Dear Delegates,

I have the privilege to welcome you to an Interactive Case Based discussion on Systemic Fungal Infections. Fungal infections are an increasing cause of morbidity and mortality in immunocompromised and critically ill patients. As we treat an increasingly aging population, prolong life with immunosuppressive therapy for a variety of disorders and administer broad spectrum antibiotics, the risk of fungal infections increases. An increasing incidence of invasive candidiasis, aspergillosis and zygomycosis has been reported from India. As we do not have a subspeciality of infectious diseases, an Internal Medicine specialist is often called upon to give advice regarding the diagnosis and treatment of suspected or proven fungal infection. It is therefore important to know the diagnostic criteria and therapeutic options for treating such disorders.

There is a paucity of good mycological laboratories in the country. Fortunately the options for therapy have increased in the past decade but many clinicians may not be familiar with these newly licensed agents. Most of the evidence based guidelines for management of systemic fungal infections are based on experience of patients of acute leukemia and bone marrow transplantation due to the high incidence of fungal infections in this population. These can provide a framework for management in general medical patients who acquire similar infections.

In this symposium we have invited a number of eminent authorities from India and Canada, to provide a comprehensive discussion of the new perspectives and strategies in managing systemic fungal infections. The proceedings should be of value to the practicing internist.

The format of this CME will allow adequate participation by the delegates. I would welcome a feedback from all of you to help us plan our future activities. Please give a free and frank opinion in the enclosed feedback form.

Happy New Year!!

01 January 2009

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Chairman Scientific Committee APICON 2009 & President-Elect, Association of Physicians of India (API)
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- Rohini Handa  
- Ashutosh Mohan  
- A. K. Varshney
Faculty

- Dr EJ Bow (Canada)
- Brig AC Anand VSM* (Delhi)
- Dr Farah Jijina (Mumbai)
- Col Jyoti Kotwal (Pune)
- Dr Rajat Kumar (Canada)-Moderator

Program Agenda
1520-1650hr: 31 January 2009

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<th>Dr Rajat Kumar</th>
</tr>
</thead>
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<td>Case 1, Autopsy findings</td>
<td>Col J Kotwal</td>
</tr>
<tr>
<td>Fungal Infections in ICU and General Medical Patients</td>
<td>Brig AC Anand, VSM</td>
</tr>
<tr>
<td>Case 2</td>
<td>Dr Rajat Kumar</td>
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<tr>
<td>Fungal Infections in Neutropenic Patients</td>
<td>Dr Farah Jijina</td>
</tr>
<tr>
<td>Diagnosis of Fungal Infections</td>
<td>Col J Kotwal</td>
</tr>
<tr>
<td>Guidelines to Manage Systemic Fungal Infections</td>
<td>Dr EJ Bow</td>
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<tr>
<td>Questions and Feedback</td>
<td>All Faculty</td>
</tr>
</tbody>
</table>

Course Objectives

- Know the incidence and prevalence of Fungal Infections in India
- Diagnosis of Systemic Fungal Infections (excluding endemic mycoses)
- Anti Fungal Agents for Systemic Fungal Infections
- Diagnosis and Therapy of
  - Candidiasis
  - Aspergillosis
  - Zygomycosis
Abstract

Fungal infections are an increasing cause for mortality throughout the world. Invasive fungal infections commonly affect those who are immunocompromised, neutropenic, on immunosuppressive drugs or with HIV infection. Others emerging risk factors include use of corticosteroids even for short periods, COPD and cirrhosis of the liver. Fungal infections can be intrinsic, such as candidemia, or extrinsic, such as invasive aspergillosis or zygomycosis. Most fungi are ubiquitous soil inhabitants and India, with its dusty atmosphere along with a warm and humid climate, offers an ideal environment for a wide variety of fungal infections. A high prevalence is expected in Indian hospitals where construction activities continue in the hospital vicinity without the use of any impervious barrier.

Candida species are part of the flora of the human skin, mucosa, gastrointestinal tract (GIT) and genito-urinary systems. The most frequent origins of candidemia are the GIT via bacterial translocation and skin. [1] Diagnosis is mainly by culture of blood or other body fluids.

