Review Article

Systemic Fungal Infections in Immunocompromised Patients

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Abstract :

In the last 25 years, the frequency of invasive fungal infections has increased remarkably. Unbiased data concerning the true incidence and prevalence of invasive fungal infection in different patient population is limited. Opportunistic invasive fungal infections (IFIs) is major cause of morbidity and mortality in immunocompromised patients. However, there still remains much uncertainty and controversy regarding the best methods for establishing the diagnosis of most IFIs.

Introduction:

In the last 25 years, the frequency of invasive fungal infections has increased remarkably. Unbiased data concerning the true incidence and prevalence of invasive fungal infection in different patient population is limited. Opportunistic invasive fungal infections (IFIs) is major cause of morbidity and mortality in immunocompromised patients. However, there still remains much uncertainty and controversy regarding the best methods for establishing the diagnosis of most IFIs.

Hart et al (1966)[1]reported 132 invasive fungal infections in normal and immunocompromised patients out of which 81% were caused by *Cadida SPP., Aspergillus SPP,* and *Zygomycete SPP*. Muller et al (1988)[2] reported the following incidence of opportunistic deep seated mycosis in various immunocompromised patients, candidiasis 92.6%, aspergillosis 6.7%, cryptococcosis 0.35% and zygomycosis 0.35%.[3] In a comprehensive review of invasive fungal infections, Rose and Varkey (1975) [4] reported per 10,000 hospital discharges the following rates of fungal infections in immunocompromised hosts*:* *Candidia SPP*. 7.08%, *Aspergillus SPP.* 1.4%, and *Zygomycet SPP*. 0.23%. Data from the National Nosocomial Infections Surveillance Program (CDC)[5] in 1984 showed that *Candida SPP. a*ccounted for 5.5% of all isolates and was the eighth most common nosocomial pathogen.

The definition:-

The definition for a new classification based on the level of certainty for the diagnosis of IFIsis given by a committee headed by Ascioglu S (2001)[6]This definition includes both diagnostic criteria for proven IFIs and also classification criteria for probable and possible diseases that are intended to promote a more uniform description of the patients.

The committee chose the terms “proven,” “probable,” and “possible” to express disease certainty. Three elements form the basis of the proposed definitions. These elements are host factors, clinical manifestations, and mycological factors. [7]

The invading organisms

The systemic fungal infections in immunocompromized hosts can be classified into two major categories. These are true pathogenic organisms and opportunistic fungal infections. The true pathogenic fungi cause

Infection in normal hosts and the infections are always self limited. These infections do not clinically manifest as clinical features of fungal infections. The opportunistic fungal infections invade the persons who are immunocompromised due to any cause. The organisms are Candida Infections, Aspergillosis, Cryptococcosis, Histoplasmosis, Coccidioidomycosis, P. Jirovecii, Blastomycosis and Sporotrichosis.[8]

Pathogenesis

The systemic fungal infections invade the affected individual by entry of organisms through four common routes. Approximately in 60 % individuals the organisms enter the body through lungs while in 25% individuals' organisms gets access through Gastro intestinal tract. Entry of organisms through skin occurs in 10% cases and only in 5% cases the route of entry is haematogenous in nature.

There are three common sources of various organisms to get access to the individuals. In 60% cases the source of organisms is anthrophilic that is the organisms present in the air. These organisms commonly enter the body through

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respiratory tract and pulmonary fungal infections are the common manifestations in such cases. Approximately 25% of various invading fungi are from soil i.e. geophilic and enter the body through food. The systemic fungal infections of Gastro intestinal tract are common in such cases. The source of fungi in immunocompromised hosts in 15% affected individuals is from animal source being called as zoophilic source.

In all such individuals who are affected by any of the fungal infections and present with systemic fungal infections present first with invasion of the specific tissue and causing colonization of the organisms at the organ affected. Lung is the commonest organ affected in this way. The microscopic examination of the tissue/ secretions obtained at this stage will demonstrate the invading organisms but it is extremely difficult to establish the fact that the isolated organism is the real cause of the disease. In such cases other parameters like clinical manifestations, presence of predisposing factors and presence of various host factors should be considered to differentiate between diseases versus colonization of the invading fungal infections.

Once the organisms get access to the affected tissue and colonize at the tissue involved, the organisms then multiply at the site of invasion. At this stage also there will be no specific clinical manifestations of fungal infections of the organ involved. Instead, the general constitutional manifestations like fever, asthenia, and generalized weakness are the common presenting features.

The organisms after a variable period of time actually invade the affected tissue by variety of ways and present with the clinical manifestations of the disease.

These stages from colonization to multiplication and finally overt infection depend on two important factors. These factors are host response and immunity of the individual affected. It has been shown that lower the immunity and lower the host response to an infection higher are the chances of developing systemic fungal infections.

