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Medical fungi

Lecture1

Introduction to medical fungi

Mycology is the branch of biology concerned with the study of fungi, including their genetic and biochemical properties, their taxonomy and their use to humans as a source for tinder, medicine, food, and entheogens, as well as their dangers, such as toxicity or infection.

In contrast to the bacteria and viruses, the fungi are eukaryotes (like animals and plants). This is medically relevant in that it impacts how fungal infections are attacked by the immune system and how they are treated pharmacologically. Fungi are scavengers. Environmentally, they play a vital role in the decomposition of dead biological materials and the maintenance of the carbon cycle. Fungi also have industrial uses, chiefly in the production of wine, beer, cheese and antibiotics (e.g., penicillin). These useful characteristics can be contrasted with the more negative roles that fungi play as pathogens of plants and animals. The fungi that infect humans fall into four main categories; superficial (hair, skin and nails only), subcutaneous, true systemic (pathogenic) and opportunistic.

Fungi are ubiquitous and nearly 1.5 million fungal species exist in the universe, but only few fungi were known to be pathogenic to humans. The temperature of 37 °C, low redox potential in tissues and immune barrier prevent majority of fungi from invading human hosts. However, with the change of host environment due to co-morbidities, several saprophytic fungi get the opportunity to adapt to human tissue. The impact of modern medical interventions and fungi adapting to this environment are reasons why many fungi are now known to cause invasive human disease.

Fungus consists of microscopic (observed only under the microscope, it could be unicellular like yeast or multi cellular) and macroscopic organisms (observed with naked eyes like mushrooms and puffballs).

Fungal Metabolism

Metabolism is a term that is used to describe all chemical reactions involved in maintaining the living state of the cells and the organism. Metabolism can be conveniently divided into two categories:

- Catabolism - the breakdown of molecules to obtain energy.

- Anabolism - the synthesis of all compounds needed by the cells.

Primary metabolites: are essential compounds for growth to occur and include proteins, carbohydrates, nucleic acids and lipids. these primary products must be synthesized if they cannot be obtained from the growth medium. These primary metabolites have essential and obvious roles to play in the growth of the fungus. Typically, primary metabolites are associated with the rapid initial growth phase of the organism and maximal production occurs near the end of this phase. Once the fungus enters the stationary phase of growth, however, primary metabolites may be further metabolized. Examples of primary metabolites produced in abundance: enzymes, fats, alcohol and organic acids as well as, low molecular weight compounds.

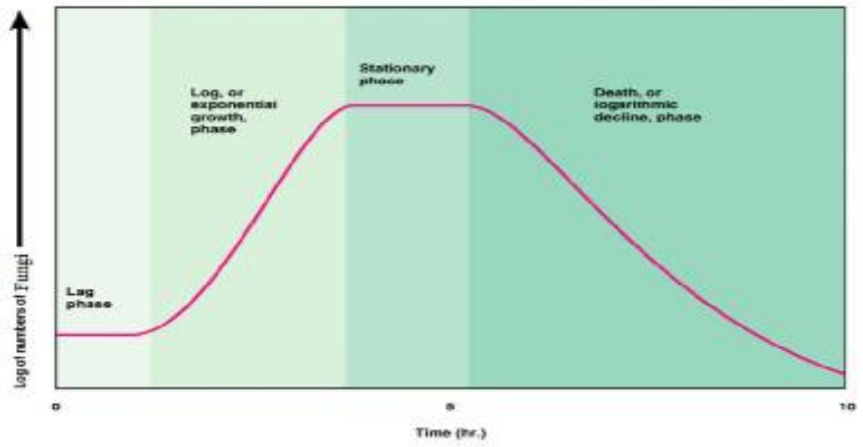


Fig.1: Growth curve or phases of the fungal growth

Primary metabolism is used for

1 Growth and development of hyphal structure

2 Energy metabolism

3 Regulation of metabolism

4 Intermediate in biosynthesis of compound.

Secondary metabolites;

Organic compounds, with low molecular weight, which are not essential for fungal growth but their natural production have certain significances. Furthermore, secondary metabolites are derived from a few common biosynthetic pathways which branch off the primary metabolic pathways and are often produced as families of related compounds, often specific for a group of organisms. Fungi are a rich source of secondary metabolites and have been of interest for humans for thousands of years.

Secondary metabolism is used for:

1 competition

2 antagonism

3 self-defense mechanisms against other living organisms to allow the fungus to occupy the niche and utilize the food.

Types of Fungal secondary metabolites

1. Strobilurin (antifungal)

2. Gibberellins (growth hormones)

3. Herbicides (control weeds)

4. Mycotoxins (poisneous)

5. Insecticides (control insects)

6. Enzymes (proteins)

7. Pigments (dyes)

8. Antibiotics (drugs)

9. Pharmacological drugs

Importance or the reasons for interest in secondary metabolites

1. industries:

