

## MODULE 2

### SPECIFIC OPPORTUNISTIC INFECTIONS

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- Pneumocystis carinii
- Candidiasis
- Cryptococcosis
- Histoplasmosis
- Microsporidiosis
- Cryptosporidiosis

#### Learning Objectives

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When you have completed this module you should:

- Understand that the major causes of death in persons with HIV infection are infections that can be treated or prevented
  - Be able to recognise clinical features suggestive of opportunistic infections
  - Recognise when to refer patients for investigations and specialist opinion
  - Know what treatment may be given to persons with certain opportunistic infections
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#### 2.1 PNEUMOCYSTIS JIROVECI PNEUMONIA

*Pneumocystis* pneumonia (PCP) is a common HIV-associated opportunistic infection. Patients usually present with cough, shortness of breath and fever. Usually patients with PCP have a sudden onset of severe dyspnoea but PCP may also present in persons with more chronic symptoms. Symptoms may be very severe and an attack of PCP may lead to death if not treated early and effectively.

#### Diagnosis

The diagnosis is often made on clinical grounds when a patient with HIV infection presents with shortness of breath. The patient may have a cough but the main feature is the extreme dyspnoea. Chest x-ray may be completely normal or there may be evidence of patchy infiltrates in both lung fields. The classic chest x-ray appearance of a ground glass

opacification in the middle zones of both lung fields may also be found. The diagnosis is confirmed upon the finding of cysts of *Pneumocystis* in sputum or in bronchial lavage aspirate.

### Treatment

Patients with pneumocystis pneumonia usually are in respiratory failure and should ideally be admitted to hospital for management. Supportive therapy includes oxygen by facemask and adequate hydration. Intravenous fluids may be necessary but may lead to over hydration. Details of specific treatment are given in the table below:

| <b>PCP<br/>FIRST LINE TREATMENT</b>                   |             |           |       |          |
|---|-------------|-----------|-------|----------|
| Antimicrobial agent                                   | Dose        | Frequency | Route | Duration |
| <b>Trimethoprim/sulphamethoxazole (Cotrimoxazole)</b> | 320mg/960mg | TID       | PO    | 21 days  |
|   |             |           |       |          |

| <b>PCP<br/>SECOND LINE TREATMENT</b> |       |           |       |          |
|--------------------------------------|-------|-----------|-------|----------|
| Antimicrobial agent                  | Dose  | Frequency | Route | Duration |
| <b>Clindamycin</b>                   | 600mg | QID       | PO    | 21 days  |
| <b>PLUS</b>                          |       |           |       |          |
| <b>Primaquine</b>                    | 15mg  | OD        | PO    | 21 days  |

Severely ill patients may require prednisolone 60mg PO daily for 5 days reducing to 40mg PO OD for 5 days and then to 20mg PO OD for 10 days. After successfully treating the acute episode of pneumocystis pneumonia it is necessary to continue secondary prophylaxis with trimethoprim 160mg/sulphamethoxazole 800mg on a long-term basis.

Some patients are sensitive to cotrimoxazole and may need desensitisation.

**Rapid cotrimoxazole desensitization regimen (for PCP)**

(suitable for prophylactic dose cotrimoxazole or high dose cotrimoxazole for treatment of PCP).

- Do not desensitize anyone who has had an anaphylactic reaction to cotrimoxazole or a severe skin rash such as a Stevens-Johnson syndrome. Usually about 60% effective. Rapid desensitization ideally should be performed during the day in a setting where emergency resuscitation can be provided and adrenaline can be given.
- Observations during rapid desensitization should be done every 30 minutes before each dose is given and include temperature, pulse and BP.
- If mild rash or pruritus only occur, administer antihistamine (e.g. chlorpheniramine or promethazine) and continue. If more serious side - effects occur such as severe wheeze, severe or symptomatic hypotension, severe rash etc, discontinue desensitization, manage appropriately and do not try to restart desensitization.
- Once cotrimoxazole has been started it can be continued indefinitely as long as no reactions are noted, but if the drug is stopped at any time, there may be a risk of reaction when it is restarted.

