HIV Associated Opportunistic Pneumonias

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SUMMARY

Opportunistic pneumonias are major causes of morbidity and mortality in HIV infected individuals. The majority of new HIV infections in Malaysia are adults aged 20 to 39 years old and many are unaware of their HIV status until they present with an opportunistic infection. HIV associated opportunistic pneumonias can progress rapidly without appropriate therapy. Therefore a proper diagnostic evaluation is vital and prompt empiric treatment of the suspected diagnosis should be commenced while waiting for the results of the diagnostic studies. Tuberculosis, *Pneumocystis* pneumonia (PCP) and recurrent bacterial pneumonias are common causes of AIDS-defining diseases and are discussed in this article.

KEY WORDS:
HIV, Oppotunistic pneumonia, Pulmonary tuberculosis, Pneumocystis pneumonia, Recurrent bacterial pneumonia

INTRODUCTION

The World Health Organisation has estimated that 25 million people have died of HIV/AIDS, including 2 million people who died in 2007[1]. A significant proportion of these deaths were due to opportunistic pneumonias. The Ministry of Health of Malaysia has reported a total of 84,630 HIV infections and 11,384 deaths from AIDS since 1986 till 31st December 2008. The majority of new HIV infections are in adults aged 20 to 39 years old[2]. With the introduction of HAART antiretroviral therapy, patients are living longer and the incidence and severity of opportunistic pneumonias have decreased. However, HIV–associated opportunistic pneumonias remain a major cause of morbidity and mortality. Many patients in developing countries are unaware of their HIV infection until they present with an opportunistic pneumonia. Patients whom are aware of their HIV status but have poor adherence to antiretroviral treatment and prophylaxis are also at risk of opportunistic pneumonias. The range of HIV associated opportunistic pneumonias is broad and includes bacterial, mycobacterial, fungal, viral and parasitic pneumonias.

Tuberculosis, *Pneumocystis* pneumonia (PCP) and recurrent bacterial pneumonias (defined as two episodes occurring within a 12 month period) are frequent causes of AIDS-defining diseases [3,4]. Doctors are frequently faced with challenges in making an accurate diagnosis for these 3 conditions. These 3 conditions often require prompt treatment decisions before microbiological confirmation is available. The majority of new cases in Malaysia (70% of cases in 2003 and 53.2% of cases in 2008) were intravenous drug users[2] and this group have been found to be at higher risk of TB and bacterial pneumonias compared to other HIV infected groups[5].

ASSESSMENT OF PATIENT

Since the treatment and management of these 3 diseases are different, the aim of assessment of a HIV infected patient with suspected opportunistic pneumonia is to obtain a definite diagnosis[6]. This will minimise inappropriate therapy with its potential side effects, reduce the duration of hospital stay and identify suspected TB patients requiring isolation.

Despite clinical assessment, basic laboratory tests and chest radiograph, a definite diagnosis may not be necessarily achievable in all cases. This may require more invasive diagnostic procedures such as bronchoscopy and more complex laboratory techniques, which may only be available in tertiary centres in the country.

A detailed clinical history is warranted and the history should include the onset and duration of the symptoms, HIV risk factors, history of previous opportunistic infections and current use of opportunistic infection prophylaxis and combination antiretroviral therapy, recent travel and most recent CD4 cell count. Physical examination may also detect extrapulmonary or disseminated disease.

Following the history and physical examination, chest x ray is indicated for suspected pneumonia. The appearance on chest x ray with the combination of history, physical examination and CD4 cell count often will suggest a differential diagnosis. Specific laboratory investigations, for example serum, sputum and bronchoalveolar lavage are indicated to confirm the diagnosis or assess disease severity (e.g. arterial blood gases). CT scan of the thorax may be indicated in certain cases if the chest radiograph is not specific or to evaluate the lungs more closely.

The challenge of HIV infection is that there is an overlap of clinical and radiological appearance of opportunistic pneumonias and the HIV infected person may present with more than one concurrent pneumonia[6]. Persons with HIV opportunistic pneumonias are at risk of rapid deterioration to respiratory failure and septicaemia if appropriate treatment is not administered promptly. Empirical treatment should be commenced while waiting for the results of the confirmatory investigations.

