VOLUME-9, ISSUE-6, JUNE-2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Laboratory Medicine

MIND-BOGGLING LOWER AIRWAY FUNGAL INFECTIONS

Raghavendra Rao M. V*	Department of Laboratory Medicine, Scientist Emeritus, and Director of Research central Laboratory, Apollo Institute of Medical Sciences and Research, TS, India. *Corresponding Author
Abrar A. Khan	Dean , American University School of Medicine Aruba, Aruba Campus: Wilhelminastraat 59, Oranjestad, Aruba, Central America
Dilip Mathai	Professor, Dean, Department of Medicine, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India
Vijay Kumar C	Professor, Department of Pulmonology, Apollo Hospitals, Jubilee Hills, Hyderabad, Telangana, India
Khizer Hussain Junaidy	Resident, Department of Pharmacology, Gandhi Medical College, Hyderabad, TS, India
Tiara Calvo Leon	Associate professor, Department of Pharmacology, American University School of Medicine Aruba, Central America
Pamphil Igman	Assistant Professor of Epidemiology and Biostatistics, American University School of Medicine Aruba, Central America
Surekha Bhat	Professor, Department of Biochemistry and genetics, American University School of Medicine Aruba, Central America
Mohammed Ismail Nizami	Department of Emergency Medicine NIMS, Punjagutta, Hyderabad, TS, India
Mahendra K. Verma	Scientist, Centre for Molecular Biology Research Bhopal, Madhya Pradesh, India

ABSTRACT Most fungi encountered by man are harmless saprophytes, but some species may in certain circumstances infect human tissue or promote damaging allergic reactions. The term mycosis is applied to disease caused by fungal infection. Predisposing factors include metabolic disorders ,such as diabetes mellitus, toxic states such as chronic alcoholism, diseases such as leukemia and myelomatosis in which immunological responses are disturbed, treatment with corticosteroids and immunosuppressive drugs, and radiotherapy. Local factors such as tissue damage by suppuration or necrosis and the elimination of the competitive influence of a normal bacterial flora by anti-biotic may also facilitates0 fungal infection. The pulmonarymycoses are difficult and unsatisfactory. The administration of antibacterial drugs should be stopped, and anti-fungal agents substituted. Nystatin or natamycin by inhalation may control the more superficial respiratory mycoses involving the trachea and bronchi. For grave pulmonary infectionsAmphotericin,a potent but highly toxic antifungal agent may have to be given intravenously.Flucytocine and the anti-fungal imidazole may be useful in the treatment of less severe infections. The effective dose of Amphotericin,and thus its toxic effects on the kidney can be reduced by combining it with flucytocine. Surgical treatment may have to be considered if severe hemoptysis occurs

KEYWORDS : Acquired immune deficiency syndrome patients (AIDS), Pneumocystis pneumonia (PCP), Bronchoalveolar lavage (lung rinse). Mucormycosis ,*Candidaalbicans*, *Curvularia*, *Geotrichum* and *Helminthosporium*

INTRODUCTION

Pneumocystis pneumonia (PCP) is a form of pneumonia that is caused by the yeast-like fungus *Pneumocystis jirovecii*.It is also known as **PJP**, for Pneumocystis jiroveci Pneumoniae (1) *Pneumocystis* specimens are commonly found in the lungs of healthy people although it is usually not a cause for disease..However, they are a source of opportunistic infection and can cause a lung infection in people with a weak immune system. PCP is especially seen in people with cancer undergoing chemotherapy, HIV/AIDS cases, and the use of medications that suppress the immune system (2) The diagnosis can be definitively confirmed by histological identification of the causative organism in sputum or bronchoalveolar lavage (lung rinse). Staining with toluidine blue, silver stain, periodic acid-Schiff stain, or an immunofluorescence assay shows the characteristic cysts.The cysts resemble crushed ping-pong balls and are present in aggregates of two to eight (and not to be confused with *Histoplasma* or *Cryptococcus*, which typically do not form aggregates of spores or cells). A lung biopsy would show thickened alveolar septa with fluffy eosinophilic exudate in the alveoli. Both the thickened septa and the fluffy exudate contribute to dysfunctional diffusion capacity that is characteristic of this pneumonia.(3)*Pneumocystis* infection can also be diagnosed by immunofluorescent or histochemical staining of the specimen, and more recently by molecular analysis of polymerase chain reaction products comparing DNA samples. Notably, simple molecular detection of *P. jirovecii* in lung fluids does not mean that a person has PCP or infection by HIV. The fungus appears to be present in healthy individuals in the general population (4)

