Respiratory infections in patients with HIV

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The lung is an important site of infection in HIV-infected individuals. Bacterial and opportunistic pathogens are commonly implicated and, despite the introduction of effective prophylaxis and the use of highly active antiretroviral therapy (HAART), these infections remain significant causes of morbidity and mortality.

Common bacterial infections

Upper respiratory tract infections are seen frequently, and present acutely as in non-HIV infected people. One study reported an incidence of 33% of such infections after 18 months of follow-up, with Streptococcus pneumoniae, Haemophilus influenzae and Pseudomonas aeruginosa commonly isolated. Sinusitis is common and may be a more chronic problem, often presenting with headache and requiring the exclusion of more sinister pathology.

HIV predisposes patients to bacterial chest infections even at relatively high CD4 counts, although the incidence increases with more advanced immunosuppression. Organisms isolated are the same as in a non-HIV setting. Intravenous (IV) drug use is a strong risk factor. Primary prophylaxis against Pneumocystis carinii pneumonia (PCP) with co-trimoxazole appears to provide some protection in those with more advanced disease. Radiological findings may be atypical in almost half the cases and possibly difficult to distinguish from PCP (Fig 1). P. aeruginosa is a cause of nosocomial and community-acquired pneumonia, both of which are associated with advanced HIV, poor response to treatment and high rates of relapse. A recent report has suggested that persistent colonisation may clear with the use of HAART.

Pneumocystis carinii

PCP has been the most frequent AIDS-defining illness for many years, even after the introduction of effective prophylaxis. It occurs predominantly in patients with an absolute CD4 count below 200 cells/mm³, and is thought to occur by airborne reinfection. Presentation is with symptoms of dry cough, progressive breathlessness, fever and malaise. Clinical signs in the chest are usually notable by their paucity. Arterial desaturation on exercise testing is characteristic. Although chest radiographs may be normal early in the infection, they are abnormal at presentation in over 90% of patients. The most common appearance is bilateral, perihilar air space shadowing which may become more confluent as the infection progresses (Fig 2). In a minority of cases the appearances are atypical, with unilateral consolidation, nodules and lymphadenopathy all described.

There is debate about the need to confirm the diagnosis by bronchoscopy in patients presenting with typical clinical and radiological findings, and many centres treat PCP empirically. However, bronchoscopy need not be performed before starting treatment, but can be left for up to five days if the patient is too unwell at presentation to tolerate the procedure.

Treatment

All patients presenting with features suggestive of PCP should begin treatment immediately. First-line therapy is high-dose co-trimoxazole (120 mg/kg) in divided doses, given either IV or
orally. For those intolerant of co-trimoxazole, IV pentamidine, dapsone with trimethoprim, clindamycin with primaquine, atovaquone and trimetrexate are alternatives. Patients with a resting PaO₂ below 9.3 should receive adjuvant corticosteroids.

Treatment with high-dose co-trimoxazole may be complicated by the development of a drug reaction; this occurs at around the tenth day, and is manifest by a maculopapular rash, fever, neutropenia and derangement of liver function tests. If possible, treatment with co-trimoxazole should be continued while the patient is given systemic antihistamines, topical relief and, if symptoms are severe, systemic corticosteroids (see also below).

Prophylaxis

Primary prophylaxis for PCP was first recommended in 1989⁶, and its widespread introduction led to a substantially reduced incidence of infection. It is recommended in patients with CD4 counts below 200 cells/mm³ and in those with a previous AIDS diagnosis who are not stabilised on antiretroviral therapy. Co-trimoxazole, daily or three times a week, is the first choice. Monthly inhaled pentamidine with oral dapsone is also effective. Side effects occur in up to 25% of patients receiving co-trimoxazole; this is a higher incidence than seen in the non-HIV infected population, the reason for which is not clear. In patients who experience adverse reactions, desensitisation should be attempted as this may be successful in up to 80%. Secondary prophylaxis is recommended following an episode of PCP.

Since the widespread introduction of HAART in 1996, many patients with previous nadir CD4 counts below 200 cells/mm³ have seen a marked recovery of their CD4 count and reduction of HIV viral load. This begs the question of how quickly immune function is restored, and whether prophylaxis can be stopped if the CD4 count remains above 200 cells/mm³. Several small studies have suggested that it is safe to discontinue PCP prophylaxis in such patients;

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Fig 1. Severe bacterial pneumonia (Mycoplasma pneumoniae).

Fig 2. Typical appearance of Pneumocystis carinii pneumonia.
this view has been supported by two large, observational studies7,8. The patients included were mainly undergoing primary prophylaxis but there were also smaller secondary prophylaxis groups. It has not yet been clearly defined how long CD4 counts need to be maintained above 200 cells/mm³ before prophylaxis can be stopped.