TUBERCULOSIS (TB)

WHO estimates that TB is the cause of death for 13% of AIDS patients. Tuberculosis was estimated to cause death in 200,000 persons with HIV/AIDS in 2006[7]. TB infection occurs when a susceptible person inhales mycobacterium tuberculosis organisms and within 2-12 weeks after infection, the immune system limits multiplication of the tubercle bacilli. These tubercle bacilli can persist in the body for years,

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a condition referred to as latent TB infection (LTBI)[8]. Persons with HIV infection have reduced cell mediated immune response in proportion to the degree of HIV related immunosupression which compromises the defence against progression of primary infection with M. tuberculosis or reactivation of LTBI[9,10].

Individuals with LTBI are asymptomatic and are not infectious. However, persons with HIV infection have a significant increase risk of progression from latent TB infection to active TB compared with persons without HIV infection. The rate of progression to active TB in persons infected with HIV is around 10% per annum compared to a 10% lifetime risk of progression to active TB in non HIV infected person[11]. Tuberculosis can occur at any stage of HIV disease but as the CD4 cell counts declines, the risk of developing pulmonary and extra pulmonary TB increases[12].

The clinical and radiological presentation of TB may be altered in the presence of HIV co-infection due to reduced cell mediated immune response. The classical symptoms of TB in persons without HIV including cough, haemoptysis, fever, night sweats, anorexia and weight loss occurs with CD4 cell count of above 350-400 cells/µL. Extrapulmonary sites are more often involved in those with a lower CD4 cell count of below 200 cells/µL. The lymph nodes are the most common extrapulmonary site of tuberculosis disease in HIV infected persons and studies have also reported higher rates of TB meningitis, pleural TB and TB pericarditis[13].

The classical TB changes on chest x ray of fibronodular infiltrates with or without cavitation in the upper lobes are similar to that in persons without HIV infection[7]. However with a low CD4 cell count of below 200 cells/µL, lower lobe involvement, miliary pattern and pleural effusion is seen more often and cavities are less common. Mediastinal lymphadenopathy is more common than non HIV infected TB patients[14,15].

At least three sputum AFB smears and culture should be obtained, preferably in three separate mornings in patients with pulmonary symptoms and chest x ray abnormalities. The HIV status does not affect the yield from sputum smear and culture examinations. Sputum smear is more likely to be positive in cavitating pulmonary disease[16]. The presence of normal CXR usually excludes the diagnosis of active pulmonary TB but in the presence of symptoms, sputum samples for acid fast bacilli smear should be obtained[8]. If the sputum acid fast bacilli smears are negative and the suspicion of TB is high, the patient should be referred for bronchoscopy and bronchoalveolar lavage. For patients with signs of extrapulmonary disease, needle aspiration or tissue biopsy of lymph nodes, pleural, skin or any other suspected organ should be performed.

Mantoux test should not be relied upon for the diagnosis of TB disease as about one fourth of HIV infected persons with pulmonary TB have false negative results. This false negative result is increasingly likely with increasing immunosuppression[17]. A positive AFB smear result should be presumed to be *M. Tuberculosis* as it is the most virulent mycobacterial pathogen and treatment should be initiated while waiting for the mycobacterial species to be identified. Culture specimen must still be obtained with drug susceptibility testing and the treatment adjusted accordingly to ensure a successful eradication of the mycobacterium.

The anti-TB treatment in HIV infected adults follows the same principles as for adults without HIV infection according to the Malaysian Clinical Practice Guideline on Tuberculosis[18]. DOT and other adherence-promoting strategies are recommended for all patients with HIV related TB. Initial treatment of drug susceptible TB disease should include the standard 4 drug regime of rifampicin, isoniazid (with pyridoxine), pyrazinamide and ethambutol in the initial 2 months (Table I). Careful clinical, radiological and sputum examination is required and once the organism has been confirmed to be fully sensitive at 2 months follow up, ethambutol and pyrazinamide can be stopped. Treatment can be switched to a 2 drug regime of isoniazid and rifampicin for the remaining 4 months to complete a 6 months regime. Patients with cavitating lung disease and repeat sputum culture that remains positive after completion of 2 months therapy, treatment with isoniazid and rifampicin should be extended to another 3 months for a total of 9 months[19]. Patients with extrapulmonary TB should receive 6-9 months of treatment apart from central nervous system, bone and joint diseases should receive 9-12 months. The respond rate to standard TB treatment regime is similar in HIV infected and uninfected patients, although the mortality rate is higher in HIV infected patients because of the complications of HIV infection. Failing to response to the standard 4 drug regimen should alert the clinician to suspect drug resistance and consultation with a TB expert is warranted.

