Host-Pathogen Interaction (Immunology)
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Lecture - 77
Fungal Infection – 1

Hi. So we have approached to the last week of this course and so far we have learned various aspects of immunology. We have learned innate immunity, adaptive immunity. Some topic we learned in quite depth and some topic we have touched upon and we learned that how overall immune system works. After that we have discussed about the virus infection, we have learned about the bacterial infection and now we are toward end of this course and we are going to learn about the fungal infection.

So fungal infection in general it is not very common and it is mainly associated with immunocompromised individual and this immunocompromise it could be acquired or it could be a congenital. In healthy individual, they do not cause any severity in general, but fungus do cause disease. So in this session we will discuss about the fungal infection.

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So fungus is very well known for various food products as you may aware that a lot of things basically we produce with the help of a fungus. To example few the best example is vinegar, bread, every morning probably you might be taking the bread, you may be occasionally taking

beer or wine and you may be taking the cheese and in hospital setting we use antibiotic. So antibiotics are produced by several fungi.

Probably you may remember the discovery of Alexander Fleming, he discovered penicillin. So the fungus has a more positive impact on our life, but there are some fungi which cause disease and this disease is mainly associated with immunocompromised individual. There are some bad products produced by the fungus. Some fungus produces toxic substance, some fungus produces agent which can cause the cancer in human, we call it as carcinogens.

Some fungal product causes the hallucination, some of hallucinogenic drugs like lysergic acid is coming from the fungus, raye ergot fungus, it is a Claviceps purpurea. And some of very common disease which is a mainly associated with small kids or whose immunity is not yet well developed, one of the best example is ringworm infection. The name is misleading, so the ringworm is not associated with worm, it is basically the fungal infection.

Which is fungal skin infection and it is caused by Microsporum and Trichophyton species and probably you might have heard that the people who are working in the field or farmers they develop athlete's foot. Basically, there are some kinds of decay in between the fingers of feet. So these are some of very simple diseases associated with fungus. So, there are approximately a million fungi known.

And out of million fungus or 10 to the power 6 fungus, there are only 400 species of fungus which cause disease to the human which is quite a small in numbers, if you look at the number is about 0.04 percent. So these fungi can cause disease in human. Fungal infection could be exogenous, more superficial, as I have explained you they can infect skin, they can gain access through injury, inhalation through respiratory tract or ingestion and they can cause disease.

There could be endogenous fungal infection which basically sometimes these fungi when the individual's immunity is somehow compromised, then they may breach or gain access to the sterile part of our body and then over there they can cause severe diseases. I will discuss all those things in subsequent slides in this session and upcoming session.

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So fungal diseases are commonly called as a mycosis and the study of fungus probably you are aware that we call it as a mycology. Fungus do cause diseases in human, animal and they are also causing disease in plants, probably you might aware about that. This fungal infection is mainly opportunistic and fungal infection could be various level as I told you exogenous or endogenous and this could be very superficial like athlete's foot.

It could be a cutaneous, it could be a subcutaneous, it could be deep in tissues and this can be systemic. So that depends on the host immunity as well as the pathogenicity of fungus. So some infections start from cutaneous and it may reach to the lung. There is a one very good example coccidiomycosis or it is also known as Valley fever. So this infection starts from skin and then this reaches to the lung, so this is quite life-threatening.

Fungal infection is basically associated with acquired or congenital immunodeficiency or it may be associated with malnutrition. If the kids or individual is not getting a proper food then that may also cause the fungal infection.

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Immunity to the fungal infection, the immune responses which is developed against the fungal infection they are very clear cut. One of the probably you have learned about the innate immunity and over there you have learned there are some friendly microbes. So competitive inhibition by commensal microbe organism because if the individual receives long term antibiotic treatment they may suffer from oral and vulvovaginal infection by Candida albicans.

So this is a kind of proof that when you take a long term antibiotic at that time your microflora which is present in the gut that are severely affected and because of this the individual may susceptible to the various fungal infection as you have seen in this point that there could be some oral infection, there could be some vulvovaginal infection, a fungus and the fungus could be the Candida albicans. So this microbial barrier, if you remember in innate immunity.

