CHAPTER

30

Opportunistic Infections in HIV

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INTRODUCTION

An opportunistic infection may be caused by various pathogens - bacteria, viruses, fungi, or protozoa. Many people living with HIV(PLHIV) may remain asyptomatic and first diagnosed when they face serious health threats from opportunistic infections (OIs). OIs are responsible as important contributing factor for mortility in PLHIV.

WHAT IS OPPORTUNISTIC INFECTION (OI)

Some infections are called "opportunistic" because they usually do not infect people of healthy immune system but take advantage of weakened immune system of the affected person. We all know HIV is the most important cause of compromised immunity.

ARE OIS UNIQUE FOR PLHIV?

HIV infection is definitely very important cause for immune suppression but there are many other clinical conditions where a non-HIV person may fall prey to opportunistic infections. Following conditions are some examples not uncommon to be associated with opportunistic infections

- Chemotherapy for cancer
- Immunosuppressing agents for organ transplant recipients
- Genetic predisposition
- Pregnancy
- Ageing
- Malnutrition

PLHIV can face serious health threats from opportunistic infections (OIs). OIs usually occur when CD4 count is below 200. However, certain OIs in HIV infected person indicate the person is having AIDS irrespective of the CD4 count.

In general, OIs are treated first before initiation of anti retroviral therapy (ART).

OIS IN HIV

There are host of OIs - viral, bacterial, fungal,protozoal & description of all is beyond scope here. Important aspects of some selected OIs are described here.

Majority of OIs (asteric ones) here are AIDS defining diseases also according to CDC.[1]

Viral

- Cytomegalovirus (CMV): CMV retinitis*, colitis, esophagitis, pneumonitis.
- Herpes simplex virus (HSV): chronic ulcer >1 month's duration, bronchitis, pneumonia, esophagitis.
- Human herpes virus 8 (HHV-8): Kaposi's sarcoma.*
- Human papillomavirus (HPV): Cervical cancer(Invasive).
- Epstein barr virus (EBV): Primary CNS lymphoma*, HIV associated Burkitt's lymphoma.
- JC virus: PML (progressive multifocal leukoencephalopathy).*

Bacterial

- Mycobacterium tubercrulosis (pulmonary or extrapulmonary)*.
- Mycobacterium avium complex (MAC)* or other species, disseminated or extrapulmonary.
- Recurrent pneumonia.
- Recurrent Salmonella septicaemia*

Fungal

- Candida: oropharyngeal thrush, esophageal candidiasis ,* candidiasis of bronchi, trachea and lungs.
- Pneumocystis jirovecii pneumonia.*
- Cryptococcosis, extrapulmonary*
- Histoplasmosis, disseminated or extrapulmonary*
- Coccidioidomycosis, disseminated or extrapulmonary*
- Microsporidiosis.

Protozoal

- Toxoplasmosis of brain.*
- Cryptosporidiosis: chronic intestinal >1 month duration*
- Isosporiasis: chronic intestinal >1 month duration*

VIRAL INFECTIONS

Cytomegalovirus disease (CMV)

- Causes retinitis, colitis, esophagitis, pneumonitis
- Retinitis is the commonest manifestation. Patients with CD4 <100/μL are at higher risk. [1]

- Clinical features of CMV retinitis :- Painless progressive irreversible loss of vision (due to necrotic inflammatory process) but patients may also complain of blurred vision, floaters, scintillations. The disease is usually bilateral but typically asymmetric.
- Fundoscopy :- Perivascular hemorrhage and exudate. When in doubt, vitreous or aqueous humor sampling with molecular diagnosis technique may be of value.
- Treament :

  Oral valganciclovir, IV ganciclovir, or IV foscarnet, with cidofovir as an alternative.

  A 3-week induction course is followed by maintenance therapy with oral valganciclovir.

  Maintenance therapy is continued until the CD4 count remains >100–150/μL for >6 months.

