AIDS and the lung · 7 *Series editors: D M Mitchell, A A Woodcock*

Treatment of lung disease in patients with the acquired immune deficiency syndrome

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At present the most common major opportunist infection affecting the lung in patients with AIDS is *Pneumocystis carinii* pneumonia. This may change with the use of primary and secondary prophylaxis, which by reducing the incidence of pneumocystis pneumonia may unmask other infections. This article will focus on the treatment of pneumocystis pneumonia, in addition to discussing the management of other pulmonary infections and tumours affecting the lung in patients with AIDS. Antimicrobial treatment for the prophylaxis of pneumocystis and other pulmonary infections, the management of respiratory failure in patients with AIDS, and the effects of antiretroviral treatment with zidovudine on pulmonary disease in AIDS are discussed in other articles in this series.

Pneumocystis carinii pneumonia

Pneumocystis pneumonia is the most common opportunist infection in patients with AIDS in Europe and North America.[1] Until recently it was also a common cause of death but this is probably changing as a result of earlier diagnosis and improved treatment. In the United States pneumocystis pneumonia is still the initial diagnosis in AIDS in about 64% of cases[2] and overall 80% of all patients with AIDS will have one or more episodes of this infection.[3] The mortality from a single episode of pneumocystis pneumonia is 10–30% overall,[4,5] but is over 90% in those who present in respiratory failure.[6–8] Before the widespread introduction of prophylaxis for pneumocystis pneumonia the annual incidence of this infection in patients with AIDS was 35%, and after one episode the relapse rate was about 35% at six months and 50–60% at one year.[9] At presentation the clinical features that determine a poor prognosis are: long duration of symptoms, prior episodes of pneumocystis pneumonia, extensive radiographic shadowing, severe hypoxaemia, increased serum lactate dehydrogenase, low serum albumin concentration, additional pulmonary infections, and extensive interstitial oedema in transbronchial biopsy specimens. The degree of immunosuppression does not seem to increase mortality from pneumocystis pneumonia.[4,5]

Co-trimoxazole (trimethoprim-sulphamethoxazole) was first shown to be effective in the treatment of pneumocystis pneumonia in man in 1975[10] and remains the best antimicrobial combination for this form of pneumonia. A high dose regimen is used. The recommended dose of trimethoprim is 15–20 mg/kg/day and sulphamethoxazole 75–100 mg/kg/day administered intravenously in three or four divided doses a day, or as a continuous intravenous infusion. The recommended serum concentration for trimethoprim is 5–8 μg/ml. Concentrations of less than 5 μg/ml have been associated with treatment failure.[9] Although co-trimoxazole is the most effective antimicrobial combination for pneumocystis pneumonia, side effects are common and occur in 50–80% of patients with AIDS.[11] The reason for this very high incidence is not understood, but a characteristic feature of patients with AIDS generally is the high incidence of adverse drug reactions, in particular hypersensitivity reactions. The most common side effects seen with co-trimoxazole are nausea with vomiting and rash. These side effects are usually seen during the first week and often subside thereafter; nausea and vomiting are often reduced to a tolerable level by antiemetics and rashes by antihistimines. Bone marrow suppression is also a common side effect, with neutropenia, thrombocytopenia, and megaloblastic anaemia.[11–13] Myelotoxicity may be minimised by reduction of the dose and some authorities recommend the routine addition of folinic acid supplements. More unusual side effects are hepatoxicity, tremor, nephrotoxicity, and very rarely the Stevens-Johnson syndrome. The duration of treatment required for pneumocystis pneumonia is three weeks, and as co-trimoxazole is well absorbed oral treatment can usually be started after a few days of treatment, when defervescence has occurred; mild cases may be treated with oral co-trimoxazole from the outset.

Pentamidine has been used for the treatment of trypanosomiasis and leishmaniasis for about 50 years. It was shown to be effective in the epidemic childhood form of pneumocystis pneumonia in 1958.[14] Unlike co-trimoxazole, it is ineffective orally and has to be given intravenously, intramuscularly, or by inhalation. The recommended dose for parenteral treatment is 4 mg/kg a day.[9] Intramuscular injections should be avoided as they are painful and may be followed by sterile muscle abscesses and localised myositis. As with co-trimox-

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azole, adverse reactions are common, occurring in about half of the patients, and may be severe; they include nausea and vomiting, rash, flushing, tachycardia, hypertension, hypoglycaemia and hyperglycaemia, pancreatitis, hepatotoxicity, and nephrotoxicity.[11-13] The nephrotoxicity probably results from drug deposition in the kidney.