I have discussed about the microbial barrier, so this microbial barrier is very important for the defense against fungal infection because there is a competition if this the good fungus or good microbes are reduced, then these pathogenic microbes can increase or they can cause the health issues. Another the most important innate immune component is the functional neutrophils. So neutrophils are playing extremely important role against fungal infection.

And it has been noticed that the neutropenia or reduced number of neutrophil or malfunction neutrophil in the host can result to the fungal infection. So, this suggests that neutrophils are playing very important role against the fungal infection. Another is, you probably remember that there are various complement pathways, so among those complement pathways if you remember there is alternative pathway and there is a lectin pathway.

So these complement pathways are also playing very important role against the fungal infection. So you probably remember that this complement basically cause three major function. One is inflammation, it induces inflammation. It opsonizes so you can understand that fungus can produce the spores. So if this spore is opsonized by say C 3 b then it will be readily phagocytosed by the phagocytic cells.

And the spore or the fungal hyphae can be can be destroyed by membrane attack complex which is the outcome of this complement pathway. So in that way this alternative and particularly lectin pathway plays a very important role against fungus. Lectin pathways basically they sense the sugar moiety which is a present over the fungus and then this will trigger the complement pathway and then as I explained you it will induce the inflammation, opsonization and cytolysis through formation of membrane attack complex.

Another is there are several antimicrobial peptide and there is a protein known as MBP, mannose-binding protein, they play a very important role against fungal infection, particularly against Candida albicans. Here you can see that there is another fungus like Aspergillus fumigatus and I will discuss about this neoformans in more detail in subsequent session. So over there this mannose-binding protein plays a very important role against the fungal infection.

There are some surfactant proteins, mainly these proteins are present in the lungs and they lay a very important role against fungal infection in lungs. So, this is very important protein. In addition, TLR2, TLR4 has been shown to play a very important role against the fungal infection, of course once they are sensed then there will be a production of pro-inflammatory cytokine and then there will be a recruitment of the immune cell.

Particularly may be neutrophil, macrophages and then the fungal infection can be taken care by the host immune system. So this is all about the innate immunity. The adaptive immunity it has been shown that T cell mediated immune responses are playing extremely important role against the fungal infection. However, the role of B cell or B cell mediated immunity or antibody production it is not very well understood.

So this can be very easily demonstrated if you knock out some T gene which is playing important role in T cell development, then you can show that T cell mediated immunity is playing very important role against the fungal infection, however B cells are not playing that much important role.

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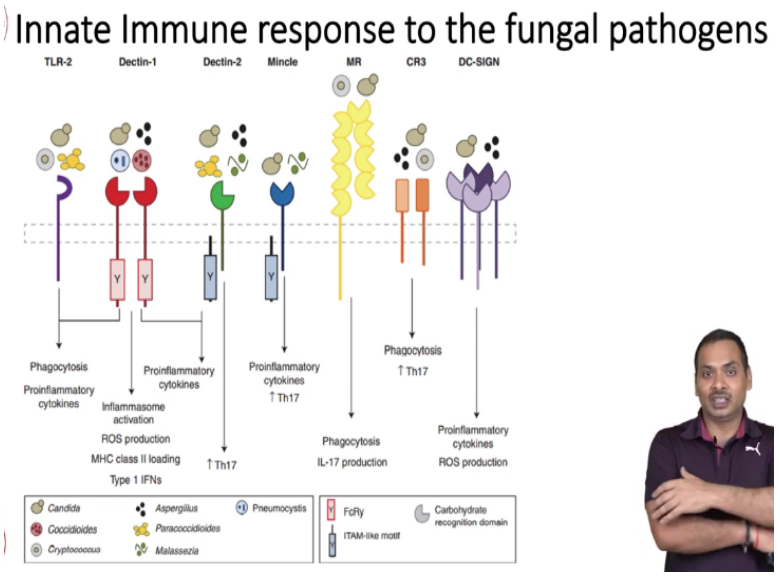

Here again I am showing that this is a very complete information for the innate immune responses to the fungal infection. Here you can see that there are various ligands here. On top you can see that there is a TLR-2, there are Dectin-1. So Dectin-1, Dectin-2, Mincle this mannose receptor, complement receptor and DC-SIGN. So all these receptors basically belong to the CLR family sensors, CLR stands for C-type lectin receptor sensors.