KAPOSI'S SARCOMA (KS)

- HHV-8 has been implicated in the pathogenesis of KS.
- May be seen at any stage of HIV infection, even in the presence of a normal CD4 count.[1]
- It is a multicentric neoplasm consisting of multiple vascular nodules appearing in the skin, mucous membranes, and viscera. Lesions often appear in sun-exposed areas and shows Koebner phenomenon (tends to occur in areas of trauma)
- Clinical features:

  Depends upon according to organ involvement.

  Disease limited to the lymph nodes show good prognosis.

  Pulmonary involvemrnt may cause dyspnoea. Chest x-ray may show bilateral lower lobe infiltrates and pleural effusion.

  Gastrointestinal (GI) involvement may cause bleeding due to mucosal involveement or may cause GI obstruction.

  Infiltration of the gallbladder and biliary tract may lead to obstructive jaundice.
- Diagnosis - by biopsy of a suspicious lesion.
- Treatment

  ART has been associated with the spontaneous regression of KS lesions.

  In single/a few lesions that are causing significant discomfort or cosmetic problems can be treated with localized radiation, intralesional vinblastine or cryotherapy.

  Extensive disease can be treated with IFN-α, liposomal daunorubicin, liposomal doxorubicin and paclitaxel with a varying response rate.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

- JC virus related disease and unlike other OI it can occur even when CD4 count >100-200/μL and in patients on ART.[2]
- Demyelination occurs in subcortical white matter that eventually coalesce. The cerebral hemispheres, cerebellum, and brainstem may all be involved.
- Patients may have seizure, ataxia, hemiparesis, visual field defects, aphasia and sensory defects with or without changes in mental status.
- MRI reveals multiple, nonenhancing white matter lesions that may coalesce and have a predilection for the occipital and parietal lobes. Measurement of JC virus DNA levels in CSF has diagnostic value.

  No definitive treatment available. Favourable prognosis occurs when CD4 count >100/μL

BACTERIAL INFECTION

Mycobacterium tuberculosis (Pulmonary & extra-pulmonary) infection

We Indians go through discussions on tuberculosis in various forams and here only some important points are mentioned:

- Leading cause of isolated fever or fever with respiratory symptoms [3]
- Patients with HIV infection are more likely to have active TB by a factor of 100 when compared with an HIV negative population. [3]
- Levels of plasma HIV RNA increase in the setting of active TB. In patients with lower CD4 counts, disseminated disease is more common.
- Patient may be asymptomatic. Thus screening for TB should be part of tlhe initial evaluation of every patient with HIV infection.
- Management : Important points to be kept in mind in the management -

- ART is delayed for a period of 2-8 weeks following initiation of antitubercular therapy (ATT) to prevent IRIS (Immune reconstitution inflammatory syndrome).
- Nevirapine is substituted with efavirenz in a patient receiving ATT.
- However, adjusted doses of rifabutin should be substituted for rifampin in patients receiving the HIV protease inhibitors.

Mycobacterium avium complex disease

- Occurs in patients with CD4 count <50/μL and average CD4 count at the time of diagnosis is 10/μL. [1]
- Prior infection with tuberculosis decreases the risk of MAC infection.

- Clinical features & Diagnosis:

  The disease is disseminated with multi organ involvement.

  Presents with fever, wight loss, night sweats, abdominal pain, diarrhoea, lymphadenopathy.

  Anemia and elevated liver alkaline phosphatase are common. Chest x-ray is abnormal in 25% of cases and may show bilateral lower lobe infiltrate.

  Diagnosis is made by culture of blood or involved tissue.

- Treatment :-

  Macrolide (usually clarithromycin) with ethambutol.

  Third drug (in extensive disease) – Rifabutin/ Ciprofloxacin/or Amikacin

  Therapy may be stopped when CD4 count is >100/ µL for 3-6 months.