Co-trimoxazole was originally shown, in 1978, to be as effective as pentamidine in patients with pneumocystis pneumonia not suffering from AIDS, with the advantage of fewer side effects.[15] At least two studies have compared co-trimoxazole with pentamidine for the treatment of pneumocystis pneumonia in patients with AIDS.[11 12] In a randomised, prospective study of the efficacy of the two drugs[12] 40 patients with their first episode of pneumocystis pneumonia received either pentamidine or co-trimoxazole for three weeks. Six of the 40 patients died (15%). There was no difference between the two drugs in the incidence of side effects or the apparent efficacy of treatment. Eleven of the 20 patients having pentamidine changed to co-trimoxazole after a mean of 10·4 days as a result of side effects, and 10 of those having co-trimoxazole changed to pentamidine after a mean of 11·5 days as a result of side effects. In the patients who were successfully treated there was no recurrence at three months. Perhaps not surprisingly, there was no detectable difference between the two treatments as over half the patients changed to the alternative treatment. In a second randomised prospective study 36 patients were treated with co-trimoxazole and 33 with pentamidine.[11] Patients received three weeks' treatment and did not go over to the alternative treatment if side effects occurred. All side effects were managed satisfactorily either symptomatically or by reductions in dose. Co-trimoxazole treatment was monitored so that the serum trimethoprim concentration could be maintained at 5–8 μg/ml. Pentamidine was administered as an intravenous infusion over 90 minutes, starting at 4 mg/kg body weight. Dose reductions were made if the serum creatinine concentration rose. Among the patients treated with co-trimoxazole leucopenia occurred in 72%, anaemia in 39%, rash in 44%, nausea and vomiting in 25%, and nephrotoxicity in 14%. Dose reductions were required in 70% of patients. The mean time from the start of treatment to improvement in blood gases was seven days and survival was 86%. Among the patients treated with pentamidine nephrotoxicity occurred in 64%, leucopenia in 47%, anaemia in 24%, nausea and vomiting in 24%, hypotension in 27%, and rash in 15%. Dose reduction was required in 24% and the mean time until clinical improvement was 15 days. Sixty one per cent survived. The authors conclude that with both drugs toxicity is usually mild and may be managed by dose reduction without loss of efficacy. Rash and nausea and vomiting are usually transient and can be managed by symptomatic treatment. Most cases of pneumocystis pneumonia may be fully treated with one drug, improvements are seen more quickly with co-trimoxazole, and mortality was lower with co-trimoxazole (14%) than with pentamidine (39%). No relapse had occurred by 90 days in either group of patients. On the basis of these studies and extensive clinical experience over the last decade, most physicians use high dose co-trimoxazole as first line treatment for pneumocystis pneumonia, unless an adverse reaction to it is known to have occurred previously.

The combination of dapsone and trimethoprim is also effective in the treatment of pneumocystis pneumonia though no comparative studies with co-trimoxazole have so far been done. This combination may be useful where severe side effects occur with co-trimoxazole or pentamidine (but it should not be used in glucose 6-phosphate dehydrogenase deficiency). The recommended dose is dapsone 100 mg a day and trimethoprim 20 mg/kg a day. In one study[16] all 15 patients entered into the study improved, though side effects occurred in 14 and two had to be withdrawn. Nausea, vomiting, marrow suppression, haemolytic anaemia, and methaemoglobinaemia were seen. The authors conclude that combination treatment with dapsone and timethoprim is probably as effective as co-trimoxazole treatment, and in pneumocystis pneumonia it is a useful substitute for co-trimoxazole where this has induced side effects. Further comparative studies are, however, needed. More recently the combination of clindamycin and primaquine has been shown to be effective for pneumocystis pneumonia.[17] Clindamycin was given intravenously (600 mg four times daily) and primaquine orally (15 mg base). Twenty eight episodes of pneumocystis pneumonia occurring in 25 patients unresponsive or intolerant to first line treatment were treated with clindamycin and primaquine. In only two episodes was there no improvement. Rash occurred in 14 patients, leucopenia in two, and nausea in two. Again, this encouraging preliminary observation requires confirmation by further comparative studies.