Aspergillus infection is mainly acquired by inhalation and is a major cause of mortality in immunocompromised and neutropenic patients. Invasive aspergillus infection mainly affects the lungs and sinuses, while in neutropenic patients, lesions may be widespread. Blood cultures are of limited utility because the results are usually negative even in disseminated infection. Tissue biopsy or bronchioalveolar lavage is needed to establish the diagnosis, but lack of positive culture or direct smears does not rule out invasive aspergillosis. It is often impractical to obtain tissue specimens in critically ill and unstable patients. Radiological signs are characteristic but not specific. The availability of the galactomannan antigen assay for invasive aspergillosis has made the diagnosis simpler in the neutropenic patients. In the non-neutropenic patient this test and the radiological signs have not been validated. [2]

Limited data from a few tertiary care centers in India suggests that there is an increasing incidence of invasive candidiasis, aspergillosis and zygomycosis in the country. The most important risk factor for invasive zygomycosis is uncontrolled diabetes mellitus while renal zygomycosis has been reported in apparently healthy hosts. These diseases are difficult to diagnose ante-mortem unless there is a high index of suspicion and as autopsies are not routinely performed, the diagnosis of invasive fungal infections is underestimated. [3]

Despite the lack of diagnostic facilities in India, the newly approved antifungal agents are widely available. An awareness of the advances in diagnostic and therapeutic aspects of fungal infections should be of value to the hematologists, oncologists, infectious disease specialists, critical care physicians and also to the general
internists who often perform all these functions. The Faculty for this symposium has varied Indian and International experience and the format of case based discussion is designed to involve the delegates in interactive participation. Endemic fungal infections are not being covered due to time constraints. As HIV infections are being discussed in another session, fungal infections in that setting will not be discussed. The aim of this symposium has been stated in the Objectives.

References


Case 1

- A 60 yrs old known case of Ischemic heart disease, diabetes mellitus for 10 years, developed Fever with Cough
- X-Ray chest was suggestive of consolidation RMZ with ? breakdown.
- Sputum culture grew Klebsiella spp. Blood sugar reading of 300 mg % for which insulin was added.
- Appropriate Antibiotics initiated
- Patient developed sepsis, required ventilatory support and succumbed to disease within 3 days

Autopsy was Performed

- Slides to be presented by Col Kotwal

Question 1: The following Statement is True

- Aspergillosis is best diagnosed by blood culture
- In renal failure, Liposomal Amphotericin is the drug of choice for systemic Candida infection
- Worldwide, the highest number of Invasive Zygomycosis have been reported from India, especially in uncontrolled Diabetes.
Question 2: In ICUs, which is the commonest fungal infection

- Candida
- Aspergillus
- Cryptococcus
- Zygomycosis

Question to Brig AC Anand, VSM

- What is the status of Fungal Infections in ICU and General Medical Patients?
Abstract

Fungal infections are increasingly being recognized as a cause of the high mortality noted in ICUs across the world. Data from India is meager as we have very few good diagnostic mycology laboratories, and many clinicians are still not aware of the emerging trends in diagnosis & Management of Fungal Disease. What ever report are available, indicate an increasing incidence of invasive candidacies, aspergillus’s, zygomycosis and several other fungal infections. Invasive candidiasis is the most common opportunistic mycosis; while Invasive aspergillosis may be the second contender. Invasive zygomycosis is an important concern as the world’s highest number of cases of this disease is reported from India in patients with uncontrolled diabetes mellitus. Emergence of fungal rhinosinusitis, penicilliosis marneffi and zygomycosis due to Apophysomyces elegans is unique in the Indian scenario. Among HIV infected patients Candidiasis (41.7 %), Cryptococcosis (10.0 %), Pneumocystosis (8.3%), Aspergillosis (8.3%) and Histoplasmosis were commonly diagnosed.

Systemic fungal infections are being increasingly diagnosed in ICUs due to Increasing use of broad spectrum antibiotics, enhanced survival on intensive care, increasingly complex therapies being undertaken (i.e.organ transplantations), increased frequency of instrumentation & catheterization, novel and more aggressive immunosuppressive regimens and increasing awareness among clinicians coupled with better diagnostic approaches.

