

Host-Pathogen Interaction (Immunology)
Prof. Himanshu Kumar
Laboratory of Immunology and Infectious Disease Biology
Department of Biological Sciences
Indian Institute of Science Education and Research (IISER) – Bhopal

Lecture - 78
Fungal Infection – 2

Hi. So in previous session we have learnt about the fungus and we have mainly learnt about that how our innate immunity to take care of fungal infection. So in this session again we will take this topic in more detail, means in which individual this fungal infection is more prominent and then we will discuss about some list prepared by the WHO, there are different levels of some fungus which is quite dangerous.

Some are less dangerous and some are not so dangerous. And we will also discuss about the two fungal diseases which is caused by a *Cryptococcus neoformans* and *Aspergillus* species. So let us begin this.

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Invasive fungal disease (IFD) by Fungal infection

- Fungal pathogens are associated with people who are at risk due to underlying health problems.
- Weakened immune system, such as chronic lung disease, prior tuberculosis (TB), HIV, cancer, and diabetes mellitus.
- Critically ill patients in an intensive care unit (ICU), patients undergoing invasive medical procedures and receiving broad-spectrum antibiotics, and those taking immune-suppressing medicines are also at risk.



So, there is invasive fungal diseases by fungal infection and the fungal pathogens are associated with people who are risked due to underlying health problems. So here I want to say that many individuals or in society there are many people who has some or other diseases and they have some other health problem. Mainly the health problems are associated with this metabolic in nature. The diseases associated with metabolic disease are like diabetes, hypertension and to some extent cardiovascular diseases.

So those individuals are at or those individuals are more prone to this kind of infection. Weakened immune system as I have discussed in previous session, some individual has some congenital problem, congenital problem may be if you remember my previous session, I have discussed about there are some individuals who have a deficiency in functional neutrophil. There is an impaired ROS production due to mutation in NADPH oxidase okay if you remember that session.

So weakened immune system such as chronic lung diseases, if individual is having some prior tuberculosis history, individual who are infected with human immunodeficiency virus, individual who had cancer or diabetes mellitus, so these individuals are more susceptible. So diabetes mellitus and all these things are metabolic diseases. Critically ill patient in intensive care unit, so individuals who are in intensive care unit.

Patients undergo invasive medical procedure and receiving broad spectrum antibiotics, so too much antibiotic is also not good, broad-spectrum antibiotic and those taking immunosuppressive medicine are also at risk. So you can understand the individual who is undergoing major surgery, generally major surgery is taken place when there is an organ transplant.

So during organ transplant, this is a major surgery plus those individuals are kept over the immunosuppressive drug and this basically causes two-layer complications, one is major surgery, another is immunosuppressive drug. So, these individuals are highly prone to the fungal infection.

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Who are at risk?

It is rising as the risk population continues to expand, due to:

- **Advancements in modern medicine and accessibility to therapies.**
- **Interventions that impair the immune system, such as chemotherapy and immunotherapy for cancer, and**
- **Solid organ transplantation.**
- **Patients with chronic obstructive pulmonary disease (COPD), liver or kidney disease, viral respiratory tract infections such as influenza and those with prior non-tuberculous mycobacterial infections.**
- **The coronavirus disease (COVID-19) pandemic has been associated with an increase in the incidence of comorbid invasive fungal infections.**
 - **Three groups of COVID-19 associated fungal infections; aspergillosis; mucormycosis; and candidaemia**
- **Finally, there is evidence to suggest that both the incidence and geographic range of fungal infections are expanding globally due to climate change.**



Who are at risk? It is rising as the risk population continue to expand due to following reasons. So advancement in modern medicine and accessibility to the therapies. So these days people very quickly take any medicine so that is also not good that may invite the fungal infection or some kind of therapy right, individual is having allergy and those individual can quickly take some immuno, maybe some steroidal molecules or drugs which can basically suppress the immunity.

So those individuals can be prone to the fungal infection. Intervention that impairs the immune system such as chemotherapy, immunotherapy for cancer and solid organ transplantation. So these individuals as I explained you they are highly susceptible to the fungal infection. The patients with a chronic obstructive pulmonary disease or a patient with liver or kidney disease, viral respiratory tract infection such as influenza.