Tuberculosis

Co-infection with Mycobacterium tuberculosis is well recognised in HIV patients and is an increasing problem worldwide. Tuberculosis is more common as the CD4 count falls, but may occur at any stage of immunosuppression9. Infection may be primary, reactivation or exogenous reinfection. In vitro work has shown that M. tuberculosis increases HIV replication and so accelerates the course of HIV infection. Thus, prompt and effective treatment of tuberculosis can significantly improve immune function.

Tuberculosis in patients with good CD4 counts tends to be similar to that seen in HIV-negative patients. As the CD4 count falls, more mycobacteraemia and extrapulmonary disease are found, with a lower rate of sputum smear-positive cases. The typical chest radiograph findings of upper lobe infiltrates and cavitation are seen more commonly with CD4 counts around 200 cells/mm³ and above (Fig 3). At lower counts, mediastinal adenopathy is increasingly seen (as is found in children with primary tuberculosis).

Diagnosis

Rapid diagnostic tests using the polymerase chain reaction have recently been introduced. These tests have not superseded acid-fast staining, culture and drug-susceptibility testing, which ideally should be carried out in all cases. Their role in management is not yet clear, and a negative result should not deter the initiation of treatment when there is a high clinical suspicion of tuberculosis.

Treatment

Current guidelines advise a six-month treatment course as for HIV-negative patients10. Four drugs are recommended for the initial two months (or until sensitivities are known) because HIV is associated with an increased incidence of drug resistance. For the remaining four months, a regimen including isoniazid and rifampicin should be continued for fully sensitive organisms. The initial priority is treatment of tuberculosis, but some patients develop tuberculosis having already started antiretrovirals, and others with advanced disease will require early treatment of their HIV to prevent further disease progression. The use of HAART together with antituber-

Key Points

- Bacterial upper and lower respiratory tract infections occur frequently, and common pathogens are usually isolated
- Pneumocystis carinii (PCP) is the most frequent AIDS-defining illness
- Primary PCP prophylaxis can be stopped in patients on highly active antiretroviral therapy (HAART) with a sustained CD4 count above 200 cells/mm³
- Patients with tuberculosis should receive standard short-course chemotherapy with four drugs in the first two months
- Care should be taken in co-prescribing antituberculosis and anti-HIV drugs as significant interactions may occur
- Tuberculosis may appear to worsen (paradoxical reaction) following the start of HAART

Fig 3. Pulmonary tuberculosis in a patient with a CD4 count of 192 cells/mm³.
culous medication is complicated by interactions involving the liver enzyme cytochrome P450 CYP3A11. Rifampicin, a potent inducer of this enzyme, reduces the levels of both protease inhibitors and non-nucleoside reverse-transcriptase inhibitors to subtherapeutic levels; this may lead to incomplete viral suppression and the development of resistance to antivirals. The use of rifampicin with these drugs is therefore not recommended. Rifabutin is a less potent inducer of CYP3A, with efficacy similar to rifampicin. It can be used with the protease inhibitors indinavir and nelfinavir, although increased doses of these drugs are recommended. Rifabutin metabolism is decreased by protease inhibitors, so it should be given at a reduced dose (150 mg daily).

Prophylaxis

Recognition of HIV-infected patients at high risk of developing tuberculosis is complicated by loss of response to tuberculin skin testing and atypical radiology. In view of these problems and worries over the emergence of drug resistance with the use of single agent isoniazid, it is currently recommended that chemoprophylaxis be given only if there is a clear history of recent contact with a smear-positive index case. A six-month course of isoniazid is recommended. The use of lifelong isoniazid therapy as secondary prophylaxis is also no longer recommended due to a lack of supporting data and worries about encouraging drug resistance.

Paradoxical reaction

Transient worsening of tuberculosis (paradoxical reaction) has previously been described following the initiation of antituberculosis therapy. Such episodes, which may consist of recurrent fever, weight loss, worsening of existing lesions and the development of new lesions, have now been well described following the commencement of HAART12. These paradoxical reactions are associated with a rise in CD4 count and fall in viral load, and are thought to reflect the reconstitution of the immune response. The episodes are self-limiting but, if severe, may require treatment with corticosteroids. They also require the exclusion of intercurrent infections and/or non-compliance with antituberculous medication.

Other infections

*Mycobacterium avium intracellulare* (MAI) infection is common at CD4 counts below 100 cells/mm³. It tends to cause disseminated disease, and the organism can often be isolated from sputum and bronchoalveolar lavage specimens as well as from blood and urine. The presenting features of MAI are generally non-specific. Standard antituberculous therapy is not effective, and first-line treatment is a combination of rifabutin, ethambutol and clarithromycin. IV amikacin may also be used if fevers persist.

Fungal infections of the lung are not common in HIV patients in the UK but are commonly seen abroad. *Cryptococcus neoformans* may cause pneumonia but is more frequently found as part of a disseminated infection, including meningitis.

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