Aspergillusfumigatus is a species of fungus in the genus *Aspergillus*, and is one of the most common *Aspergillus* species to cause disease in individuals with an immunodeficiency.*Aspergillusfumigatus*, a saprotroph widespread in nature, is typically found in soil and decaying organic matter, such as compost heaps, where it plays an

essential role in carbon and nitrogen recycling (5) Colonies of the fungus produce from conidiophores; thousands of minute grey-green conidia (2–3 μm) which readily become airborne. For many years, *A. fumigatus* was thought to only reproduce asexually, as neither mating nor meiosis had ever been observed. In 2008, *A. fumigatus* was shown to possess a fully functional sexual reproductive cycle, 145 years after its original description by Fresenius (6) Although *A. fumigatus* occurs in areas with widely different climates and environments, it displays low genetic variation and a lack of population genetic differentiation on a global scale. Thus, the capability for sex is maintained, though little genetic variation is produced (7).*Histoplasmacapsulatum* is "distributed worldwide, except in Antarctica, but most often associated with river valleys"and occurs chiefly in the "central and eastern United States"followed by "Central and South America, and other areas of the world". It is most prevalent in the Ohio and Mississippi river valleys. It was discovered by Samuel Taylor Darling in 1906. (8,9)

Blastomycosis is a systemic pyogranulomatous infection usually caused by the inhalation of (spores) conidia of *Blastomycesdermatitidis*. Clinical presentations vary widely, ranging from an asymptomatic, self-limited pulmonary infection to acute respiratory distress syndrome (ARDS), a life-threatening disease (10) The extracutaneous or disseminated forms are characterized by the involvement of organs and systems. Skin, eyes, lungs, liver, kidney, heart, central nervous system (CNS) and genitalia have already been described as affected sites. The osteoarticular form may occur by contiguity of the primary lesion or hematogenous spread dissemination from lungs (11) Infection with *C. neoformans* is termed cryptococcosis. Most infections with *C. neoformans* occur in the lungs (12) Pulmonary candidiasis may be a secondary process arising from hematogenous dissemination or rarely a primary bronchopneumonia (13) In general, *Candida* pneumonia occurs in two forms: either local or diffuse bronchopneumonia originating from endobronchial inoculation of the lung, a rare event, or as a hematogenously seeded, finely nodular, diffuse infiltrate, which in its early stages may be difficult to distinguish from congestive heart failure or *Pneumocystis* pneumonia (14) .Symptoms and signs first appear usually in the body area infected and may occur as fever, headache, reddish and swollen skin over nose and sinuses, dark scabbing in nose by eye(s), visual problems, eye(s) swelling, facial pain, coughing sometimes with bloody or dark fluid production, shortness of breath, diffuse abdominal pain occurs (15). Allergic Bronchopulmonary MycosesMost frequently, (ABPM)_ is caused by *Aspergillusfumigatus*, which may grow in the bronchial lumen, leading to a persistent bronchial inflammation inducing bronchiectasis in asthmatic patients. Seven to 22% of asthmatic patients suffer from allergic bronchopulmonary as per gillosis (ABPA).Besides *A. fumigatus,* ABPM is induced by *Candida albicans*, *Curvularia*, *Geotrichum* and *Helminthosporium*(16)