**Desensitization process**

Using a 1ml syringe put 0.5ml of paediatric cotrimoxazole 240mg/5ml syrup in 1000ml of 5% Dextrose and mix well. Give as follows:

| Minutes | Quantity of above mixture given orally |
|---------|--|
| 0       | 1ml (use 10ml syringe)                 |
| 30      | 10ml (use 10ml syringe)                |
| 60      | 100ml (use 10ml syringe)               |

The switch to paediatric cotrimoxazole 240mg / 5ml syrup.

| Minutes | Quantity                                    |
|---------|---|
| 90      | 0.5ml                                       |
| 120     | 5ml   |
| 150     | 480mg tablet                                |
| 180     | Start full prophylactic or therapeutic dose |

Slow Desensitization regimen for adults allergic to cotrimoxazole (excluding those with Stevens-Johnson syndrome, acute anaphylaxis, and fixed drug reaction to cotrimoxazole)

**Use a 1ml syringe and cotrimoxazole syrup 240mg/5ml**

| Day | Dose of cotrimoxazole syrup |
|-----|-----------------------------|
| 1   | 0.05ml = 2.4mg              |
| 2   | 0.1ml = 4.8mg               |
| 3   | 0.2ml = 9.6mg               |
| 4   | 0.4ml = 19.2mg              |
| 5   | 0.6ml = 28.8mg              |
| 6   | 1.0ml = 48mg                |
| 7   | 2.5ml = 120mg = ½ teaspoon  |
| 8   | 5ml = 240mg = 1 teaspoon    |
| 9   | 480mg = 1 tablet            |
| 10  | 480mg = 1 tablet            |
| 11  | 960mg = 2 tablets           |

Stop cotrimoxazole at any point if there is evidence of a skin rash.

**Activity 2.1**

**This is an individual exercise**

A 37-year old man HIV positive man who has been well and has been attending regularly at the OIP Clinic attends 10 days before his scheduled appointment. At this visit he states that over the last 4 days he has been coughing and that today he has become short of breath. The shortness of breath is present even at rest.

- List the causes of shortness of breath in this patient.
- What further information would you want to obtain from this patient to assist you with the differential diagnosis?

**There will be a discussion when this exercise has been completed**

## 2.2 CANDIDIASIS

The two main types of candidiasis are localized disease (of the mouth and throat, and of the vagina), and systemic disease (of the oesophagus, skin and nails and other viscera). The mouth and throat variant (oropharyngeal candidiasis (OPC) is believed to occur at least once in the lifetime in all HIV-infected patients. The symptoms of oesophageal candidiasis are difficulty in swallowing and pain in the chest that increases with swallowing. Disseminated candidiasis causes fever and symptoms in the organs affected by the disease (for example, blindness when it affects the eyes).

### Diagnosis

The diagnosis of oro-pharyngeal candidiasis is made on clinical grounds. The diagnosis may be confirmed by the microscopic examination of material obtained from lesions. The diagnosis of oesophageal candidiasis is made by direct visualization of oesophageal lesions by upper gastrointestinal endoscopic examination. In other sites the diagnosis is made by histologic examination of tissue biopsies.

### Treatment

Localized disease is treated first with topical drugs such as aqueous GV paint, nystatin, miconazole, or clotrimazole. If there is a failure to respond to local treatment systemic antifungal agents may be used. In patients with disseminated candidiasis and in those in whom topical therapy has failed antifungal agents such as ketoconazole, itraconazole, fluconazole or amphotericin B may be given.

### 1. Oral candidiasis

#### **FIRST LINE TREATMENT**

#### **Oral candidiasis**

| <b>Antifungal agent</b>              | <b>Dose</b>   | <b>Frequency</b> | <b>Route</b> | <b>Duration</b> |
|--------------------------------------|---------------|------------------|--------------|-----------------|
| <b>Nystatin lozenges to suck</b>     | 200 000 units | 5 times a day    | PO           | 14 days         |
| <b>OR</b>                            |               |                  |              |                 |
| <b>Clotrimazole lozenges to suck</b> | 10mg          | 5 times a day    | PO           | 14 days         |
| <b>OR Aqueous GV paint</b>           |               | 5 times a day    | PO           | 14 days         |

**SECOND LINE TREATMENT**

**Oral candidiasis**

| Antifungal agent | Dose  | Frequency | Route  | Duration |
|------------------|-------|-----------|--------|----------|
| Fluconazole      | 100mg | OD        | PO     | 14 days  |
| <b>OR</b>        |       |           |        |          |
| Itraconazole     | 100mg | OD        | Gargle | 21 days  |

**2. Vaginal candidiasis**

**FIRST LINE TREATMENT**

**Vaginal candidiasis**

| Antifungal agent             | Dose  | Frequency   | Route   | Duration    |
|------------------------------|-------|-------------|---------|-------------|
| Fluconazole                  | 100mg | Single dose | PO      | Single dose |
| <b>OR</b>                    |       |             |         |             |
| Miconazole cream/pessaries   | 200mg | Once a day  | Vaginal | 3 days      |
| <b>OR</b>                    |       |             |         |             |
| Clotrimazole cream/pessaries | 100mg | Twice daily | Vaginal | 3 days      |