FUNGAL

Pneumocystis Pneumonia (PCP)

- Caused by Pneumocystis jirovecii.
- CD4 count <200/µL & previous history of PCP are risk factors for developing PCP. [1]
- Clinical features :- fever, nonproductive cough, dyspnoea, night sweats, unexplained weight loss and thrush.
- Investigations :

- Chest x-ray may be normal at early stage or shows faint bilateral interstitial infiltrate rather than classic dense peri-hilar infiltrate in patients with AIDS.
- HRCT (Chest) - Shows diffuse ground-glass opacities. Cysts and pneumothoraces are common radiological finding.
- ABG - decline in PaO2, increase in the arterial-alveolar (a–A) oxygen gradient. Blood - lactate dehydrogenase is elevated.
- Definitive diagnosis - By showing organism in sputum, broncho-alveolar lavage, lung biopsy (with methenamine silver, toluidine blue O or Giemsa staining).
- DNA PCR for P.jirovecii (may be used when histology is non-confirmatory).

- Treatment

  Trimethoprim (5mg/kg) + sulfamethoxazole (25mg/ kg) orally or IV for 14-21 days. Skin rash, cytopenia, hepatitis may occur. Alternatively

  Dapsone/ Trimethoprim, clindamycin/primaquine, atovaquone or IV pentamidine may be used alternatively.

  Glucocorticoids improve survival in moderate to severe disease (Pa O2 <70 mmHg or a- A oxygen gradient ≥ 35 mmHg).

Cryptococcosis

- Causative organism - C. Neoformans occurs in patients with CD4 <100/µL.[1]
- Clinical features - Commonly manifests as subacute meningitis or meningoencephalitis, cryptococcoma, cranial nerve involvement.

  Patient usually presents with fever, headache, nausea, vomiting, altered mental status, personality changes, ± neck stiffness.

  Raised ICT due to impaired resorption CSF caused by debris from Cryptoccal polysaccharide capsule. [3] So subacute presentation with worsening of headache is usally initial manifestation.

  Approximately one-third of patients have pulmonary disease.

- Investigations :

- CSF analysis : Investigation of choice for diagnosis.

  - Modest rise in leucocytes (usually ≤ 20) and protein and decrease in glucose. These parameters may remain normal. [3]
  - Confirmation is by identification of organism in spinal fluid with India ink preparation (less sensitive) or by detection of cryptococcal antigen(far more sensitive).[3]

- Blood culture for fungus is often positive.
- Biopsy may be needed rarely to diagnose CNS cryptococcoma.

- Treatment :

- Amphotericin B (0.7 mg/kg) but preferably liposomal amphotericin(4–6 mg/kg) daily, with flucytosine 25 mg/kg qid for at least 2 weeks and, if possible, until the CSF culture turns negative

  ↓ Followed by

  Fluconazole 400 mg/d PO for 8 weeks

  ↓ Then

  Fluconazole 200 mg/d until the CD4+ T cell count has increased to >200 cells/L for 6 months in response to ART.

- Fluconazole 800-1200 mg / day is to be given with Amphotericin B, if Flucytocine is intolerable/ unavailable (as in India)[4]
- ICT is usually elevated & failure to relieve it satisfactorily with therapy is important underlying pathophysiology for morbidity & mortality.[4]

Histoplasmosis

- Caused by H. Capsulatum (dimorphic fungus) in persons with CD4 count <150/µL.[5]
- Clinical features & diagnosis :-

Table 1: Prophylactic Medications which are commonly in use in HIV patients

Infection	When to Give Prophylaxis	Agent
Pneumocystis jirovecii	CD4 < 200 cells/mm3 or oropharyngeal candidasis (thrush)	TMP-SMX
Toxoplasma gondii	CD4 < 100 cells/ mm3 and positive Toxoplasma gondii IgG immunoassay	TMP-SMX
Mycobacterium avium complex	CD4 < 50	Azithromycin

- Disseminated disease with common features are fever, weight loss, hepatosplenomegaly, lymphadenopathy.
- Maculopapular rash of skin and oral ulcer develops in 7% of patients.
- Cytopenia occurs in 33% of patients.
- Diagnosis :
- By culturing the organisms from blood/bone marrow/tissue
- By detecting antigen in blood or urine [3]
- Treatment :

  Liposomal amphotericin B followed by maintenance therapy with oral itraconazole until the serum histoplasma antigen is < 2 units, the patient has been on antiretrovirals for at least 6 months and the CD4 count is >150 cells/μL.