A. Antibiotic: Penicillin and cephalosporin.

B. Itaconic acid: cloth industries.

C. Gibberellin: plant growth regulator.

D. Animal feed.

2. Pigment.

3. Bioluminescence.

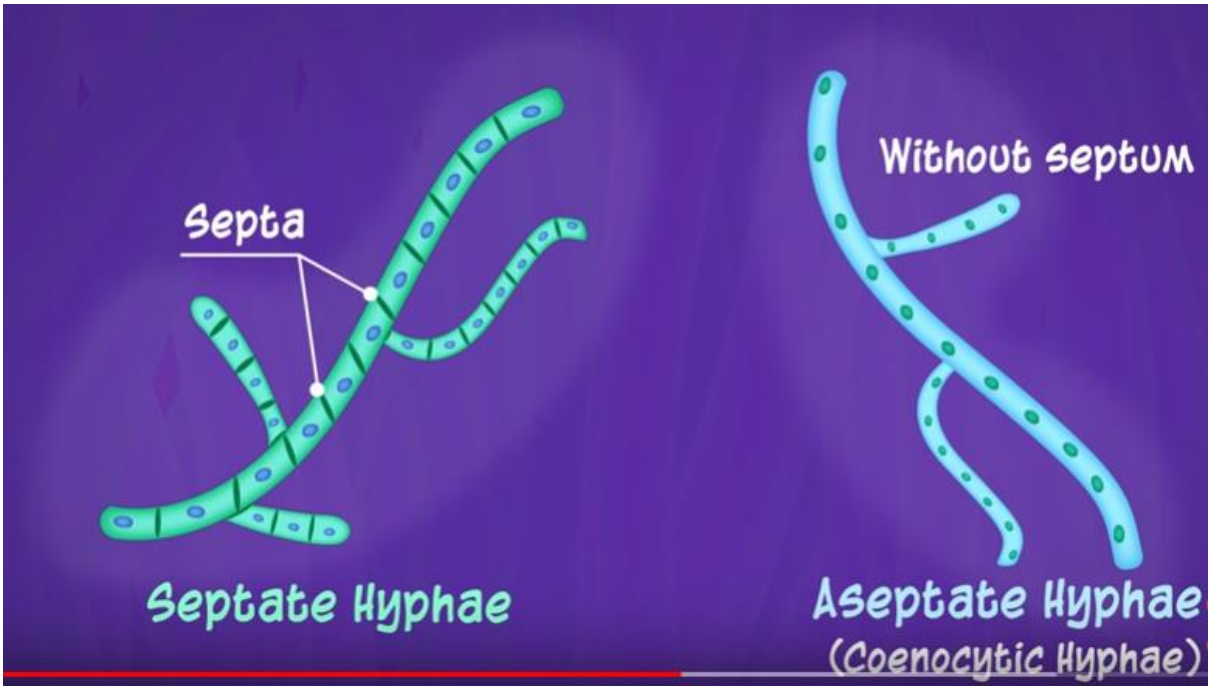
Lecture2

Structure, reproduction and classification

Structure of fungi

Except for yeasts, which grow as single cells, most fungi grow as thread-like filaments,. The filaments are called **hyphae** (singular, hypha). Each hypha consists of one or more cells surrounded by a tubular cell wall. A mass of hyphae makes up the body of a fungus, which is called a **mycelium** (plural, mycelia).

The hyphae of most fungi are divided into cells by internal walls called **septa** (singular, septum). Septa usually have little pores that are large enough to allow ribosomes, mitochondria and sometimes nuclei to flow among cells. Hyphae that are divided into cells are called **septate hyphae**. However, the hyphae of some fungi are not separated by septa. Hyphae without septate are called **coenocytic hyphae**. Coenocytic hyphae are big, multinucleated cells.



Dimorphic Fungi

Some fungi take on different shapes, depending on their environmental conditions. These fungi are called **dimorphic fungi**, because they have "two forms." For example, the fungus *Histoplasma capsulatum*, which causes the disease histoplasmosis, is thermally dimorphic; it has two forms that are dependent on temperature. In temperatures of about 25°C, it grows as a brownish mycelium, and looks like a mass of threads. At body temperature (37°C in humans), it grows as single, round yeast cells.

Reproduction of Fungi

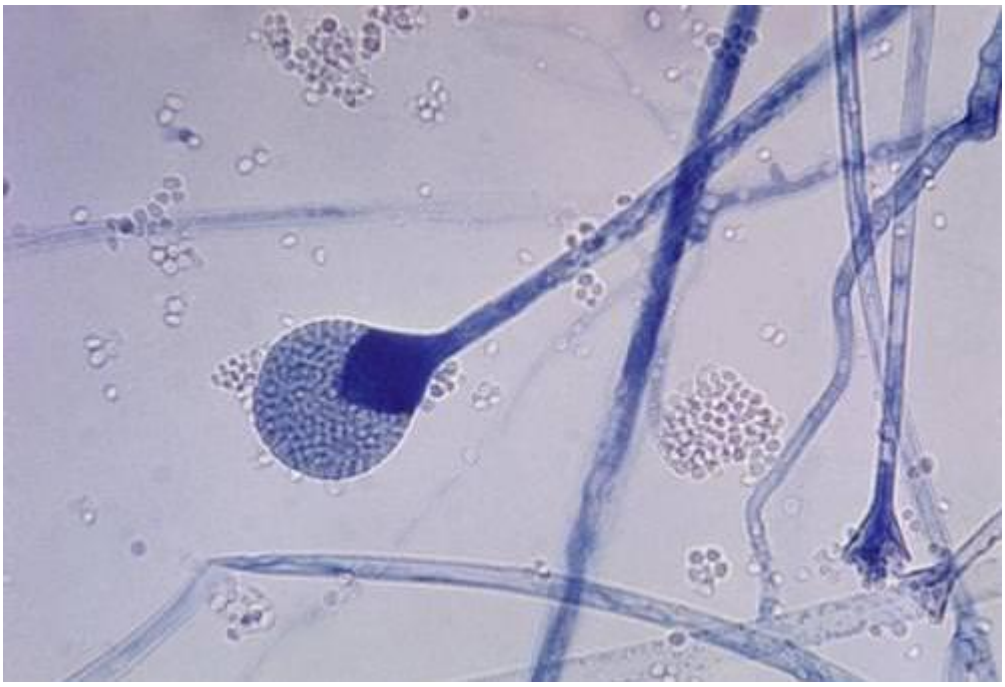
Asexual Reproduction

Most fungi are able to reproduce both sexually and asexually. Most fungi are haploid for the majority of their lifecycle. This is unlike other eukaryotes; for example, humans spend the majority of their lives as diploid organisms.