**SECOND LINE TREATMENT**

**Vaginal candidiasis**

| Antifungal agent | Dose  | Frequency | Route | Duration |
|------------------|-------|-----------|-------|----------|
| Ketoconazole     | 200mg | BID       | PO    | 3 days   |
| <b>OR</b>        |       |           |       |          |
| Ketoconazole     | 200mg | OD        | PO    | 7 days   |

**3. Oesophageal candidiasis**

**FIRST LINE TREATMENT**

**Oesophageal thrush**

| Antifungal agent | Dose           | Frequency | Route | Duration   |
|------------------|----------------|-----------|-------|------------|
| Fluconazole      | 200mg to 400mg | OD        | PO    | 14-21 days |

**SECOND LINE TREATMENT****Oesophageal thrush**

| Antifungal agent | Dose         | Frequency | Route | Duration  |
|------------------|--------------|-----------|-------|-----------|
| Ketoconazole     | 200mg-400mg  | BID       | PO    | 2-3 weeks |
| <b>OR</b>        |              |           |       |           |
| Itraconazole     | 200mg        | OD        | PO    | 2-3 weeks |
| <b>OR</b>        |              |           |       |           |
| Amphotericin B   | 0.3-0.5mg/kg | OD        | IV    | 2-3 weeks |

**2.3 CRYPTOCOCCOSIS**

Systemic mycoses such as cryptococcosis probably cause up to 10% of all HIV-associated deaths worldwide. Cryptococcosis most often appears as

- meningitis,
- occasionally as pulmonary or
- disseminated disease.

Cryptococcal meningitis is the most frequent systemic fungal infection in HIV-infected persons. Patients present with headache, fever, neck stiffness, and may be comatose. Commonly fever is absent in patients with cryptococcal meningitis. Without treatment, life expectancy is probably less than a month.

Diagnosis

Cryptococcosis is relatively easy to diagnose. The centrifuged deposit of the cerebrospinal fluid is examined microscopically after a drop of India skin is added. The yeasts are seen as organisms surrounded by a thick capsule.

Treatment

The treatment of cryptococcal meningitis is summarised in the tables below. Note that lifelong secondary chemoprophylaxis is necessary and this may be achieved with fluconazole 200mg orally daily for life. Alternate long term secondary prophylaxis may be achieved with itraconazole 200mg orally daily for life.

**FIRST LINE TREATMENT****Cryptococcal meningitis**

| Antifungal agent      | Dose       | Frequency | Route | Duration |
|-----------------------|------------|-----------|-------|----------|
| <b>Amphotericin B</b> | 0.7mg/kg   | OD        | IV    | 14 days  |
| <b>PLUS</b>           |            |           |       |          |
| <b>5-flucytosine</b>  | 15-25mg/kg | QID       | PO    | 14 days  |
| <b>THEN</b>           |            |           |       |          |
| <b>Fluconazole</b>    | 400mg      | OD        | PO    | 8 weeks  |
| <b>THEN</b>           |            |           |       |          |
| <b>Fluconazole</b>    | 200mg      | OD        | PO    | For life |

**2.4 HISTOPLASMOSIS**

This infection is caused by *Histoplasma capsulatum*, a fungus that can cause an acute or chronic illness. Intact cell mediated immunity is essential for preventing its dissemination. Reactivation of previous infection as well as acquisition of new infection can lead to dissemination. Infection occurs by inhalation of spores. The outcome of exposure depends on immune status of host as well as size of inoculum. The acute illness is influenza-like with fever, anorexia, arthralgia, myalgia, a dry cough and chest pain. Dissemination occurs soon after initial infection in immunosuppressed hosts who develop weight loss, chest symptoms, liver, spleen and lymph node enlargement and oral and skin lesions. The skin lesions may be follicular, maculopapular, pustular, erythematous, nodular or papulo-necrotic. While buccal lesions may be ulcers, nodules, or perforated palate.

Diagnosis

The diagnosis is made on clinical grounds and is confirmed on fungal cultures or histological examination of biopsied tissues. A chest x-ray in the acute illness may show hilar lymphadenopathy, scattered infiltrates and lower lobe nodules. Blood and skin tests have been developed for the diagnosis of histoplasmosis but these are not readily available.

