Chapter 10
Impact of Aerial Fungal Spores on Human Health

Sadia Alam, Maryam Nisar, Syeda Asma Bano, and Toqeer Ahmad

Abstract Fungal spores are present in almost all types of environments and prevail in certain environmental conditions. The composition of aeromycoflora of a particular area plays an important role in the spreading of many respiratory allergies. The indoor and outdoor aerial fungal spores may be different due to many factors. The aerial fungal spores play an important role in public health as many fungal spores are potent allergens for human population. These fungal spores may also cause some important mycolic infections. Indoor environments are possible sources of fungal spores which can be injurious to human health. These fungal spores can endure for months in suitable conditions. Many environmental factors such as high temperature, high humidity, dampness physical activity, and the wind speed play effective role in the release and distribution of fungal spores in air and which can impede wellness of local population. Aerial fungal spores are the major cause of allergic diseases and infections in immunocompromised patients in many parts of the world. The aerial fungal spores of *Alternaria, Aspergillus, Cladosporium, Candida, Curvularia, Epicoccum, Fusarium, Geotrichum, Helminthosporium, Mucor, Penicillium, Rhizopus, Trichoderma*, and *Trichothecium* were found as dominant in the air of many cities of the world. Variations in composition of aerial fungal spores occur due to environmental and meteorological factors. Some fungal spores are seasonal, and therefore, these spores are linked with some seasonal mycotic infections. They are also established to cause Type I hypersensitive diseases with IgE-mediated response. Fungal spores are present in both outdoor and indoor environments and behave as suspended bio pollutants of the air. Many aerial

S. Alam (✉) · M. Nisar · S. A. Bano
Department of Microbiology, The University of Haripur,
Haripur, Khyberpukhtunkhwa, Pakistan
e-mail: sadia.alam1@uoh.edu.pk

T. Ahmad
Centre for Climate Research and Development (CCRD), COMSATS University Islamabad (CUI), Islamabad, Pakistan
e-mail: Toqeer.ahmed@comsats.edu.pk

T. Ahmed, M. Z. Hashmi (eds.), *Hazardous Environmental Micro-pollutants, Health Impacts and Allied Treatment Technologies*, Emerging Contaminants and Associated Treatment Technologies, https://doi.org/10.1007/978-3-030-96523-5_10

fungal spores are found as main cause of respiratory tract allergies. Many fungal spores can penetrate in lower respiratory airways of human lungs and intercede allergic reactions. These fungal spores can be a serious health hazard for immunocompromised persons. The sensitization to fungal spores may cause some fungal allergies in local population. The seasonal data of aerial fungal spores and their pattern of distribution can help to prevent fungal allergies and mycotic diseases.

10.1 Introduction

10.1.1 Composition of Aeromycoflora

Fungi are omnipresent in the world's environment and are an integral part of airborne microbiome. Particulate matter dispended in air includes bacteria, fungi, clay, and sand particles of 10 μm or smaller to below 0.1 μm and gases including ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) (Ministry of Environmental Protection of the People's Republic 2017). *Alternaria* is the most common fungus present in outdoor and indoor environment. Indoor environment also contains *Aspergillus fumigatus* and *Alternaria* spp. Both species have positive impact on developing asthma (Shabankarefard et al. 2017). Humans are continuously affected by aerosols because of domesticated animals, plants, plumbing systems, heating and cooling systems, and saprophytic molds along with suspended dust particles that contribute to a type of airborne fungus. Yamamoto et al. (2015) detected different types of yeasts in classroom environment including *Rhodotorula*, *Candida*, *Cryptococcus*, *Malassezia*, and *Trichosporon.* Certain researchers have indicated that most of the fungi found in indoor environment comprise of the genera prevailing in outdoor environment (Barberan et al. 2015). Goh et al. (2000) studied library environment and found that indoor fungi concentration was 50 times less than that of outdoor environment.

10.1.1.1 Allergenicity of Airborne Fungal Spore

The huge diversity of fungal kingdom is well known. A variable lot of fungal species exist; some of them disseminate airborne spores, conidia hyphae, or other fragments that are inhaled by human beings. Three taxonomic groups of fungi and their 112 fungal genera including Basidiomycota, Ascomycota, and the Deuteromycota release those allergens which spread allergic diseases. Associated components of fungal conidia are unlike any other bio aerosol in that these are heterogeneous; those which have pathogenic and inflammatory properties are actively secreted by biological dynamic particles. In several multi-studies sensitization of fungi has been identified which is considered to be a risk factor for severe asthmatic patients. The hypersensitivity to fungal allergens ranges from as low as 2% to as high as 90% (Arbes et al. 2005; Zureik et al. 2002), and it was reported that sensitization of fungi

is dependent on different exposure as with most allergens just like source and commercial skin test extracts, based on selection criteria of test subject and analysis methods. There are several subject methods which are used to measure exposure such as spore count, endure assessments of visible growth of fungi, and this procedure is also used to understand the relationship of exposure to clinical outcome. Fungi including *Aspergillus*, *Cladosporium*, *Penicillium*, and *Alternaria* species have been investigated for human exposure. These genera have been found in abundance and a cause of maximum human exposure to airborne fungal spores. These have been detected in vast geographic area and can be detected through various diagnostic means (Cruz et al. 1997).

10.1.1.2 Fragments of Fungi in the Environment

Indoor environment is polluted by airborne fungal spore which is characterized by numerous diagnostic methods. The particulate matter in air have been studied rarely for personal exposure. Many studies' procedures have been promulgated to verify presence of hyphal fragments in indoor environment that indicates the amount of particles in air amounting to 6–56% of total fungal particles (Li and Kendrick 1995; Foto et al. 2005). These fragments of aerosols actually originate from indoor polluted surfaces, and these particles may even persist in indoor environment for quite long in viable form thus aiding to fungal dispersion (Madelin and Madelin 2020). It has been detected from different epidemiological studies that multitudinous fragments of fungal hyphae are associated with acute high expiratory flow rates (Delfino et al. 1997).

Submicron Fungal Fragments

Those particles which are derived for intracellular and extracellular structure are known as submicron fungal fragments that have been aerosolized from fungal colony (Górny et al. 2002). Their usual size is around 1mm and they lack morphological features. Reports related to submicron fungal fragments are few as it is a bit difficult to collect and identify fungal fragments from polluted environment and its isolation is totally based on experimental conditions (Gorny et al. 2002; Gorny 2004; Cho et al. 2005). Dr. Tinna Reponen and Rafal Gorny developed aerosolization chamber, and its purpose was to assess gradual release and collection of bio aerosols. Aerosolization of submicron fungal fragments studied by different authors from culture medium vessels, building internal tiles were found polluted with *Aspergillus versicolor* (Górny et al. 2002, 2003). An aerosolization chamber was designed by researchers group of Dr. Tinna Reponen and Rafal Gorny, and different researchers found different fungal species involved in formation of submicron fragments on internal tiles of buildings and culture vessels. The species involved were *Aspergillus versicolor*, *Penicillium melinii*, *Cladosporium cladosporioides*, and *Stachybotrys chartarum*. The small hyphal segments related to these species have

been indicated in aerosols with spores but to large concentration (320–514 times higher). These findings depict that colony structure, desiccation stress, air velocity, degree of vibration, and moisture conditions may all affect aerosolization rate (Górny et al. 2002; Górny 2004). Various study methods have investigated respiratory disposition of submicron fungal fragments and inflammation. All are based on computer-based models. Cho and colleagues currently explained that the presence of *S. chartarum* fragments is in higher concentration than spores, but in case of *A. versicolor*, a total count 230–250 was similar to the spore. The model was utilized to predict infants' environment, and it was known that sedimentation rate was a 4–5 times multitude of the value associated with young ones (Cho et al. 2005). Further investigation is needed to determine personal fungal exposure from a clinical point of view.

