Review Article

The spectrum of diseases caused by *Aspergillus fumigatus*

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Abstract

Abstract.

The opportunistic mould *Aspergillus* is a ubiquitous fungus. Diseases caused by *Aspergillus* species are most commonly caused by *Aspergillus fumigatus.* The spectrum of disease caused by *Aspergillus* is dependent on the health of the immune system. The ranges of illnesses individuals acquire are aspergilloma, allergic bronchopulmonary aspergillosis, invasive aspergillosis, sinusitis, otomycosis, ocular infections, CNS infection, osteomyelitis, cutaneous aspergillosis, endocarditis, urinary tract infection.

Aspergilloma is the most common clinical presentations of lung infections due to *Aspergillus* species. Allergic Bronchopulmonary Aspergillosis is a result of an immune reaction to colonization of *Aspergillus fumigatus* within the airways of patients. Invasive aspergillosis is generally seen in severely immunocompromised individuals. *Aspergillus* sinonasal infections may or may not be invasive and can follow a fulminant or an indolent course. Otomycosis has typically been described as fungal infection of the external auditory canal. *Aspergillus* endophthalmitis may occur by several mechanisms, including direct inoculation by trauma after surgical procedures or by hematogenous spread. Central nervous system (CNS) aspergillosis is a rare and uniformly fatal complication of disseminated disease, involving the cerebral hemispheres and cerebellum. The mechanism for *Aspergillus* bone infections is by direct extension, traumatic injury, inoculation by a surgical intervention, hematogenous spread and injection drug abusers. Primary cutaneous disease is a rare disease caused by *Aspergillus fumigatus. Aspergillus* species have been reported as a cause of both native and prosthetic valve endocarditis. Aspergillosis of urinary tract may occur by three ways namely, by ascending infection from the lower tract, from haematogenous dissemination or due to *Aspergillus* cast in renal pelvis.

Keywords: *Aspergillus fumigatus*, disease, aspergilloma, invasive aspergillosis.

Introduction

The opportunistic mould *Aspergillus* is one of the most ubiquitous filamentous fungi in the world. It is a soil saprophytic fungus that plays a significant role in the aerobic decomposition of organic materials recycling of environmental carbon and nitrogen. These species produce abundant conidia that are released into the atmosphere. The small size of conidia makes them present in the air at concentration 1 to 100 conidia per m3. For many years, *A. fumigatus* was not thought to only reproduce asexually, as neither mating nor meiosis had ever been observed. However, *A. fumigatus* was shown to possess a fully functional sexual reproductive cycle, 145 years after its original description by Fresenius(1). All human inhale several hundred conidia of *Aspergillus* per day, but it rarely results in disease in immunocompetent persons, since conidia are easily eliminated. Ten teleomorph of *Aspergillus* have been described to date, being classified in the Ascomycota division, Eurotiales: Trichomaceae (2).

The genus *Aspergillus* includes over 185 species. Approximately 40 species have so far been reported as causative agents of opportunistic infections in human and animals (3). Diseases caused by *Aspergillus* species are most commonly caused by *Aspergillus fumigatus.* Other species reportedto cause disease include *Aspergillus amstelodami, Aspergillusavenaceus, Aspergillus candidus, Aspergillus carneus, Aspergilluscaesiellus, Aspergillus clavatus, Aspergillus glaucus, Aspergillusgranulosus, Aspergillus nidulans, Aspergillus niger, Aspergillus oryzae, Aspergillus quadrilineatus, Aspergillus restrictus, Aspergillus sydowi, Aspergillus terreus, Aspergillus ustus,* and *Aspergillus versicolor. A. fumigatus* is the most frequent cause of invasive fungal infection in immunosuppressed individuals, which include patients receiving immunosuppressive therapy for autoimmune or neoplastic disease, organ transplant recipients, and AIDs patients(4, 5).

The spectrum of disease caused by *Aspergillus* is dependent on the health of the immune system. The ranges of illnesses individuals acquire (from usually less severe illness in an immunocompetent individual to more severe illness in the immunocompromised) are aspergilloma, allergic bronchopulmonary aspergillosis, invasive aspergillosis, sinusitis, otomycosis, ocular infections, CNS infection, osteomyelitis, cutaneous aspergillosis, endocarditis, urinary tract infection. Invasive aspergillosis can disseminate to any organ, but most frequently involves the respiratory system. However, CNS involvement in invasive aspergillosis is not uncommon(6).