Patients on concurrent treatment for HIV infection and TB have a higher likelihood of complications of drug interactions and adverse events such as cutaneous reaction and hepatotoxicity[8]. It is also important to be aware that HIV infected patients on both antiretroviral therapy and anti-TB treatment may develop the immune reconstitution inflammatory syndrome (IRIS). IRIS is thought to be the result of immune reconstitution as a consequence of effective antiretroviral therapy and the symptoms cannot be explained by a newly acquired infection or inflammatory condition. The frequency of IRS is estimated to occur in 10%– 25% of patients especially those with CD4 cell count of below 200 cells/µL and receive antiretroviral therapy which decreases the HIV-1RNA levels[20].

Symptoms and signs of IRIS include high fevers, new or worsening lymphadenopathy, worsening of chest symptoms and chest x ray findings. Non pulmonary presentations may include expanding central nervous system lesions. Most of the patients recover without any change in antiTB or antiretroviral therapy. Nonsteroidal anti-inflammatory may help with the symptoms and with severe reactions, steroids may be beneficial. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other etiologies, particularly tuberculosis treatment failure. In a patient who is receiving therapy for active TB, the onset of TB IRIS typically occurs in the first 3 months after the patient begins antiretroviral therapy[8].

HIV patients with diagnosis of LTBI based on either a positive Mantoux test (≥ 5mm of induration at 48-72 hours) or IFN-gamma release assays (IGRAs) should be considered to be infected with *M tuberculosis* and have a high risk of progression to TB, therefore should be treated for LTBI[18,19]. Prophylactic TB treatment should also be considered for anergic HIV infected patients who are known contacts of persons with infectious TB[18]. Before commencing on treatment for LTBI, it is important to exclude active TB based on clinical assessment, radiological findings and sputum examination (smear for acid fast bacilli and culture). Treatment options for LTBI include isoniazid for 9 months with pyridoxine to minimise the risk of peripheral neuropathy[18,19].

PNEUMOCYSTIS PNEUMONIA (PCP)

PCP is caused by *Pneumocystis jirovecii*, an organism classified as fungus. PCP was the AIDS defining illness for approximately two- thirds of adults with AIDS in the United States during the 1980's. With the introduction of PCP prophylaxis and combination antiretroviral therapy, the incidence of PCP had significantly declined in the developed countries. PCP however remains the most frequent serious opportunistic infection among HIV infected patients. The incidence of PCP has been increasingly reported in low-or middle income countries[22,23]. It may be the first presentation in persons who are unaware of their HIV infection, those who fail to access medical care and poor adherence to antiretroviral therapy or prophylaxis[6,24].

The clinical presentation of PCP in HIV infected patients differs from the presentation in other immunocompromised patients. The clinical presentation of HIV infected patients usually follows a subacute course with longer symptom duration, higher arterial oxygen level and the bronchoalveolar lavage specimens contains significantly higher numbers of Pneumocystis organisms compared with non HIV infected patients[25].

The mortality rate is 10-20% during initial infection in patients with AIDS and PCP, but the rate increases significantly with the need for mechanical ventilation[26]. The majority of cases with PCP occur in HIV infected persons whose cell count is below 200 cells/μL[24]. Usually the symptoms are subacute, occurring within days to weeks. Classically, the patient presents with non productive cough, fever and progressively worsening dyspnoea. Physical examination may reveal inspiratory crepitations but is often unremarkable especially in mild cases. In more severe cases, hypoxia may be present. Oxygen desaturation on exercise and elevated LDH level reflects underlying lung inflammation and injury rather than a specific marker for the disease. The chest x ray typically shows bilateral, symmetrical, interstitial infiltrates that become increasingly homogenous and diffuse as the disease progresses but may also be normal[27]. High resolution chest CT is more sensitive than chest x ray and typically shows ground glass attenuation and less commonly thin walled cysts, nodules and blebs. The occurrence of pneumothorax in a HIV patient should raise the suspicion of PCP[28].