Treatment

Acute histoplasmosis is self-limiting with normal immunity and does not require treatment. Immunosuppressed patients may be treated as follows:

**FIRST LINE TREATMENT****Histoplasmosis**

| Antifungal agent | Dose       | Frequency | Route | Duration  |
|------------------|------------|-----------|-------|-----------|
| Amphotericin B   | 0.7-1mg/kg | OD        | IV    | 3-14 days |
| <b>THEN</b>      |            |           |       |           |
| Itraconazole     | 200mg      | BID       | PO    | Long term |

Long-term secondary prophylaxis may be achieved with itraconazole or fluconazole 200mg orally daily for life.

## 2.5 MICROSPORIDIOSIS

Microsporidia are intracellular protozoan parasites. There are over 1200 species of microsporidia, though human disease is caused by about 14 species. The pathogens produce resistant spores and at least three species that infect humans are found in domestic animals.

These include,

- **Encephalitozoon cuniculi**
- **Encephalitozoon intestinalis**
- **Encephalitozoon bieneusi**

Infection occurs with the ingestion of spores. The infection is an opportunistic disease, occurring mainly in immunocompromised patients. The clinical manifestations of microsporidiosis vary according to the causal species with diarrhoea being the most common manifestation. Infections of the eyes, respiratory tract, gall bladder, genitourinary tract and muscles have also been described.

### Diagnosis

The diagnosis is made on finding the spores in stool smears stained by the Chromotrope 2R method.

### Treatment

Albendazole has been found to be effective in treating ocular and intestinal infections. In

addition for ocular infection, topical fumagillin is recommended.

### Important points to remember

- Fungal infections occur commonly in immunosuppressed persons
- The incidence of fungal opportunistic infections in persons with HIV infection increases as the cell mediated immunity decreases
- The type of fungal infections that occur varies geographically
- Candidial infections are probably the commonest fungal infections seen in HIV infected individuals
- Pneumocystis pneumonia (PCP) and cryptococcal meningitis are life threatening fungal infections and may be treated adequately in most patients but recurrences commonly occur and secondary prophylaxis with appropriate antimicrobial agents is necessary
- PCP and cryptococcal meningitis are common causes of death in HIV infected persons

## 2.6 CRYPTOSPORIDIOSIS

*Cryptosporidiosis* is a diarrhoeal disease caused by a *Cryptosporidium parvum*. It can live in the intestine of humans and animals and is passed in the stool of an infected person or animal. The parasite can form cysts allowing it to survive outside the body for long periods of time and makes it resistant to chlorine disinfection. Cryptosporidiosis a common cause of waterborne disease. The organisms cause a secretory diarrhoea and malabsorption. Infection may ascend from the intestine to the biliary tree resulting in cholangitis

Symptoms include diarrhoea, abdominal pain with mild fever. The infection may remain completely asymptomatic. Symptoms usually start 2 to 10 days after infection and in immunocompetent hosts symptoms last about 2 weeks. The organisms (cysts) may be found in soil, food, and water, and on surfaces contaminated with faeces of infected persons.

Infected persons pass millions of cysts in the faeces. HIV infected persons who become infected develop repeated bouts of diarrhoea and a severe chronic illness and wasting. Infection is easily transmitted to family members of infected patients. Cholangitis, cholecystitis, hepatitis, pancreatitis and respiratory tract infections may also occur.

Diagnosis

The diagnosis is made on finding the organisms in stool smears stained by the modified acid fast staining method.

Treatment

HIV-infected persons should be educated and counseled about the ways that *Cryptosporidium* can be transmitted. Modes of transmission include having direct contact with infected adults and children, and infected animals; drinking contaminated water; and eating contaminated food. HIV-infected persons should avoid contact with human and animal feces. They should be advised to wash their hands after contact with human faeces (e.g., napkin changing), after handling pets, and after gardening or contact with soil. Supportive treatment is with oral rehydration fluid and codeine or loperamide. Drinking boiled water is advisable.

**Recovery from cryptosporidiosis depends on the immune status. With effective antiretroviral therapy the incidence of infection has been reduced. Antiretroviral therapy usually results in a good response with session of the chronic diarrhea. The following may be used in treating the infection:**

| <b>RECOMMENDED TREATMENT</b> |       |           |       |          |
|------------------------------|-------|-----------|-------|----------|
| Antimicrobial agent          | Dose  | Frequency | Route | Duration |
| <b>Paromomycin</b>           | 1g    | BID       | PO    | 4 weeks  |
| <b>PLUS</b>                  |       |           |       |          |
| <b>Azithromycin</b>          | 600mg | OD        | PO    | 4 weeks  |

**Activity 2.3**

**This is an individual exercise**

How would you assess dehydration in an adult?

**There will be a discussion when this exercise has been completed**