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Aspergilloma

Aspergilloma is the most common clinical presentations of lung infections due to *Aspergillus* species and also is a common complication of sarcoidosis, particularly in patients with cystic parenchymal damage, and fatal haemoptysis is a potentially lethal complication of this infection. It is the result of saprophytic proliferation of *Aspergillus* mycelia within a pre-formed cavity in the lungs of patients who are generally immunocompetent and asymptomatic. Mycelial invasion of lung or vasculature is not a feature of aspergilloma. Other common causes of the pre-formed cystic host cavity of the aspergilloma include end-stage sarcoidosis or other interstitial lung disease such as pneumoconiosis, bronchiectasis as in cystic fibrosis and/or ABPA, lung abscess, cavitating lung neoplasm, pulmonary infarct, atypical mycobacterial infection, bullous emphysema, hematoma, Pneumocystis jirovecii (formerly P.carinii) pneumonia (PCP), lung surger ankylosing spondylitis and the cavitary residue of invasive fungal infection. Unusually, aspergilloma has been described in immunocompetent patients who do not appear to have had a pre-existing dilated lung space. The presumptive diagnosis of aspergilloma is made by imaging, but the definite diagnosis relies on other clinical data.

The diagnosis of aspergilloma is usually made clinically without a lung biopsy, and the chest radiographic features are of utmost importance in making the presumptive diagnosis. On radiographs, pulmonary aspergilloma appears as a solid rounded mass, sometimes mobile, of water density, within a spherical or ovoid cavity, and separated from the wall of the cavity by an airspace of variable size and shape(7).

Treatment

When surgery is not feasible, itraconazole is the drug commonly used for the medical treatment of aspergilloma (5). Nevertheless, there have been some reports of in vitro itraconazole resistance in *A. fumigatus*. Both de novo and acquired resistance during long-term therapy have been reported(8). It has been demonstrated that voriconazole is an effective treatment for invasive pulmonary aspergillosis (9), but has been seldom used for treatment of aspergilloma. Although voriconazole possesses a similar mechanism of action to itraconazole, it has a good in vitro activity against most of the itraconazole-resistant strains of *A. fumigatus*(10, 11), and it can be considered as an alternative to itraconazole therapy. In conclusion, long-term therapy with itraconazole in patients with aspergilloma caused by *A. fumigatus* can be associated with the development of itraconazole resistance, and voriconazole therapy may be a good alternative for treatment in cases of itraconazole resistance(12).

Allergic Bronchopulmonary Aspergillosis (ABPA).

Allergic Bronchopulmonary Aspergillosis (ABPA) is the archetype of allergic aspergillosis. It is a result of an immune reaction to colonization of *Aspergillus fumigatus* within the airways of patients who are likely to be atopic and immunocompetent. The syndrome is clinically characterized by chronic asthma, mucus production, elevated *Aspergillus* -specific and total IgE, and eosinophilia. A small but significant fraction of patients who suffer from chronic asthma have underlying ABPA, including patients with cystic fibrosis. The main clinical-imaging challenge posed by ABPA is to differentiate between patients with simple chronic asthma and those who might have steroid-responsive asthma due to ABPA.

It was initially described (13) as a disease characterized by episodic wheezing, pulmonary infiltrates, sputum and blood eosinophilia, pyrexia and sputum containing brown flecks or plugs. Two decades later, 7 primary diagnostic criteria for ABPA were proposed (14): episodic bronchial obstruction (asthma), peripheral blood eosinophilia, immediate scratch test reactivity to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated serum immunoglobulin E (IgE) concentrations, history of pulmonary infiltrates (transient or fixed) and central bronchiectasis. The diagnosis of ABPA was felt likely if the first 6 diagnostic criteria were present, and the presence of all 7 made the diagnosis certain. Secondary diagnostic criteria included repeated detection of *Aspergillus* in sputum by use of stain and/or culture, a history of expectoration of brown plugs or flecks, elevated specific IgE directed against *Aspergillus* antigen, Arthus reaction (late skin reactivity) to *Aspergillus* antigen, and characteristic defects on intrabronchial challenge with *Aspergillus.*

Treatment

While early efforts to treat ABPA with amphotericin B, ketoconazole and nystatin were largely unsuccessful, recent experiences with newer generation antifungals, particularly intraconazole, have shown promise(15). Recent studies demonstrated that itraconazole produced a significant reduction in the number of exacerbations. Newer antifungal agents have been shown to be highly effective against *Aspergillus* spp. Azoles remain the preferred class of antifungals for *Aspergillus*. The newer agents in this class, voriconazole, have been shown to be more effective than itraconazole in other *Aspergillus*-related pulmonary diseases. However, its utility in ABPA has not been established. Echinocandins, such as capsofungin, micafungin and anidulafungin, are also effective therapy and show excellent tolerability (16, 17).