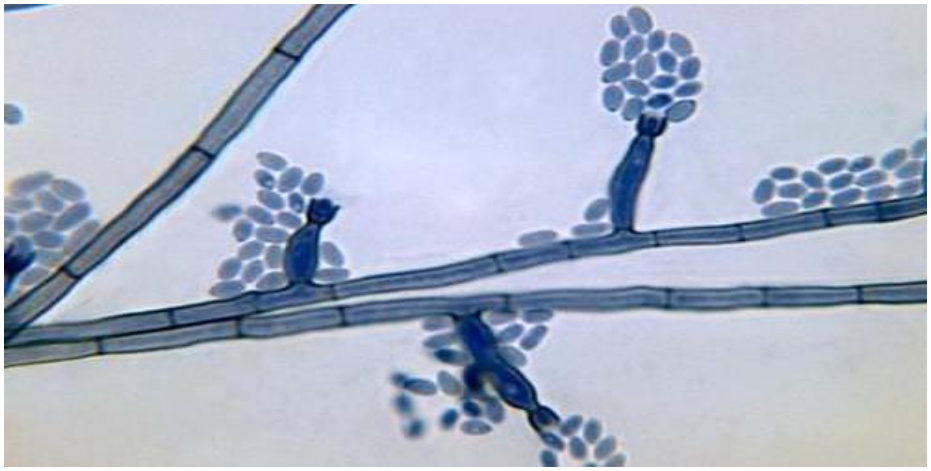
Fungi reproduce asexually by producing genetically identical spores or by breaking off pieces of mycelia. A **spore** is a reproductive cell made by fungi and other organisms. Spores can grow into an individual without being fertilized. Asexual reproduction is common in many fungal species, and it allows for more rapid spreading of the fungus than sexual reproduction does.

There is great variety of asexual reproductive structures. These structures can be used to identify certain fungi. Some fungi produce spores within a protective sac called a **sporangium**, while others produce spores that are not surrounded by a protective sac. In some cases, **sporogenesis**, or the creation of spores, occurs by mitosis. Other fungi produce spores by mitosis and meiosis.

Sporogenesis begins with the growth of special reproductive hyphae called **sporangiophores**. At the end of a sporangiophore is a structure called a **sporangium** (plural, **sporangia**), shown in **Figure** below. Spores are produced by the mitotic division of haploid spore mother cells within the sporangium.



Conidia (singular, **conidium**) are the asexual, non-motile spores of certain genera of fungi. They too are made by mitosis. Conidia are not enclosed in a protective sac like sporangiospores are. Conidia are haploid cells that are genetically identical to the haploid parent. They develop into a new organism when conditions are favorable for growth, such as when a food source is readily available or when humidity levels are right. Fungi of the genus *Penicillium*, which are used to make the antibiotic penicillin and to flavor certain cheeses, produce conidia, as shown in **Figure** below.



Spores may be dispersed by water, wind, or other organisms. Some fungi even have “cannons” that “shoot” the spores far from the parent organism. You are probably familiar with puffballs. They release a cloud of spores when knocked or stepped on. Wherever the spores happen to land, they do not germinate until conditions are favorable for growth. Then they develop into new **hyphae**.

Yeasts do not produce spores, instead they reproduce asexually by budding. **Budding** is the asexual formation of a new organism by “pinching off” from the parent organism, as shown in **Figure** below. The offspring yeast cell is always genetically identical to the parent cell.

Sexual Reproduction

Sexual reproduction via meiosis exists in all fungal phyla, except for the class Deuteromycota. Fungal sexual reproduction differs in many ways from sexual reproduction in animals or plants. Many differences also exist between fungal groups, and differences such as morphology, types of sexual structures, and types of spores have been used to classify fungi. Many fungal species have complex systems that allow mating only between individuals of opposite mating type (see below), while others can mate and sexually reproduce with any other individual, including themselves

Fungal gametes usually look alike, and they are often referred to as "+" and "-" instead of "male" and "female". Each mating type can signal its presence to other individuals. This is done using chemical signals such as pheromones, steroids, or carotenoids. The two haploid mycelia eventually grow toward each other and fuse. After the fusion of the mycelia, some fungi go through a heterokaryotic stage in which cells contain two genetically distinct haploid nuclei that do not fuse right away. It may take hours, days, or even centuries before the parental nuclei fuse in the short-lived diploid phase.

The results of sexual reproduction are spores, called zygospores, that are genetically different from the parents. After they are released, the zygospores will germinate to form a haploid hyphae, and the lifecycle continues. The ability of some fungi to reproduce both sexually and asexually is a form of adaption to changes in the environment. This ability gives fungi an adaptive advantage and allows them to spread quickly into new areas.

Summary

- Fungi reproduce asexually by producing genetically identical spores either by mitosis or by breaking off pieces of mycelia.
- In sexual reproduction, fungal gametes fuse to produce zygospores.
- Sporogenesis begins with the growth of special reproductive hyphae called sporangiophores. At the end of a sporangiophore is a structure called a sporangium, which is where spores are produced.
- Spores may be dispersed by water, wind, or other organisms.

Classification of fungi

Both plants and fungi have cell walls, while members of the Animal Kingdom do not have cell walls. However, the fungi are now considered a separate kingdom, distinct from both plants and animals. Many studies have identified several distinct morphological, biochemical, and genetic features in fungi that clearly distinguish them from the other kingdoms. For these reasons, fungi are placed in their own kingdom, separate from plants.

The major divisions (phyla) of fungi have been classified based mainly on their sexual reproductive structures. Currently, seven fungal divisions are proposed.