Recent advances in proteomics and glycomics have contributed to the identification of candidate antigens for use in subunit vaccines, novel adjuvants, and delivery systems to boost the efficacy of protective vaccination responses that are becoming available, and several targets are being exploited in immunotherapeutic approaches. (17) Successful treatment of infectious diseases requires choice of the most suitable antimicrobial agent, comprising consideration of drug pharmacokinetics (PK), including penetration into infection site, pathogen susceptibility, optimal route of drug administration, drug dose, frequency of administration, duration of therapy, and drug toxicity.(18) Antifungal pharmacokinetics and pharmacodynamics (PK–PD) has been used to develop currently available antifungal agents, and further optimize their use for critically ill patients. New experimental models have been developed to enable drug concentration–effect relationships to be characterized (19) Recognition of fungal ligands by these receptors initiates a cascade of signaling events that result in activation of inflammatory cytokine and chemokine expression, driving recruitment and activation of innate phagocytic cells such as neutrophils and monocytes to the site of infection. Dendritic cells take up fungal particles in this cytokine-rich microenvironment, integrate these activating signals through PRRs and cytokine/chemokine receptors, migrate to site-draining lymph nodes, and subsequently activate naïve fungal-specific T cells. (20)

Chronological record of significant events

The rediscovery of *Pneumocystis* cysts was reported by Antonio Carini in 1910, also in Brazil .The genus was again discovered in 1912 by Delanoë and Delanoë, this time at the Pasteur Institute in Paris, who found it in rats and proposed the genus and species name *Pneumocystis carinii* after Carini. *Pneumocystis* was redescribed as a human pathogen in 1942 by two Dutch investigators, van der Meer and Brug, who found it in three new cases: a 3-month-old infant with congenital heart disease and in two of 104 autopsy cases - a 4-month-old infant and a 21-year-old adult. There being only one described species in the genus, they considered the human parasite to be *P. carinii*. Nine years later (1951), Dr. Josef Vanek at Charles University in Prague, Czechoslovakia, showed in a study of lung sections from 16 children that the organism labelled "*P. carinii*" was the causative agent of pneumonia in these children.The following year, Jírovec reported "*P. carinii*" as the cause of interstitial pneumonia in neonates.Following the realization that *Pneumocystis* from humans could not infect experimental animals such as rats, and that the rat form of *Pneumocystis* differed physiologically and had different antigenic properties, Frenkel was the first to recognize the human pathogen as a distinct species. He named it "*Pneumocystis jiroveci*" (corrected to *P. jirovecii* - see nomenclature above).

Controversy existed over the relabeling of *P. carinii* in humans as *P. jirovecii*,(22) which is why both names still appear in publications. However, only the name *P. jirovecii* is used exclusively for the human pathogen, whereas the name *P. carinii* has had a broader application to many species (23) Frenkel and those before him believed that all *Pneumocystis* were protozoans, but soon afterwards evidence began accumulating that *Pneumocystis* was a fungal genus. Recent studies show it to be an unusual, in some ways a primitive genus of Ascomycota, related to a group of yeasts.Every tested primate, including humans, appears to have its own type of *Pneumocystis* that is incapable of cross-infecting other host species and has co-evolved with each species (24)Currently, only five species have been formally named: *P. jirovecii* from humans, *P. carinii* as originally named from rats, *P. murina* from mice,*P. wakefieldiae* also from rats, and *P. oryctolagi* from rabbits (25) Historical and even recent reports of *P. carinii* from humans are based upon older classifications (still used by many, or those still debating the recognition of distinct species in the genus *Pneumocystis*) which does not mean that the true *P. carinii* from rats actually infects humans. In an intermediate classification system, the various taxa in different mammals have been called *formaespeciales* or forms. For example, the human "form" was called *Pneumocystis carinii* f. [or f. sp.] *hominis*, while the original rat infecting form was called *Pneumocystis carinii* f. [or f. sp.] *carinii*. This terminology is still used by some researchers. The species of *Pneumocystis* originally seen by Chagas have not yet been named as distinct species (26)

