Infections in HIV disease

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Infection in the era of antiretroviral drugs

The course of HIV infection has changed dramatically over the past five years in much of the developed world. The use of potent antiretroviral drugs in combinations of at least three agents (highly active antiretroviral therapy (HAART)) has become routine, with an impressive improvement both in HIV-associated mortality and in the incidence of AIDS-defining opportunistic infections[1,2]. *Pneumocystis carinii* pneumonia (PCP), cryptococcal meningitis and toxoplasmosis are now much less common causes of death for those on an effective HAART regimen. Nonetheless, intercurrent infection continues to cause major and often fatal complications in HIV disease. A variety of viral infections (eg hepatitis B and C, Epstein-Barr virus (EBV)) and their associated complications appears to be less successfully controlled by HAART – indeed, a variety of new presentations of old foes is being recognised.

For those who are unaware of being HIV-positive, acute opportunistic infection continues to be a common first presentation. Not all those who take HAART are able to restore adequate immunity to avoid opportunistic pathogens. Adherence to treatment, tolerability, drug interactions and toxicity, plus the emergence of viral resistance are all factors that reduce the efficacy of antiretrovirals. Crucially, these drugs are not available to the majority of people with HIV who live in resource poor areas.

HIV and susceptibility to infection

Immune deficits associated with HIV result in infectious complications. The central mechanism is progressive depletion of CD4 T lymphocytes, cells which are pivotal to the overall functioning of the immune system. In response to antigen presentation, they proliferate and release cytokines. Two of the most important are interleukin (IL)-2 and interferon (IFN) gamma. IL-2 stimulates cytotoxic T cells that eliminate viral infections, while IFN gamma stimulates antibody production in B cells and the cytotoxic effects of natural killer cells and macrophages to act against intracellular organisms. Impaired macrophage function consequent upon reduced IFN gamma production means that individuals with HIV infection are at particular risk both for primary and reactivated tuberculosis[3].

HIV also affects other cell types. Polyclonal activation of B cells by components of HIV envelope proteins results in hypersensitivity reactions. Examples include autoimmune thrombocytopenia and allergic drug reactions. Abnormalities of B cell function lead to reduced immunoglobulin G2 production, leaving the host particularly susceptible to encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. These abnormalities occur prior to the onset of immunosuppression and the clinical consequences may be seen early in the course of HIV disease.

CD4 lymphocyte count is a marker for the likelihood of opportunistic infection. For individuals with a CD4 count consistently above 200 cells/ml the risk is low, but it increases as the CD4 count falls lower.

Many of the organisms that cause illness may have been previously encountered. They are kept in abeyance while the immune system is competent, but re-emerge as immunosuppression progresses. Examples include herpes zoster, cytomegalovirus (CMV) and EBV. Others (eg cryptosporidiosis, cryptococcus) can be acquired *de novo* if the immune system is sufficiently compromised. The particular clinical problems of an individual patient will be a consequence of their existing microbiological repertoire, the pathogenicity of the organism, and the level of immunosuppression (Table 1).

An inflammatory syndrome associated with immune restitution on initiating HAART has been described in people who have been profoundly immunosuppressed on starting therapy[4,5]. As the immune system recovers, an inflammatory response may be mounted to a range of co-existing and possibly silent pathogens. Unexpected symptoms and signs may develop. Examples include:

- inflammatory vitritis in those with CMV eye disease
- mass lesions, and lymphadenopathy associated with *Mycobacterium avium intracellulare*
- atypical lymphadenopathy with cryptococcal infection
- acute deterioration of liver function in those with coexisting hepatitis B infection
- exuberant vesicular eruptions with herpes zoster.

Key Points

Although the incidence and pattern of infection associated with HIV has changed with the introduction of potent antiretroviral medications, intercurrent infections remain major – often fatal – complications of HIV

Diagnosis often depends on direct culture or microscopic examination of clinical specimens

Inflammatory immune restitution may occur on initiating highly active antiretroviral therapy (HAART). This can lead to unusual symptoms and signs associated with infectious agents that may previously have been clinically silent

Drug interactions and toxicities may complicate therapy of intercurrent infections, particularly in patients taking HAART

Table 1. Important pathogens associated with HIV infection.