Invasive Aspergillosis

Invasive aspergillosis is generally seen in severely immunocompromised individuals and carries a high mortality rate. Risk factors for invasive aspergillosis include neutropenia, immunosuppressive therapy, high-dose systemic corticosteroids, AIDS, solid organtransplant and haematopoietic stem cell transplant. An aggressive diagnostic approach in patients at risk and prompt institution of antifungal therapy may be essential for patient survival. The lungs are the most common site of primary invasive disease. The CNS is the most common secondary site of invasive disease(5).

Treatment

The effective management of Invasive Aspergillosis includes strategies to optimize prevention and early antifungal treatment, immunomodulation, and, in some cases, the role of surgery. Three classes of antifungal agents are available for the treatment of aspergillosis: polyenes, azoles, and echinocandins. Amphotericin B deoxycholate is the major antifungal drug used in patients with invasive aspergillosis, which should begiven at maximum tolerated doses (e.g., 1–1.5 mg/kg/d) and should be continued, despite modest increases in serum creatinine levels. Lipid formulations of amphotericin are indicated for the patient who has impaired renal function or who develops nephrotoxicity while receiving deoxycholate amphotericin(18, 19). Oral itraconazole is an alternative for patients who can take oral medication, are likely to be adherent, can be demonstrated (by serum level monitoring) to absorb the drug, and lack the potential for interaction with other drugs(20, 21). Currently, the drug of choice for Invasive Aspergillosis is voriconazole (22).

Sinusitis

Aspergillus sinonasal infections may or may not be invasive and can follow a fulminant or an indolent course (23). The disease manifestations and the subsequent treatment approach may also vary, depending on the degree of immune competence of the host. Acute invasive infection is the subtype of sinonasal aspergillosis that occurs in the immunocompromised host. These infections are characterized by mucosal invasion with infarction and spread of infection in centrifugal fashion to contiguous structures. Mortality is high, ranging from 20% in patients with leukemia in remission who are undergoing maintenance therapy, to up to 100% in patients with relapsed leukemia or those undergoing bone marrow transplantation (24, 25). A high index of suspicion is necessary in immunocompromised patients. Although surveillance nasal cultures are of questionable value, baseline sinus radiographs or limited CT should be considered in these high risk patients. Early diagnosis is imperative, and the onset of new local symptoms, such as epistaxis, nasoorbital pain, a positive nasal swab culture in a febrile, susceptible host, or an abnormal sinus radiographic finding should lead to immediate otolaryngologic evaluation, including careful inspection of the nasal turbinates. Biopsy and subsequent fungal culture of suspicious lesions are important not only to demonstrate mucosal invasion but also to differentiate *Aspergillus* infections from those caused by other isolates, such as those due to *Mucorales* or *Alternaria* species.

Treatment

Treatment should combine medical with surgical approaches. Although surgical debridement alone may be curative in immunocompetent hosts, it may increase mortality among patients with neutropenia.

Acute sinusitis. Emergent treatment is necessary once this condition is suspected. Initiate systemic antifungal treatment after surgical debridement. High doses of amphotericin B (1-1.5 mg/kg/d) are recommended(26, 27). Oral itraconazole (400 mg/d) can replace amphotericin B once the acute stage has passed. Treatment of the underlying immune deficiency, if possible, is desirable(28, 29).

Chronic sinusitis. Surgical treatment is mandatory. Initiate medical treatment with systemic antifungal once invasion is diagnosed. Amphotericin B (2 g/d) is recommended; this can be replaced by ketoconazole or itraconazole once the disease is under control(30, 31).

Otomycosis

Otomycosis or fungal otitis externa has typically been described as fungal infection of the external auditory canal with infrequent complications involving the middle ear.*Aspergillus* species may colonize the ceruminous debris in the external canal, with no resulting infection. However, invasive infection of the external ear canal has been described in patients with AIDS and in patients with acute leukemia. *Aspergillus* mastoiditis may follow *Aspergillus* otitis(5).