1. The Blastocladiomycota are commonly known as **blastocladiomycetes.** They are fungi that are saprotrophs and are parasites of all eukaryotic groups. They undergo meiosis in their spores unlike their close relatives, the chytrids, which mostly undergo meiosis of zygotes.
2. The Neocallimastigomycota are commonly known as **neocallimastigomycetes.** They are anaerobic fungi that live in the digestive system of large herbivorous mammals. They do not have mitochondria, instead they have organelles called **hydrogenosomes** that produce ATP. Similar to chrytrids, neocallimastigomycetes form zoospores that have a single or many flagella.
3. Members of the **Glomeromycota** are fungi that form mycorrhizae with higher plants. Only one species has been observed forming zygospores; all other species solely reproduce asexually. The symbiotic association between the Glomeromycota and plants is ancient, with evidence dating back to 400 million years ago.
4. The **Zygomycota** reproduce sexually with spores called zygospores and asexually with sporangiospores. Black bread mold (*Rhizopus stolonifer*) is a common species that belongs to this group. Members of this phyla that can cause disease and food spoilage include *Mucor, Rhizomucor,* and *Rhizopus.*
5. Members of the **Basidiomycota,** produce spores called basidiospores on stalks called **basidia.** Most common mushrooms belong to this group, as well as rust and smut fungi, which are major pathogens of grains. Other important Basidiomyces include the maize pathogen, *Ustilago maydis* and commensal species of the genus *Malassezia.*
6. The **Ascomycota** are commonly known as **sac fungi.** These fungi form meiotic spores called ascospores, which are enclosed in a special sac-like structure called an **ascus.** This division includes morels, a few mushrooms, truffles, single-celled yeasts, and many filamentous fungi living as saprotrophs, parasites, and mutualistic symbionts. Important genera of filamentous Ascomycetes include *Aspergillus* and *Penicillium*, which are used in food production, and *Claviceps*, a parasite of cereal crops. Many Ascomycetes species have only been observed undergoing asexual reproduction.
7. The **Chytridiomycota** are commonly known as **chytrids.** These fungi are found worldwide. Chytrids produce zoospores that are able to move through aqueous environments with a single flagellum.

Lecture3

Types of mycoses

Mycosis is a fungal infection of animals, including humans. Mycoses are common and a variety of environmental and physiological conditions can contribute to the development of fungal diseases. Inhalation of fungal spores or localized colonization of the skin may initiate persistent infections; therefore, mycoses often start in the lungs or on the skin.

Types of mycoses:

Superficial mycoses

As listed above, in superficial mycoses infection is localized to the skin, the hair, and the nails. an example is "ringworm" or "tinea", an infection of the skin by a dermatophyte. Ringworm refers to the characteristic central clearing that often occurs in dermatophyte infections of the skin. Candida albicans is a yeast causing candidiasis or "thrush" in humans. As a superficial mycosis, candidiasis typically infects the mouth or vagina. C. albicans is part of the normal flora of the vagina and gastrointestinal tract and is termed a "commensal". However, during times of ill health or impaired immunity the balance can alter and the organism multiplies to cause disease. Antibiotic treatment can also alter the normal bacterial flora allowing C. albicans to flourish.

Subcutaneous mycoses

These are infections confined to the dermis, subcutaneous tissue or adjacent structures. Infection may arise following the wounding of the skin. These mycoses are rare and confined mainly to tropical regions. They tend to be slow in onset and chronic in duration. An example is sporotrichosis caused by sporothrix schenckii. The fungus is dimorphic, being a mold that can convert to a yeast form at 37°c on rich laboratory media or in infection. Infection usually follows and insect bite, thorn prick or scratch from a fish spine. Certain occupation groups appear to have increased risk from infection. These include florists, farm workers and others who handle hay and moss. The most common symptom is an ulcerative lesion that may develop into lymphangitis.

Systemic mycoses (primary and opportunistic)

these are invasive infections of the internal organs with the organism gaining entry by the lungs, gastrointestinal tract or through intravenous lines. They may be caused by: (i) primary pathogenic fungi or (ii) by opportunistic fungi that are of marginal pathogenicity but can infect the immunocompromised host.

primary pathogenic fungi

Infection occurs in previously healthy persons and arises through the respiratory route. Examples include histoplasmosis, blastomycosis, coccidiomycosis and Paracoccidioidomycosis.

Opportunistic fungi

Here, patients usually have some serious immune or metabolic defect, or have undergone surgery. The diseases include aspergillosis, systemic candidiasis and cryptococcosis. Exceptionally, other fungi that are normally not pathogenic, such as trichosporon, fusarium or penicillium, may cause systemic infections.

Aspergillosis: this is the name given to a number of different diseases caused by the mold aspergillus. It produces large numbers of spores and occurs world-wide. in the United Kingdom, a. fumigatus is the most common species causing disease. The organism can infect the lungs, inner ear, sinuses and, rarely, the eye of previously healthy persons. In the immunosuppressed host, aspergillus can disseminate throughout the body.

Candidiasis: in severely immunocompromised patients (e.g. those receiving chemotherapy) C. albicans, that is part of the normal human flora (see above), can proliferate and disseminate throughout the body.

Cryptococcosis: this is a systemic infection caused by the yeast cryptococcus neoformans. The commonest manifestation is a subacute or chronic form of meningitis resulting from the inhalation of the organism. Pulmonary infection can also occur. The disease affects both healthy and immunosuppressed individuals and occurs worldwide. C. neoformans can be isolated in large numbers from pigeon droppings in the environment, although such birds do not appear to harbor the yeast.

Lecture4

General principle in treatment

PRINCIPLE 1: KNOW THE SPECTRUM OF ACTIVITY OF COMMONLY USED ANTIFUNGALS

The three major classes of modern antifungals used in the treatment of mold infections consist of: the triazole antifungals (posaconazole, voriconazole), the echinocandins (caspofungin, micafungin, anidulafungin) and AMB-based therapy (Amphotericin B lipid complex). All those classes of drugs have their own limitations in terms of coverage for different molds. For example, voriconazole has excellent activity against *Aspergillus* species and modest activity against *Fusarium* species. Voriconazole also has good activity against *Scedosporium apiospermum*. However, it lacks an important coverage against the *Mucorales* and *Scedosporium prolificans*. Unlike voriconazole, posaconazole is active *Mucorales*, although some isolates have intrinsically high MICs (minimum inhibitory concentration) that may be untreatable with the current oral formulation.

The echinocandins inhibit growth of *Aspergillus* species, even though this class lacks true fungicidal activity in vitro and in vivo. Hence, many clinicians use echinocandins as monotherapy for invasive aspergillosis only in situations of less severe disease, after immune reconstitution, as a second-line agent when other drugs cannot be tolerated, or in combination with a second antifungal.

Finally, AMB-based regimens have a broad spectrum of activity with the exception of some uncommon molds, such as *Scedosporium, Fusarium* species. Thus, the prescribing physician, who treats patients with a variety of mold infections, would benefit from knowing the full spectrum of activity of drugs, especially in the context of preemptive and targeted treatment of invasive mold infections.