Infection with the human immunodeficiency virus (HIV) results in progressive deterioration in host immunity. Although HIV infection most consistently alters T-helper cell function, in reality the aberrations in immunity are potentially more global. Thus, defects in B-lymphocyte, neutrophil, and monocyte/macrophage function as well as in the modulation of immune function by various cytokines are now well-recognized as being associated with HIV infection and as contributing to the profound immunodeficiency seen in many infected persons. Fungi are widely distributed throughout the environment. The lungs are the common portal of entry for most fungi into the human host. Multiple components of the normal host defence mechanism usually control fungal infections, thereby preventing local progression or dissemination.

Systemic Fungal Infections (SFI) occurs in 3 settings

1. Neutropaenic patients following chemotherapy, and other oncology patients with immune suppression
2. Immune compromised patients like HIV/AIDS
3. Patients in intensive care (ICU) due to long term IV line, breaches in their skin, severe systemic illness or burns, and prolonged use of broad-spectrum antibiotics.

During the process of systemic fungal infections, the Phagocytes and dendritic cells sense fungal organisms by lectin-like receptors - dectins. Neutrophils (PNL) liberate fungicidal substances, such as reactive oxygen species and lysosomal enzymes, and phagocytose fungi. In affected individuals Fungi elicit strong TH17 responses & activate dendritic cells binding to the dectin receptor by releasing cytokines (IL-6 & IL-23).The TH17 cells stimulate inflammation, recruit PNL & Monocytes and destroy Fungi. Finally, The decrease of PNL leads fungi to grow & SFI.

Predisposing conditions for SFI

The systemic fungal infections in immunocompromized hosts can occur in presence of various predisposing factors. In an extensive study by Johrami et al (2005), various predisposing factors are identified and include

1.HIV/AIDS	30.24%
2.Diabetes Mellitus	28.49%
3. Renalm failure on Hemodialysis or transplantation	15.99%
4. Hematological Malignancy	14.89%
5. Infectious diseases like Tuberculosis	10.29%
6. Autoimmune disorders like SLE, RA WG	6.68%
7. Chronic Glomerular diseases	5.57%
8. Patients on immunosuppressive therapy	5.57%
9. Recurrent GI surgery or perforation	4.55%
10. APACHE score > 10	3.35%
11. Long term catheterization	3.35%

Classification of SFI in Immunocompromised cases

It is proposed to have a new classification based on the level of certainty for the diagnosis of systemic fungal infections. This classification includes the diagnostic criteria for proven systemic fungal infections and also classification criteria for probable and possible diseases. This classification promotes a more uniform description

of the patients

In a study on Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus by Ascioglu et al(2001) a committee is formed to promote the diagnosis of systemic fungal infections in immunocompromised hosts.

The committee chose the terms "proven," "probable," and "possible" to express disease certainty. Although other terms could be used, literature review showed a clear trend among investigators favoring the use of these terms.

Diagnostic criteria for Diagnosis of systemic fungal Infections

Disease	Criteria
Proven	1. Positive culture from tissue (except Urine & mucous membrane. 2. Histopathologic or cytopathologic evidence of presence of fungus 3. Positive Blood culture for invasive fungus
Probable	1 Microbial criteria 1 major or 2 minor clinical criteria 1 host factor
Possible	1 Microbial criteria 1 major or 3 minor clinical criteria 1 host factor E/O predisposing factor

Host factors:-
Thevarious host factors include;

Type of Criteria	Criteria
Host Factors	1.Neutropenia (<500 neutrophils/mm3 for 10 d) 2. Persistent fever for >96 h refractory to appropriate broad-spectrum antibacterial treatment in high-risk patients. 3. Body temperature either >38^{0}C or <36^{0}C and any of the following predisposing conditions: • prolonged neutropenia in previous 60 days • Recent or current use of immuno suppressive agents in previous 30 days. • Proven or probable invasive fungal infection during previous episode of neutropenia • coexistence of symptomatic AIDS

Clinical Criteria:

Apart from Microbiological criteria, various clinical criteria are also important for diagnosis of systemic fungal infections. These criteria are related to the site and current episode of infection

Criteria	Findings
LRT Inf. – Major criteria	Any of the following - new infiltrates on CT imaging, halo sign, or cavity within consolidation
LRT Inf. – Minor Criteria	Symptoms of LRT infection (cough, chest pain, hemoptysis, dyspnea); physical finding of pl. rub; any new infiltrate not fulfilling major criterion; effusion
Sino-nasal Inf. – Major criteria	invasive sinus infection erosion of sinus wall or extension of infection to neighbouring structures like extensive skull base destruction
Sino nasal Inf. – Minor Criteria	Upper respiratory symptoms nasal discharge or stuffiness epistaxis or maxillary tenderness nose ulceration or; periorbital swelling; black necrotic lesions or perforation of hard palate
CNS Inf.- Major Criteria	E/O Infection - mastoiditis or parameningeal foci, extradural empyema, intraparenchymal brain or spinal cord mass lesion
CNS Inf.–Minor Criteria	S/S - seizures, hemiparesis, cranial nerve palsies, mental changes, meningeal irritation, abnormalities in CSF biochemistry and cell counts