Like TLR, there is CLR also. So here you can see that TLR-2 can sense there is a scheme below you can find out the panel which is explaining what this sensor can sense. So in case of TLR-2 this can sense the Candida, this can sense the Paracoccidioides and this can also sense the Cryptococcus. So this upon sensing they can induce the phagocytosis, they can induce the pro-inflammatory cytokine.

And there are Dectin-1 receptor which has a carbohydrate recognition domain and this can sense variety of microbes such as a Candida, Aspergillus, so and so, Pneumocystis, Coccidioides this is also sensed and then they can induce the inflammasome activation, they can produce ROS production and they can also induce the MHC class 2 loading and it can also produce type 1 interferon.

So Dectin-1 is a quite well characterized sensor in case of fungal infection. There is another receptor which is Dectin-2, Mincle mannose receptor and complement receptor 3 and DC-SIGN. So all this thing if you see very carefully basically upon sensing various fungus they can induce the pro-inflammatory cytokine and like Dectin-2, Mincle, this mannose receptor and complement receptor can induce the activation of Th17 immune response.

So in that way these various pattern recognition receptors they are not playing very important role in innate immune defense, they are also linking with the adaptive immune response, they basically activate the Th17 cell response in order to get rid of from this fungal infection.

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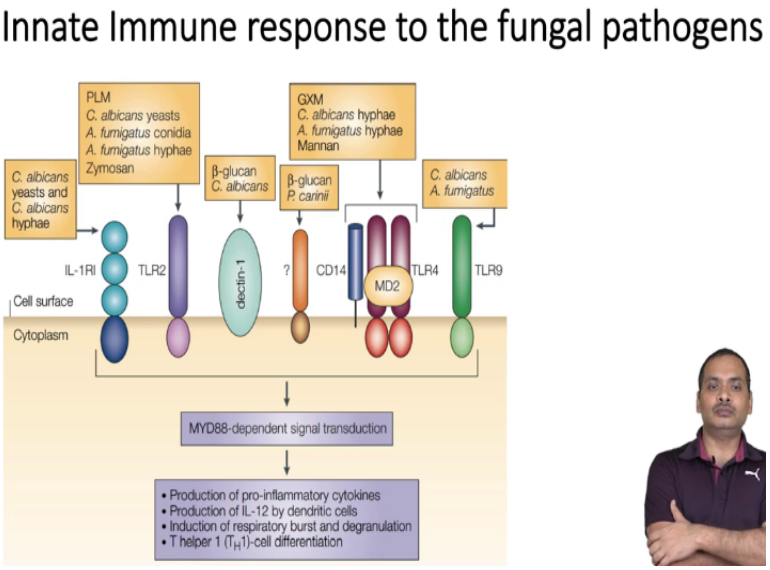

Here this is another quite a detailed slide. Here you can see there are various sensors. You can see that there is IL 1 receptor 1 which is also sensing the Candida albicans yeast and Candida albicans hyphae. And TLR2 can also sense the variety of fungal pathogen including the fungal pathogen originated the PAMP that is zymosan. The zymosan is a basically a beta-glucan. dectin-1 can also sense the beta-glucan.

And there are some sensors which is not known they can also sense the beta-glucan and there are TLR4 receptor complex, they can also sensed some other fungus. And TLR9 also sense the Candida albicans and Aspergillus fumigatus and basically they activate the MyYD88 dependent signaling and this will obviously produce the pro-inflammatory cytokine, they can also induce the IL-12 by in entering dendritic cells and induce the respiratory burst as you remember that there is ROS and RNMS.

So ROS and RNMS basically kill the microbe inside the phagocytic cells and this can also trigger the degranulation and overall they can also trigger the Th1 response, which will basically trigger the killing of intracellular spores or some various stages of fungal like yeast form of fungus. So this can be phagocytose and then this can be cleared by activation of Th1 immune responses.