Larger Fungal Fragments

Conidia in broken form and visible septate hyphae or mycelium are considered as larger fungal fragments. Their size exceeds 1mm and comprised of fragmented hyphae (Green et al. 2005). As compared to submicron particle, these fungal fragments are larger in size, easier to be visualized by light microscopy and environmental air samples. In some geographical locations, their concentration can range up to 56% of the total aerospora (Li and Kendrick 1995). Larger fungal fragments related research is scarce as compared to submicron fragments in aerosols. But it is evident that their presence is based on a number of similar variables including substrate disturbance, wind, speed, and wind direction (Green et al. 2005). Filamentous fungi reproduce through hyphal fragmentation. Fragmentation is continued by vacuole formation following a reduction in nutrients that may be induced by environmental stress (Papagianni et al. 1999; Paul et al. 1994). This stress and nutrient depletion zone proceeds towards hyphal separation at septal junctions, and their dissemination is made through wind blowing (Marfenina et al. 1994). The process of conidial fragments formation has not yet been investigated thoroughly and remains undiscovered. It is considered that multicellular conidia get rupture near cross walls of hyphae due to different osmotic potential or when they differ in moisture content (Taylor and Jonsson 2004; Schäppi et al. 1999).

10.1.2 Taxonomy of Allergic Fungi

Kingdom fungi have huge diversity of eukaryotic organisms including mushrooms, molds, bracket fungi, puffballs, smuts, plant rusts, and yeast. Fungi contain different metabolic processes which differ from animals to plants. They secrete enzyme into environment, and their function is also to absorb the breakdown product of enzyme action. Some of these enzymes are also well-classified allergens. Phylogenetic relationships were unclear among different classes of fungi, but currently its classification is based upon morphological characterization and sexual state. Deuteromycetes

or fungi imperfecti at fungal phyla are resolved by DNA sequencing. On the basis of DNA sequencing, it has been found out that three fungal phyla are mostly associated with important aeroallergens; Basidiomycota, Ascomycota, and Zygomycota. Many fungal allergens have been categorized. Specific immunoglobulin E (igE) level in individuals sensitized to fungi has a close relationship between fungal phylogeny, and this is a great benefit from this study. This strong correlation between molecular fungal systematics and IgE sensitization gives a strong evidence about cross reactivity of fungal allergens with human immunity response (Levetin et al. 2016).

10.1.3 Common Fungal Aeroallergens

Aeroallergens are the substances that are dispersed in air as spore or pollens and are able to cause an allergic reaction.

10.1.3.1 Pollens

Aeroallergens are found in certain seasonal plants, and when pollens acting as aeroallergens cause sensitivity reactions in patients, the response is called "hay fever." Because it is the most common illness during haying season in summer months of May and June in Northern areas, some individuals may suffer from this seasonal allergy throughout the year. Hay fever caused by pollens differs from region to region and person to person; small, hardly visible pollens of wind pollinated plants are the main cause of hay fever. The insect pollinated plants have larger pollens that are much larger to remain in air and cause no risk. The plants responsible for pollen allergy or hay fever include trees: alder (*Alnus*), birch (*Betula*), hornbeam (*Carpinus*), cedar (*Cedrus*), hazel (*Corylus*), willow (*Salix*), olive (*Olea*), poplar (*Populus*), linden lime (*Tilia*), horse chestnut (*Aesculus*), and plane (*Platanus*). Grasses [family Poaceae] especially ryegrass (*Lolium* sp.) and timothy (*Phleum pratense*) are involved in causing allergies. An estimated proportion of 90% of hay fever sufferers are allergic to grass pollens. Plantain (plantain), ragweed (ambrosia), nettles/*Parietaria* (Urticaceae), fat hen (*Chenopodium*), sorrel/dock (*Rumex*), and mugwort (*Artemisia*) also cause allergic immune sensitivity.

Ranging from the mid spring to early summer, the pollen count is the highest in a year. The pollen-sensitive patients may anticipate at the onset of the season and when the season ends.

10.1.3.2 Spores

Both sexual and asexual spores in many fungi actively spread by strong ejection from their reproductive structure or sporangium, which spread through the air to distant area. Many fungi have special physiological and mechanical processes as

well as spore structure and surface structure formation like hydrophobic characteristics for spore ejection. This process consists of strong discharge of ascospores enabled by structure of ascus and accumulation of solutes causing osmotic potential in the fluid that push the spores towards dispersal at high velocity into the air (Trail 2007). When single spores get discharged, this process is known as ballistospore dispersal and involves small water droplet formation (Buller's drop), which when link with spore it moves toward projectile ejection with a starting acceleration rate of more than 10,000 g. Other fungi depend on alternative mechanisms for spore ejection which include mechanical forces like puffballs.

Peanuts and other food material may become airborne thus causing allergic reactions in disease-prone individuals like children, immunocompromised people, pregnant women, and elderly adults. Currently concern has been raised about peanuts protein related allergens in the air that may cause a full-blown anaphylaxis and in the result respiratory exposure can occur. In schools setting as a protein food for children, even in well-ventilated restaurants, when airborne peanut protein exposure occurs, different allergic responses were explored. Children have been detected with peanut-associated allergic reaction. No peanut allergen was found in air after subjects consumed peanut (Perry et al. 2004). Dr. Michael Young (2006) reported that peanut allergy may result in life-threating anaphylactic response, but its association with airborne allergy is unconfirmed. Eosinophilic gastroenteritis is an uncommon and heterogeneous condition involving eosinophilic infiltration of gastrointestinal tissue first described by Kaijser in 1937 (Whitaker et al. 2004).

The stomach is the type of organ which is mostly affected followed by the small intestine and colon. Eosinophil is commonly found in gastrointestinal mucosa, like a part of host immunity mechanism; its finding in deeper areas is mostly pathologic. Pathogenic mechanism of disease occurs. Viable IgE and food allergy correlation have been observed in some patients. Eosinophilic aggregation in tissue for inflammation is a complicated process which occurs by different processes of accumulation of cytokines. Cytokines IL 3, IL 5, and granulocytes macrophages colony stimulating factor [GM –CF] are involved in activation, and it has been observed in histological examination of the intestinal wall. Stomach/intestinal allergies are treated by corticosteroids, and its response rate is much positive.

10.1.4 Respiratory Disease Caused by Aeromycoflora

Fungal flora is found everywhere in the environment. Mycopathogens are omnipresent in the environment. Serological reports have revealed that major human population proportion have been affected with fungus respiratory diseases during their life span. Even symptomatic infections by these fungi are infrequent in healthy and vigorous individuals. This indicates the possible hazard of developing a respiratory system disease.

10.1.4.1 Histoplasmosis

Histoplasmosis is a respiratory disease caused by fungal pathogens and commonly occurs in the South America, Africa, Australia, Asia, and Mississippi Valley of the United States. *Histoplasma* is a dimorphic fungus that grows in the environment as a filamentous mold, but during human infections they occur as budding yeast. Soil is the primary reservoir of this fungal pathogen, especially in location rich in bird and bat feces. *Histoplasma* is not transmitted from human to human, and its acquisition is made through inhalation of microconidial spores in the air. In endemic areas, histoplasmosis is high, and the 60–90% of population harbor anti-*Histoplasma* antibodies depending on the locating habitat, but few individuals experience symptoms. Young ones are most likely to be affected and immunodeficient adults. The disease pattern of histoplasmosis is similar to tuberculosis in many ways. Following inhalation this disease gets symptoms similar to tuberculosis because spores go to the respiratory organs and are engulfed by alveolar macrophages. Fungal cells increase in number and sustain even after being engulfed by these phagocytes. Granulomatous lesions caused by focal infections are similar to the Ghon complexes of tuberculosis even in symptomless conditions. Histoplasmosis can become severe and reactivate and spread to other areas of the body such as the spleen and liver. Symptoms and signs of histoplasmosis contain headache, fever, chest discomfort, and weakness. Initial diagnosis of this disease depends on cultures grown on fungal-selective media (Sabouraud Dextrose Agar) and chest radiographs. Giemsa staining and direct fluorescence antibody staining technique can also be utilized for detection of the disease. In some conditions this infection may be restricted and antifungal therapy is not necessary. Yet in case of complexities, the disease is treated by antifungal agents like ketoconazole and amphotericin B; in immunocompromised patients, itraconazole is more effective.

