetoma produced by the fungus in air cavities of the lungs. It causes scarring or fibrosis of the lung tissues developing the lung cavities allowing the fungus balls to grow in them. One or more fungal balls may be present in the lungs. Aspergilloma is a tangled mass of fungal fibers, mucus, tissue debris, inflammatory cells, WBCs and the blood clotting protein fibrin. The people having more air cavities are in more risk of developing aspergilloma in their lungs. Therefore, CPA is sometimes more specifically called as the chronic cavitary pulmonary aspergillosis. But, in some cases of CPA, exceptionally *Aspergillus* nodules are also observed in lungs without the formation of cavities. These are the tiny masses without the formation of infected tissues (Denning *et al.* 2003 & 2013 and Yun *et al.* 2017) [6, 7,18].

Invasive aspergillosis occurs when an individual suffering from CPA is not cured properly. This is a most life-threatening and lethal condition in human in which the infections are spread in other parts of the body causing damage and failure of different organs including brain, heart, liver and kidneys. It occurs mostly in immunocompromised patients due to chemotherapy, bone marrow transplantation or suffering from other disorders (Mahedano *et al.* 2018) [25].

Further, invasive pulmonary aspergillosis in patients with liver failure or liver cirrhosis has always been fatal (Bbosa *et al.*2013 and Xuan *et al.*2018) [42,43]. This is hypothesized that the fatality might be due to the result of toxins produced by the same fungus. Similarly, neuroaspergillosis developed brain infections having devastating consequences as brain abscess, meningitis, cerebritis, cranial sinus thrombosis and ventriculitis. It penetrated the blood – brain barrier to cause damage to the CNS (Marisa 2019) [40]. *Aspergillus* infection in human heart is rare appearing very difficult to treat as the high mortality rate is achieved. The infection when enters the blood stream it travelled to the heart. Invasive pulmonary aspergillosis (IPA) sometimes also appeared as a lethal complication after heart transplant and surgery. Nearly 20% of deaths occur in the first year after transplantation (Ameeta *et al.*2010, Beata *et al.*2019, Christina *et al.*2018 and Eduardo *et al.*2021) [44 - 47].

A kidney infection is a type of urinary tract infection (UTI) usually called as pyelonephritis. Although, *Aspergillus* pyelonephritis is rare but often observed in immunocompromised individuals. Kidney and bladder are more frequently involved in invasive aspergillosis. Nearly half the patients suffering from renal aspergillosis had renal failure (Sakamoto *et al.*1978, Godec *et al.*1989, Wise and Silver 1993 and Zhou *et al.*2017 [48 - 51]. Similarly, *Aspergillus* infection in renal transplant (Maanes *et al.*1996, Hadaya *et al.*1998, Guleria *et al.* 1998, Shirwany *et al.* 1998, Sagorika *et al.*2013 and Antonio *et al.*2020) [52 - 57] and prostatic aspergillosis have also been reported (Karayannopoulos and stylianea 1981, Khawand *et al.* 1989, Campbell *et al.* 1992, Abbas *et al.* 1995, Hemal *et al.*1999 and Valerio *et al.* 2009) [58 - 63]. Lastly, the role of genetic and immune dysregulation caused by the pathogenicity of aspergillosis is still a matter of further research (Bongomin *et al.* 2020) [29].