Bacteria	*Streptococcus pneumoniae* *Staphylococcus aureus* *Haemophilus influenzae* Salmonella spp *Mycobacterium tuberculosis* *Mycobacterium avium intracellulare* *Moraxella catarrhalis*
Viruses	Herpes simplex and zoster Cytomegalovirus Epstein–Barr Human papilloma Papovavirus Hepatitis B and C
Protozoa	*Toxoplasma gondii* *Cryptosporidium parvum* *Leishmania donovanii* Microsporidia spp
Fungi and yeasts	*Pneumocystis carinii* *Cryptococcus neoformans* Candida spp *Histoplasma capsulatum* *Aspergillus fumigatus* Dermatophytes

HIV and diagnosis of infection

Appropriate management is based on accurate diagnosis. The problem is complex because a variety of infections may present with a similar clinical picture. HAART has introduced additional complications. The causes of fever may include:

- acute infection
- inflammatory reactions due to an immune restitution phenomenon
- an adverse reaction to HAART or other medication.

Management of each of these situations is substantially different. Helpful pointers in the history are:

- details of medication, particularly initiation or change of antiretroviral agents
- adherence to chemoprophylaxis
- previous medical diagnoses
- travel
- possible exposure to potential sources of infectious agents (eg food hygiene, pets, contacts with acute infections or TB, sexually transmitted infections).

Physical examination may reveal clinical evidence of immunosuppression, for example:

- oral candida
- hairy oral leukoplakia
- signs of disseminated sepsis
- indicators of adverse drug reactions (eg skin rash or oral ulceration).

Focal neurological signs and/or meningism may be present, as may evidence of an altered mental state (which may be either organic or functional).

Defective immune responses resulting in impaired inflammatory responses alter the clinical presentation of infections. Diagnosis in an immunosuppressed patient may be complicated

Table 2. Major HIV-associated infections and their treatment.

Condition	Features	First-line treatment
Cryptococcal meningitis	Headache, fevers, fits, altered mental state Meningism may be absent Positive cryptococcal antigen and/or culture in blood and CSF Yeast seen in CSF on India ink stain	Amphotericin B IV 0.5–1.0 mg/kg/day for 6 weeks May add flucytosine
PCP	Shortness of breath, non-productive cough, fevers Oxygen desaturation on exercise CXR interstitial shadows, but may be normal Organisms identified in washings from bronchial lavage	Trimethoprim 20 mg/kg/day and sulfamethoxazole 100 mg/kg/day for 14–21 days May require adjuvant corticosteroids in severe cases
Cerebral toxoplasmosis	Focal neurological signs, fits, fevers Multiple ring-enhancing lesions on CT scan or MRI	Sulfadiazine 4–6 g/day & pyrimethamine 50 mg/day for 6 weeks
CMV	Retinitis, loss of vision, floaters Exudates & haemorrhage on fundoscopy Colitis, diarrhoea, fevers, abdominal pain, rebound tenderness Pneumonitis, encephalitis, myelitis, radiculopathy can occur Blood CMV PCR- and/or culture-positive Biopsy demonstration of viral inclusion bodies	Ganciclovir 10 mg/kg/day or foscarnet 90 mg/kg bd IV for 2–3 weeks depending on response
Mycobacterium tuberculosis	Frequently disseminated Chest & generalised lymph node involvement Immunosuppression means Mantoux tests of little value Granuloma formation poor & histology atypical CXR may be normal Smear test often negative despite positive cultures	At least a four-drug regimen (standard is isoniazid, rifampicin, ethambutol, pyrazinamide) until sensitivities known. Beware drug interactions with antiretrovirals Notify
Pyogenic respiratory infections	Pyogenic chest & sinus infections common, particularly in smokers & those with Ig abnormalities (eg IgG2 subclass deficiency) *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*	Broad-spectrum antibiotic cover with activity against staphylococci until cultures and sensitivities known

bd = twice daily; CMV = cytomegalovirus; CSF = cerebrospinal fluid; CT = computed tomography; CXR = chest X-ray; Ig = immunoglobulin; IV = intravenous; MRI = magnetic resonance imaging; PCP = *Pneumocystis carinii* pneumonia; PCR = polymerase chain reaction.

by a lack of typical signs. Examples are lack of neck stiffness in cryptococcal meningitis and minimal clinical or radiological findings in early PCP. Serological responses are blunted, and standard diagnostic tests are therefore frequently unreliable. These factors mean that the diagnosis may require direct examination or culture of material from appropriate sites.