No combination of symptoms, signs and chest radiographic features is diagnostic of PCP and the diagnosis is further complicated with the use of prophylactic drugs in the treatment of HIV infected individuals and simultaneous infection with multiple organisms[24]. Since *pneumocystis* cannot be cultured, its diagnosis is currently made from microscopic visualisation of the characteristic cysts or trophic forms on stained respiratory specimens from sputum induction, bronchoalveolar lavage or lung tissue. Sputum induction with hypertonic saline has a diagnostic yield of 50-90% and should be the initial procedure performed to diagnose PCP[29]. If the induced sputum is negative for pneumocystis, bronchoscopy with bronchoalveolar lavage will be the next step of investigation. Lung tissues from transbronchial (potential risk of pneumothorax) and open lung biopsies may be used to diagnose PCP when other procedures have failed.

Treatment can be started before making the diagnosis because the organisms persist in clinical specimens for days or weeks after effective therapy is initiated. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended first line treatment for PCP and the recommended duration of treatment for PCP is 21 days. This fixed-dose medication has excellent tissue penetration and is available in intravenous and oral formulations that achieve comparable serum levels. Alternatives to TMP-SMX include intravenous pentamidine, oral atovaquone and clindamycin plus primaquine (Table II)[24]. Patients with moderate to severe PCP with pO_2 < 70mmHg or arterial-alveolar O_2 gradient >35 mmHg should receive adjunctive corticosteroids. A consensus panel recommended a regimen of prednisolone 40mg twice daily for 5 days, then 40mg daily on days 6 -11, followed by 20mg daily thereafter to complete a 21 day course. The corticosteroids should be commenced within 72 hours after starting PCP therapy[30].

TMP-SMX (160mg/800mg or 80mg/400mg daily) is the recommended agent for primary and secondary prophylaxis. Patients with CD4 cell count below 200 cells/μL or a history of oropharyngeal candidiasis regardless of CD4 cell count should be started on primary PCP prophylaxis. Persons who have a CD4 cell percentage of <14% or a history of an AIDS defining illness should also be considered for prophylaxis. If monitoring of CD4 counts cannot be performed regularly

Table I: Adult doses of first line antituberculosis drugs[18]

Drug	Daily dose (max)
Rifampicin	10-15mg/kg (600mg)
Isoniazid	5-8mg/kg (300mg)
Pyrazinamide	20-40mg/kg (1.5g)
Ethambutol	15-25mg/kg (1.2g)
Streptomycin	15-20mg/kg (1g)

Table II: Treatment of Pneumocystis Pneumonia[24]

Drug	Dose	Route
Trimethoprim – Sulfamethoxazole	15-20mg/kg 75-100mg/kg Daily in divided doses	Oral or intravenous
Primaquine plus clindamycin	30mg daily 600mg three times daily	Oral
Atovaquone	750mg two times daily	Oral
Pentamidine	4mg/kg daily 600mg daily	Intravenous Aerosol

Table III: Adapted from National Antibiotic Guideline 2008[41]

Infection/Condition & Likely Organism	Suggested Treatment	
	Preferred	**Alternative**
Mild CAP (out-patient) **a. No comorbidity** *Streptococcus Pneumonia* *Mycoplasma Pneumoniae*	**No recent antibiotic therapy** EES 800mg PO q12h for 1 week **PLUS** Amoxycillin 500mg PO q8h for 1 week **Recent Antibiotic Therapy** Treat as b *(Presence of comorbidity* or *History of recent antibiotic therapy) as below*	*β-lactam/β-lactamase inhibitors, e.g.* Amoxycillin/Clavulanate 625mg PO q12h for 1 week **OR** Ampicillin/Sulbactam 375mg PO q12h for 1 week **OR** Doxycycline 100mg PO q12h for 1 week
b. Presence of comorbidity or History of recent antibiotic *Streptococcus Pneumoniae* *Mycoplasma Pneumoniae* *Haemophilus Influenzae*	Azithromycin 500mg PO q24h for 3 days **OR** EES 800mg PO q12h for 1 week **PLUS** *β-lactam/β-lactamase inhibitors, e.g.* Amoxycillin/Clavulanate 625mg PO q12hr 1 week	Levofloxacin* 500mg PO q24h for 1 week
Moderate & Severe CAP (not requiring mechanical ventilation) *Streptococcus Pneumoniae* *Mycoplasma Pneumoniae* *Haemophilus Influenzae* *Klebsiella Pneumoniae* *Legionella* *Staphylococcus Aureus* *Other Gram Negative Bacilli* *- Enterobacter* *- Escherichia Coli*	Azithromycin 500mg IV/PO q24h **OR** Erythromycin 500mg IV q6h/EES 800mg PO q12h **PLUS** *3rd gen. Cephalosporins,e.g.* Ceftriaxone 1-2g IV q24h **OR** β-*lactam/β-lactamase inhibitors, e.g.* (Amoxycillin/Clavulanate OR Ampicillin/Sulbactam) Duration: 1 week	Levoflaxacin* 500mg IV/PO q24h for 1 week
Pseudomonas Infection	Piperacillin/Tazobactam 4.5g IV q8h for 1 week **OR** Cefepime 2g IV q12h for 1 week **PLUS** Gentamicin 5mg/kg IV q24h **PLUS** Azithromycin 500mg IV q24h for 1 week	Piperacillin/Tazobactam 4.5g IV q8h for 1 week **OR** Cefepime 2g IV q12h for 1 week **PLUS** Ciprofloxacin* 500mg IV q12h for 1 week
Severe community-acquired pneumonia requiring mechanical ventilation *S. Pneumoniae* *H. Influenzae* *S. Aureus* *K. Pneumoniae* *M. Pneumoniae* *L. Pneumophilia* *C. Pneumoniae*	*3rd gen. Cephalosporins, e.g.* Ceftriaxone 2g IV q24h **PLUS** Erythromycin 500mg IV q6h **OR** Azithromycin 500mg IV q24h	*β -lactam/β- lactamase inhibitors, e.g.* Amoxycillin/Clavulanate 1.2g IV q8h **PLUS** Erythromycin 500mg IV q6h **OR** Azithromycin 500mg IV q24h