Patients with high risk for developing fungal infections include those with Neutropenia (neutrophil count, <500 neutrophils/mm3), Hematological malignancies, Allogeneic > Autologous bone marrow transplantation, Prolonged treatment with corticosteroids before admission to the ICU, Liver cirrhosis with a duration of stay in the ICU >7 days, Solid-organ cancer, HIV infection, Systemic diseases requiring immunosuppressive therapy and so on. The source of infection is usually Fungal colonization of the lungs and may be present before entry into the hospital. Primary ecological niche remains decomposing material and infections in ICUs can also occur through aerosolized spores through improperly cleaned ventilation systems, water systems, or even computer consoles. The use of high-efficiency particulate air filtration reduces the risk of invasive fungal infections

Diagnostic & Therapeutic approaches are evolving thanks to Bone Marrow Transplantation data, which may not be the same in ICU patients as for other hematology patients. In general, a diagnosis is made on the basis of a combination of High risk situation, Compatible clinical findings, Abnormal radiologic findings, and if possible, Microbiologic confirmation or histologic proof of tissue invasion.
Fungal Infections in the ICU

1. Are Fungal Infections A Problem in ICU?
2. What Is The Situation In India?
3. Do Patients Acquire Fungal Infections In The ICU?
4. Which Fungal Infections Are Common In ICU?
5. Who is at Risk in ICU?
6. Are Available Diagnostic Tools Applicable In ICU

Trends of fungal infections in ICU

 Contribution of ICU in fungal infection

305 episodes of candidiasis 305 episodes of candidiasis


Mortality Due to Invasive Mycoses


What Is The Situation In India?

- Very few good diagnostic mycology labs
- Clinicians still not aware of the emerging trends in diagnosis & Management of Fungal Disease
- Limited data available
  - An increasing incidence of invasive candidiasis, aspergillosis, and zygomycosis are reported.

Chakrabarti A, Chatterjee SS, Shivaprakash MR,
Overview of Opportunistic Fungal Infections in India.

Indian Data

- The emergence of fungal rhinosinusitis, penicilliosis marneffei and zygomycosis due to Apophysomyces elegans is unique in the Indian scenario.
- Invasive candidiasis is the most common opportunistic mycosis; while Invasive aspergillosis is the second contender.
- Invasive zygomycosis is an important concern as the world’s highest number of cases of this disease is reported from India in patients with uncontrolled diabetes mellitus.

**Fungal Infections in the ICU**

**Which Fungal Infections Are Common In ICU?**

- 11x increase in candidemia in late 1980s, and further 18x increase in the early 1990s.
- Rising trend in invasive zygomycosis during 1990-99
- Cryptococcosis has increased 15x compared to pre-AIDS era.
  - Fungemia due to unusual yeast – Pichia anomala in neonates and children (4.2%)
  - Emergence of Apophysomyces elegans infection in India

*Chakrabarti A. J Postgrad Med 2005 Vol 51 Suppl 1*

**Fungi: Main Players**

- **Yeast**
  - Candida
  - Cryptococcus

- **Mould**
  - Aspergillus
  - Mucomycosis

**AIDS-related opportunistic mycoses**

- Candidiasis (41.7%)
- Cryptococcosis (10.0%)
- Pneumocystinosis (8.3%)
- Aspergillosis (8.3%)
- Histoplasmosis were also diagnosed.

Why Are Systemic Fungal Infections Becoming More Common In ICUs?

- Increasing use of broad spectrum antibiotics
- Enhanced survival in intensive care
- More complex treatments undertaken, namely organ transplantsations
- Increased frequency of instrumentation & catheterization
- Novel and more aggressive immunosuppressive regimens
- Better Therapy of other complications of immunosuppression
- Increasing awareness among clinicians
- Better diagnostic approaches.

Who is at Risk in ICU?