HIV and treatment of infection (Table 2)

Ideally, therapy is based on a firm diagnosis, but this can take time and patients are frequently extremely sick. Empirical therapy is often instituted based on the most likely or most dangerous diagnosis. Response to therapy may in itself provide diagnostic clues, for example radiological improvement of an intracerebral mass to antitoxoplasma treatment. Some infections take days or even weeks to show a response and it is important that a trial of empirical treatment is continued for an adequate time. Multiple pathology is common; if the patient does not respond as expected to treatment for a diagnosed problem, a further search for additional pathology should be initiated.

All HIV protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors are metabolised by, and have an impact on, the cytochrome P450 enzyme system, primarily by the 3A4 isoform (CYP3A4). Metabolism of a wide range of medications is affected and drug interactions can become a dominant feature of patient management. Not only do HIV PIs affect the metabolism of certain drugs but their own metabolism is altered by other inducers or inhibitors of cytochrome activity. Falls in plasma drug concentrations facilitate viral resistance and subsequent treatment failure. For this reason, rifampicin should not be used in conjunction with PIs. Rifabutin may be substituted but, to prevent associated toxicity, the dose should be lowered to compensate for reduced clearance in the presence of PIs[6]. These factors complicate the management of tuberculosis, a common intercurrent infection. Updated guidelines for using rifabutin and rifampicin in patients receiving antiretroviral drugs have recently been issued by the Centers for Disease Control and Prevention[7].

Prevention of infections in HIV

Avoiding action can be taken to prevent exposure to new pathogens:

- Good food hygiene and thorough cooking will reduce the risk of salmonella and toxoplasmosis.
- Exposure to herpes simplex virus, papilloma virus, hepatitis B and syphilis is reduced by safer sex.
- Appropriate travel advice should be sought.
- CMV-negative patients should be given CMV-negative blood products.

Although the response to immunisation may be impaired in HIV-infected individuals, hepatitis A and B vaccines should be considered for those without natural immunity, particularly if there is coexisting liver pathology (eg hepatitis C). Influenza vaccine is not routinely recommended unless there is coexisting cardiac or respiratory pathology. Live vaccines (eg yellow fever, live polio, BCG) are contraindicated.

Prophylaxis

Antibiotic prophylaxis to prevent infection has done much to improve survival, even before the advent of widespread antiretroviral drug use. However, many of the organisms associated with HIV infection cannot be eradicated by antimicrobials in the absence of a normal immune response and the recurrence rate is high.

Primary prophylaxis against PCP is recommended for all HIV-infected patients with a CD4 count below 200 cells/ml. Co-trimoxazole 960 mg thrice weekly is a common regimen in the UK. It reduces recurrence in patients with positive serology for *Toxoplasmosis gondii* and a CD4 count below 100 cells/ml. If the CD4 count is below 50 cells/ml, azithromycin or rifabutin will reduce the risk of *Mycobacterium avium intracellulare* (MAC) infection. Primary prophylaxis is not normally recommended against CMV, herpes viruses or fungi. Long-term secondary prophylaxis has been advocated in life-threatening conditions (eg *P. carinii, cryptococcus*) or those which have serious long-term sequelae (eg CMV retinitis)[8].

The need for ongoing chemoprophylaxis is being reviewed following the introduction of HAART and immune reconstitution[9]. In patients receiving HAART whose CD4 count has increased to at least 200 cells/ml for upwards of three months, primary and secondary prophylaxis against PCP can be safely discontinued[10,11]. This also applies to secondary CMV prophylaxis in patients taking HAART with a CD4+ T lymphocyte count above 100-150 cells/ml[9], and for MAC if CD4+ cell counts have increased to more than 100 cells/ml[12].

Decisions about stopping or restarting prophylaxis should be regularly reviewed as clinical and laboratory parameters change.

Conclusion

Far from disappearing, the well-recognised opportunistic infections continue to occur and a variety of newly appreciated issues is surfacing. Diagnosis, management and prevention of infection remain central to the care of HIV-infected patients, even in the age of antiretroviral therapy.

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