Pneumocystis carinii pneumonia (PCP) remains the most common serious opportunistic infection affecting HIV-infected adults and children, despite a decline in its incidence since the widespread introduction of prophylaxis.\textsuperscript{1–3} Both in the USA and Europe, more than a quarter of cases of first-time PCP still occur in persons unaware of their HIV status,\textsuperscript{4,5} highlighting the importance of early identification of HIV infection by encouraging those at high risk of becoming HIV-infected to undergo testing. Once found to be HIV seropositive, all patients should have regular medical follow-up to ensure that primary PCP prophylaxis is initiated at the appropriate time.

The clinical presentation, diagnosis and management of PCP have been comprehensively reviewed recently.\textsuperscript{6} We address here several management issues, including the selection of optimal anti-pneumocystis treatment, the role of steroids and options for salvage therapy, the current status of prophylactic regimens for adults and children, and the management of intolerance to prophylaxis.

Whatever the severity of disease, the cornerstone of PCP treatment remains co-trimoxazole, given at a total daily dose of 20 mg/kg of trimethoprim and 100 mg/kg of sulphamethoxazole in two to four divided doses, either intravenously or orally. Treatment is for 21 days, and should be followed by continuous prophylaxis. Side-effects, which usually become apparent after 1–2 weeks of therapy, are common, and include fever, rash (40%), bone marrow suppression (40%), nausea and vomiting (25%), and liver function abnormalities (20%).\textsuperscript{7} These are sufficiently severe to require discontinuation of co-trimoxazole therapy in about a third of cases.\textsuperscript{8} The second-line therapy for severe PCP, if co-trimoxazole cannot be tolerated, is intravenous pentamidine, at a daily dose of 4 mg/kg for 21 days. Again, a gain, adverse effects are frequent and include nephrotoxicity (60%), leucopenia (45%), hypotension (25%), nausea and vomiting (25%), hypoglycaemia and/or hypocalcaemia (20%).\textsuperscript{7} Close monitoring of serum electrolytes, glucose, calcium and blood pressure during therapy is required. A further regimen for patients with mild or moderately severe PCP who cannot tolerate co-trimoxazole, is dapsone with trimethoprim for 21 days. A recent trial showed comparable rates of efficacy and dose-limiting toxicity with dapsone as with co-trimoxazole or clindamycin with primaquine.\textsuperscript{8} Methaemoglobinemia due to dapsone occurs in most patients but only rarely is symptomatic or necessitates cessation of therapy.

Although unlicensed in the UK for PCP treatment, combination clindamycin/primaquine is being widely used as an alternative to iv pentamidine. Clindamycin is usually given orally at a dose of 600 mg three times daily together with a daily 30 mg oral dose of primaquine.\textsuperscript{8–10} Important haematological toxicity occurs in over 25% of patients, and a rash in 20%, but in general this combination is very well tolerated.\textsuperscript{8} Clostridium difficile infection should be remembered as a possible cause of diarrhoea in these patients. A tolvazone, a hydroxynaphthoquinone originally developed as an antimalarial agent but with powerful cidal activity against pneumocystis in the animal model,\textsuperscript{11} has now been approved in the UK for the treatment of mild or moderately severe PCP, at a dose of 750 mg three times daily.\textsuperscript{12} Its high failure rate\textsuperscript{12} and apparently low toxicity profile\textsuperscript{13} reflect the poor absorption and bioavailability of the current formulation. For this reason, it is usually reserved for patients with mild PCP who are intolerant of both co-trimoxazole and the second-line regimens. It should not be considered a therapeutic option in patients with severe PCP or those who have diarrhoea or malabsorption. Other unlicensed drugs with a role limited to ‘salvage’ therapy include trimetrexate/folinic acid, and efornithine. Experimental drugs under study are albendazole, terbinafine, and 1-671,329, a 1,3-\beta-glucan synthesis inhibitor.

The use of adjuvant corticosteroid therapy in adult patients with moderate to severe PCP is well established. In severe disease, when arterial oxygen saturation is below 91% and the partial pressure below 8.0 kPa, adjuvant high-dose corticosteroids reduce both the risk of respiratory failure and death,\textsuperscript{14–16} as well as the rate of intolerance to co-trimoxazole.\textsuperscript{17} Results from a small paediatric study suggest that its use in children is also associated with
improved survival. However, some reports suggest that adjunctive corticosteroids may exacerbate co-existing CMV disease in those with advanced immunosuppression. Several reports of outbreak clusters of PCP infection, together with the frequent failure of even the most sensitive methods to detect P. carinii in immunocompetent individuals, suggest that PCP may be due to re-infection rather than reactivation. As a result, some authorities have recommended the re-evaluation of infection control guidelines with regard to limiting direct exposure of those at risk to known cases of PCP. However, data are insufficient to support this recommendation as standard practice, and more research is needed to identify routes of transmission for PCP.