PRINCIPLE 2: KNOWLEDGE OF THE PATHOGENESIS AND NATURAL HISTORY OF MOLD INFECTIONS IS ESSENTIAL FOR EFFECTIVE USE OF ANTIFUNGAL THERAPY IN HIGH-RISK PATIENTS

Most antifungals are prescribed for prophylaxis or empirical treatment based on clinical signs and symptoms such as persistent fever. Preemptive and targeted treatment courses of antifungals generally account for no more than 30% of those treatment episodes.

In the United States, and many other countries, empiric therapy remains the predominant approach for antifungal use, especially in the setting of persistent neutropenic fever.

Finally, clinicians must recognize that cultures and histopathology are rarely positive until relatively late in the course of an invasive mold infection, when the fungal burden is high. Even so, culture and histopathology data are often essential for targeting current therapy and future secondary prophylaxis approaches, especially with respect to orally administered agents against specific fungi.

PRINCIPLE 3: IT IS IMPORTANT FOR THE CLINICIAN TO KNOW THE PHARMACOKINETIC AND PHARMACODYNAMIC BEHAVIOR OF ANTIFUNGALS

Even the most broad-spectrum antifungals have notable pharmacokinetic limitations. These limitations are driven by the fact that these agents when given orally may not be absorbed in the setting of mucositis or poor appetite, as is the case with posaconazole.

In addition, several antifungals have limitations in penetration of some sites of infection, such as the brain and eye (e.g., the echinocandins, posaconazole, itraconazole) or the urine (e.g., the echinocandins, voriconazole, posaconazole). Therefore, “staging” of the infection for potential or likely sites of dissemination is essential for choosing an appropriate antifungal that will target critical sites of infection.

Knowledge of concomitant medications and potential pharmacokinetic and toxicodynamic interactions of antifungal agents with other drugs used in the transplant or oncology setting is essential.

PRINCIPLE 4: KNOW THE ADVERSE EFFECTS OF ANTIFUNGALS

Antifungal medications target fungi that are eukaryotic organisms. Not surprisingly, these drugs have some toxicities in humans that can be magnified or accelerated in medically complex patients receiving multiple medications.

PRINCIPLE 5: EARLY DIAGNOSIS IS THE MOST IMPORTANT VARIABLE IN TREATMENT RESPONSE

Antifungal drugs work well when the inoculum is lowest and the risk of dissemination to other organs is low. Improved survival attributed to newer

antifungals often occurred in the background of increasingly earlier diagnosis and treatment.

More sensitive biomarkers that allow for earlier diagnosis should translate to better strategies for the use of antifungals. Therefore, there is a consensus in the mycology field that in the future, we shall see an increased reliance and introduction of new, even better biomarkers that would allow us to move away from empiric antifungal therapy (even if we are not quite there yet) and start treatment preemptively for a mold infection.

PRINCIPLE 6: KNOW YOUR LOCAL EPIDEMIOLOGY

Analysis of the local epidemiology of invasive fungal infections is essential for effective infection control programs and antifungal stewardship. This knowledge is developed through quality improvement processes in the clinical microbiology laboratory that uses traditional and culture-independent diagnostic methods and with an attempt to increase autopsy rates.

Knowledge of the local epidemiology plays a key role for guiding empiric treatment approaches. For example, if early pulmonary mucormycosis is treated as invasive pulmonary aspergillosis with voriconazole-based regimen, the in-hospital mortality doubles, unless AMB-based therapy is introduced in the first 6 days from the onset of the symptoms.

PRINCIPLE 7: THE PROGNOSIS OF INFECTION IS HEAVILY DEPENDENT ON THE DEGREE AND COURSE OF IMMUNOSUPPRESSION IN THE PATIENT

Immunosuppression, like immunity itself, is highly individualized and sometimes difficult to define objectively. Nevertheless, clinicians must have a concept of the patient's "net state of immunosuppression" and understanding of future immunosuppression risks when developing an individualized treatment plan. The most common variables in the hematology/oncology patients include: (1) the duration and sequence of immunosuppressive therapy; (2) depth and duration of neutropenia; (3) the number of episodes of neutropenia; (4) the presence of mucositis; and (5) whether the patient has ongoing metabolic issues (e.g., diabetes, or iron overload) or severe catabolic state (malnutrition, hyperglycemia), which is frequently encountered in the late stages of relapsed malignancy.

PRINCIPLE 8: VARIABLES INFLUENCING THE SELECTION OF AN ANTIFUNGAL AGENT CHANGE IN THE ACUTE VERSUS CHRONIC STATES OF TREATMENT

For an acutely ill patient, selection of an antifungal should initially focus on agents with the broadest spectrum of activity and pharmacokinetic predictability over patient convenience and risks of future toxicity.

PRINCIPLE 9: THE MANAGEMENT OF OPPORTUNISTIC MOLD INFECTION NEEDS MULTIDISCIPLINARY APPROACH

A coordinated approach by an expert clinical mycologist, in close collaboration with a hematologist, is of paramount importance. An experienced microbiologist, pathologist, and pharmacist also play important roles in the management of complex patients.

PRINCIPLE 10: EVIDENCE-BASED TREATMENT GUIDELINES ARE A STARTING POINT, NOT A ROADMAP, FOR MANAGING PATIENTS WITH INVASIVE FUNGAL INFECTIONS

Consensus treatment guidelines have been published that provide evidence-based recommendations for the diagnosis and treatment of invasive aspergillosis and empiric treatment of invasive fungal infections in the setting of febrile neutropenia. European guidelines for the management of mucormycosis have been recently developed, but are still lacking for other molds such as *Fusarium* or *Scedosporium* spp. The treatment recommendations are based, whenever possible, on data from prospective, multicenter randomized trials and graded according to the strength of evidence.