- Neutropenia (neutrophil count, <500 neutrophils/mm³)
- Haematological and other malignancy chemotherapy
- Allogeneic > Autologous bone marrow transplantation
- Prolonged treatment with corticosteroids before admission to the ICU
- Liver cirrhosis with a duration of stay in the ICU > 7 days
- Hemodialysis, azotemia
- Broad spectrum antibiotics
- Central venous catheter
- GVHD, Mucous barrier injury
- Hyper-alimentation (trifatoids)
- Mechanical ventilation
- GI perforations, recurrent abdominal surgery
- HIV infection
- Systemic diseases requiring immunosuppressive therapy
- Chronic obstructive pulmonary disease
- Neonatal ICU (Low APGAR, LOS, shock, H2 blockers, intubation)

Clin Infect Dis 2001; 33: 177-186

Opportunistic Fungi: Candida

- 4th most common nosocomial bloodstream infection

Maulana Azad Medical College:
- n=101 ICU patients
- Candidemia in 7 (6.9%)
- Risk factors:
  - The length of hospitalization (p=0.018)
  - Broad-spectrum antibiotics (p=0.045)
  - Central venous catheters (p=0.005)
  - Mechanical ventilation (p=0.013)
  - Total parenteral nutrition (p=0.001)

Sahai et al JAPI 2005
Risk factors for invasive candidiasis in the intensive care setting

Adults:
- Prolonged stay in ICU
- High APACHE II score (>20)
- Renal failure
- Hemodialysis
- Broad-spectrum antibiotics
- Central venous catheter
- Parenteral nutrition
- Immunosuppressive drugs
- Cancer and chemotherapy
- Severe acute pancreatitis
- Candida colonization at multiple sites
- Surgery
- Transplantation

Neonates and children:
- In addition to the adult risk factors:
  - Prematurity
  - Low Apgar score
  - Congenital malformations

Candida species causing blood stream infection worldwide

<table>
<thead>
<tr>
<th>Species</th>
<th>USA</th>
<th>Canada</th>
<th>Mexico</th>
<th>Hungary</th>
<th>Russia</th>
<th>India</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>56</td>
<td>53</td>
<td>53</td>
<td>41</td>
<td>60</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>9</td>
<td>23</td>
<td>21</td>
<td>7</td>
<td>38</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>19</td>
<td>11</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>C. krusei</td>
<td></td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Other Candida species</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>13</td>
<td>3</td>
<td>26</td>
</tr>
</tbody>
</table>

Zygomycosis

The etiologic agents encountered in India:
- Rhizopus oryzae
- Apophysomyces elegans
- Saksenaea vasiformis
- Cunninghamella bertholletiae
- Absidia corymbifera
- Basidiobolus ranarum
- Conidiobolus coronatus

In the developed world:
- transplant recipients & patients with haematological malignancies seem to be most vulnerable to zygomycosis
- In India: the most common risk was uncontrolled diabetes mellitus

Dixwade et al., Zygomycosis in India
Mycoses (2007), 50, 247-254
**Cryptococcosis in India: the awakening of a giant?**

U. Banerjee, K. Datta, T. Maji, and S.K. Gupta
Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India

Cryptococcus in CSF


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**Do Patients Acquire Fungal Infections In The ICU?**

- Fungal colonization of the lungs may be present before entry into the hospital.
- Primary ecological niche remains decomposing material.
- Aerosolized spores may be a potential source of infection through improperly cleaned ventilation systems, water systems, or even computer consoles.
- The use of high-efficiency particulate air filtration reduces the risk of invasive fungal infections.
- Contaminated water has been implicated as a source of infection.

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**Are Available Diagnostic Tools Applicable In ICU?**

- Diagnostic & Therapeutic approaches are evolving thanks to BMT, which may not be same in ICU patients as for other hematology patients.
- In general, a diagnosis is made on the basis of a combination of:
  - High risk situation
  - Compatible clinical findings
  - Abnormal radiologic findings
  - Microbiologic confirmation or histologic proof of tissue invasion.

Fungal Infections in the ICU

**Systemic Fungal Infection: Who Is at Risk?**

<table>
<thead>
<tr>
<th></th>
<th>Moulds</th>
<th>Yeasts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematopoietic Stem Cell Transplant (HSCT)</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Allergenic</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Non-hyperalveolar allogenic</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Autologous</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other hematologic malignancy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Solid organ transplant (SOT)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Critical Care</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Congestive lung disease/Critical Care</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>General Surgery</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(Data vary by case. Key not for GI and anology.)