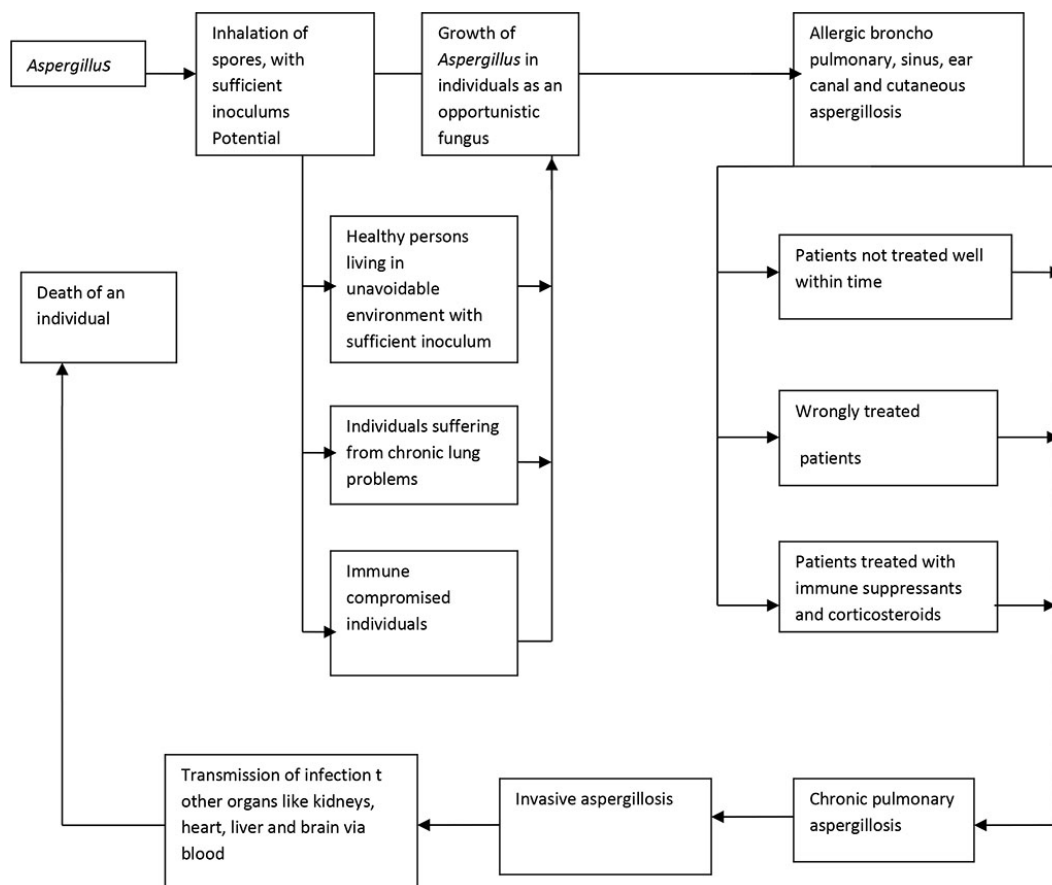


Figure 1. A functional model of developing aspergillosis in human

TREATMENT OF ASPERGILLOSIS

While the prognosis for patients with allergic pulmonary and sinus aspergillosis is good unless the lungs and sinuses are not severely damaged, this is quite poor with the invasive aspergillosis patients. If the infections are spread to other organs of the body especially CNS, heart, liver and kidneys, the mortality rate observed is very high (Alastruey *et al.* 2018) [64]. Sometimes, a very weird situation is also developed when a medical practitioner differentially misdiagnosed and treated a patient as a case of pulmonary tuberculosis.

The aspergillosis patients are treated with some antifungal drugs like variconazole, posaconazole, itraconazole and amphotericin B. Variconazole is the first choice of drug for physicians. Amphotericin B, though effective, usually not prescribed due to its adverse side effects. Sometimes, caspofungin is used for resistant strains of *Aspergillus*. Micafungin has also been tried. The most common drug of choice for

physicians as corticosteroids are prednisone, prednisolon and methylprednisolon. As usual, allergic bronchopulmonary aspergillosis is being treated with itraconazole and corticosteroids (Jenks and Hoenigl 2018)[65]. Moreover, physicians should always be acquainted that all antifungal drugs can have serious side effects including kidney and liver damage, if used for a longer period of time. Similarly, triazole antifungal drugs are the primary treatment for aspergillosis. However, the patients treated with azoles if developed azole resistant *A. fumigatus* are 33% more likely to die than the patients simply treated azoles (Shelders *et al.* 2012 and Helene *et al.* 2021) [22,23].

