

New Era of Antifungal Agents

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Fungal infections particularly nosocomial ones have increased greatly in recent years, mainly due to the rising number of immunocompromised patients and cause wide-ranging morbidity and mortality. However, the current antifungal therapy in total is limited, and the development of unique drugs has been slow. Yet only a few drug classes are available to treat fungal infections, and this problem is compounded by the emergence of antifungal resistance. Current drug therapy is often toxic, long-term, and expensive and has limited effectiveness.

Natural products such as plants have been the most productive source for new drug development and could produce a variety of medicinal components that can inhibit fungal growth. Nano particles (NPs) have also been considered as novel antifungal agents with high surface area and high reactivity.

It is hoped that the new agents e.g. natural & nano products will usher in a new era of antifungal therapy.

Brain Infection Due to Black Yeast like Fungi; How Come We Are Alive?

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Cerebral phaeohyphomycosis is the collective name for a group of cerebral fungal infections that are characterized by black necrotic tissue or black CSF. If untreated, the infection leads to death within weeks, months, or, occasionally, years. This infection is caused by a group of black fungi, and emerging pathogens from this group are still being encountered. The thought is a bit frightening, but perfectly healthy people may suddenly die of a fungal brain infection. This type of disease has been known for 100 years. Nevertheless, there has been very little progress in early diagnoses. The disorder is often overlooked because symptoms are similar to those of cerebral carcinoma, and the option of a fungal infection will not be mostly considered by the physician. In current clinical practice, a fungal brain infection is, therefore, diagnosed mostly at a late stage of infection or even post mortem. Although rare, *Rhinoctadiella*, *mackenziei* and *Cladophialophora bantiana* are extremely lethal neurotropic filamentous fungi related to the black yeasts. Despite therapy, the mortality rates reach up exceeding 75%. The infection also occurs in patients with decreased immunity due to organ transplants, long-term corticosteroid administration, in which case survival chances are even lower. Currently, most clinicians would be inclined to use amphotericin B as a standard therapy for severe infections; however, posaconazole seems to be a good option instead of inadequate amphotericin treatment.

Clinical Mycology: New Challenges and Controversies Surrounding Fungal Infections

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In the recent decades, a new wave of challenges and controversies surrounding medically important fungi and their infections has prevailed. But still, many questions are unanswered and controversies persist relating to new picture of fungal infections. Medical mycologists try to solve these contradictions and reach to a common understanding of their views and hypotheses. The present lecture will discuss most recent challenges and different views of scientists in pathogenicity of fungi proposed in publications and conferences. Based on expanding our knowledge in interaction of clinical mycology and host physiology along with living environment, the target and concept of mycosis is also changing and new terminology and disease classifications are emerging. Until 1970 there were less species noted as pathogens for man, but today the species surrounding controversies for

pathogenicity are increasing with a noticeable rate. A recent example of contradiction is the pathogenic role of *Malassezia spp.*, *Candida spp.* and non-dermatophyte moulds which are human commensal, and has always been a matter of speculative among researchers. Their role in the pathogenesis is less clear, and in some cases, controversies among mycologists get so tense where, some deny any association of these commensal with infections. Some other new challenges will rise in this speech are: a) plant pathogens breaking their boundaries and become potentially pathogenic for human. b) increase rate of hosts with intact immune system affected with mycoses. c) challenges associated with resistance to current antifungal treatment. Fortunately clinical mycologists have overcome with the past challenges concerning accurate diagnosis of mycoses using molecular techniques alongside traditional methods. Hopefully this talk could shed some light on these contradictions to make mycologists more aware of new ideas for further research.

Misdiagnosis of Dermal Fungal Infections with Parasitic or Bacterial Skin Diseases

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Dermal fungal diseases have different clinical forms. The superficial form refers to tinea versicolor. Cutaneous form, known as dermatomycosis, is caused by dermatophytes, *Candida spp.*, and sometime opportunistic fungi. Each form may in turn have several clinical presentations. Several clinical manifestations of different fungal skin diseases and similarity between clinical presentations of dermatomycosis with other skin diseases may lead to misdiagnosis of the disease.

During 30 years (1984-2014), more than 20000 patients admitted to mycology Lab., Emam Reza hospital, Mashhad University of Medical Sciences. All patients had primarily referred to dermatologists and clinically diagnosed with mycotic or parasitic skin diseases. They requested for laboratory examination to reconfirm the clinical diagnosis.