Many other undescribed species presumably exist and those that have been detected in many mammals are only known from molecular sample detection from lung tissue or fluids,

rather than by direct physical observation (27,28) The history of the discovery and naming of Candida extends from the ancient Greeks to modern day researchers. The perception of Candida has evolved from the presence of an exudate in the human host to a known infectious agent. 200 years of medical history was recorded before the etiological agent of oral thrush, the first form of candidiasis described, was correctly identified as a fungal pathogen. "Thrush" appears as whitish plagues within the oropharynx or the buccal mucosa or tongue. One of the main points of contention when defining thrush was whether it originated from the host or was an infectious agent, or a combination of the two. The earliest reports of thrush predated the concept of a microbial pathogen. In "Of the Epidemics," Hippocrates described oral candidiasis (around 400 B.C.) as "mouths affected with aphthous ulcerations" . In 1665, Pepys Diary reported "a patient hath a fever, a thrush and a hiccup" , perpetuating the idea that oral thrush originates from the host. Mycologists accepted this perception as late as the early 1900s where Castellani quoted previous accounts of thrush as "morbid secretions of the oral mucosa " (29) However, a few clinicians and mycologists swayed popular belief towards the idea of an infectious agent causing thrush. In 1771, Rosen von Rosenstein defined an invasive form of thrush In 1839, Langenbeck was credited with first recognizing a fungus in a patient with typhoid fever. Oropharyngeal and esophageal thrush with pseudomembranes were found at autopsy. "Under the microscope magnified, the pseudomembranes consisted of an immense number of fungi" (translated from German) .

He describes in detail what is now referred to as septate hyphae, branched pseudohyphae and blastoconidia However, he ascribed the entity to the typhoid bacterium rather than the fungus (30). In 1844, J.H. Bennett observed a similar fungus in the sputum and the lungs of a patient with a pneumothorax and criticized the conclusion by Lagenbach Descriptions of what sounds like oral thrush go back to the time of Hippocrates circa 460–370 BCE (31) Vulvo vaginal candidiasis was first described in 1849 by Wilkinson. (32)With the advent of antibiotics following World War II, the rates of candidiasis increased. The rates then decreased in the 1950s following the development of nystatin (33) The colloquial term "thrush" refers to the resemblance of the white flecks.(34)The current classification of Candida authorized for use by the International Botanical Congress (IBC) (35) The genus *Candida* includes about 150 different species; however, only a few are known to cause human infections. *C. albicans* is the most significant pathogenic species. Other species pathogenic in humans include *C. auris, C. tropicalis, C. glabrata, C. krusei, C. parapsilosis, C. dubliniensis, and C. lusitaniae*.The name Candida was proposed by Berkhout.The specific epithet *C.albicans* also come from Latin, albicare meaning "to whiten".These names refer to the generally white appearance of *Candida* species when cultured.(36)Candida comes from the Latin term "candidus" which has the meaning of "glowing white" and also refers to as smooth and glistering (37) Phenotypic, chemotaxonomic and phylogenetic analyses established *C. auris* as a new strain of the genus *Candida* (38)

Main research hypothesis of fungal colonization of respiratory tract

Endoscopic signs of bronchial or anastomotic aspergillosis infection were assessed by senior pneumologists of LT department. Bronchial or anastomotic aspergillosis infections were defined as isolation of *Aspergillus* in culture with histopathologic evidence of tissue invasion or necrosis, ulceration or pseudo membranes on bronchoscopy, as previously reported in lung transplant recipients (39) AC was defined as identification of *Aspergillus* spp. via culture of a bronchopulmonary sample in patients with no radiologic or endoscopic signs of pulmonary or tracheobronchial invasive aspergillosis. Colonization was considered certain if two consecutive cultures were positive in expectorations or aspirations, or if a single BAL was positive in culture. Colonization was considered probable when a culture was positive in a single expectoration or aspiration. (40)

Why the problem of Fungus infections of the lung is important?

While the incidence of pulmonary fungal infections has increased over the years, advances in diagnostic techniques and treatments have improved. Despite these advances, patient outcomes remain poor owing to a lack of early infection identification. Therefore, treatment should begin as soon as a diagnosis is made. With the expansion of antifungal treatment options, pharmacists should be aware of specific recommended doses, available drug formulations, drug–drug interactions, and potential side effects when assisting with the prescribing of anti fungal agents. Luckily, enhancements in diagnostic measures and treatment modalities have expanded early detection of infection and available treatment choices.(41)

What is lacking in current knowledge ?(Fungus Lung)

The impact of the diversity and composition of the lung mycobiome in chronic and fungal lung diseases is poorly understood. Most studies involve detection of fungi in respiratory samples by culture. However, such methods lack sensitivity and the emergence of next-generation sequencing technologies is an important advance. However, differences in the sequencing methodologies limit study comparisons. Well-designed methodological approaches and large cohort studies are needed to evaluate the impact of the lung mycobiome in respiratory diseases (42)

What are we learning about fungal lung infection research?