Treatment

In immunocompromised patients, systemic antifungal therapy appears necessary. However, infections of lesser severity (without tissue invasion) or those that occur in immunocompetentpatients may be managed with local measures, including cerumen removal. A variety of such topical therapeutic options has been used, which includes cresylate, alcohol, nystatin (ointment, powder), amphotericin B 3% topicalsolution, boric acid, thymol, gentian violet, iodochlorhydroxyquin (powder, lotion), 5-fluorocytosine ointment, nitrofungin, clotrimazole, and ketoconazole. Topical ketoconazole is a preferred antifungal agent for its efficacy against *Aspergillus* (32).

Ocular infections

Aspergillus endophthalmitis may occur by several mechanisms, including direct inoculation by trauma after surgical procedures, such as cataract extraction, or by hematogenous spread, which is seen most commonly in immunocompromised patients, injection drug abusers, or patients with *Aspergillus* endocarditis(33). Diagnosis in these cases requires smear and culture of vitreous and/or aqueous humor.

Treatment

Penetration of systemic amphotericin B and itraconazole into the vitreous and aqueous humors is often inadequate and treatment is unsuccessful. Because of this, intravitreal amphotericin B (10 mg dose) may be employed, usually after pars plana vitrectomy. Various approaches have been used for corneal infections, including the application of collagen shields impregnated with amphotericinB (0.5%), 0.15%–1% amphotericin B eye drops, amphotericinB corneal baths, topical clotrimazole (1%), pimaricin (5%), miconazole(1%), or ketoconazole (2%) (34, 35). Oral itraconazole may also play a role in these more superficial infections, since this agent penetratesthe deeper corneal layers (36, 37). Voriconazole is a triazole

antifungal agent and is a second- generation synthetic derivative of fluconazole. It is effective against yeast and filamentous fungi. The primary mode of action of voriconazole is the inhibition of cytochrome P-450-mediated 14-α-lanosterol demethylation and the resulting ergosterol depletion causes fungal cell wall destruction. It is well tolerated after oral administration; therapeutic aqueous and vitreous levels are achieved after administration of up to 200 mg twice a day (38, 39).

CNS infection

Central nervous system (CNS) aspergillosis is a rare and uniformly fatal complication of disseminated disease, involving the cerebral hemispheres and cerebellum in the majority of cases. *Aspergillus* infections of the CNS may manifest as single or multiple cerebral abscesses, meningitis, an epidural abscess, or a subarachnoid hemorrhage (40). In patients with few risk factors, the entire disease period can last from 9.5 months to four years. Diabetes mellitus type II seems to be a predisposing condition(41).Because *Aspergillus* spp are difficult to detect in CSF smears and cultures, the determination of serum *Aspergillus* galactomannan, with two positive results, coupled with typical radiological findings, is highly sensitive and specific to support the diagnosis(42).

Treatment

Although surgery alone may be sufficient in the setting of well-encapsulated single lesions inless immunocompromised patients, systemic antifungal therapy is also used in the majority of cases. Flucytosine in conjunction with amphotericin may have a role here because of its CNS penetration. There are reports of successes with lipid complex amphotericin, itraconazole, or voriconazole (43, 44); aggressive dosing may be important. *Aspergillus* meningitis is unusual; cases are reported in injection drug abusers; neutropenic, diabetic, or tuberculosis patients; or patients on prolonged corticosteroid therapy. It may present as an extension of paranasal sinus disease, as a complicationof intrathecal antibiotic therapy or in the post operative setting after trans sphenoidal surgery (45), and presents rarely in patients with no underlying disease. Amphotericin B and other clinical and surgical alternatives showed few encouraging results(46). Although intravenous amphotericin B has been the mainstay treatment for CNS aspergillosis, two new drugs for IV use—voriconazole and caspofungin—are promising agents, with a good tolerability profile(47)The triazoles, itraconazole and voriconazole are probably slightly better than amphotericin B for treatment of cerebral aspergillosis. *Aspergillus* antigen may be detectable in the CSF and may be used for serial observations of the course of therapy (48).

Osteomyelitis

The mechanism for *Aspergillus* bone infections is by direct extension, traumatic injury, inoculation by a surgical intervention, or hematogenous spread, especially in patients with the previously described predisposing risk factors, particularly those with chronic granulomatous disease, or injection drug abusers (49, 50). Vertebral osteomyelitis or diskitis is the most frequent bone infection caused by *Aspergillus* species, with joint infections being distinctly uncommon. Surgical debridement is generally required for these infections.