10.1.4.2 Coccidioidomycosis

Coccidioidomycosis infection is caused by dimorphic fungi known as *Coccidioides immitis*. This disease is sometimes mentioned as valley fever because it is endemic to the San Joaquin Valley of California. Same infection is found in arid and semi-arid area of southwestern United states, central and South America, and Mexico. Coccidioidomycotic infection is caused by inhalation of fungal spores. In epidemiology of this disease, the arthospores are produced when the fungal hyphae breaks into fragments. When fungus gets entry in host cells, it is distinguished into spherules filled with endospore. Some *C. immitis* infections are self-limiting and asymptomatic. Yet, the infection can be chronic for immunocompromised patients (Fig. 10.1). Endospore may be elated in the blood, spreading the infection and formed granulomatous lesions on the nose and face. In chronic situation some other organs can be infected and cause serious complex diseases such as untreatable meningitis. This disease can be diagnosed by isolation of fungal pathogens from clinical specimen. *C. immitis* can be cultured on Sabouraud Dextrose Agar when incubated

Fig. 10.1 (**a**) The patients have facial lesion due to *Coccidioides* infection. (**b**) The fluorescent micrograph shows a spherule (Source: http://www.cdc.gov/fungal/diseases/coccidioidomycosis/index.html)

at 35 °C. It is very dangerous to grow in laboratory environment because it is the most infectious mycopathogens capable of surpassing human immune system in the laboratory. This pathogen is rendered as Risk Group 3 agent and can be experimented only in BSL-3 lab facility. The serology of patient may be utilized for its diagnosis through presence of antibody against the pathogen in the patient serum. Though minor cases do not require thorough treatment, but severe pathologies can be treated with **amphotericin B.**

10.1.4.3 Blastomycosis

Another dimorphic fungus *Blastomyces dermatitidis* causes disease termed as blastomycosis. Like *Coccidioides* and *Histoplasma*, *Blastomyces* spread through soil, and fungal spores can be breathed with dust from eroded soil. Symptoms and signs of blastomycosis are mild flu-like and treat with time without medication. It can spread in immunocompromised people and is able to produce severe cutaneous disease with underlying skin lesions on the hand and face. These abrasions are ultimately converted into discolored and crusty surface and can cause deforming scars on skin. Systemic blastomycosis is uncommon, but when it is left untreated, it always results in fatality. Urine antigen tests are now available for diagnosis of pulmonary blastomycosis. Further tests include serological assays such as EIA or immunodiffusion tests. **Ketoconazole** or **amphotericin B** are used for the treatment of blastomycosis.

10.1.4.4 Mucormycosis

The diversity of fungi in the order Mucorales causes disease termed as **mucormycosis**, uncommon mold infection. These include bread molds, like *Mucor* and *Rhizopus*, generally related species is *Rhizopus arrhizus (oryzae)*. In immunocompromised patients, these fungi can establish itself in many different organs but cause infection in the sinuses, respiratory organs, and human dermal region. From the environment the spores enter through breathing in spore-laden air, but spore can also infect the derma layer through gastrointestinal tract if ingested or wound. Sever infection can occur in immunocompromised individuals such as a patient who had a transplant or with cancer. When spores are inhaled into the host's tissue, the fungi grow by spreading hyphae. Infection causes disease in both lower and upper respiratory tracts. In some severe cases the host brain and sinuses are also affected, and the disease is rhinocerebral mucormycosis. Its pathological manifestations are pyretic response, headache, congestion, and tissue death resulting in formation of black lesions in the oral cavity and facial swelling. Infection of the lungs is termed as pulmonary mucormycosis; symptoms include shortness of breath, fever, chest pain, and cough. In chronic cases, the pathogen may disperse to the central nervous system paralyzing the patient in coma and cause death. Currently, for diagnosis there are no PCR-based or ELISA available for detection of pathogens in medical specimens. Tissue biopsy specimens is the only detection strategy to assess the presence of the fungal pathogens. Infections are treated by intravenous administration of **amphotericin B,** and surgical procedures are utilized for removal of superficial infections.

10.1.4.5 Aspergillosis

Aspergillus is a fungus having a mycelial mat comprising of large filaments found in organic debris and soils. This fungus is the most common fungal pathogens; however rarely people become sick. *Aspergillus* may colonize the host and cause infection called aspergillosis. In immunocompromised patients, when its spores are inhaled, the patient can develop allergic asthma-like reactions. Clinical manifestations commonly include wheezing, flue, coughing, headaches, and shortness of breath. Aspergilloma or fungal balls are formed when colonies of hyphae are accumulated in the lungs (Fig. 10.2). In the lungs the *Aspergillus* mycelium damages the host tissues and causes pulmonary hemorrhage and bloody cough. When the infection worsens, the disease becomes fatal because of disseminated fungal mycelium, and it may take the patient to unrecoverable stage of brain hemorrhages and pneumonia. Laboratory diagnosis mostly requires radiography of chest and microscopic testing of tissues and respiratory samples of fluid. *Aspergillus* antigens are identified from serological test. If a person is exposed to fungus, skin test can also be performed for its determination. These tests are similar to that performed for tuberculosis.

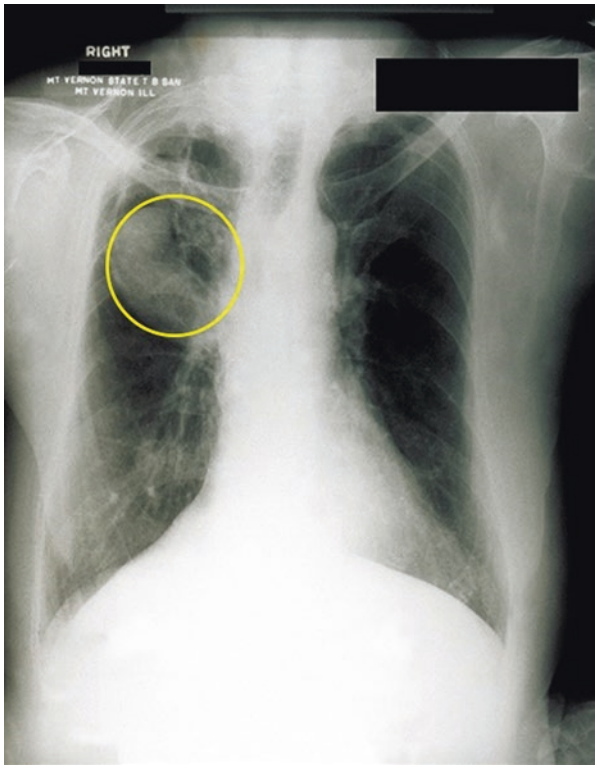

Fig. 10.2 An Aspergilloma (fungal ball) can be observed in the upper lobe of the right lung in this chest radiograph of patients with aspergilloma (Source: Modified image by Centers for Disease Control and Prevention)

10.1.4.6 *Pneumocystis* Pneumonia

Pneumocystis pneumonia (PCP) is a type of pneumonia caused by *Pneumocystis jirovecii*. Initially supposed to be a protozoan, this microbe was previously classified as *P. carinii,* but after genetic analyses and biochemical tests it is regrouped as a fungus (*Pneumocystis jirovecii*) (Fig. 10.3). Immunodeficiency syndrome (AIDS) patients acquire *Pneumocystis* pneumonia, and some of premature infants may get infected also. When lungs are infected shortness of breath is inevitable with cough and fever. These infections are difficult to diagnose. The pathogen is normally identified by slide identification under microscope. Usually fluid and tissue samples from the infected organ are used. Molecular detection may also be used using PCR assay to probe *P. jirovecii* in symptomless patients with immunodeficiency disease. A combo drug **trimethoprim-sulfamethoxazole** is successfully utilized for treatment of the disease.