Trimetrexate is a lipid soluble analogue of methotrexate and is a potent dihydrofolate reductase inhibitor. When it is given with folinic acid toxicity for mammalian cells is minimal and yet the inhibitory effect on *P carinii* is maintained. It has to be administered intravenously at a dose of 30–60 mg/m^2. In a study of 49 patients with pneumocystis pneumonia 16 patients received trimetrexate for three weeks after failing to improve with first line treatment (co-trimoxazole or pentamidine); the response rate was 69%.[18] A further 16 patients in the study received trimetrexate as primary treatment for pneumocystis pneumonia and showed a 63% response rate, and a further 17 received trimetrexate plus sulfadiazine as primary treatment and had a 71% response. Overall 68% of the patients responded but the relapse rate was high, 40% of patients developing a further episode of pneumocystis pneumonia within three months. Difluoromethylornithine (DFMO), a polyamine synthesis inhibitor, has been evaluated for salvage treatment. In a study

of 345 patients who had failed to respond to first line treatment, of whom 151 were receiving intermittent positive pressure ventilation, the overall survival was 36%. Thrombocytopenia occurred in 48%, leucopenia in 16%, anaemia in 15%, and diarrhoea in 20%.[19] Both these experimental agents require further evaluation as first line agents. At the moment their use is confined to the occasional case of pneumocystis pneumonia that has clearly failed to respond to one of the first line drugs.

On account of the troublesome side effects and the need for intravenous access for parenteral treatment with both co-trimoxazole and pentamidine, treatment of pneumocystis pneumonia by pentamidine inhaled via a nebuliser has recently aroused considerable interest. In an early study 15 patients with mild or moderate first episodes of pneumocystis pneumonia received 600 mg of pentamidine daily via a jet nebuliser. Thirteen patients improved (87%), there were no systemic side effects, serum pentamidine concentrations were undetectable or extremely low, and the only major local side effect was cough, which occurred in 12 patients.[20] In a further study nine of 13 similarly treated patients (70%) improved.[21] In this study both cough and bronchospasm occurred as side effects and three patients had an early relapse of pneumocystis pneumonia. Since these studies it has become clear that the particle size generated by the nebuliser is critical in determining therapeutic outcome. Generally particles smaller than those generated by the standard jet nebulisers used for bronchodilator treatment are required. The initial successful study of Montgomery *et al* used the Respirgard II nebuliser, which produced small particles of mass median aerodynamic diameter (MMAD) 0·8 μm with a geometric standard deviation (GSD) of 1·5.[22] In a comparative study only three of 14 patients with pneumocystis pneumonia responded to nebulised pentamidine delivered by a standard jet nebuliser (Acorn, system 22: aerosol droplet size 2·6 μm MMAD (GSD 2·9), with 46% of droplets less than 3·9 μm); whereas 13 of 16 patients responded to nebulised pentamidine via a Respirgard II nebuliser (MMAD 0·8 μm (GSD 1·5), with 98% of droplets less than 3·9 μm).[22] Alternative nebuliser systems that are as effective are now available and are considerably cheaper than the Respirgaard II nebuliser; these include the Acorn system 22 Miser.[23,24] Subsequent experience with nebulised pentamidine for the treatment of pneumocystis pneumonia has shown that the overall response rate for mild and moderate disease is about 70%. The response to treatment is less rapid than with systemic treatment and early relapse after nebulised pentamidine is relatively frequent,[21] whereas it is unusual after treatment with co-trimoxazole. In view of these findings and the lack of large controlled studies of efficacy, treatment of pneumocystis pneumonia with nebulised pentamidine should probably be reserved for patients who either have mild disease or have developed serious side effects during parenteral treatment.[25]

During an episode of pneumocystis pneumonia response to treatment is normally seen between the second and sixth day with a fall in temperature and respiratory rate, and improvement in arterial hypoxaemia. If no improvement is seen by the seventh day, or the patient is deteriorating, the diagnosis of pneumocystis pneumonia should be reviewed. This may require consideration of further bronchoscopy or a search for a respiratory copathogen. If pneumocystis pneumonia remains the main problem, alternative antimicrobial treatment should be considered, with possibly a second line agent, as should the possible use of additional support measures (see article in February issue, p140). (In an early series patients who changed from co-trimoxazole to pentamidine because of failure to respond had an 88% mortality.)[1] Finally, after the particular episode of pneumocystis pneumonia has been considered in the context of the patient's overall state and other HIV related complications, further active measures may be thought inappropriate.