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Innate Immune response to the fungal pathogens

	Selected disease(s)	Barriers breached/site of infection	Selected PRRs involved in protective immunity	Selected references
Ascomycota				
Candida albicans	Disseminated candidiasis	Blood, kidneys, brain, heart	TLR-2/TLR-4/TLR-6	Ferwerda et al. 2009 Saijo et al. 2010
	Vulvovaginal candidiasis	Vagina	Dectin-1	Wells et al. 2008
	Mucosal candidiasis	GI tract, oral mucosa	Dectin-2 CR3, DC-SIGN	
Candida glabrata	Disseminated candidiasis	Blood, kidneys, brain, heart	Mincle, MR	
Aspergillus fumigatus	Invasive pulmonary aspergillosis	Lung, blood	TLR-9/TLR-3 Dectin-1,	Ramirez-Ortiz et al. 2011
	Allergic bronchopulmonary aspergillosis	Lung	Dectin-2 CR3 DC-SIGN	Werner et al. 2009 Sainz et al. 2012
Pneumocystis carinii	Pneumonia	Lung	Dectin-1	Saijo et al. 2007
Blastomyces dermatitidis	Blastomycosis (pneumonia)	Lung	??	Wüthrich et al. 2011
Histoplasma capsulatum	Histoplasmosis (pneumonia)	Lung	??	Wüthrich et al. 2011
Paracoccidioides brasiliensis	Paracoccidioidomycosis	Lung	TLR-2/TLR-4	Loures et al. 2011
Coccidioides immitus *Coccidioides posadasii*	Coccidioidomycosis (Valley fever)	Lung, blood	Dectin-1	Viriyakosol et al. 2013
Fonsecaea pedrosi	Chromoblastomycosis	Skin	TLRs Mincle	Da Glória Sousa et al. 2011

So here I am giving a quite detailed information about the innate immune responses to the fungal pathogen. Here you can see that the Candida albicans can cause a variety of disseminated candidiasis. This can cause the vulvovaginal candidiasis. Mucosal candidiasis and basically which barriers breach or the site of infection will be blood, kidney, brain, heart, vagina, gastrointestinal tract, oral mucosa.

And this Candida can be sensed by TLR-2, 4, 6, Dectin-1, Dectin-2, complement receptor 3, DC-SIGN and this is quite detailed information. Similarly, this is given for various fungus like Candida glabrata which causes disseminated candidiasis and they affect again blood, kidney, brain and heart. Aspergillus fumigatus they can infect the lungs can cause the aspergillosis. This can also cause the allergy or bronchopulmonary aspergillosis and basically it affects the blood and lungs.

And this can be sensed by TLR-9, 3, Dectin-1, Dectin-2, complement receptor 3 and DC-SIGN. Similarly, all details are given about the Pneumocystis carinii, this pneumocystis carinii is mainly associated with the individual who is infected with HIV human

immunodeficiency virus. So those individuals are quite susceptible to the Pneumocystis carinii or pneumocystis species fungus, so these are all details.

So, all these fungi basically belong to the Ascomycota and Ascomycota is basically the family of fungus which makes hyphae and there will be septa. Septum is there will be a kind of partition in the hyphae and that is why they call it as Ascomycota.

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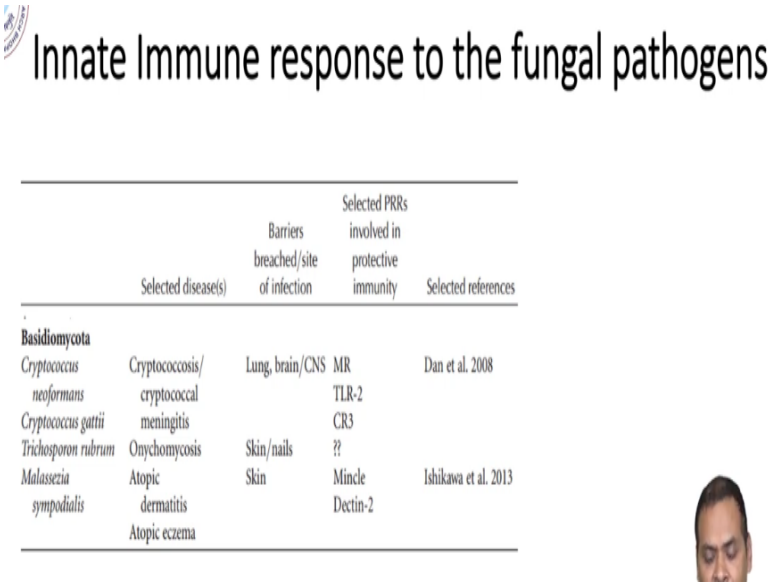