And those with prior non-tuberculosis mycobacterial infection, so these individuals are also highly susceptible to the fungal infection. Probably you may remember one disease which is quite a prominent worldwide after the Covid or not after the Covid, during the Covid, so the Covid or coronavirus disease pandemic has been also associated with an increase in incidence of comorbid invasive fungal infection.

And if you remember there are three groups of Covid-19 associated fungal infection. One is aspergillosis and there is a mucormycosis, mucormycosis is that black fungal disease, it is very well reported in various news channels and all those resources. So this mucormycosis is

also associated with this Covid-19 infection besides aspergillosis and there is also candidemia, There is a presence of candida in the blood.

So here you can see very good association between the fungal infection and other diseases, these viral diseases are associated with fungal diseases. And this mucormycosis is a quite dangerous disease. This infection can take place in various place, it can take place in the brain, it can take place in the nose, it can affect the lungs, pulmonary mucormycosis is also there and this can affect the central nervous system and various organs.

So this is quite dangerous disease. Finally, there is evidence to suggest that both incidence and geographic range of fungal infection are expanding globally due to climate change. So this fungal infection is also associated with the climate change. So there are some dried place but those places are receiving too much rain and so all those things that will increase the humidity and then that will make the individual prone to the fungal infection.

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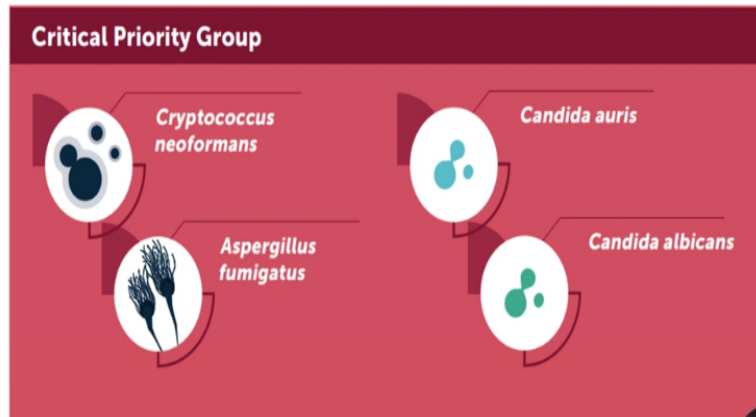
Fungal Infection were enhanced due to

- Rapid emergence of antifungal resistance and, in many settings, limited access to quality diagnostics and treatment.
- Antifungal resistance has major implications for human health. It generally leads to prolonged therapy and hospital stays.

So fungal infections were enhanced due to rapid emergence of antifungal resistance in many setting, limited access to the quality diagnostic and treatment. So, generally the fungal infection detection or diagnosis is a little complicated and it is not so common. So that is why the treatment is not very effective, so these are another reason. So antifungal resistance has major implications for human health. It generally leads to prolonged therapy and hospital stay, so do not underestimate the fungal diseases. Fungal diseases are more complicated to manage.

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WHO fungal priority pathogens list



Here this is I want to talk, the WHO made some kind of list and this is WHO fungal priority pathogen list and this is a critical priority group. So these fungus like a *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida auris* and *Candida albicans*, so they are very critical priority groups. They are quite dangerous fungus. So I will talk about the *Cryptococcus neoformans* and *Aspergillus fumigatus*, the disease caused by these fungus.

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Cryptococcosis

- Overall, approximately one million new cases of cryptococcosis occur annually, and the mortality approaches 50%.
- *Cryptococcus neoformans*, *C. gattii* occurs worldwide in nature and is isolated readily from dry pigeon feces, as well as trees, soil, and other sites.
- From the lungs, these neurotropic yeasts typically migrate to the central nervous system where they cause meningoencephalitis.
- They can also have the capacity to infect many other organs (eg, skin, eyes, prostate).
- *C. neoformans* occurs in immunocompetent persons but more often in patients with HIV/AIDS, hematogenous malignancies, and other immunosuppressive conditions.