**Clinical Features: Zygomycetosis**

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus disease</td>
<td>Fever, headache, nasal congestion, facial pain, ear pain, epistaxis, anosmia</td>
</tr>
<tr>
<td>Rhino-orbital</td>
<td>Proptosis, ophthalmoplegia, blindness, facial anhidrosis</td>
</tr>
<tr>
<td>Rhinocerebral</td>
<td>Alteration in level of consciousness, focal neurological defects, invasion into carotid artery &amp; jugular veins</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Fever, cough, hypoxemia, pleurisy, pleural effusions, hemoptysis</td>
</tr>
<tr>
<td>Cutaneous disease</td>
<td>Fever, eschar</td>
</tr>
<tr>
<td>GI disease</td>
<td>Nausea, vomiting, abdominal distension, pain, hematohemorrhage</td>
</tr>
</tbody>
</table>
Stays Alert!

To believe is very dull.
To doubt is intensely engrossing.

—Oscar Wilde
Question 3: In neutropenic patients, a major cause for mortality is

- Candida
- Aspergillus
- Zygomycosis
- Cryptococcus

Case 2

- A 28 year male
- Fever 1 month, symptomatic anemia
- Hb 6.2g/dl, TLC 3000/cu mm, Plat 3400/cu mm, Absolute Neutrophil Count (ANC) =20/cu mm
- BM: Acute Myeloid Leukemia- M4

Clinical Course

- Fever with Neutropenia: from 22/12/05 Inj Cefaperazone+Sublactam (Magnex) + Amikacin
- Nasal Stuffiness, Sinusitis
- X-Ray PNS and CT Sinuses: ? Fungal
Clinical Course

- No response: Added Inj Vancomycin + Inj Amphotericin (25/12/05)
- Afebrile from 27/12/05
Clinical Course

- Induction with Daunorubicin (3) + Cytosine arabinoside (7) wef 27/12/05.
- Afebrile from Day + 3
- Fever from Day + 13 (8/1/06). ANC=20
- Antibiotics: Inj Meronem
- X-Ray Chest : Patch +ve

Day + 13

- Patient has high grade fever, cough with hemoptysis, Severe neutropenia
- Blood cultures negative, Hyperglycemia
- CT Scan Chest: Day + 17
Question 4: The following sign on CT scan Chest suggests Probable Invasive Fungal Infection EXCEPT

- Dense, well circumscribed lesion ± Halo sign
- Lobar consolidation
- Air-crescent sign
- Cavity

Question to Dr Farah Jijina

- How do You Manage a Neutropenic Patient with Suspected Fungal Infection?
Abstract

Neutropenia is defined as an ANC of < 500 /mm3 and is one of the major causes of defects in the host defense. Besides bacterial infections, fungal infections add to the morbidity & mortality in febrile neutropenia. This is especially more prevalent in the present day, due to intensive anticancer therapy leading to prolonged severe myelosuppression and the use of broad spectrum antimicrobial drugs.

Thus invasive fungal infections (IFI) are seen in up to 20 % of febrile neutropenia patients; with a high mortality, up to 80%.

The most common fungal infections are due to:

- Candida
- Aspergillus
- Environmental moulds

Over the years there has been a shift from Systemic Candidiasis (SC) to Invasive Aspergillosis; and within SC a shift from C. albicans to non-albicans C. spp

Invasive fungal infection (IFI) is suspected when antibacterial drugs have failed to reduce fever during a period of neutropenia or sustained immunosuppression.

A probable diagnosis of IFI is made on the basis of a combination of host factors, presence of fever, neutropenia and resistance of fever to broad-spectrum antibacterial drugs. Thus clinical features, radiological criteria and microbiological evidence, all need to be taken into consideration. Early and repeated CT scans of chest and head are essential for high risk patients. All bacteriological samples should be investigated for fungi and a biopsy of suspected lesions must be done whenever possible.

However, it must be borne in mind that investigations are often not conclusive and ante-mortem diagnosis is less than optimal.

The treatment is therefore often empirical. The main drugs used in the treatment are Amphotericin, Voriconazole and Caspofungin. Numerous guidelines are available for the use of these drugs. However, one of the major factors for the choice of drug in our country is its cost. Newer anti fungal drugs can be prohibitively expensive and many of our patients are unable to afford them. Thus we may not always be able to follow the recommended guidelines.

As mortality remains high, the real challenge is to institute early, adequate treatment to the patients before they develop severe IFI and succumb!