Macrolide monotherapy should not be given because of increased risk for drug resistant Streptococcus pneumonia in HIV infected patient
*Fluroquinolone should be used with caution in whom patients with TB are suspected who are not being treated with the standard 4 drug therapy TB regime

(e.g. every 1-3 months), initiating prophylaxis at a CD4 cell count of >200, but <250 cells/μL should also be considered. Secondary PCP prophylaxis is recommended for persons with a history of PCP. Primary or secondary prophylaxis is recommended for life but can be safely discontinued in patients whose CD4 cell count rise above 200 cells/μL for at least 3 months as a result of antiretroviral therapy and should be reintroduced if the CD4 cell count falls less than 200 cells/μL[31]. For those allergic to TMP-SMX, monthly nebulised pentamidine 300mg or dapsone 100mg daily are suitable alternatives.

Patients receiving dual therapy for HIV infection and PCP may develop Pneumocystis associated IRIS although the incidence appears to be less than TB associated IRIS. This paradoxical worsening of PCP with worsening symptoms and occasionally respiratory failure occurs as a result of improved immune response directed against active infection or residual antigen[32]. The majority of patients recover but the antiretroviral therapy may be temporarily discontinued and a short course of corticosteroids can be considered in severe cases.

RECURRENT BACTERIAL PNEUMONIAS

HIV infection should be considered in any person with recurrent bacterial pneumonias as bacterial infections are the most common respiratory complications in patients with HIV infection[33]. The cummulative incidence of bacterial pneumonia in hospitalised patients with HIV infection may be as high as 12.5 per 100 person-years and is a major cause of death in patients with HIV, with a hospital and 4 weeks discharge mortality rate ranging from 2.6-27%[34]. Respiratory bacterial infections occur at all levels of CD4 count but become more frequent as the CD4 count declines[35].

The most common organisms are similar to organisms causing community acquired pneumonia in non HIV infected persons[8]. *Streptococcus pneumonia, Haemophilus influenza, Staphylococcus aureus, Klebsiella pneumonia* and *Pseudomonas aeruginosa* are the most commonly identified. *Pseudomonas aeruginosa* are more frequently reported as community acquired causes of pneumonia in persons with HIV infection especially in patients with low leukocyte and CD4 count [36,37]. Risk factors associated with an increased risk for bacterial pneumonia includes low CD4 cell count, use of injection drugs and cigarette smoking[35].

Given the increased incidence of *M tuberculosis* in HIV infected persons, the diagnosis of TB should always be suspected in HIV infected persons with pneumonia especially if the patient has not responded to the standard antibiotic therapy. The clinical and radiological changes of bacterial pneumonia in HIV infected persons are similar to that in persons without HIV infection. Typically the symptoms are acute on onset (3-5 days) with dyspnoea, fever, chills, rigors, cough productive of purulent sputum and pleuritic chest pain. Physical examination reveals lung consolidation and not uncommonly parapneumonic effusion. Blood culture and sputum samples for gram staining and culture are indicated in hospitalised patients[38]. Blood investigations show elevated white blood cell and inflammatory markers. Chest x-ray findings depend on the underlying bacterial pathogen and typically shows unilateral, focal, segmental or lobar consolidation with or without pleural effusion. A diagnostic pleural tap should be performed in the presence of pleural effusion to exclude empyema.

