Important opportunistic infections in HIV

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Abstract

People living with HIV (PLWH) develop common infections such as influenza and community-acquired pneumonia. They also remain at risk of opportunistic infection (OI) if they are diagnosed with late-stage human immunodeficiency virus (HIV) infection and fail to reconstitute their immune system after diagnosis, for example due to lack of adherence to antiretroviral therapy (ART). When PLWH present unwell, it is helpful to gather a past history of HIV-associated illness and previous ART exposure. Acute issues should be addressed, and treatment of common infections commenced in line with local guidelines. The incidence of OI correlates with the diminishing CD4 count. Symptoms and signs of specific OIs should be assessed and empirical therapy commenced where indicated clinically. Appropriate serological, microbiological and histological investigations, as well as cross-sectional imaging, are often used to confirm a suspected diagnosis and guide further management. Transfer to a specialist HIV inpatient centre for continuing management of suspected OI should be considered at the earliest opportunity.

Keywords Bacterial pneumonia; Candida; *Cryptococcus*; cytomegalovirus; immunosuppression; Kaposi sarcoma; MRCP; *Pneumocystis*; toxoplasmosis; tuberculosis; varicella-zoster virus

Key points

- People living with HIV are susceptible to non-opportunistic and opportunistic infections
- Careful exploration of the history of the HIV infection and presenting complaint, complete systems review and a whole-body examination (including fundoscopy) are indicated to look for evidence of immunosuppression and opportunistic infections
- Management should involve a multidisciplinary specialist HIV inpatient team

Introduction

Increased access to human immunodeficiency virus (HIV) testing combined with the development and uptake of antiretroviral therapy (ART) has resulted in a substantial decline in the morbidity and mortality previously associated with HIV infection.[1] As opportunistic infections (OIs) become rarer, the relative contribution of common infections such as influenza and community-acquired pneumonia rises, and the distinction between these groups becomes less clear (Table 1).[2] Nevertheless, a significant proportion of people living with HIV (PLWH) remain at risk of severe disability and death if they are diagnosed with late-stage HIV infection or fail to adhere to appropriate ART treatment regimens following diagnosis.

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General considerations

When PLWH present unwell, it is helpful to gather information on current CD4 count, HIV viral load, previous OIs (including treatment and prophylaxis) and ART exposure. The centre(s) previously responsible for managing the HIV infection should be identified, so outstanding information can be gathered at the earliest opportunity. Referral for HIV specialist advice is always indicated; this is particularly important with uncontrolled HIV infection and/or immunosuppression, or if this information is unknown. In all cases, an up-to-date CD4 count and HIV viral load should be requested, as a CD4 count <200 cells/microlitre lowers the threshold for treating OI empirically.

PLWH can present with many symptoms, and it is useful to approach each systematically and identify those which should be addressed urgently. Fever is a common finding and is rarely caused by HIV itself (unless in seroconversion);[2] it should therefore prompt further evaluation to localize a source of infection. Suspected sepsis should be managed without delay and according to local guidelines. Country of birth, travel history and risk factors such as intravenous drug use and sexual exposure are relevant and often overlooked. Transfer as an inpatient to a specialist centre for continuing management of suspected OI should be considered at the earliest opportunity[2] (Table 1).

Respiratory system

The presentation of an acute onset of fever, dyspnoea, productive cough and chest pain with examination and radiological findings consistent with lung consolidation should be managed empirically as bacterial pneumonia according to local guidelines, taking personal and situational risk factors into account. Every effort should be made to identify a causative organism by culturing blood and sputum. A throat swab for viral nucleic acid detection is useful in excluding influenza, an important and treatable cause of this presentation in the winter months.[2]

Pneumocystis jirovecii (formerly *P. carinii*) is a fungal infection that causes pneumonia (PCP) in immunocompromised hosts. This typically presents as insidious, progressive exertional dyspnoea associated with a dry cough and malaise, with or without fever. The patient may have an increased respiratory rate and appear short of breath but have only subtle

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Summary of conditions discussed

Respiratory system	Central nervous system	Gastrointestinal system	Eyes	Skin
Bacterial pneumonia/Influenza	Bacterial/viral meningoencephalitis	Candida	Cytomegalovirus retinitis	Varicella-zoster virus
Pneumocystis jirovecii pneumonia	Cryptococcal meningitis	Bacterial gastroenteritis		Kaposi sarcoma
Pulmonary tuberculosis (TB)	Cerebral toxoplasmosis	*Clostridium difficile* infection		
	Central nervous system TB	*Mycobacterium avium* complex		