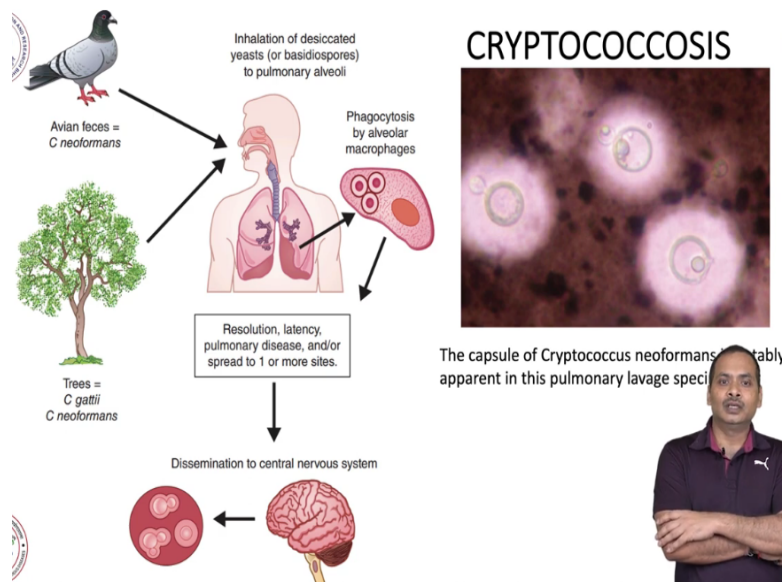
So cryptococcosis is caused by *Cryptococcus neoformans*. So overall approximately 1 million new cases of cryptococcosis occur annually and the mortality is approaching about 50 percent. This is quite frightening number, right. It is a quite high, right, 50 percent people die by fungal infection. It is really quite point of worry. *Cryptococcus neoformans* is the key pathogen which can cause this disease, besides this *cryptococcus gattii* occur worldwide in nature and is isolated readily from dried pigeon feces.

So here please note that this fungus is coming from pigeon feces and so they basically harbor this cryptococcus neoformans as well as a tree, soil and other sites are also there, but be careful with the pigeon. From lung, these neurotropic yeasts typically migrate to the central nervous system, so they are basically not only affecting the lung they are reaching to the central nervous system where they cause meningoencephalitis.

They basically cause the inflammation of meninges. They can also have a capacity to infect many other organs. They can infect the skin, they can infect the eyes, they can infect the prostate. So this fungus has quite well-developed potential to cause very dangerous disease, so now you can understand it is not surprising that about 50 percent people die if they have this infection. So cryptococcus neoformans occur in immunocompetent persons.

So please note this infection can be also present in the immunocompetent individual, it is not only associated with immunocompromised individual, but it is quite often or it is a more readily associated with patient with HIV or hematogenous malignancy, it is a blood related cancer and other immunosuppressive condition, generally the individual who receive this organ, so they are on immunosuppressive drugs.

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So here I am just presenting the life cycle of this fungus. Basically, here you can see that this fungus is coming from pigeon feces and this cryptococcus neoformans, and this is basically inhaled or inhalation of this desiccated yeast to the pulmonary alveoli. This can also come

from the trees and basically it affects the lungs. There is a phagocytosis by alveolar macrophages and then there will be a resolution or latency pulmonary diseases.

And or spread to one or more sites, they can affect the brain and this will cause the wide range of pathology. Not only brain then it can infect the skin and so on so. Here you can see this cryptococcus which is depicted here, the capsule of a cryptococcus neoformans is notably apparent in the pulmonary lavage specimen.

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Aspergillosis

- **Caused by a number of *Aspergillus* species. *A fumigatus* is the most common human pathogen, but many others, including *A flavus*, *A niger*, *A terreus*, and *A lentulus* may cause disease.**
- **This mold produces abundant small conidia that are easily aerosolized.**
- **In immunocompromised patients—especially those with leukemia, stem cell transplant patients, and individuals taking corticosteroids—the conidia may germinate to produce hyphae that invade the lungs and other tissues.**
- **In the lungs, alveolar macrophages are able to engulf and destroy the conidia. However, macrophages from corticosteroid-treated animals or immunocompromised patients have a diminished ability to contain the inoculum. In the lung, conidia swell and germinate to produce hyphae that have a tendency to invade preexisting cavities (aspergilloma or fungus ball) or blood vessels**

Now I will talk about another fungus that is aspergillosis which is caused by the *Aspergillus* species. This is caused by *Aspergillus* species and *Aspergillus fumigatus* is a one of main pathogens. It is most common human pathogen, but many other including *Aspergillus flavus*, *Aspergillus niger* and there are various species may cause the disease. This mold produces abundant small conidia that are easily aerosolized.