Treatment

Amphotericin B levels in bone are low, which may necessitate other drugs that have good penetration. Itraconazole may play a role in the treatment of *Aspergillus* osteomyelitis, since there is some evidence that it penetrates bone, and there have been anecdotal reports of its efficacy in fungal osteomyelitis. Compared with Amphotericin B and Itraconazole, posaconazole has the highest in vitro activity against *Aspergillus* species. Moreover, clinical success has been demonstrated with posaconazole in the treatment of invasive aspergillosis in patients in whom Amphotericin B or Itraconazole therapy has failed. Since posaconazole is metabolized by the liver, it offers an attractive treatment choice for patients with impaired renal function(51).

Cutaneous aspergillosis

Cutaneous aspergillosis is usually a cutaneous manifestation of disseminated infection with the fungus *Aspergillus.* Primary cutaneous disease is rare and is most commonly caused by *Aspergillus fumigatus*. Colonization of burn eschars by *Aspergillus* is common, and reports have described primary cutaneous infection in immunocompetent patients in association with agricultural trauma(52).Usually, however, aspergillosis begins as a pulmonary infection subsequent to inhalation of fungal spores. In the immunocompromised host, hematogenous dissemination and invasion of other organ systems, including the skin, often follows the initial pulmonary infection. Dermatologic manifestations of disseminated aspergillosis include single or multiple erythematous-to-violaceous plaques or papules, often characterized by a central necrotic ulcer or eschar. Skin lesions occur in 5-10% of patients with disseminated aspergillosis. In primary cutaneous aspergillosis, the most typical presentation is implantation of the fungus following trauma, including infections at the site of intravenous cannulas, or venipuncture wounds, especially those that have been covered with occlusive dressings. *Aspergillus* is a frequent contaminant found in cultures of dystrophic nails, but it can occasionally cause a true onychomycosis.

Treatment

The role of biopsy of cutaneous lesions for a definitive fungal diagnosis has been emphasized. Systemic antifungal therapy is the mainstay of therapy, and the results are generally good. Surgical excision may occasionally be necessary when the local infection cannot be controlled in the neutropenic setting (53). In catheter site infections, removal of the catheter in addition to systemic antifungal therapy is indicated. Burn wound

aspergillosis and posttraumatic soft tissue infections arebest managed by surgical debridement in addition to systemic therapy. voriconazole is approved as a first-line agent for aspergillosis and is being used with increased frequency. Other treatment options for aspergillosis include itraconazole, caspofungin, or voriconazole in combination with terbinafine(54, 55). Topical voriconazole solution combined with a systemic antifungal has also been reported as effective for secondary cutaneous aspergillosis(56, 57).

Endocarditis

Aspergillus species have been reported as a cause of both native and prosthetic valve endocarditis, which is occasionally a manifestation of disseminated aspergillosis. The fungus is rarely isolated from blood cultures. The resultant vegetations are often large and friable, and carry a high risk of embolic complications.

Treatment

Because of the poor penetration of amphotericin B into theheart valves, in addition to the risk of embolic complications, early surgical intervention with valve replacement is generally undertaken, especially in the setting of prosthetic valve endocarditis(58). Hence, survival without valve surgery is rare and this should be recommended in all cases. Liposomal amphotericin B at a dose of 3 – 5mg/kg/ day should be used as initial therapy, a 4-week minimum duration is recommended assuming a good initial response. Combination therapy involving liposomal amphotericin B with voriconazole and an echinocandin may be used but the evidence of its superiority over liposomal amphotericin B alone is weak; and Secondary prophylaxis with long-term oral voriconazole for at least two years is recommended, in many cases this may need to be continued lifelong (59).

Urinary tract infection

Urinary (Renal) aspergillosis is a rare entity. Patients with compromised immune status, such as diabetics, those on corticosteroid therapy and HIV positive individuals are more vulnerable to infection by *Aspergillus* species (60). Aspergillosis of urinary tract may occur by three ways namely, by ascending infection from the lower tract, from haematogenous dissemination or due to *Aspergillus* cast in renal pelvis (61). Renal aspergillosis due to haematogenous dissemination is the most common while localized infection is rare (62).

Treatment

Systemic antifungal therapy is generally used for parenchymal disease. For management of abscesses and fungus balls, surgical removal may be indicated.Therapy is confounded by the low concentrations achieved in urine by itraconazole or polyenes. Renal, ureteral, or prostaticdisease has been managed with systemic amphotericin B or its liposomal preparations (63); the addition of flucytosine maybe helpful since this agent reaches high concentrations in the urine.

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