Table 1

if any chest findings. The chest radiograph can be normal or show perihilar haze or interstitial infiltrates. Pneumatoceles and pneumothoraces may be associated with acute pleuritic symptoms. If the chest X-ray is normal, a fall in oxygen saturation on exertion is suggestive but not diagnostic of PCP. Arterial blood gas measurement is obligatory, and suspected cases of PCP should be stratified according to severity of hypoxia. A diagnosis of PCP is strongly supported by typical findings seen on high-resolution computed tomography (CT) of the chest and confirmed by direct identification of *P. jirovecii* from bronchial washings.[2]

Empirical treatment of PCP is indicated where signs of respiratory failure are seen in the context of advanced immunosuppression, and early discussion of both non-invasive and invasive ventilation in the intensive therapy unit is recommended. Treatment in moderate to severe cases consists of intravenous trimethoprim–sulfamethoxazole (Septrin) 120 mg/kg daily in 2–4 divided doses with oral prednisolone 40 mg twice daily. Prophylaxis with oral Septrin 480 mg once daily should be prescribed for PLWH with a CD4 count <200 cells/microlitre. Patients should be screened for glucose 6-phosphate dehydrogenase deficiency to avoid drug-induced haemolysis. However, this should not delay commencing therapy in the first instance.[2]

Pulmonary tuberculosis (TB) can present at any CD4 count and should be considered in the differential diagnosis of anyone presenting with cough, particularly in association with weight loss, night sweats or lymphadenopathy. If pulmonary TB is suspected, the patient should be isolated and referred for TB/HIV specialist management. Sputum or bronchial washings should be examined for acid-fast bacilli (AFB) and *Mycobacterium tuberculosis* (Mtb) culture and DNA polymerase chain reaction (PCR).[3] Evidence of disseminated (miliary) TB in the chest should prompt magnetic resonance imaging (MRI) of the brain to look for central nervous system (CNS) involvement.

Central nervous system

Immunosuppressed individuals presenting with fever and headache, meningism, new confusion or behavioural change, new seizures, focal neurology or a reduced level of consciousness should undergo urgent cross-sectional brain imaging (MRI is always preferable to CT) before proceeding to lumbar puncture for cerebrospinal fluid (CSF) analysis.[2] Suspected meningoencephalitis should be treated according to local guidelines at the earliest opportunity.

Lumbar puncture should be performed with the patient in the left lateral position, and a manometer should be used to record the CSF opening and closing pressures. CSF should be routinely analysed for microscopy, culture and sensitivities, viral nucleic acids, protein and glucose, along with a contemporaneous serum glucose measurement. It is important to collect a sufficient volume of CSF as specific tests, for example HIV viral load, AFB microscopy and cytology, require large volumes to be diagnostic. The CSF sample should also be analysed for cryptococcal antigen (CrAg): a positive result is diagnostic of cryptococcal meningitis.[2]

Cryptococcus neoformans is an encapsulated yeast that is found throughout the environment. Following inhalation, *Cryptococcus* infects the lungs and can cause respiratory symptoms before spreading to the blood and then rapidly to the CNS. It is therefore important to request a fungal culture of blood and a serum CrAg when cryptococcosis is suspected. A positive serum CrAg necessitates CSF analysis regardless of symptomatology. Cryptococcal meningitis is treated with induction therapy of intravenous liposomal amphotericin B 4 mg/kg once daily plus intravenous flucytosine 100 mg/kg daily in 4 divided doses. Cryptococcal meningitis classically results in raised CSF pressure. If >250 mmH_2O, it should be reduced to <200 mmH_2O or to 50% of the original value. Lumbar puncture with CSF manometry should be performed daily until the CSF pressure is stable or if a change in neurological symptoms or signs occurs. If the CSF pressure is persistently raised, referral to neurosurgery is advised for consideration of ventriculoperitoneal shunt insertion.[2]

Focal neurology with a CNS space-occupying lesion (SOL) has numerous infective and non-infective causes in immunosuppressed hosts; the most common is toxoplasmosis. Abscesses result from reactivation of chronic infection with the obligate intracellular protozoan *Toxoplasma gondii*. Obtaining a microbiological diagnosis is a challenge, but the classical appearance of multiple ring-enhancing lesions on MRI of the brain is usually sufficient to commence empirical therapy (Figure 1)[2].

First-line treatment consists of a loading dose of oral pyrimethamine 200 mg followed by 50 mg (<60 kg) to 75 mg (>60 kg) daily plus oral folinic acid 15–30 mg daily and oral sulfadiazine 1–2 g four times daily. The patient should be screened for glucose-6-phosphate dehydrogenase deficiency. As a clinical and radiological response is routinely used to confirm the diagnosis, corticosteroids can cloud the picture and should only be employed when signs of raised intracranial pressure are present. In this case, dexamethasone 4 mg four times daily is the treatment of choice. A lack of radiological response to treatment should always lead to a consideration of primary CNS lymphoma in the differential diagnosis of ring-enhancing lesions on brain MRI.[2]

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