10.1.4.7 *Cryptococcosis*

Cryptococcosis infection caused by encapsulated yeast termed as *Cryptococcus neoformans. This fungus mostly resides in soil and can be detected in avian feces. If inhaled basidiospores found in air the spores may cause disease in infected*

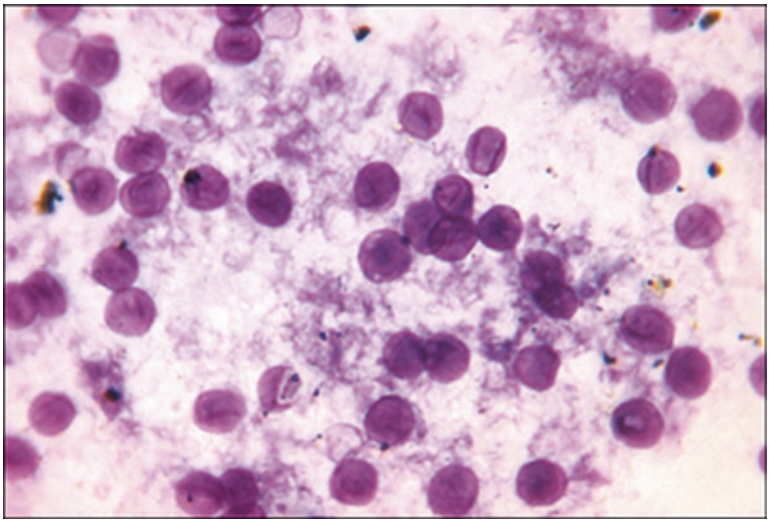

Fig. 10.3 A light micrograph of smear containing *Pneumocystis jirovecii* obtained from human lungs tissue (Source: Modified image by Centers for Disease Control and Prevention)

immunocompromised patients. This microbe is surrounded by thick polysaccharide capsule and enables them to evade the response of alveolar macrophages. Early manifestations of infection include a dry cough, malaise, and fever. Pulmonary infection is often disseminated to the brain in immunocompromised patients. The resultant **meningitis** produces confusion, sensitivity to light, and headaches. This infection is diagnosed on the basis of microscopic examination of cerebrospinal fluids or lung tissues. Indian ink can be used to locate the capsules bordering outer wall of the fungal pathogen. ELISA technique is also performed to endorse the detection. For the initial treatment of pulmonary infection, **flucytosine combination with** Amphotericin B can be used. Amphotericin B is a broad-spectrum drug against fungus that targets cell membranes of fungus. In immunocompromised and those with AIDS patients, cryptococcal infections are more common.

10.1.4.8 Dermatophytes

Dermatophytes are fungi able to cause contagious diseases of the skin, hair, and nails. The disease is termed as dermatophytosis. Dermatophytes have enzymes that can degrade keratin proteins of the scalp, hair, nails, feathers, horns, and hooves. Dermatophytes are mostly soil resident microorganisms and decompose the organic matter. The decomposing ability also enables these microbes to infect hosts when alive. Some dermatophytes (anthropophilic species) are habituated and are transmissible to person to person. When dermatophytes are habituated to animals, these are zoophilic species. A few (geophilic) species frequently reside in the environment and can be parasitic when these get the opportunity. Zoonotic transfer of some of the zoophilic and geophilic species may also occur. There is also evidence of

reverse zoonosis, i.e., human to animals route of disease transmission is also noted. The epidermis, nails, and hair of living host are the target residing areas for dermatophytes. The infection may limit itself, but sometimes the illness may cause facial or tissue impairment and discomfort, when spread widely. Economic effects, such as damage to obnubilate, are additionally consequential in livestock. Infrequently, dermatophytes may invade subcutaneous tissues and (very infrequently) other sites, especially in immunocompromised hosts (Cafarchia et al. 2004).

Tinea capitis Most often children get infection on the scalp and hair, and it is known as tinea capitis. The disease is caused by diverse groups of pathogens like *M. canis*, a zoophilic species causing the same infection in continental Europe, while *T. tonsurans* is mostly associated anthropophilic infection in human population of the USA and the UK. Variable pathogenic organisms have been isolated and include *T. violaceum*, *M. audouinii*, *T. schoenleinii*, and *T. soudanense*. Some fungi are zoophilic only and include *T. mentagrophytes*, *T. verrucosum*, and *M. persicolor*. *M. gypseum* and *M. nanum* (uncommonly) have been detected as geophilic species in some the infection in some area. Tinea capitis is manifested when scaly, erythema and baldness grow rapidly on the scalp. Some human-residing dermatophytic species may result in bald crusts with slight inflamed tissue at follicle point. Dermatophytes associated with animals are able to cause swelling in the infected area called kerions. "Favus" is an infective manifestation of anthropophilic *T. schoenleinii*. This a chronic infection and hairs are surrounded by yellow crusts. When untreated the disease may last up to years (Nweze and Okafor 2005).

Tinea corporis or ringworm occurs on the main body and in extreme parts of the body including face sometimes. Neck and hand wrists also get infected more often from children to adults. Human-infecting microbes are *T. rubrum* and *E. floccosum*. Both of these infect the skin only. The other causative agents are *M. audouinii*, *T. schoenleinii*, *T. tonsurans*, and *T. violaceum*. The fungal pathogens causing this dermatophytic infections in animals are mostly *M. canis*, *T. verrucosum*, *T. equinum*, *T. mentagrophytes*, and *M. persicolor*. The geophilic pathogenic flora comprised of *M. gypseum* and *M. nanum*. Tinea corporis may be characterized by one or more lesions of pink or red or even scaly with annular ring appearance. The ring borders may have follicular papules or vesicles mostly when the infecting pathogen is zoophilic or geophilic in origin. The zoophilic fungus *Trichophyton quinckeanum* can form yellow crusts on the skin called scutulae. Itching gets started in lesions. The remedial measures include treatment with corticosteroids. Tinea corporis may take few months to be cured naturally if left untreated.

Tinea faciei and tinea barbae are dermatophytic face infections, and the causative agents are usually acquired from pets or livestock. The target area for fungal pathogenesis includes the scalp or torso. Tinea barbae include fungal infection in hair and skin of beard or mustache. The victims are usually men. *Trichophyton rubrum* is the causing agent, and follicular pustules are formed along with scaling and redness of skin. The cattle associated pathogen *T. verrucosum* and *T. mentagrophytes* may have a large inflammation of infected area with pustular folliculitis or kerions. The other fungal species involved include *M. canis*, *T. tonsurans*, *T. megnini*, and *T. violaceum*. Tinea barbae is sometimes considered as a similar condition

as tinea faciei by some researchers. Tinea faciei is visually perceived on the hairless facial area. The causing pathogens are *T. rubrum*, *T. tonsurans*, *T. schoenleinii*, *T. mentagrophytes*, *M. canis*, and *T. erinacei*. The itching sensation increases when skin is exposed to sunlight and even burning starts. In some cases this condition resembles tinea corporis.

Tinea cruris Anthropophilic fungal dermatophytes infect groin and groin associated area. *T. rubrum*, *T. mentagrophytes* var. interdigitale, and *E. floccosum* are common causative agents. The clinical manifestations include itching, burning, pruritus, and formation of red lesions with clear centers. The edges of the ring are sharp and raised. Vesicles or pustules may be formed that may exude out and are moist when macerated. The moist acute cases may resemble eczema while dry pustular forms of lesions are chronic in nature. As the lesion increases, in size hyperpigmentation occurs in the central part. Both tinea cruris and tinea pedis are conditions caused by the same fungal pathogen and can occur simultaneously.