Lecture5

Dermatophytes and Candidiasis

Dermatophytes

Dermatophytes are fungi that require keratin for growth. These fungi can cause superficial infections of the skin, hair, and nails. Dermatophytes are spread by direct contact from other people (anthropophilic organisms), animals (zoophilic organisms), and soil (geophilic organisms), as well as indirectly from fomites. Dermatophyte infections can be readily diagnosed based on the history, physical examination, and potassium hydroxide (KOH) microscopy. Diagnosis occasionally requires Wood's lamp examination and fungal culture or histologic examination. Topical therapy is used for most dermatophyte infections. Oral

Tinea Capitis

therapy is preferred for tinea capitis, tinea barbae, and onychomycosis.

Microsporum, Trichophyton, and Epider-mophyton species are the most common pathogens in skin infections.

Tinea capitis, the most common dermatophytosis in children, is an infection of the scalp and hair shafts. Transmission is fostered by poor hygiene and overcrowding, and can occur through contaminated hats, brushes, pillowcases, and other inanimate objects. After being shed, affected hairs can harbor viable organisms for more than one year.

Tinea Corporis

Tinea corporis, or ringworm, typically appears as single or multiple, annular, scaly lesions with central clearing, a slightly elevated, reddened edge, and sharp margination (abrupt transition from abnormal to normal skin) on the trunk, extremities, or face.

Tinea Barbae

Tinea barbae involves the skin and coarse hairs of the beard and mustache area. This dermatophyte infection occurs in adult men and hirsute women. Because the usual cause is a zoophilic organism, farm workers are most often affected. Tinea barbae may cause scaling, follicular pustules, and erythema.

Tinea Faciei

Tinea faciei tends to occur in the non-bearded area of the face. The patient may complain of itching and burning, which become worse after sunlight exposure.

Tinea Manuum

Tinea manuum is a fungal infection of one or, occasionally, both hands.

Tinea Cruris

Tinea cruris, frequently called “jock itch,” is a dermatophyte infection of the groin. This dermatophytosis is more common in men than in women and is frequently associated with *tinea pedis*. *Tinea cruris* occurs when ambient temperature and humidity are high. Occlusion from wet or tight-fitting clothing provides an optimal environment for infection.

Tinea Pedis

Tinea pedis, or athlete's foot. The interdigital form of *tinea pedis* is most common. It is characterized by fissuring, maceration, and scaling in the interdigital spaces of the fourth and fifth toes.

Tinea Unguium

Tinea unguium, a dermatophyte infection of the nail, is a subset of onychomycosis, which also may be caused by yeast and non-dermatophyte molds. Risk factors for this infection include aging, diabetes, poorly fitting shoes, and the presence of *tinea pedis*.

Candidiasis

There are many kinds of fungus that live in the human body. One type is called candida. It's a type of yeast that normally lives in small amounts in places like your mouth and belly, or on your skin without causing any problems. But when the environment is right, the yeast can multiply and grow out of control.

The infection it causes is called candidiasis. **Candidiasis** is a fungal infection due to any type of *Candida* (a type of yeast).

There are several different types of it. Most can be easily treated with over-the-counter or prescription medications.

Thrush (Oropharyngeal Candidiasis)

More than 20 types of *Candida* can cause infection with *Candida albicans* being the most common. When the candida yeast spreads in the mouth and throat, it can cause an infection called thrush. It's most common in newborns, the elderly and people with weakened immune systems. Also, more likely to get it are adults who:

- Are being treated for cancer
- Take medications like corticosteroids and wide-spectrum antibiotics
- Wear dentures
- Have diabetes

The symptoms include:

- White or yellow patches on the tongue, lips, gums, roof of mouth, and inner cheeks
- Redness or soreness in the mouth and throat
- Cracking at the corners of the mouth
- Pain when swallowing, if it spreads to the throat

Thrush is treated with antifungal medicines like nystatin, clotrimazole, and fluconazole. Rinsing the mouth with chlorhexidine (CHX) mouthwash may help prevent infections in people with weakened immune systems.

Genital Yeast Infection (Genital Candidiasis)

Three out of four adult women will get at least one yeast infection during their lifetime. This occurs when too much yeast grows in the vagina. (Men also can get a genital yeast infection, but it's much less common).

A yeast infection typically happens when the balance in the vagina changes. This can be caused by pregnancy, diabetes, use of some medicines, lubricants, or spermicides, or a weakened immune system. Occasionally, the infection can be passed from person to person during sex.

The symptoms include:

- Extreme itchiness in the vagina
- Redness and swelling of the vagina and vulva (the outer part of the female genitals)
- Pain and burning when you pee
- A thick, white “cottage cheese” discharge from the vagina

A man with a yeast infection may have an itchy rash on his penis.

Because the symptoms in women can be similar to other infections like bacterial vaginosis (bacterial overgrowth in the vagina) and sexually transmitted diseases, it's important to visit your doctor.

Most times, an over-the-counter antifungal suppository, tablet, or cream will knock out the infection. Your doctor might also prescribe a single dose of a prescription antifungal medicine like fluconazole. Tell your doctor if you get yeast infections more than four times a year. She may recommend regular doses of antifungal medication over several months to fight the repeated infections.

Diaper Rash from Yeast Infection

Though diaper rashes are usually caused by leaving a wet or soiled diaper on too long, once your baby's skin is irritated, infection is more likely. If his diaper rash isn't going away, check to see if his bottom is red and sensitive, and if there's a raised red border around the sores. If so, have your pediatrician check for candidiasis. It can be treated with an antifungal cream.

Keeping your baby's bottom clean and dry is a good start to help prevent diaper rash and candidiasis.

Invasive Candidiasis

If candida yeast enters the blood stream (usually through medical equipment or devices), it can travel to the heart, brain, blood, eyes, and bones. This can cause a serious, life-threatening infection.

This happens most often to people who have recently been admitted to a hospital or live in a health care facility, such as a nursing home. Like other types of yeast infections, if you have diabetes, a weakened immune system, kidney failure, or are on antibiotics, your chances of getting it are greater.

The symptoms include fever and chills. Since it's likely a person with this infection is already sick with another condition, it can be hard to diagnose.

Invasive candidiasis is treated with an oral or intravenous dose of antifungal medication. If you are having surgery and have higher odds of a yeast infection, your doctor might prescribe a series of antifungal medicines before the procedure.