Several studies have observed the profound effect of the introduction of widespread PCP prophylaxis on overall survival, quality of life and resource utilization in HIV infection. But questions remain as to who should receive prophylaxis. Evidence from numerous well-designed, randomized, controlled trials has confirmed the benefits of prophylaxis in: (i) patients with absolute CD4+ lymphocyte counts below 200 x 10^6/L (or a CD4+ percentage below 14-16%) and those with higher counts who have oropharyngeal thrush or unexplained fever for more than 2 weeks; and (ii) all patients with a previous episode of PCP. No data support the initiation of prophylaxis in patients who do not meet these standards, and the premature use of prophylaxis carries a risk of sensitization. A at least until more data are available, the substantial increases in circulating CD4+ lymphocyte numbers seen with the advent of powerful anti-retroviral drug combinations cannot be assumed to reflect complete restoration of the immune repertoire. The risk, therefore, of PCP (as with other opportunistic infections) is determined by the life-time CD4+ lymphocyte nadir, and prophylaxis should be continued (Masur, H., data presented at Fourth Conference on Retroviruses and Opportunistic Infections, Washington DC, USA, 1997). For the moment, resistance to PCP prophylaxis is initiated for all HIV-exposed children at 4–6 weeks of age, while they are still undergoing evaluation for HIV infection, regardless of their CD4+ lymphocyte count. Prophylaxis should be discontinued in children who are subsequently found not to be HIV-infected, but should be continued through the first year of life in those whose infection status remains unknown.

The choice of which of the three standard prophylaxis regimens (co-trimoxazole, dapsone and aerosolized pentamidine) to use in clinical practice is often problematic, since regimens of varying dose and frequency are available. Oral regimens are effective and inexpensive but have a high incidence of side-effects. Aerosolized pentamidine is better tolerated but is more expensive and lacks the antitoxoplasma activity of either co-trimoxazole or dapsone with pyrimethamine, and the antibacterial effect of co-trimoxazole (protective against, for example, sinusitis, bronchitis, pneumonia and bacteraemia).

A large clinical trial of these primary prophylaxis regimens confirmed that use of co-trimoxazole 960 mg was the regimen of choice. A handful of studies have compared the use of aerosolized pentamidine 300 mg fortnightly via a Microcirus nebulizer, Intersurgical, Wokingham, U.K. A recent meta-analysis of 35 randomized trials involving 6538 patients confirmed the superior efficacy of co-trimoxazole in preventing both PCP and toxoplasmosis, but also that the rate of adverse events was reduced by 43%, without loss of efficacy, if 480 mg was given daily or 960 mg was given three times a week, instead of daily. Dose reduction diminished the toxicity of dapsone, but at the expense of efficacy. The analysis also showed that for those patients who were intolerant of the oral regimens, a dose increase in aerosolized pentamidine from 300 mg per month to 300 mg twice monthly halved the prophylaxis failure rate. A major predictor of prophylaxis failure is a fall in the CD4+ lymphocyte count to below 75 x 10^6/L. Further PCP prophylactic activity may be achieved in such severely immunosuppressed patients by the addition of weekly azithromycin, similar to the prophylactic regimen for atypical mycobacterial disease.

Despite numerous descriptive studies of the adverse events associated with co-trimoxazole, there are relatively few data on the optimal management of toxicity. With a non-life-threatening adverse reaction, such as a mild rash or abnormalities in liver function, there is little guidance on whether it is preferable to continue therapy, reduce the drug at a lower and gradually increasing dose or use a desensitization regimen. However, desensitization to co-trimoxazole should only be attempted if rash or fever occurs without evidence of associated mucositis or exfoliation. In a recent study, rapid desensitization to co-trimoxazole was achieved in 71% of patients long-term. However, the reported success rate varies considerably according to the protocol adopted. In co-trimoxazole-intolerant patients, the use of dapsone may also be problematic, because of the similarity between dapsone and co-trimoxazole. In a retrospective review, 40% of co-trimoxazole-intolerant patients were also subsequently intolerant of dapsone. Interestingly, it has been recently reported that gradual initiation of co-trimoxazole...
as primary PCP prophylaxis reduces the incidence of treatment-limiting adverse effects within the first 12 weeks, compared with commencing immediately with the full dose (960 mg).

PCP prophylaxis should be administered to pregnant women, and co-trimoxazole is the preferred oral agent, although owing to concerns about teratogenicity some physicians may choose to initiate therapy after the first trimester, or minimize systemic drug absorption by using inhaled pentamidine. However, a retrospective review of pregnant HIV-infected women indicated no increased risk of congenital malformations with the use of co-trimoxazole. Less clinical experience has been accumulated for other agents, but pyrimethamine should be used with great caution because of its reported teratogenicity even at low doses.

References