The microbiological criteria are also defined. These include;

Microbiological Criteria	
	1. sputum or BAL -Positive culture for mold (including Aspergillus, Fusarium, or Scedosporium species or Zygomycetes) or Cryptococcus neoformans or an endemic fungal pathogens or any other fungal species 2. Sinus Aspirate - Positive culture or findings of cytologic/direct Microscopic evaluation for mold , BAL, CSF or Blood – Positive for Aspergillus antigen or cryptococcal antigen in blood samples or any other fungus 3. Sterile body fluid samples - Positive on direct microscopic examination for fungal elements e.g., Cryptococcus 4. Blood, Urine or CSF – Positive for H. cap. antigen 5. Urine -Two positive urine cultures for yeasts in absence of catheterization or Candida casts in urine in absence of urinary catheter 6. Blood -Positive blood culture for Candida sp.

There can be various predisposing conditions for the diagnosis of systemic fungal infections. These can be multiple and the presence of multiple factors further enhances the development of systemic fungal infections. The various predisposing factors are already mentioned above.

Candidiasis:- *Candida albicans are extremely common. Other sp are C. Krusei, C. Guillermundii, c. tropicalis* [9]

Oral candidiasis (thrush) commonest lesion. Thrush is predictor for progression of AIDS.

Esophageal candidiasis second commonest lesion.

other system involvement - CNS, eye, Liver, spleen, Kidneys & gall bladder. These are commonly involved with disseminated. Candidiasis.

Predisposing factors - long term use of antibiotics, indwelling catheters, patients on cytotoxic drugs.

The defect in cellular immunity characteristic of HIV infection predisposes to mucocutaneous *Candida infections but is protective against other fungal pathogens*

Marked neutropeniais important.

In HIV patients-humoral immunity –Antibodies directed against a 47-kD antigen of C. *albicuns is more common*

47-KD-produced as a result of polyclonal B-cell activation & may limit dissemination.

Practical Points

- Do not assume that the Candida infection you have encountered is C. albicans
- Resistance to azole antifungals is on the increase!
- Health care workers commonly transmit yeasts by hand.

Aspergillosis

The commonst organisms are *Asp. Fumigatus, A. niger, A. terreus* [10]

RS most commonly involved.

Three forms – Allergic Br. pulm. Aspergillosis (APA)

- Invasive aspergillosis and
- Pulmonary Aspergilloma

Depletion of neutrophils & Monocyte/macrophages is important pathologic change in these cases.

CNS, heart, kidney, para-nasal sinuses, and the skin may be involved alone or in combination.

Involvement depends on Intensity of exposure, Immune status & underlying lung architecture.

Major manifestations of Aspergillosis

Organ	Invasive (Acute or Subacute)	Chronic	Saprophytic	Allergic
Lung	Angioinvasive, non angio invasive, granulomatous	Chronic cavity Chr. Fibrosing Aspergillosis	Aspergilloma (single with airway colonization.)	ABPA Severe Asthma Extrinsic Allergic Alveolitis
Sinus	Acute invasive	Chr. invasive	Max. fungal ball	Allergic Fungal Sinusitis Eosinophilic rhinosinusitis
Brain	Abscess, Hemorrhagic Infarct, Meningitis, Mycotic anurysm	Gr. Meningitis	None	None
Heart	Endocarditis, Pericarditis	None	None	None
Eye	Keratitis Endophthalmitis	None	None	None

Halo Sign

In a cavity with a fungus ball, there is a crescentic radiolucent space along the upper portion of the density giving the appearance of a halo. This phenomenon is seen with two clinical presentations of pulmonary aspergillosis:
Fungus ball,

Necrotizing subacute pneumonia and

During recovery phase from leukopenic episodes

Galactomannan test

- Galactomannan is a component of the cell wall of the mold *Aspergillus* and is released during growth.
- Detection of galactomannan in blood is used to diagnose invasive aspergillosis infections in humans.
- The test is performed with monoclonal antibodies in a double-sandwich ELISA.

Practical Points

- Aspergillosis is a major cause of infective mortality in oncology patients in some centres
- It is often missed.
- Do you *know* that it's not causing deaths in your hospital?

Cryptococosis

The commonest organisms are *Crypto. neoformans, c. gatti.* It is one of the most common systemic fungal infection. The Incidence is 6-10 %.

The CNS is most commonly involved as meningitis. Meningitis is of long duration. Meningismus is usually absent.