Most pulmonary fungal infections occur after inhalation of fungi that have been aerosolized because their natural habitat was disturbed. Once in the lungs' alveoli (air sacs), the fungus is engulfed by macrophages and other cells involved in the primary immune response. Macrophages are usually able to neutralize and destroy the pathogens that they attack, but many fungi have developed a way to disable the macrophage's weapons, and some fungi have actually developed the ability to grow and multiply inside macrophages. Secondary or adaptive immunity cells are called to the site of infection, and in healthy individuals, this action can usually control the infection's spread. The fungus is contained, but the sites of initial infection can remain as granulomas, collections of different types of immune cells. The granulomas later degenerate to scars and often calcify. Calcified granulomas may be seen years later on x-ray images. When cellular immunity is impaired, as it is, for instance, in AIDS, infection with an endemic fungus cannot be controlled. Almost any organ can be involved as the infection spreads throughout the body. The presence of structural lung disease, such as emphysema, impairs the clearance of the infection and allows a chronic condition to take hold. White blood cells (especially neutrophils) are critical to fight certain fungal infections such as those due to the fungus Aspergillus (43)

New fungal pathogens, new tricks: and future prospects for antifungal therapeutics

Fungal pathogens are a growing threat to public health. As human immunodeficiency becomes increasingly common, fungal infections are becoming more prevalent. The use of antifungal agents for prophylaxis and treatment of fungal infections has favored the emergence of previously rare or unidentified species of drug resistant fungal pathogens, including several *Candida* and *Cryptococcus* species, as well as mold pathogens. As these new and increasingly drug resistant fungal pathogens continue to emerge, strategies for rapid identification and treatment are necessary

to combat these life threatening infections. (44)

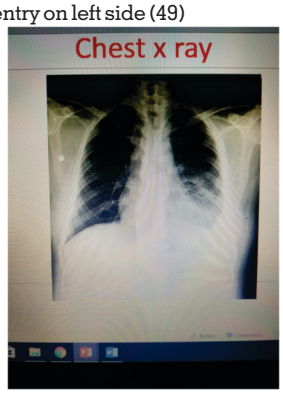
Broncho pulmonary infections

Though fungal spores are being inhaled all the time,infection is very rare.It is commonest in agricultural workers,who either have pre-existing pulmonary disease or are on steroids and the organism is most frequently a species of *Aspergillus*.The most important species is *A. fumigatus*,which also causes pulmonary infection in birds and mycotic abortion in cattle and *A.niger* When yeast persistently present in sputum it is ussally because they have colonized pockets of secretion in a bronchial tree damaged by bronchiectasis tuberculosis or carcinoma.The sputum then contains many yeasts but is often mucoid and gelatinous rather than purulent.Systemic infection may occur when the organism is inoculated directly into the tissues as in drug addicts,after heart valve operationsIn severe organized disease such as leukaemia especially when treated with cytotoxic drugs,steroids and antibiotics and occasionally in small children with no clear predisposing condition (45)