Tinea pedis and tinea manuum *T. rubrum*, *T. mentagrophytes* var. interdigitale, and *E. floccosum* cause tinea pedis infection mostly, and these pathogens are anthropophilic. Interdigital tinea pedis (athlete's foot) is an infection of the foot, characterized either by dryness, fissures, and scales or white, moist macerated lesions in some or all of the spaces between the toes. Tinea pedis also exists in the chronic, erythematosquamous type. This condition is evident when scales appear on the feet; swelling and dryness are also visible on the feet. Another form of tinea pedis appears on feet soles and manifests itself in the form of redness and withdrawal of foot nails. **Tinea manuum** is a dermatophytic fungal pathologic reaction condition on human hands. When these fungi infect hands, palms become dry; red coloration due to erythematous response and scaling also occurs. Anthropophilic dermatophytes are mostly isolated for tinea manuum condition (*T. rubrum*), zoophilic fungi *M. canis*, *T. mentagrophytes*, *T. verrucosum*, and *T. erinacei*, or the geophilic organism *M. gypseum* are also isolated in some cases. **Tinea unguium** (or onychomycosis) is a condition when nails are infected with dermatophytic fungus. Its manifestation is evident when nail shape is distorted and the color is changed (Microsporum 2004).

10.1.4.9 Allergen in Respiratory Allergic Patients

At the start of the eighteenth century, it was detected that fungi in air environment cause many respiratory ailments (Huber 2006). Sir Floyer in 1726 has mentioned a patient with an astringent asthmatic attack who visited a brewery where fermentation was going on. After a century, Blackley detected that chest tightness and bronchial catarrh were caused by *Penicillium glaucum* spores were inhaled (Blackley 1873). Storm van Leeuwen was the scientist who declared that asthma is also caused by fungal spore inhalation. The initial discovery of fungi as respiratory allergen was made 300 years ago, but the disease could not be studied much (Crameri et al. 2014). Presently enormous data is available where fungi as respiratory allergen have caused several ailments both in indoor and outdoor environments. Many asthmatic patients are prone to aeromycoflora and develop infections when exposed to fungal

spores, and some patients may become asthmatic even if they were previously not (Jo et al. 2014). Home dampness, visible mold magnification, and moldy odor are indication of huge fungal load inside homes and are the main causes of asthmatic reactions in children and elderly (Meng et al. 2012). A correlation exists between fungal spores load and asthmatic reactions in patients. Mortality may be caused when asthma patients are not treated within time. It was noted in Chicago that double deaths from asthma occurred on days when fungal spores in air were more as compared to days when fungal spores load was less (Targonski et al. 1995). In rural areas when crops ripen the spores load in air is also increased. This increase is further augmented when crops are harvested and stored (RodrÍGuez-Rajo et al. 2005). Respiratory ailments associated with fungi mostly belong to Ascomycota and Basidiomycota group (Pulimood et al. 2007).

The allergic response was indicated in experiment when IgE-mediated reactions were increased. The histamines in basophils were released in sensitive patients. This was detected by skin testing (Fadel et al. 1992). Earlier bronchial and nasal challenge experiments for spores and mycelia inhalation concluded that it may produce rhinitis, asthma, and eosinophilic infiltration reactions (Licorish et al. 1985). There is evidence that fungal spores and mycelium both have certain components that can cause allergic reactions. *Alternaria alternata* allergen (Alt a 1) is present in both spores and mycelium of fungus and detected by electron microscopy (Twaroch et al. 2016). Fungi have the ability to activate further the innate immune system which may result in inflammation enhancement by other allergens like pollens.

It is a prerequisite if patients are tested in hospital environment for sensitization against fungal allergens. Air is always laden with fungal spores, and it is almost unavoidable to find a fungal spore-free environment. Different sizes of fungal air contamination have been investigated in recent years, and several fungal species have been identified (Oh et al. 2014). DNA sequence analysis of different fungal abundant species in air and dust particles in different seasons were studied. It was found that fine particles contain more fungal allergens than coarse particle which in turn harbored more human pathogens (Oh et al. 2014). There are certain other factors that influence fungal allergen presence in air. These include climatic factors like temperature, precipitation, wind, and moisture content in air. Sunlight is also an important factor that affects fungal spore presence in air (Kilic et al. 2010). The spores level increases in hot months and autumn season and greatly reduces when winter approaches. If we note daily variation in spores count early evening and afternoon have more spores load.

Collectively the human body is exposed to fungal spores through air inhalation, skin exposure, or when ingested with contaminated food. The lungs route is most prominent route for getting fungal allergens of various shapes and sizes. Usually 2–250 μm spores are able to cause respiratory allergic reactions. Certain small spores get entry to the lower respiratory part of lungs. The threshold level for each allergen is different to start sensitizing symptoms like in *Alternaria* 100 spores/m^3 are able to induce allergic manifestations, whereas in *Cladosporium* 3000 spores/m^3 are needed to create allergic symptoms. Halogen Immunoassay (HIA) is used to quantify fungal fragments and submicron fungal particles (Green et al. 2006). It is

generally found that large fungal fragments and submicron particles colonize air more than spores. It is also detected that air allergens are not necessarily dependent on spores number or fragments count (Brito et al. 2012). Major *Alternaria* allergen Alt concentration varies with developmental stage of producing pathogen.

10.1.5 Prevalence of Sensitization

Fungi are omnipresent in all types of environment, and this characteristic creates fungal sensitization everywhere in the earth environment. A range of 3–10% population is affected by fungal sensitivity reactions globally. Similarly atopic patients' response to the atmospheric fungus was found magnified (Park et al. 2014). A study conducted in different European countries indicated *Alternaria* and *Cladosporium* sensitive allergy in a population of children and adults of 5–60 years of age with rhinitis and/or asthma. A estimate of 9.5% patients were sensitive to either *Alternaria* or *Cladosporium* species as detected by skin prick method. Spain had maximum sensitization (20%) while Portugal had minimum values (3%) (D'amato et al. 1997). Rivera-Mariani et al. (2011) reported that Early Aversion of Asthma in Atopic Children (EPAAC) surveyed infant population of 10 European countries, Australia, and South Africa, for IgE antibodies against aeroallergens. Data from the USA indicated 12.9% of the population developed *Alternaria alternata* sensitivity. Another study showed allergic response against *Ganoderma applanatum* with the prevalence of 30%. On the basis of different studies conducted, it is evident that fungal sensitivity is also an age-dependent phenomenon and individual immunity plays a main role. Children particularly infants are more susceptible to get aeromycoflora infection (Moral et al. 2008). IgE antibody levels against *Alternaria* increase with age, and after a certain age their titer in blood is decreased with growing age. Fungi do not cause monosensitization, and polysensitization is observed usually. A study by Cantani and Ciaschi (2004) has revealed involvement of genetic factors in population for molds sensitization. Aeromycoflora is usually identified on the basis of spore morphology as time consuming and an expert is required for the identification. IgE level and skin tests of allergic patients do not sufficiently depict exact prevalence of aeromycoflora influence on respiratory allergies. Fungal allergens extraction is also a bit difficult task as pure form of the allergen is seldom extracted (Kespohl et al. 2013).

10.1.6 Fungal Detection in Air

Usually culture techniques are used to isolate air fungus. Different fungal media are used to isolate on Potato Dextrose Agar and Sabouraud Dextrose Agar. Czapek dox agar is also utilized to grow air fungus. The petri dish containing sterilized medium is exposed for 5 minutes in air and then closed with lid and incubated. These

cultured fungi are identified through microscopy. This method is time consuming, and a special expert is required to identify the culture. DNA sequencing is another method to detect exact species through molecular technique using 18srRNA analysis. This technique is quite expensive and lengthy. Present-day researchers identify fungal species in air samples or clinical samples on the basis of molecular analysis. Suchorab et al. (2019) have devised an E nose containing gas two sensors for detection of fungi in air. The air samples are collected through polyamide tubes. Clinical diagnosis of fungal allergen is usually symptoms based and clinical manifestations are categorized. Skin test and in vitro tests (particularly the RAST) are utilized to assess fungal allergens. Usually people are allergic to different allergens along with the fungal allergens. This makes it difficult to exactly identify the fungal allergens. It is different to extract the fungal allergen in pure form, but still *Alternaria alternata*, *Aspergillus fumigatus*, and *Cladosporium herbarum* have been characterized and can be utilized for rapid detection of fungal allergy. Further studies should be conducted to characterize different fungal allergens.