So, there is another family of fungus and their details are given and here you can see that this Cryptococcus neoformans, this is a quite dangerous fungal infection and this is also associated with immunodeficiency. This can cause very fatal disease, about 50 percent people die due to this fungal infection which is a quite surprising. And this fungus can affect the lungs, brain and central nervous system and this can be sensed by this mannose receptor, TLR-2 and CR3. There are different another fungus this is Cryptococcus gattii.

This is also causing similar disease as a Cryptococcus neoformans, it can cause the meningitis and this is quite severe. There is another fungus and all these fungi basically cause a variety of diseases in the human and just for your information in next session I will discuss that. There are some very dangerous fungi are reported and WHO made a priority if this fungus is there then that will be a really high risk. And this fungus is also developing a drug resistance, so that is the point of worry, anyway that I will discuss in upcoming session.

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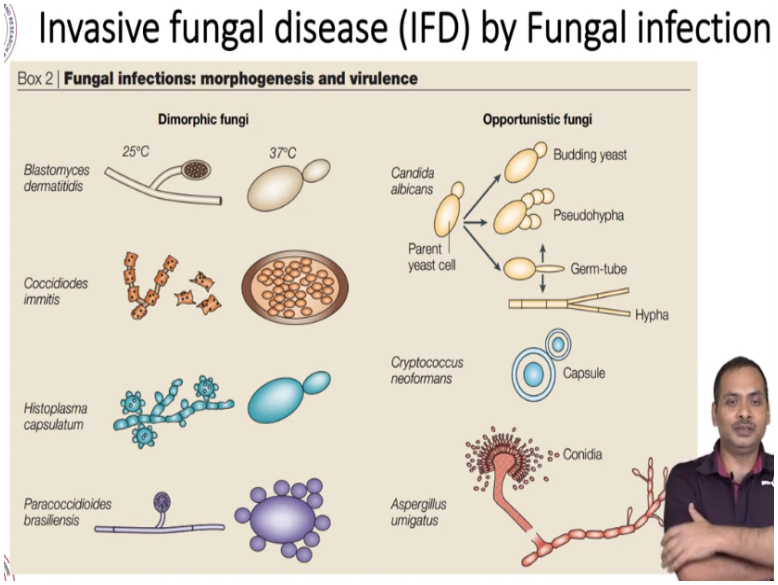

Here I am showing that invasive fungal diseases by a fungal infection and because this is fungal infection morphogenesis and is playing a very important role in virulence. So you probably might be aware that fungus has different stages, some fungus they make hyphae, they can also make spores, they can also make different structure. But some structures are highly pathogenic and those structures are associated with virulence.

Here you can see that there are dimorphic fungi. Here you can see there is Blastomyces dermatitidis, this has a hyphae structure and this has like yeast kind of a structure. Coccidioides immitis, this is also having different stages or there are two morpho forms, there are two phenotypic forms are there like histoplasma, this is also having different kinds of morphology. Paracoccidioides, this is also having different kind of structure and it is possible that the one structure is much more virulent.

There is opportunistic fungus like Candida albicans, here you can see that this Candida albicans can be present in various form, the budding yeast form, pseudohypha form and they can make a germ-tube or hypha with septa. Cryptococcus neoformans also make a spore with a capsule. Aspergillus fumigatus, they can also make different kind or different form of fungus. here you can see that there is Conidia and there are hyphae with septa.

So this is a very good strategy of fungus in order to evade the immunity. Different morphological form will definitely have a different biochemical composition and different virulence factor. So this is very easy way to evade the immunity.