Treatment typically consists of oral or intravenous antifungal medications. In candida infections of the blood, intravenous fluconazole or an echinocandin such as caspofungin may be used. Amphotericin B is another option.

Lecture6

What is Histoplasmosis?

Histoplasmosis is a type of lung infection. It is caused by inhaling *Histoplasma capsulatum* fungal spores. These spores are found in soil and in the droppings of bats and birds. This fungus mainly grows in the central, southeastern, and mid-Atlantic states.

Most cases of histoplasmosis don't require treatment. However, people with weaker immune systems may experience serious problems. The disease may progress and spread to other areas of the body. Skin lesions have been reported in 10 to 15 percent of cases of histoplasmosis that has spread throughout the body.

What Should I Watch For?

Most people who are infected with this fungus have no symptoms. However, the risk of symptoms increases as you breathe in more spores. If you are going to have symptoms, they generally show up about 10 days after exposure.

Possible symptoms include:

- fever
- dry cough
- chest pain
- joint pain
- red bumps on your lower legs

In severe cases, symptoms may include:

- excessive sweating
- shortness of breath
- coughing up blood

Widespread histoplasmosis causes inflammation and irritation. Symptoms may include:

- chest pain, caused by swelling around the heart
- high fever
- stiff neck and headaches, from swelling around the brain and spinal cord

Types of Histoplasmosis

*Acute

Acute, or short-term, histoplasmosis is typically mild. It rarely leads to complications.

*Chronic

Chronic, or long-term, histoplasmosis occurs far less often than the acute form. In rare cases, it can spread throughout the body. Once histoplasmosis has spread throughout your body it is life-threatening if it isn't treated.

Sporotrichosis

What is sporotrichosis?
Sporotrichosis (also known as "rose gardener's disease") is an infection caused by a fungus called *Sporothrix*. This fungus lives throughout the world in soil and on plant matter such as sphagnum moss, rose bushes, and hay. People get sporotrichosis by coming in contact with the fungal spores in the environment. Cutaneous (skin) infection is the most common form of the infection. It occurs when the fungus enters the skin through a small cut or scrape, usually after someone touches contaminated plant matter. Skin on the hands or arms is most commonly affected.

Types of sporotrichosis

- **Cutaneous (skin) sporotrichosis** is the most common form of the infection. It usually occurs on a person's hand or the arm after touching contaminated plant matter.
- **Pulmonary (lung) sporotrichosis** is rare but can happen after someone breathes in fungal spores from the environment.
- **Disseminated sporotrichosis** occurs when the infection spreads to another part of the body, such as bones, joints, or central nervous system. This form of sporotrichosis usually affects people with health problems or who take medicines that lower the body's ability to fight germs and sickness.

Symptoms

The symptoms of sporotrichosis depend on where the fungus is growing in the body. Contact your healthcare provider if you have symptoms that you think are related to sporotrichosis.

Sporotrichosis usually affects the skin or tissues underneath the skin. The first symptom of **cutaneous (skin) sporotrichosis** is usually a small, painless bump that can develop any time from 1 to 12 weeks after exposure to the fungus. The bump can be red, pink, or purple, and usually appears on the finger, hand, or arm where the fungus has entered through a break in the skin. The bump will eventually grow larger and may look like an open sore or ulcer that is very slow to heal. Additional bumps or sores may appear later near the original one.

Pulmonary (lung) sporotrichosis is rare. Symptoms include cough, shortness of breath, chest pain, and fever.

Symptoms of **disseminated sporotrichosis** depend on the body part affected. For example, infection of the joints can cause joint pain that may be confused with rheumatoid arthritis. Infections of the central nervous system can involve difficulty thinking, headache, and seizures.

Lecture7

Rhizopus& Penicillium

Rhizopus is a genus of common saprophytic fungi on plants and specialized parasites on animals. They are found in a wide variety of organic substances, including "mature fruits and vegetables", jellies, syrups, leather, bread, peanuts,

and tobacco. They are multicellular. Some Rhizopus species are opportunistic agents of human zygomycosis (fungal infection) and can be fatal. This widespread genus includes at least eight species. Rhizopus species grow as filamentous, branching hyphae that generally lack cross-walls (i.e., they are coenocytic). They reproduce by forming asexual and sexual spores. In asexual reproduction, sporangiospores are produced inside a spherical structure, the sporangium. Sporangia are supported by the sporangiophore. Sporangiophores arise among distinctive, root-like rhizoids. In sexual reproduction, a dark zygospore is produced at the point where two compatible mycelia fuse. Upon germination, a zygospore produces colonies that are genetically different from either parent.

- R. oligosporus is used to make tempeh, a fermented food derived from soybeans.

Note: Tempeh or tempe is a traditional Indonesian soy product, that is made from fermented soybeans. It is made by a natural culturing and controlled fermentation process that binds soybeans into a cake form. Here a special fungus is used, which has the Latin name Rhizopus oligosporus, usually marketed under the name tempeh starter.

- R. oryzae is used in the production of alcoholic beverages in parts of Asia and Africa.

- Rhizopus stolonifer (black bread mold) causes fruit rot on strawberry, tomato, and sweet potato and used in commercial production of fumaric acid and cortisone.

Note: Fumaric acid is an organic compound with the formula $HO_2CCH=CHCO_2H$. A white solid, fumaric acid occurs widely in nature. It has a fruit-like taste and has been used as a food additive.

Note: Cortisone is a pregnane (21-carbon) steroid hormone. Cortisone suppresses the immune system, thus reducing inflammation and attendant pain and swelling at the site of the injury.

Penicillium (Division: Ascomycota) ascomycetous fungi are of major importance in the natural environment as well as food and drug production.

Some members of the genus produce penicillin, a molecule that is used as an antibiotic, which kills or stops the growth of certain kinds of bacteria. Other species are used in cheese making. According to the Dictionary of the Fungi (10th edition, 2008), the widespread genus contains over 300 species

which produced a brush-like conidiophore (asexual fruiting structure).