All patients with pneumonia should be assessed on the severity of pneumonia to decide whether the patient can be treated at home or require hospitalisation in a general ward or considered for closer monitoring in high dependency or intensive care unit[38]. There are several valid tools of risk assessment in community acquired pneumonia such as CURB index[39] and pneumonia severity index (PSI) [40], however studies looking at these risk assessment tools did excluded patients with a diagnosis of HIV infection.

The principles of treatment of community acquired bacterial pneumonia in HIV associated pneumonia are the same as non HIV infected persons. Malaysian guideline for antibiotics therapy for community acquired pneumonia is available from the National Antibiotic Guideline 2008[41](Table III). However, unlike recommendations for community acquired pneumonia in non HIV infected persons, macrolide monotherapy is not recommended because of the increased risk for drug resistance *Streptococcus pneumoniae* in the HIV infected patient. Instead a beta-lactam plus macrolide should be given. Respiratory fluroquinolone are active against Mycobacterium tuberculosis therefore should be used with caution in patients suspected of TB but who are not being treated with the standard 4 drug TB therapy[8].

HIV infected persons have an increased incidence of bacteraemia and septicaemia accompanying the pneumonia especially if the infected organism is *Streptococcus pneumoniae*. Therefore it is vital that therapy is started promptly without waiting for the results of the diagnostic tests. Factors independently related to increased mortality among HIV infected persons with bacterial pneumonia include CD4 cell count < 100/μl, radiologic progression of disease, and shock[42].

HIV infected adults who have a CD4 cell count of > 200cells/μL should be given the 23-valent polysaccharide pneumococcal vaccine. HIV infected adults with a CD4 cell count of < 200 cells/μL can also be offered the vaccine although the efficacy may be less in those with advanced immunosuppression[8,43,44]. Inactivated influenza vaccine should also be administrated to HIV infected persons[45]. HIV infected patients on antiretroviral therapy and daily TMP-SMX for prophylaxis against PCP has been shown to have a decreased incidence of bacterial respiratory infections[46]. Smoking is associated with increased risk of bacterial pneumonia, therefore smokers should strongly be encouraged to stop smoking.

CONCLUSION

Opportunistic pneumonias are major causes of morbidity and mortality in patients infected with HIV. Making an accurate diagnosis is vital as many of these pneumonias can be treated successfully with prompt appropriate treatment. Prevention strategies play an important role in reducing the morbidity and mortality associated with opportunistic pneumonias in HIV infected patients.

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HIV Associated Opportunistic Pneumonias - Multiple Choice Questions

1. The following statements is/ are true regarding tuberculosis (TB) in the immunosuppressed patient.

A. The clinical presentation is similar with immunocompetent patient
B. Standard TB treatment should be extended to 9 months
C. The response rate to treatment is similar with immunocompetent patients
D. Mantoux test is an unreliable test to diagnose TB
E. A negative sputum acid fast bacilli smear excludes pulmonary TB

2. The following statements is/ are true regarding Pneumocystic pneumonia (PCP)

A. Bronchoalveoolar lavage is required in most cases to obtain a diagnosis
B. Non HIV infected patients with PCP have a lower load of pneumocystis in bronchoalveoolar lavage
C. A normal chest xray excludes PCP
D. Diagnosis is by culture of pneumocystis jirovecii in the sputum
E. The majority of patients occurs when the CD 4 count falls below 200 cells/μL

3. The following statements is/are true regarding treatment of PCP:

A. Treatment should be started even before a definite diagnosis is made
B. The recommended duration of treatment is 21 days
C. Corticosteroid is indicated with all cases
D. PCP prophylaxis is indicated following oropharyngeal candidiasis infection
E. Immune reconstitution inflammatory syndrome is due to improved immune response

4. In HIV infected individuals with pneumonia,

A. The incidence of bacteraemia is higher
B. The radiological changes are similar to non HIV infected individuals
C. In mild pneumonia, macrolide monotherapy is recommended
D. Pleural diagnostic aspiration is indicated if pleural effusion is present
E. A low CD 4 cell count is associated with higher mortality