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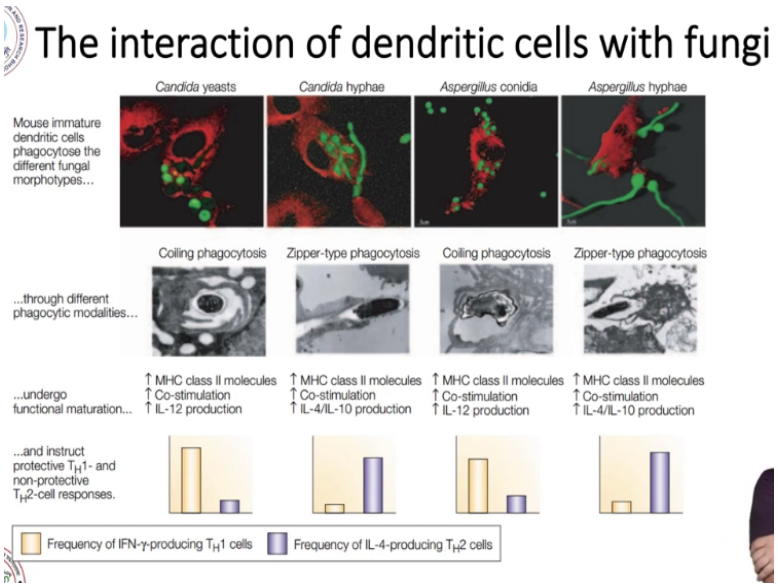

Here there is an interaction of dendritic cells with fungi. So you know that some fungi makes a hypha. So they are basically coiled and when DC phagocytose this coiling form. And if it is hyphae form, then there will be a kind of zipper type of phagocytosis and like that. And upon phagocytosis they can increase the expression of MHC class 2 molecule, co-stimulatory molecule and IL-12 production, here you can see. Various immune response, basically they can trigger the Th1 and Th2 responses, depend on the stages of fungus.

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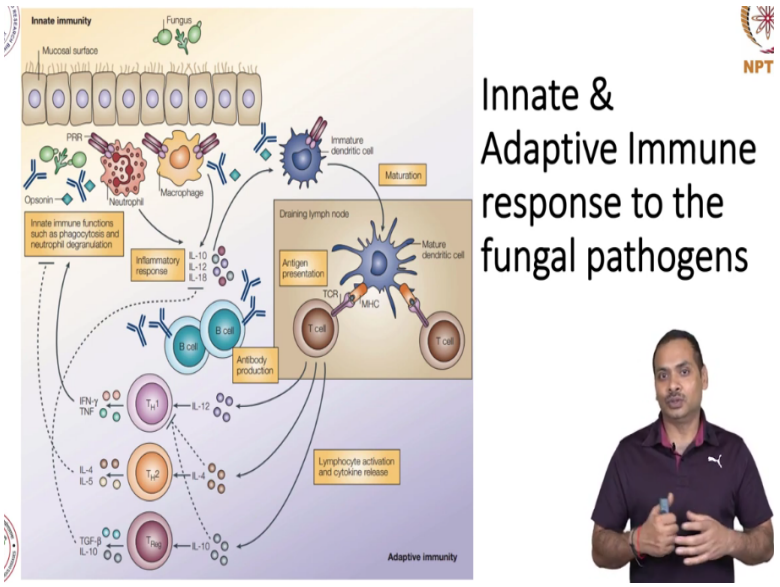

This is a kind of summary of how the innate and adaptive immunity basically take care of the fungal infection. You have seen there are various kinds of PRRSs, mainly the PRRSs belongs to the C type lectin receptor and upon sensing this can be sensed by neutrophils, macrophages and this can be opsonized by C-3-b or antibody and basically this will induce the innate

immune response and this innate immune response can also activate the T cell mediated immune response.

And then that result to the differentiation of various Th cells. Here you can see that there are Th1 cells, there are Th2 and T reg cells and depends on this immune response generated through T cell, this will regulate the innate as well as adaptive immune response. So this is a kind of complete summary about the immune responses against the fungal infection which I have discussed in several occasion in previous session.

So this is all about the defense against the fungal infection. In next session I will talk about some of the fungal diseases and I will also discuss about there is some priority list made by the WHO, some are extremely dangerous fungal infections, some are less and some are like that. So thank you and in next session we will discuss about all those things.