10.1.7 Prevention and Control of Fungal Ailments

Microclimate plays a significant role in fungal growth on walls of the buildings, bio-deterioration, and contamination of indoor environments. Fungal contamination of buildings not only deteriorate buildings and their indoor environment but also poses serious health risks to the inhabitants as they produce both allergens and toxins. About 200,000 species of fungi and microbes are known, but 60–100 are significant pathogens in indoor environment. Among these pathogens, mold is the most important contaminant having relation with sick building syndrome symptoms which is mostly present in water leakage and areas having relative humidity above 70% or condensation (Straus, 2009). Fungi have some useful or beneficial impacts (Hyde et al. 2019), but due to infections and damaging impacts, it's important to control the fungal growth in the environment. It has been observed that tensile strength and weight loss/durability of building may decrease more than 80% which can increase the biodeterioration of buildings (Kazemian et al. 2019). It is important to address the fungal growth on both indoors and outdoors of buildings to minimize the general public health, occupational health, and economic loss. Prevention and control of molds and mycotoxins in food can be minimized by adopting the various preventive measures which depend on the type of food, storage time, and techniques (Northolt and Bullerman 1982). There is no direct method to completely eliminate fungi from the environment, but surveillance methods on regular intervals and sterilization methods can inhibit the fungal growth and can decrease the chances of infections in the medical environment (Araujo and Cabral 2010; Caggiano et al. 2014). However, correlation between fungal infections and fungal contamination through genetic analysis is suggested (Caggiano et al. 2014). Molecular techniques can be helpful in differentiating the medical and environmental strains and their

pathogenicity. Preventive measures include early detection of different body parts by routine cultural through direct microscopy, histopathology, antigen detection, and serological tests (Rodrigues and Nosanchuk 2020; Seeliger and Schroter 1984). Different types of measures are adopted to control the fungus-related ailments and allergies including environmental, meteorological, and chemical treatments which are discussed in more detail:

10.1.7.1 Environmental Controls

Virtuous air quality can help in controlling the fungal growth in the more important environments like hospitals where chances of fungal growth are more, kitchens in the homes, and humid offices (Munoz et al. 2001). High Efficiency Particulate Air (HEPA) filters are recommended to install at the incoming air to maintain good quality of air. Similarly, surveillance at regular time interval for maintaining good air quality can help in controlling the fungal infections.

10.1.7.2 Meteorological Factors

Climatic factors like temperature and humidity play an important role in growth of fungi and spreading infections in the different environments. Fungi can easily adopt themselves with the changing climate, and it is important to understand the mechanism at molecular level as highlighted earlier (Hernandez and Martinez 2018). For safety and durability of food, both water activity and moisture contents are important. Water activity (aW) is defined as the ratio of the water vapor pressure of sample to be tested to the water vapor pressure of pure water under the same conditions. Water activity is important for the growth of microbes as they will not grow below a certain limit (Northolt and Bullerman 1982). For example, a_w of 0.70 is required for mold spoilage and 0.60 for all other microorganisms. Similarly, pH, temperature, oxygen contents, and many other factors can also influence the growth of microbes (Mermelstein 2009). Another study reported aW for different molds ranges between 0.6 and 0.95 like xerophilic molds have aW 0.6 and most molds 0.80 and some yeasts have 0.95 (Stanaszek-Tomal 2020).

10.1.7.3 Chemical Use

Cleaning of kitchen sinks, cabinets, and showers with detergents is recommended as these areas in homes, offices, and especially in the hospital environment can cause the growth of *A. niger*, *A. terreus*, and *Fusarium* spp. Paints can play important role in the growth of fungus as they prevent the growth of *Aureobasidium pullulans*, while *Aspergillus* and *Penicillium* species can grow quickly on paints (Nielsen 2003). In some cases, depending on the nature of the solvents, fungi may grow on

water-based or solvent-based paints. Natural preservatives like chitin, chitosan, and its derivatives are recommended for food preservatives alternative to chemical preservatives like fungicides to control the growth of post-harvest fungus. It is reported that chitosan has triple effect (De Oliveira Junior 2016). Similarly, pH, O_2, and CO_2 have influence on growth of molds but extent varies. CO_2 at 20% in air depresses mold growth and aflatoxin production and markedly depresses mold growth (Northolt and Bullerman 1982). Hot water with temperature of 70 °C for 1 h contact time is an effective disinfectant as reported. Use of hot water and steams requires no chemical for fungal growth control. Other chemical treatments include hydrogen peroxide, sodium hypochlorite, and peracetic acid, and quaternary ammonium compounds (quats) at concentration of more than 0.5% are effective against bacteria and fungi (Wolf et al. 2021). Different fungicides are also used to inhibit and kill the fungus by damaging cell membranes or by stopping energy production mechanism (NPIC 2019).

Diverse range of products are used as fungicides like ethanol, vinegar, tea tree oil, etc. A study reported that tea tree oil has the greatest inhibitor effect against Aspergillus fumigatus and Penicillium chrysogenum isolated from air samples while vinegar inhibited against P. chrysogenum and no inhibitory effect has been observed against 70% ethanol (Rogawansamy et al. 2015). Herbal medicine treatment is effective against the control of skin infection, e.g., mustard oil is effective against dermatophytes. A study reported mustard essential oil effectiveness against molds by inhibiting their growth (Mejia-Garibay et al. 2015). Similarly, another study reported the effectiveness of natural oil like cinnamon leaf, bay, clove, mustard, lemongrass, thyme, orange, sage, and rosemary and concluded that effectiveness depends on method of application (Suhr and Nielsen 2003). Nonchemical method includes genetically modified and resistant crop varieties that can combat fungal and other diseases (The Bichel Committee 1999).

10.1.7.4 Public Awareness

Fungal infections are more severe and difficult to manage because both the host cells and fungi are Eukaryotes. Public awareness about the growth and related infections is highly important to address the issues. As most of the people are unaware about the causes, spread, and control of infections (Brandt and Park 2013), public awareness about the types of fungus, their pathogenicity, and control of its spread is mandatory to save both health and food. Fungal diseases are seldomely reported on the TV talk shows or print media. Although most of the food is spoiled by growth of Aspergillus and other fungal genera, public awareness is scanty. It is treated as neglected disease as compared to other infections. It is recommended to allocate more funding for the control of fungal infections (Rodrigues and Nosanchuk 2020).

References

Araujo R, Cabral JP (2010) Fungal Air Quality in Medical Protected Environments. DOI: https://doi.org/10.5772/9766

Arbes Jr SJ, Gergen PJ, Elliott L, Zeldin, DC, (2005) Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *Journal of Allergy and Clinical Immunology*, *116*(2), pp.377–383.

Barberan A, Dunn RR, Reich BJ, Pacifici K, Laber EB, Menninger HL, et al. (2015) The ecology of microscopic life in household dust. Proc R Soc B. 2015;282:20151139.

Blackley CH, (1873) Experimental researche on the causes and nature of catarrhus aestivus (hay-fever or hay-asthma). Baillière, Tindall & Cox.

Brandt ME, Park BJ (2013) Think fungus–prevention and control of fungal infections. Emerging infectious diseases, 19(10), 1688–1689. https://doi.org/10.3201/eid1910.131092.

Brito FF, Alonso AM, Carnés J, Martín-Martín R, Fernández-Caldas E, Galindo PA, Alfaya T, Amo-Salas M, (2012) Correlation between Alt a 1 levels and clinical symptoms in Alternaria alternata-monosensitized patients. *J Investig Allergol Clin Immunol*, *22*(3), pp.154–159.