Endurance of Fungus in Lungs

Rhizopus organisms have an enzyme, ketone reductase, which allows them to thrive in high glucose, acidic conditions. Serum from healthy individuals inhibits growth of *Rhizopus*, whereas serum from individuals in diabetic ketoacidosis stimulates growth Rhino-orbital-cerebral and pulmonary mucormycosis are acquired by the inhalation of spores. In healthy individuals, cilia transport these spores to the pharynx and they are cleared through the gastrointestinal tract. In susceptible individuals, infection usually begins in the nasal turbinates or the alveoli (46) Deferoxamine and iron overload — Deferoxamine, which chelates both iron and aluminum, increases the risk of mucormycosis by enhancing growth and pathogenicity The deferoxamine-iron chelate, called feroxamine, is a siderophore for the species *Rhizopus*, increasing iron uptake by the fungus, which stimulates fungal growth and leads to tissue invasion Iron overload itself may predispose to mucormycosis in the absence of deferoxamine therapy In addition, individuals with diabetic ketoacidosis have elevated concentrations of free iron in their serum, which supports the growth of *Rhizopusoryzae* at an acidic, but not at an alkaline, pH (47)Deferoxamine was once used commonly as an aluminumchelator in patients with renal failure; however, aluminum excess is rarely seen today. Currently, patients at risk for deferoxamine-associated mucormycosis are those who have received multiple blood transfusions and are treated with this chelating agent for iron overload. The majority of patients with deferoxamine-associated infection present with disseminated disease that is rapidly fatal, with a mortality rate that approaches 90 percent (48)

A 65 year old elderly male patient presented to Emergency with complains of fever and cough associated with hemoptysis since 1 week. He was on medical management for Diabetes Milletus, Hypertension and Coronary Artery Disease. On examination – chest auscultation revealed decreased air entry on left side (49)



Biotechnology for Molecular Diagnosis of Fungus

Early diagnosis of fungal infection is critical to effective treatment. There are many impediments to diagnosis such as diminishing number of clinical mycologists,cost,time to result and requirements for sensitivity and specificity. In addition,fungal diagnostics must meet the contrasting needs presented by the increasing diversity of fungi found in association with the use of immunosuppressive agents in countries with high levels of medical care and need for diagnostics in resource-limited countries, where large numbers of opportunistic infections occur in patients with AIDs.Traditional approaches to diagnosis include direct microscopic examination of clinical samples, histopathology, culture and serology. Emerging technologies include molecular diagnostics antigen detection in clinical samples, innovative new technologies that use molecular and Immuno assay platforms have the potential to meet the needs of both resource-rich and resource limited clinical environments.(50)

Isolation of Candida albicans from sputum and other respiratory specimens is common but rarely associated with pulmonary infection. Histopathology shows yeast cells and mycelial forms, epithelial disruption with organisms invading through mucosal cells, and submucosal inflammation and mucosal candidiasis. deep tissue candidiasis shows organisms invading and disrupting infected tissue. Antibody detection has played a limited role in diagnosis In dissiminated coccidioidiomycosis.

Small ovoid cells may be detected intracellularly in histologic sections or in Giemsa stained specimens.Specificimmuno fluorescence can identify Histoplasma cells in sections or smears.Injection of organisms into mice may yield Histoplasma in lesions of spleen and liver upon culture. Massive doses of spores of *Blastomyces dermatitis* cultures injected intravenously into mice,guinea pigs or rabbits are fatal in 5-20 days,In *cryptococcusneoformans* detection of antigen is diagnostically significant.With effective treatment,antigentiterdrops.PulmonaryAspergillosis may occur in distinct forms One is "fungal ball" growing preexisting cavity(Eg Tuberculosis cavity,Para nasal sinus, bronchiectasis) in which the Aspergillus does not invade the tissues. Diagnosis of Aspergillosis rests most securely on demonstration of hyphal fragments in tissue biopsies by methenamine silver strain.They may give significant antibody responses to *Aspergillus*antigens.Inzygomycosis, the organisms are rarel;y cultured during life but are seen in histologic preparations of tissues as broad,nonseptate irregular hyphae in thrombosed vessels or sinuses with surrounding leukocyte and giant cell response.