The other organs involved are lungs, eyes, skin, prostate gland, and skeletal system. There can be Variable skin lesions like Macule, pappule, vesicle, plaque, tumour or Rash.

The disease is characterized by,

- Acute or chronic headache and fever.
- In 30% of cases, other CNS symptoms like Seizures & Focal CNS lesions or Meningitis.
- Persistent, unexplained fever and malaise may be the only symptoms.
- There might be associated Pulmonary cryptococcosis. This is characterized by patchy segmental or interstitial pneumonitis, single or multiple nodules, or tumor-like masses mimicking Carcinoma.
- The X-Ray Chest may show Lymphadenopathy, cavitation, and pleural effusions. These findings are more common in in HIV-infected patients than in non-HIV-infected individuals.

Histoplasmosis

The ICH patients living in endemic areas are at increased risk of developing Progressive Disseminated Histoplasmosis (PDH).

The incidence is variable between 5% to 25% of all fungal infections in immunocompromised cases.

- PDH is reactivation of previous infection or rapidly progressive present infection.
- Fever & weight loss commonest (75% to 50%)
- Splenomegaly and lymphadenopathy are noticed in 30% hepatomegaly in 26% cases.
- Atypical presentations - intestinal ulcers, with or without bleeding, intracerebral Histoplasmomas, meningitis, skin lesions, and DIC complicating an infection.
- Laboratory examination shows anaemia in 30%, leucopoenia in 24%, and thrombocytopenia 20%
- CXR – shows diffuse interstitial infiltrates and /or calcified nodules.

COCCIDIOIDOMYCOSIS

The commonest Organisms are C. immitis, C. posadasii. The infection is endemic in certain parts of world.

Fever (valley fever)and dyspnea are the commonest manifestations.

X-Ray chest shows bilateral diffuse reticulonodular pulmonary infiltrates, thin wall cavities and nodules in lung fields.

The disease also involves skin, lymph nodes, liver and meninges.

The risk factors for inf.are E/o immunosuppression. Living in endemic areas for more than 2 years and history of previous coccidomycosis infection.

The diagnosis is made by positive Spherulin skin test.

Pneumocystis Jirovecii

Micro-organisms	RS	GIT	CNS	CVS	Hepato splenomegaly	Eyes	Endocrine	skin
Candidiasis	++	+++ +	++	-	++	++	+	+
Aspergillosis	++++	--	++	++	+	++	+	+
Cryptococcosis	++	--	++++	--	+	--	--	+++
Histoplasmosis	++	+++	++++	+/-	+++	-	-	++
Coccidiadomycosis	+++	-	+++	-	+=+	-		+++
P. Jerovecii	++	+	+	+/-	+	-	-	-

P. jirovecii is the infection in humans while p. carinii is common in rats. Respiratory system most commonly involved. Rarely Liver, Spleen, Lymph nodes and Bone marrow may also be involved.

CXR shows Bilat diffuse infiltrations and rarely Nodular density, Cav. Lesions & peumothorax.

The condition is treated with combination therapy with – TMP/SMX or TMP + Dapsone. If these drugs do not work, Clindamycin/ Pentamidine/Primaquine along with adjuvent therapy with Prednisolone can be tried.

Summary of organs involved in SFI in Immuno Compromised Host

Treatment of Systemic Fungal Infections

The treatment of systemic fungal infections include three main types of drugs.These are Amphotericin B, Azoles and Echinocandins. The details of their preparations and route of administration is shown in the table below

Agents	Route of Administration	Comment
1. Amphotericin B deoxycholate	IV	Replaced by Lipid formulations
a) Amphotericin B Lipid formulations	IV	Less toxic
b) Liposomal Amhotericin	IV	Infusion reactions
i) Lipid complex (ABLC)	IV	Infusion reactions
ii) Colloidal dispersion (ABCD)		
2. **Azoles**	IV & Oral	Most commonly used
a) Fluconazole	IV & Oral	Multiple drug interactions
b) Variconazole		
3. Echinocandins	IV	Useful for disse.candidiasis
a) Caspofungins	IV	Useful for disse.candidiasis
b) Anidulafungin	IV	Under trial for diss. Candi.
c) Micafungin		

SUMMARY

A high index of suspicion must be maintained in the immunocompromised patient who has been receiving antibiotics and who has an elevated temperature either associated with pneumonia or of undermined origin, when that fever persists for 21 or more days. Particularly suspect is that group of patients who have been receiving adrenal corticosteroids as part of their chemotherapeutic regimen. For patient whose condition is in remission, the risk of further chemotherapy must be carefully weighed against its anticipated benefits; the high risk of recurrent fungal infection may preclude such therapy.

The appropriate body secretion should be evaluated for the presence of appropriate fungal infections. The diagnosis should be categorized as definite, probable or proven.

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