So this can easily go in the air and then individual can inhale and then they can suffer from the aspergillosis. In immunocompromised patients, especially those with leukemia, the patient who have this blood cancer leukemia or stem cell transplant patient and individual taking corticosteroids, here you can see that corticosteroid is basically an immunosuppressive drug. So those who are regularly taking this corticosteroid the conidia may germinate to produce hyphae that evade the lung and other tissues.

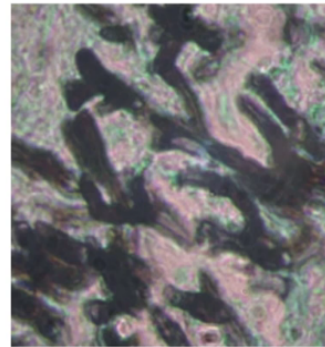
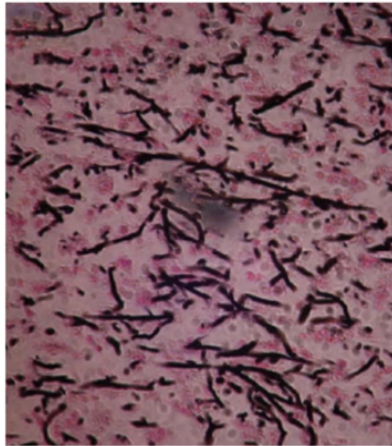
In the lungs, alveolar macrophages are able to engulf and destroy the conidia, however macrophages from the corticosteroid treated animal or immunocompromised patient have a

diminished ability to contain the inoculum. In the lung, conidia swell and germinate and produce hyphae that have a tendency to evade preexisting cavities and then there will be aspergilloma or fungal ball will be formed or it will also present maybe in the blood vessel.

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Aspergillosis

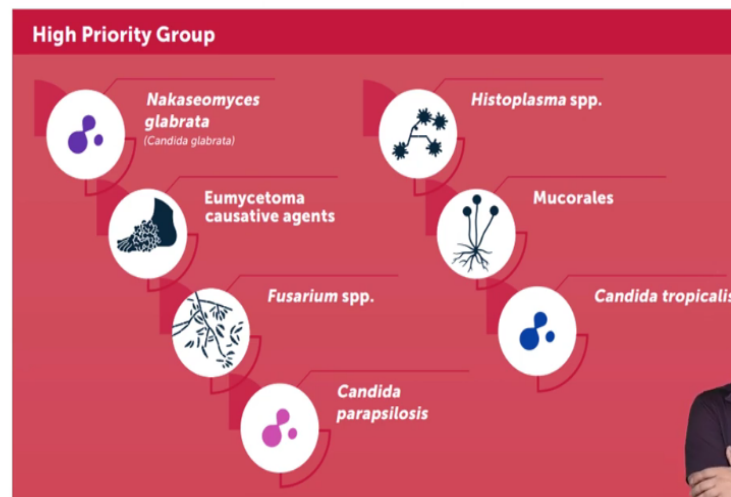


Aspergillus fumigatus in lung tissue stained with Gomori methenamine silver.

Here this is Aspergillus fumigatus image. It is recovered in the lung tissue stained with some particular fungal staining agent that is Gomori methenamine silver.

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WHO fungal priority pathogens list



This is a high priority group these fungi, as you can see that there is histoplasma, there is Mucorales, the Candida tropicalis. There is a Candida parapsilosis, fusarium species, eumycetoma causative agent and there is Nakaseomyces glabrata, it is a kind of candida species.

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WHO fungal priority pathogens list



So this is a medium priority group. Here you can see that *Cryptococcus gattii*, there is *Talaromyces*, *Pneumocystis*, *Paracoccidioides*, *Pichia Kudriavzevii* and there are some other fungi. So, these are all the fungal list which is prepared by the WHO and this is not so dangerous compared to the previous one. So with this, I am finishing all fungal diseases or about the fungus and in next session I will talk about the parasitic infection and that will be the last topic for this course. Thank you.