According to primary diagnosis as requested, direct fresh smear with 10-15 % KOH and, as needed, stained smear with Geimsa and Ziehl-Nielsen, methylene blue and gram, in addition to culture on mycological media, Löwenstein-Jensen medium, and, if necessary, other microbiological media were performed.

All of the patients had skin lesions clinically suspected to a type mycotic, parasitic or bacterial skin disease on any part of their body. The result of direct examination was mainly negative for primary clinical diagnosis, but further follow up and laboratory examinations yielded different results. More than 80% of the patient had atypical clinical presentations not matched with primary clinical diagnosis. Among whom, 12.5% of the patients with clinical presentation of mycetoma suffered from cutaneous leishmaniasis. 15% of the patients were diagnosed with cutaneous leishmaniasis, but the clinical presentations were similar to candidal onychomycosis, dermatomycosis, mycetoma, etc. Clinical presentation is not always satisfactory for definite diagnosis. The comments and suggestions of laboratory experts can play an important role to reach an exact and definite diagnosis.

Chronic Pulmonary Aspergillosis in Patients with Underlying Pulmonary Conditions: a Berg Phenomenon?

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Chronic pulmonary aspergillosis (CPA) is one of the clinical presentations of aspergillosis which affects patients with underlying pulmonary conditions. Among the many different underlying conditions, TB is the single most common primary underlying condition in the development of CPA. The CPA definition has been inconsistent in the literature because of a wide range of clinical, radiologic, and anatomopathological manifestations. Recently, it has been accepted that CPA is an umbrella term covering mainly chronic cavitary pulmonary aspergillosis (CCPA) and single aspergilloma. The morbidity and mortality of CPA remain high, even with treatment.

Diagnosis of non-invasive pulmonary aspergillosis is not easy; however, in addition to pulmonary cavitations on chest X-ray, even the presence of fungus ball and hyphae and also mass in a pulmonary cavity, with a positive culture (preferably positive direct examination), the presence of *Aspergillus* IgG antibodies must be definitively demonstrated for the diagnosis of aspergilloma or CPA. Often the diagnosis of CPA is difficult because of its overlapping clinical and radiological characteristics with tuberculosis; hence, it is important to use microbiological and serological testing for the early diagnose CPA. *Aspergillus* PCR and/or antigen in sputum or bronchoscopy may be helpful.

There is not a population study for the evaluation of CPA incidence in exposed hosts; therefore, the determination of real incidence of aspergilloma and CPA after tuberculosis has remained a dilemma because most of the existing reports are case reports or case series on previous diagnosed CPA patients.

In this review, we presented our new findings on the prevalence of CPA in patients with tuberculosis from Iran, the global epidemiology of CPA, different laboratory diagnostic methods, and a discussion on the question "are we encountering a berg phenomenon in CPA in patients with underlying pulmonary conditions."

Diagnostic Challenges in Opportunistic Invasive Fungal Infections, New Approaches for Detection, Identification and Typing

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The most critical point among challenges with opportunistic invasive fungi mainly *Aspergillus* spp. and *Candida* spp., is the reliable diagnosis of the infections. Early diagnosis and species identification are critically important for successful treatment, while strain typing is necessary for tracing infection sources and ways of transmission of infection in outbreaks as well as for pathogenesis investigations.

Conventional diagnostic methods, such as direct microscopy, histopathology and culture, which are still the gold standards, are deficient in both sensitivity and rapidity. Novel diagnostic approaches include serological and molecular methods especially the detection of fungal cell wall components or metabolites and the detection of fungal DNA mainly PCR-based methods, in clinical specimens. Galactomannan antigen test for aspergillosis and the universal β -glucan test, as well as other antigen and antibody tests, for *Cryptococcus* spp. and *Pneumocystis* spp, have already been established and implemented in routine clinical laboratories. Detection of fungal DNA is being developed, but has not had a significant impact on clinical laboratories yet, largely because these methods have not been standardized and validated. Sequencing of suitable gene targets, FISH, NASBA, MALDI-TOF MS and NMR spectroscopy are examples of recently developed tools for species identification.