Cafarchia C, Romito D, Sasanelli M, Lia R, Capelli G, Otranto D, (2004) The epidemiology of canine and feline dermatophytoses in southern Italy. *Mycoses*, *47*(11–12), pp.508–513.

Caggiano G, Napoli C, Coretti C, Lovero G, Scarafile G, Giglio OD, Montagna MT, (2014) Mold contamination in a controlled hospital environment: a 3-year surveillance in southern Italy. BMC Infect Dis 14, 595. https://doi.org/10.1186/s12879-014-0595-z.

Cantani A Ciaschi V, (2004) Epidemiology of alternaria alternata allergy: a prospective study in 6840 Italian asthmatic children. *European review for medical and pharmacological sciences*, *8*(6), pp.289–294.

a. Chapter in book titled Air Quality ISBN: 978-953-307-131-2.

Cho SH, Seo SC, Schmechel D, Grinshpun SA Reponen T, (2005) Aerodynamic characteristics and respiratory deposition of fungal fragments. *Atmospheric Environment*, *39*(30), pp.5454–5465.

Crameri R, Garbani M, Rhyner C, Huitema C, (2014) Fungi: the neglected allergenic sources. *Allergy*, *69*(2), pp.176–185.

Cruz A, Saenz de Santamaria M, Martinez J, Martinez A, Guisantes J, Palacios R, (1997) Fungal allergens from important allergenic fungi imperfecti. *Allergologia et immunopathologia*, *25*(3), pp.153–158.

D'amato G, Chatzigeorgiou G, Corsico R, Gioulekas D, Jäger L, Jäger S, Kontou-Fili K, Kouridakis S, Liccardi G, Meriggi A Palma-Carlos A, (1997) Evaluation of the prevalence of skin prick test positivity to Alternaria and Cladosporium in patients with suspected respiratory allergy: a European multicenter study promoted by the Subcommittee on Aerobiology and Environmental Aspects of Inhalant Allergens of the European Academy of Allergology and Clinical Immunology. *Allergy*, *52*(7), pp.711–716.

De Oliveira Junior EN, (2016) Fungal Growth Control by Chitosan and Derivatives. Chapter in open access peer-reviewed Edited Volume Fungal Pathogenicity. ISBN: 978-953-51-2393-4.

Delfino RJ, Zeiger RS, Seltzer JM, Street DH, Matteucci RM, Anderson PR, Koutrakis P, (1997) The effect of outdoor fungal spore concentrations on daily asthma severity. *Environmental health perspectives*, *105*(6), pp.622–635.

Fadel R, David B, Paris S, Guesdon JL, (1992) Alternaria spore and mycelium sensitivity in allergic patients: in vivo and in vitro studies. *Annals of allergy*, *69*(4), pp.329–335.

Foto M, Vrijmoed LL, Miller JD, Ruest K, Lawton M, Dales RE, (2005) A comparison of airborne ergosterol, glucan and Air-O-Cell data in relation to physical assessments of mold damage and some other parameters. *Indoor Air*, *15*(4), pp.257–266.

Goh I, Obbard J, Viswanathan S, Huang Y, (2000) Airborne bacteria and fungal spores in the indoor environment. A case study in Singapore. Acta Biotechnol. 2000;20:67–73.

Górny RL, (2004) Filamentous microorganisms and their fragments in indoor air-a review. *Annals of Agricultural and Environmental Medicine*, *11*(2), pp.185–197.

Górny RL, Mainelis G, Grinshpun SA, Willeke K, Dutkiewicz J, Reponen T, (2003) Release of *Streptomyces albus* propagules from contaminated surfaces. *Environmental Research*, *91*(1), pp.45–53.

Górny RL, Reponen T, Willeke K, Schmechel D, Robine E, Boissier M, Grinshpun SA (2002) Fungal fragments as indoor air biocontaminants. Appl Environ Microbiol 68(7): 3522–3531. https://doi.org/10.1128/AEM.68.7.3522-3531.2002. PMID: 12089037; PMCID: PMC12676.

Green BJ, Sercombe JK, Tovey ER, (2005) Fungal fragments and undocumented conidia function as new aeroallergen sources. *Journal of Allergy and Clinical Immunology*, *115*(5), pp.1043–1048.

Green BJ, Yli-Panula E, Tovey ER, (2006) Halogen immunoassay, a new method for the detection of sensitization to fungal allergens; comparisons with conventional techniques. *Allergology International*, *55*(2), pp.131–139.

Hernandez H, Martinez LR, (2018) Relationship of environmental disturbances and the infectious potential of fungi. Microbiology. 164(3): 233–241. doi: https://doi.org/10.1099/mic.0.000620.

Huber B, (2006) 100 Jahre Allergie: Clemens von Pirquet–sein Allergiebegriff und das ihm zugrunde liegende Krankheitsverständnis. *Wiener Klinische Wochenschrift*, *118*(19), pp.573–579.

Hyde KD, Xu J, Rapior S,et al. The amazing potential of fungi: 50 ways we can exploit fungi industrially. *Fungal Diversity* **97,** 1–136 (2019). https://doi.org/10.1007/s13225-019-00430-9.

JO EJ K.I.M.M.Y, LEE S, KIM M, SONG W, (2014) Eosinophilic Airways inflammation and Airways hyperresponsiveness according to aeroallergen sensitization pattern in patients with lower airway symptoms. *Allergy Asthma Immunol Res*, *6*, pp.39–46.

Kazemian N, Pakpour S, Milani AS, Klironomos J, (2019) Environmental factors influencing fungal growth on gypsum boards and their structural biodeterioration: A university campus case study. PLOS One. 14(8): e0220556. https://doi.org/10.1371/journal.pone.0220556.

Kespohl S, Maryska S, Zahradnik E, Sander I, Brüning T, Raulf-Heimsoth M, (2013) Biochemical and immunological analysis of mould skin prick test solution: current status of standardization. *Clinical & Experimental Allergy*, *43*(11), pp.1286–1296.

Kilic M, Altintas DU, Yilmaz MUSTAFA, Kendirli SG, Karakoc GB, Taskin E, Ceter T, Pinar NM, (2010) The effects of meteorological factors and Alternaria spore concentrations on children sensitised to Alternaria. *Allergologia et immunopathologia*, *38*(3), pp.122–128.

Levetin E, Horner WE, Scott JA, Barnes C, Baxi S, Chew GL, Grimes C, Kennedy K, Larenas-Linnemann D Miller JD, Phipatanakul W, (2016) Taxonomy of allergenic fungi. *The Journal of Allergy and Clinical Immunology: In Practice*, *4*(3), pp.375–385.

Li, DW, Kendrick B, (1995) A year-round comparison of fungal spores in indoor and outdoor air. *Mycologia*, *87*(2), pp.190–195.

Licorish K, Novey HS, Kozak P, Fairshter RD, Wilson AF (1985) Role of Altemaria and Penicillium spores in the pathogenesis of asthma. *Journal of Allergy and Clinical Immunology*, *76*(6), pp.819–825.

Madelin TM, Madelin MF, (2020) Biological analysis of fungi and associated molds. In *Bioaerosols handbook* (pp. 361–386). CRC Press.

Paul GC, Kent CA, Thomas CR, (1994) Hyphal vocuolation and fragmentation inpenicillium chrysogenum. *Biotechnology and bioengineering*, *44*(5), pp.655–660.

Marfenina OE, Ivanova AE, Zvyagintsev DG, (1994) The effect of fragmentation of the mycelium of various yeast species on its viability. *Microbiology (New York, NY)*, *63*(6), pp.603–606.

Mejia-Garibay B, Palou E, López-Malo A, (2015) Composition, diffusion, and antifungal activity of black mustard (Brassica nigra) essential oil when applied by direct addition or vapor phase contact. J Food Prot. 78(4):843–8. doi: https://doi.org/10.4315/0362-028X.JFP-14-485. PMID: 25836415.