Researchers struggle to develop a new treatment for Fungus

Both Itraconazole and Fluconazole are available as oral and 1V preparation. The advantage of fluconazole is its long half-life, satisfactory penetration in most body tissues and minimal toxicity. The disadvantage of Itraconazole is the varying blood levels among patients taking the oral form of the drug. Fluconazole is highly effective for the treatment of superficial and invasive Candida infections including in neutropenic patients, however, in an unstable patients and those who were receiving azoles for prophylaxis, Amphotericin B is the therapy of choice (51) Intravenous amphotericin B,0.4-0.8 mg/kg/d or double the dose 3 times weekly- continued for months may result in remissions. Systemic miconazole ketoconazole have been moderately effectiver in treatment of chronic pulmonary *coccidioidiomycosis* but have had very limited effect on disseminated disease.In disseminated Histoplasmosis, Amphotericin B,0.6 mg/kg/d,has arrested and at times,cured the disease,andketakonazole has shown some limited benefits. Ketaconazole in doses of 400 mg/d or amphotericin doses upto 50 mg/d is the current drug of choice in *Blastomyces dermatitis* Flu cytosine 150 mg/hg/d orally

effective agaist many strains of *cryptococcusneoformans* but resistant mutants m,ay develop. Amphotericin B 0.4-0.8mg/kg/d intravenously can also be effective but has many toxic side effects..PulmonaryAspergillosis may occur in distinct forms One is "fungal ball" growing preexisting cavity(Eg Tuberculosis cavity,Para nasal sinus, bronchiectasis) in which the *Aspergillus* does not invade the tissues.It requires active anti fungal drug therapy with flu cytosine and Amphotericin B. Amphoterin B and Posaconazole are effective against Zygomycosis.

Current Relevance, Challenges and way forward

Nearly half of all nursing homes do not have adequately trained infection prevention staff and their efforts to combat the over prescription of antibiotics are suffering as a result, according to a new study in the American Journal of Infection Control, the journal of the Association for Professionals in Infection Control and Epidemiology, published by Elsevier.New antigen- or DNA-based methods for early diagnosis still await clinical validation. Their routine use is hampered by methodological issues. Histoplasmosis occurs in many parts of the world. Histoplasmosis outbreaks occurred somewhat more frequently in black than in white residents.The disease is not communicable from person to person.Spraying of formaldehyde on infected soil may destroy *Histoplasma. Coccidioidisimmitis* are normally asymptomatic or mild. More severe disease may occur in migrant workers and military personnel first exposed to infected dust as adults. Progressive disease occurs only rarely. for this reason very strict precautions are necessary against the risk of laboratory infection from cultures or infected animals. Blastomyces dermatitis is relatively common finding in dogs and some other animals in endemic area.it is assumed the both animals and humans are infected by inhaling conidia from B*lastomyces*growing in soil. Direct isolation from soil has been occasionally successful, especially from beaver dams with originally rich soil.

Early Recognition and Management of Fungal lung diseases

It is important before treating a candida infection to try to identify the underlying circumstances that have allowed it to establish itself. If the underlying disturbance such as poor hygiene or diabetes can be corrected. Treatment will however shorten process. When the underlying condition cannot be altered quickly as in pregnancy, debility or serious disease, the usual treatment is to give the polyene nystatin locally. Nystatin is poorly absorbed in gut so that systemic infections must be treated with Amphotericine B, another polyene wit 5-fluorocytosine or with cotrimazole. A larger dose of Histoplasma spores, as from cleaning out old hen houses or exploring bat-infested caves,leads to an acute through usually benign pneumonitis. Primary infections may progress to chronic cavitating disease or may take that form when reactivated later in life.progressive disseminated disease, with an enlarged liver and spleen,anemia and foci in adrenals,meninges and brain,is rare but more likely to occur at the end of life and in patients who also have Hodgkin's disease,leukemia or lymphoma. Histologically,the reaction to the yeast is primarily a diffuse histocytic granuloma with large numbers of yeasts in some cells.Clinically,radiologically,in biopsies and even at necropsy the disease has been mistaken for tuberculosis. Infections with coccidioides are normally asymptomatic or mild and the patient is left with delayed type of hypersensitivity to coccidioidin and perhaps calcified focus or dry thin walled cavity in the lung.More severe disease may occur in migrant workers and military personnel first exposed to infected dust as adults.progressive disease occurs only rarely,but dissemination may then be miliary or skin, bones, central nervous system and the mortality is 50% For this reason very strict precautions are necessary against the risk of laboratory infection from cultures or infected animals.

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