Selected species include:

- Penicillium camemberti, which is used in the production of Camembert and Brie cheeses

note: Camembert is a moist, soft, creamy, surface-ripened cow's milk cheese. It was first made in the late 18th century at Camembert, Normandy, in northern France.

- Penicillium candidum, which is used in making Brie and Camembert. It has been reduced to synonymy with Penicillium camemberti
- Penicillium chrysogenum (previously known as Penicillium notatum), which produces the antibiotic penicillin

Note: Penicillium chrysogenum or P. notatum (formerly) is a species of fungus in the genus Penicillium. It is common in temperate and subtropical regions and can be found on salted food products, but it is mostly found in indoor environments, especially in damp or water-damaged buildings

- Penicillium digitatum, a plant pathogen
- Penicillium echinulatum produces Mycophenolic acid

Note: Mycophenolic acid (MPA), and also called mycophenolate, is an immunosuppressant medication used to prevent rejection following organ transplantation and to treat Crohn's disease. Specifically, it is used following kidney, heart, and liver transplantation.

- Penicillium expansum, a plant pathogen, it is a psychrophilic blue mold that is common throughout the world in soil. It causes Blue Mold of apples .
- Penicillium funiculosum, a plant pathogen infecting pineapples.
- Penicillium glaucum, which is used in making Gorgonzola cheese.

Note: Gorgonzola is a veined Italian blue cheese, made from unskimmed cow's milk.

Penicillium italicum, a plant pathogen

Characteristics

The thallus (mycelium) consists of highly branched networks of multinucleated cells located on a septum lacking hyphae that is often colorless. Conidiophores are at the end of each branch accompanied by green spherical constricted units called conidiospores. These individual units play a significant role in reproduction; conidiospores are the main dispersal route of the fungi. Sexual reproduction involves the production of ascospores.

Lecture8

Cryptococcus& Cryptococcosis

Cryptococcus is an invasive fungus that causes cryptococcosis an infection commonly associated with immunosuppressive individuals while being rare in healthy individuals. The two species of Cryptococcus that are commonly associated with infections in humans are Cryptococcus neoformans and Cryptococcus gatti. The organism is widely prevalent in certain regions of the world. However, the most common forms of exposure include a history of exposure to soil, bird droppings.

Cryptococcosis is a potentially fatal fungal disease caused by one of two species; *Cryptococcus neoformans* and *Cryptococcus gattii*. Both were previously thought to be subspecies of *C. neoformans* but have now been identified as distinct species.

Cryptococcosis is believed to be acquired by inhalation of the infectious propagule from the environment. Although the exact nature of the infectious propagule is unknown, the leading hypothesis is the basidiospore created through sexual or asexual reproduction

Etiology

Cryptococcal species are fungal pathogens which are encapsulated yeasts morphologically. Immune suppression is the major underlying mechanism that is involved in the causation of cryptococcal disease. Diseases like AIDS, diabetes, chronic liver disease, chronic renal disease, prolonged use of steroids and patients who undergo organ transplantation are commonly associated with the development of cryptococcal disease.

Epidemiology

Globally approximately 1 million cases of cryptococcosis are reported each year resulting in 625,000 deaths approximately. In the United States incidence of cryptococcosis is estimated to be about 0.4-1.3 cases per 100,000 population and 2-7 cases per 100,000 in people affected with AIDS with a case fatality ratio of about 12%. The incidence of cryptococcal infections has declined drastically over the last two decades owing to advances in the anti-retroviral therapy. Cryptococcus neoformans is usually associated with infections in immunocompromised patients while Cryptococcus gatti is associated with infections in immunocompetent patients.

Cause

Cryptococcosis is a defining opportunistic infection for AIDS, and is the second-most-common AIDS-defining illness in Africa. Other conditions that pose an increased risk include certain lymphomas (e.g., Hodgkin's lymphoma), sarcoidosis, liver cirrhosis, and patients on long-term corticosteroid therapy.

Distribution is worldwide in soil. The prevalence of cryptococcosis has been increasing over the past 20 years for many reasons, including the increase in incidence of AIDS and the expanded use of immunosuppressive drugs.

In humans, *C. neoformans* causes three types of infections:

- Wound or cutaneous cryptococcosis
- Pulmonary cryptococcosis
- Cryptococcal meningitis.

Cryptococcal meningitis (infection of the meninges, the tissue covering the brain) is believed to result from dissemination of the fungus from either an observed or unappreciated pulmonary infection. Often there is also silent dissemination throughout the brain when meningitis is present. *Cryptococcus gattii* causes infections in immunocompetent people (fully functioning immune system). People with defects in their cell-mediated immunity, for example, people with AIDS, are especially susceptible to disseminated cryptococcosis. Cryptococcosis is often fatal, even if treated. It is estimated that the three months case fatality rate is 9% in high-income regions, 55% in low/middle income regions, and 70% in sub-Saharan Africa. As of 2009 there were globally approximately 958,000 annual cases and 625,000 deaths within three months after infection.

Although the most common presentation of cryptococcosis is of *C. neoformans* infection in an immunocompromised person (such as persons living with AIDS), the *C. gattii* is being increasingly recognized as a pathogen in what is presumed to be immunocompetent hosts, especially in Canada and Australia. This may be due to rare exposure and high pathogenicity, or to unrecognised isolated defects in immunity, specific for this organism.

The majority of symptoms of cryptococcosis occur in the lungs, the brain, or both. The following is a list of the major symptoms:

- Fever
- Malaise
- Pleuritic chest pain (sharp pain that occurs over the area of inflammation and increases with breathing movements)
- Cough, usually nonproductive
- Hemoptysis (bloody or blood-tinged sputum)

  Note: **Hemoptysis** is the coughing up of blood or blood-stained mucus from the bronchi, larynx, trachea, or lungs. In other words, it is the airway bleeding.

- Headache
- Vision changes (blurry or double vision, photophobia)
- Nausea and vomiting
- Mental status changes (lethargy, confusion)
- Meningitis

- Seizures
- Coma

Some people may develop skin changes (rash, pustules, nodules, ulcers).