Meng J, Barnes CS, Rosenwasser LJ, Children's Mercy Center for Environmental Health, (2012) Identity of the fungal species present in the homes of asthmatic children. *Clinical & Experimental Allergy*, *42*(10), pp.1448–1458.

Mermelstein NH (2009) Measuring Moisture Content & Water Activity. Article in Food Tech. Magazine. IFT. https://www.ift.org/news-and-publications/food-technology-magazine/issues/2009/november/columns/laboratory [last accessed on 29 June 2021].

Microsporum T, (2004) Ringworm, Tinea.

Ministry of Environmental Protection of the People's Republic, http://www.stats.gov.cn/tjsj/ndsj/2017/indexeh.htm,(2017).

Moral L, Roig M, Garde J, Alós A, Toral T, Fuentes MJ, (2008) Allergen sensitization in children with asthma and rhinitis: marked variations related to age and microgeographical factors. *Allergologia et immunopathologia*, *36*(3), pp.128–133.

Muñoz P, Burillo A, Bouza E, (2001) Environmental surveillance and other control measures in the prevention of nosocomial fungal infections. Clinical Microbiology and Infection. 7(2): 38–45. https://doi.org/10.1111/j.1469-0691.2001.tb00008.x.

Nielsen KF (2003). Mycotoxin production by indoor molds. Fungal Genetics and Biology, 39, 103–117.

Northolt MD, Bullerman LB, (1982) Prevention of *Mold Growth* and Toxin Production through *Control* of *Environmental* Conditions. J. of Food Protection. 45(6): 519–526.

NPIC, (2019) Fungicides. http://npic.orst.edu/ingred/ptype/fungicide.html. [last accessed on 29 Jun. 21].

Nweze EI Okafor JI, (2005) Prevalence of dermatophytic fungal infections in children: a recent study in Anambra State, Nigeria. *Mycopathologia*, *160*(3), pp.239–243.

Oh SY, Fong JJ, Park MS, Chang L, Lim YW (2014) Identifying airborne fungi in Seoul, Korea using metagenomics. J Microbiol 52(6): 465–472. https://doi.org/10.1007/s12275-014-3550-1. Epub 2014 Apr 11. PMID: 24723107.

Papagianni M, Mattey M, Kristiansen B, (1999) Hyphal vacuolation and fragmentation in batch and fed-batch culture of Aspergillus niger and its relation to citric acid production. *Process Biochemistry*, *35*(3–4), pp.359–366.

Park HJ, Lee JH, Park KH, Ann HW, Jin MN, Choi SY, Lee YW, Hong CS, Park JW, (2014) A nationwide survey of inhalant allergens sensitization and levels of indoor major allergens in Korea. *Allergy, asthma & immunology research*, *6*(3), pp.222–227.

Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA (2004) The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol 114(1): 144–149. https://doi.org/10.1016/j.jaci.2004.04.009. PMID: 15241358

Pulimood TB, Corden JM, Bryden C, Sharples L, Nasser SM, (2007) Epidemic asthma and the role of the fungal mold Alternaria alternata. *Journal of Allergy and Clinical Immunology*, *120*(3), pp.610–617.

Rivera-Mariani FE, Nazario-Jiménez S, López-Malpica F, Bolaños-Rosero B, (2011) Skin test reactivity of allergic subjects to basidiomycetes' crude extracts in a tropical environment. *Medical mycology*, *49*(8), pp.887–891.

Rodrigues ML, Nosanchuk JD, (2020) Fungal diseases as neglected pathogens: A wake-up call to public health officials. PLoS Negl Trop Dis 14(2): e0007964. https://doi.org/10.1371/journal.pntd.0007964.

RodrÍGuez-Rajo FJ, Iglesias I, Victoria JATO, (2005) Variation assessment of airborne Alternaria and Cladosporium spores at different bioclimatical conditions. *Mycological research*, *109*(4), pp.497–507.

Rogawansamy S, Gaskin S, Taylor M, Pisaniello D, (2015) An Evaluation of Antifungal Agents for the Treatment of Fungal Contamination in Indoor Air Environments. *Int. J. Environ. Res. Public Health. 12*, 6319–6332. https://doi.org/10.3390/ijerph120606319.

Schäppi GF, Taylor PE, Staff IA, Rolland JM, Suphioglu C, (1999) Immunologic significance of respirable atmospheric starch granules containing major birch allergen Bet v 1. *Allergy*, *54*(5), pp.478–483.

Seeliger H P, Schröter G, (1984) Preventive measures for the control of fungal infections in the clinic. Immun Infekt. 12(3):143–50.

Shabankarefard E, Ostovar A, Farrokhi S, et al., (2017) Air- and dust-borne fungi in indoor and outdoor home of allergic patients in a dust-storm-affected area," Immunological Investigations, vol. 46, no. 6, pp. 577–589, 2017.

Stanaszek-Tomal E (2020) Environmental Factors Causing the Development of Microorganisms on the Surfaces of National Cultural Monuments Made of Mineral Building Materials-Review. Coatings, 10, 1203; doi:https://doi.org/10.3390/coatings10121203.

Straus, DC, (2009) Molds, mycotoxins, and sick building syndrome. Toxicol Ind Health 25(9–10): 617–635.

Suchorab Z, Frąc M, Guz Ł, Oszust K, Łagód G, Gryta A, Bilińska-Wielgus N, Czerwiński J, (2019) A method for early detection and identification of fungal contamination of building materials using e-nose. *PloS one*, *14*(4), e0215179. https://doi.org/10.1371/journal.pone.0215179

Suhr KI, Nielsen PV, (2003) Antifungal activity of essential oils evaluated by two differentapplication techniques against rye bread spoilage fungi. Journal of Applied Microbiology. 94: 665–674.

Targonski PV, Persky VW, Ramekrishnan V, (1995) Effect of environmental molds on risk of death from asthma during the pollen season. *Journal of Allergy and Clinical Immunology*, *95*(5), pp.955–961.

Taylor PE, Jonsson H, (2004) Thunderstorm asthma. *Current allergy and asthma reports*, *4*(5), pp.409–413.

The Bichel Committee, (1999) Report from the Sub-committee on Agriculture. Publisher 221, Danish Environmental Protection Agency. Ministry of Environment and Energy. https://www2.mst.dk/udgiv/publications/2000/87-7944-246-3/html/default_eng.htm. [last accessed on 1 July 2021].

Trail F, (2007) Fungal cannons: explosive spore discharge in the Ascomycota. *FEMS microbiology letters*, *276*(1), pp.12–18.

Twaroch TE, Curin M, Sterflinger K, Focke-Tejkl M, Swoboda I, & Valenta R (2016) Specific antibodies for the detection of Alternaria allergens and the identification of cross-reactive antigens in other fungi. International Archives Allergy Immunology, 170(4): 269–278. https://doi.org/10.1159/000449415

Whitaker IS, Gulati A, McDaid JO, Bugajska-Carr U, Arends MJ, (2004) Eosinophilic gastroenteritis presenting as obstructive jaundice. *European journal of gastroenterology & hepatology*, *16*(4), pp.407–409.

Wolf H, Urtz BE, Snel M, Schäfer W, Prevention and Control of Microbial Growth in Water-based Crop Protection Formulations. By Group (MSCSG) of the European Crop Protection Association. https://croplife.org/wp-content/uploads/pdf_files/Prevention-and-Control-of-Microbial-growth-in-Water-based-Crop-Protection-Formulations.pdf. [last accessed on 29 Jun. 2021].

Yamamoto N, Hospodsky D, Dannemiller KC, Nazaroff WW, Peccia J, (2015) Indoor emissions as a primary source of airborne allergenic fungal particles in classrooms. Environ Sci Technol. 2015;49:5098–106.

Young MC (2006) The Peanut Allergy Answer Book. Second Edition. Fair Winds Press, Massachusetts.

Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F, (2002) Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *Bmj*, *325*(7361), p.411.