PROTOZOAL

Cerebral Toxoplasmosis

- Caused by T.Gondii and occurs in patients with CD4 <200/μL.[1]
- Occurs due to reactivation of latent T.Gondii cysts in the brain.
- Clinical features - Usually fever, headache and focal neurologic deficit.
- Common differentials : Primary CNS lymphoma, TB, fungal or bacterial abscess.
- Investigations :

  MRI of brain - multiple ring enhancing lesions

  Serum for IgG and IgM antibodies to Toxoplasma – simultaneous elevation of both helps diagnosis of acute infection.

  Brain biopsy – the definitive diagnostic procedure, only considered after failure of 2-4 weeks of emperical therapy.
- Treatment
- Sulfadiazine and pyrimethamine with leucovorin for a minimum of 4–6 weeks.
- Alternative regimens include
- Clindamycin+ Pyrimethamine,
- Atovaquone+ Pyrimethamine, and
- Azithromycin+ Pyrimethamine+ Rifabutin.
- Maintenance therapy with sulfadiazine, pyrimethamine and leucovorin is required to prevent relapse as long as CD4 count is <200/μL.
- Response to therapy is usually prompt & satisfactory clinical improvement is within 1 week , otherwise alternative diagnosis is suggested.[3]

Cryptosporidiosis

- Caused by various species of Cryptosporidium which infect small bowel mucosa.
- Persons with CD4<100/μL^3 are at greater risk of developing severe manifestation. Common presenting features are diarrhoea accompanied by abdominal cramps, nausea, vomiting.
- This was important cause for mortality before initiation of HAART
- Therapy is supportive and improvement occurs in the setting of ART. Nitazoxamide upto 2000 mg/ day is effective in reducing symptoms.
- This infection could be prevented to a great extent if water is boiled before drinking [6]

PREVENTION OF OIS IN HIV

Much emphasis is to be put to prevent Ois in HIV as it may cause rapid deterioration of patients clinical status and ultimately death in many cases. This preventive approach may be addressed under following heading

Immune System Restoration

- Starting antiretroviral therapy is a very important step to reduce OIs incidence.[7,8] It helps immune reconstitution to a great extent & may provide near normal life-span in PLHIV

To Reduce Exposures to microorganisms for Ois[9]

One has to avoid

- Cat feces & firm animals with diarrhoea (source of Toxoplasma gondii, Bartonella spp)
- Eating undercooked meat or eggs, unpasteurized dairy products (M. tuberculosis)
- Soil/dust mixed with bird droppings (Histoplasmosis, Coccidiomycosis)
- Reptiles, chicks, ducklings: source of Salmonella spp.- Recurrent Salmonella septicaemia is a AIDS defining disease

Prophylactic Medications

- A patient's risk stratification for developing an opportunistic infection is approximated according to patient's CD4 T-cell count

- Prophylactic treatments are commonly in use as shown in the Table 1. [10]

CLINICAL PEARLS: OPPORTUNISTIC INFECTIONS IN HIV

1. Opportunistic Infection (OI) take advantage of weakened immune system of the affected person.
2. Though HIV infection is classical example for weakened immune system to contract OIs, some other clinical conditions (eg.: Cancer chemotherapy, ageing, malnutrition) are not uncommon to be associated with opportunistic infections.
3. In general, OIs are treated first before initiation of anti retroviral therapy (ART)
4. Cytomegalovirus disease (CMV): Retinitis is the commonest manifestation. The disease is usually bilateral but typically asymmetric.
5. Kaposis Sarcoma can occur even in the presence of a normal CD4 count. It is a rare manifestation of HIV in India.
6. Patients with HIV infection are 100 times more likely to have active TB(Pulmonary/Extrapulmonary)
7. Cryptococcus meningitis : Raised ICT is (due to organism debris induced impairment in CSF resorption) is usually responsible for morbidity & mortality of patients.
8. Toxoplasma Gondaii: Response to therapy is usually prompt & if satisfactory clinical improvement is not seen within 1 week, alternative diagnosis is suggested.

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