Further, the patients suffering from chronic pulmonary and invasive aspergillosis, the treatment should begin as early as possible. If not treated within time, lung fibrosis may occur. The treatment response is measured by the disappearance of fungus balls and decreasing the cavity lesions. Surgery with antifungal treatment is required for the removal of fungus balls or aspergilloma. The excessive bleeding caused by the aspergilloma can only be prevented by surgery. However, this is only recommended for advanced and chronic cases of aspergillosis as it does not work properly and the bleeding may recur again. It has also been observed that therapeutic embolization also does not work for long (Lang *et al.* 2020 and Fosses and Waymac 2022[66,67]. Similarly, on the off chance, surgery for the infected heart valves is also done to expel the tainted regions.

Finally, as the invasive aspergillosis is usually rapidly progressive, it eventually leads to death. Various specialists like allergists, thoracic surgeon and a radiologist are always required for the treatment of aspergillosis patients in association with a good physician.

CONCLUSION

Aspergillosis is a kind of bronchopulmonary infection caused by the fungi. The causal organism is *Aspergillus*. Initially, the *Aspergillus fumigatus* causes allergic bronchopulmonary aspergillosis (ABPA) in human. If not treated well within time, a rather more serious form of the disease developed. This is chronic pulmonary aspergillosis (CPA) damaging the lungs by developing aspergilloma. The disease is more easily developed in immunocompromised individuals. However, the healthy individuals are also not otherwise exempted from infection with the availability of sufficient inoculum potential. It has also been observed that the individuals suffering from different ailments and diseases developed the aspergillosis differently as under:

- ABPA is usually developed in persons suffering from asthma or cystic fibrosis
- CPA is developed in individuals suffering from COPD and other diseases like tuberculosis, influenza or pneumonia
- Similarly, the aspergilloma are often developed in association with tuberculosis
- Lastly, the invasive aspergillosis affects mostly the immunocompromised individuals who have undergone stem cell therapy, organ transplant, chemotherapy or kept under the treatment of immunosuppressants and the higher doses of corticosteroids

Finally, the sign and symptoms of aspergillosis may vary with the type of illnesses developed. CPA is often characterized by the rhinitis, coughs with blood and fever, chills, chest pain, night sweats, bronchitis, asthma and shortness of breath as dyspnea. The final stage of disease as invasive aspergillosis occurs when the infections are spread in other body parts via blood. The diagnosis for aspergillosis is often made with the help of sputum and blood test, thoracic x rays, CT scan, ELISA and PCR. The initial stage treatment is easy with certain antifungal medications and corticosteroids. The first choice of drug for physicians is itraconazole and corticosteroid as prednisolone. Sometimes, surgery is also required for the removal of aspergilloma. Lastly, the treatments should begin for aspergillosis as soon as possible because the survival rate for patients suffering from invasive aspergillosis is very low. Sometimes, the treatment with some antifungal medications should begin as soon as the aspergillosis is suspected, even before the diagnosis has confirmed the disease.

ABBREVIATIONS

CNS Central nervous system

HIV Human immune virus

CPA Chronic pulmonary aspergillosis

PCR Polymerase chain reaction

WBC White blood corpuscles

IPA Invasive pulmonary aspergillosis

UTI Urinary tract infection

COPD Chronic obstructive pulmonary disease

AIDS Acquired immunodeficiency syndrome

ABPA Allergic bronchopulmonary aspergillosis

SAFS Severe asthma with fungal sensitization

ELISA Enzyme linked immunosorbent assay

CT scan Computed tomography scan

CAT scan Computed axial tomography scan

ACKNOWLEDGEMENTS

This piece of research work is dedicated to the memory of marhooma Shahidan Khatoon, mother in law of my niece. She was very much loving and caring to us. She has been suffering from chronic obstructive pulmonary disease (COPD) and died recently of lung failure.

CONFLICT OF INTEREST

The authors have declared no conflict of interest. They have approved the final version of the manuscript contributing equally.

FINANCIAL SUPPORT

No financial support was granted during the course of this research work.

ETHICAL CLEARANCE

As this is purely a review article therefore, it does not require any ethical clearance.

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