Strain typing is an essential need because it helps strain identification, determining the epidemiological relationships between isolates in outbreaks, patients' monitoring and treatment follow-up, environmental monitoring, local and global epidemiology and database construction. Several sequence and non-sequence-based methods have been evaluated; namely, MLEE, PFGE, RAPD-PCR, STR, MLST, SSDP, MSP, RFLP, AFLP, PCR-SSCP, microsatellites, Rep-PCR, VNTR, and Whole genome sequencing.

In this presentation, various diagnostic approaches for detecting opportunistic invasive fungal infections and associated challenges were described.

Application of Chromatography in Antifungal Drug Discovery from Medicinal Plants

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Plants are promising sources of bioactive compounds for the development of new antifungal drugs. Although probable synergistic effect of natural compounds is still a challenging subject, isolation and characterization of natural active constituents are very considerable. Most of the antifungal natural compounds

are classified as phenols, alkaloids, and terpenoids. In screening assays of natural antifungal agents, samples of crude extracts and essential oils have usually been studied on a wide range of clinical and resistant fungi. The potent samples underwent fractionation, isolation and comprehensive analysis by various techniques such as column chromatography, GC-FID, GC-MS, HPLC, and HPTLC. Our present research program has so far led to the characterization of several active compounds among Iranian native medicinal plants by the efficient use of above techniques. Our further conducted biological screening of medicinal plants samples revealed significant antifungal effects of essential oil, extracts, and pure compounds against standard and clinical isolates of *Candida* species. In conclusion, chromatography systems help researchers to choose proper methods for the isolation and identification of natural antifungal agents.

Herbs as Antifungal Agents; an Example Derived from Traditional Persian Medicine

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Dermal fungal infections are prevalent nowadays. Treatment of this group of skin disorders is expensive to some extent. On the other hand, selecting a proper antifungal agent with fewer adverse effects is a matter of concern. Therefore, introduction of new antifungal agents could be helpful to reduce the costs and to increase the patients' satisfaction. In this regard, natural compounds and herbal products could be good substitutes. The aim of the current study was to introduce herbs with dermal antifungal properties based on traditional Persian medicine (TPM).

This was a review study focusing on outstanding masterpieces of Persian scholars such as The Canon in Medicine by Avicenna and Al-Havi by Rhazes to find out a proper herbal remedy for skin disorders equal to fungal infections in conventional mycology. One of the frequent drugs for skin disorders mentioned in TPM resources is myrrh (*Commiohora molmol* Engl.) from the family Burseraceae (*Morr-e-Makki*). According to Persian hakims, there are symptoms like itching, redness, scaly skin and even, oozing wound which are curable by myrrh either alone or in a combination dosage form. Combination of myrrh and rose oil is a famous poultice applicable for such skin lesions. Aforementioned symptoms are seen if infected by dermatophyte fungi like *Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum canis*, *M. gypseum*, and *T. verrucosum*. The antifungal effects of myrrh oil against skin dermatophytes have been established in current studies because of its active ingredients.

Some natural and herbal products have shown evidenced antifungal activities and could be used in modern mycology as inexpensive favorable substitutes for antifungal agents. Myrrh (*Commiohora molmol*) is a good example derived from TPM textbooks and could be applied as a poultice for curing cutaneous fungal infections caused by dermatophytes. New clinical studies to assess this claim are highly suggested.

Role of Fungi in Diabetic Foot Ulcer- a Superficial Colonizer or True Pathogen

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Foot ulcer is the most common problem in patients with diabetes and the leading cause of hospitalization which may proceed with limb amputation. The pathophysiology of foot ulcer in these patients is complex and is mainly due to neuropathy, peripheral vascular disease, slower wound healing and immunopathy. Secondly, it and, result from virulence, antibiotic resistance of involved pathogens. The most common pathogens responsible for acute Diabetic Foot Infection (DFI) are aerobic bacteria. The diverse causative pathogens with vast virulence factors, and polymicrobial nature of DFI have further complicated antibiotic treatment. Opportunistic and commensal fungi are rare causative agent and should be considered in chronic foot ulcer with delayed healing in diabetic patients. One of the most controversial issues

confronting the DFI is lack of widely agreed guidelines for its diagnosis, treatment, and management.

This review was aimed to address the role of fungi in chronic diabetic foot ulcer-true as pathogen or a superficial colonizer, to discuss the current diagnostic methods and report a rare case with calcaneal osteomyelitis caused by *Aspergillus ochraceus* in a patient with diabetic foot osteomyelitis.