Bacterial pneumonia

Those infected with HIV have a higher incidence of bacterial pneumonia than is found in the normal population.[26,27] This increased susceptibility to infection by capsulated bacteria is thought to be related to an inability to mount normal antibody responses in AIDS. This is coupled with the finding of selective IgG_2 deficiency in some patients with AIDS, which may be correctable with gammaglobulin.[28,29] Most of these pulmonary infections will respond to broad spectrum antibiotics (amoxycillin or erythromycin). In this group of patients sputum culture often reveals *Streptococcus pneumoniae* and *Haemophilus influenzae*, and occasionally *Branhamella catarrhalis*. Severe bacterial pneumonia due to *Staphylococcus aureus* or Gram negative organisms may be seen, particularly in the later stages of AIDS. As bacterial pneumonia in AIDS may be rapid in onset, severe, and accompanied by bacteraemia, it is advisable to cover this possibility in any severe pneumonic illness in a patient with AIDS. This is an added advantage of using co-trimoxazole for treating presumptive pneumocystis pneumonia as it is also effective for most of these bacteria. If pentamidine is used for pneumocystis pneumonia, a broad spectrum antibiotic should be considered while a firm diagnosis is awaited.

Mycobacterial infection

Both tuberculosis and non-tuberculous mycobacterial infection are seen with increased frequency in those infected with HIV. The incidence of tuberculosis in HIV infected individuals in a particular community will reflect the background prevalence of tuberculosis in the community in which these individuals live or have lived. Tuberculosis may often be the first serious infection to be seen in patients with progressive HIV disease,[30-32] and indeed non-pulmonary tuber-

culosis is now an "AIDS defining" diagnosis.[33] Patients with AIDS who develop tuberculosis frequently have false negative tuberculin skin test responses[30] and may present with atypical clinical[30-32] and radiographic features.[34] The clinical pattern often resembles primary rather than post-primary disease. Tuberculosis in patients with HIV infection generally responds well to conventional antituberculous chemotherapy (rifampicin, isoniazid, and pyrazinamide) given for six to nine months.[30-32] Relapse after conventional chemotherapy has been described in AIDS but is relatively rare.[35] The issue of maintenance treatment for life remains open at the moment, though it would seem advisable in view of the profound defect in cell mediated immunity in patients with AIDS.

MYCOBACTERIUM AVIUM-INTRACELLULARE INFECTION

Widespread disseminated infection with *Mycobacterium avium-intracellulare* is extremely common in the terminal phase of AIDS and occurs in up to half of patients with AIDS if carefully sought by blood culture or necropsy.[36] Although the infection is frequently documented in patients with AIDS, the extent to which it contributes to clinical disease varies. Many of these patients have numerous concomitant infections or tumours and are drawing towards the close of their AIDS illness. Some authorities therefore do not routinely attempt to treat *Mycobacterium avium-intracellulare*—because treating the infection may not prolong survival.[36-38] *Mycobacterium avium-intracellulare* is universally resistant to all first line antituberculous drugs in vitro and shows variable sensitivity to ansamycin (rifabutin), clofazimine, amikacin, ethionamide, cycloserine, ciprofloxacin, and azithromycin. Various combinations of these agents have been used but clearcut clinical response is rare.

OTHER NON-TUBERCULOUS MYCOBACTERIAL INFECTIONS

Infections with other non-tuberculous mycobacteria are seen less frequently than infection with *M avium-intracellulare* and include infection with *M kansasii, M gordonae,* and *M xenopi*. In patients not suffering from AIDS *M kansasii* responds well to chemotherapy and may be treated with standard chemotherapy, though this should continue for at least 18 months. Ciprofloxacin has been shown to have good in vitro activity against *M xenopi* and should probably be included in the treatment regimen.[38 39]

Cytomegalovirus infection

Cytomegalovirus is a major opportunist pathogen in patients with AIDS, causing choroidoretinitis, colitis, hepatitis, adrenalitis, radiculitis, and oesophagitis. It is also frequently isolated in bronchoalveolar lavage specimens in patients with AIDS and pneumonitis, being commonly found with *P carinii*.[40] It is now well established that cytomegalovirus causes a frequently fatal pneumonitis in recipients of allogenic renal,[41] liver,[42] heart,[43] and bone marrow transplants.[44] Whether cytomegalovirus causes appreciable pneumonitis in patients with AIDS, however, remains controversial, because where cytomegalovirus is isolated from the lavage fluid of a patient with pneumocystis pneumonia the patient frequently improves with treatment of the pneumocystis pneumonia alone. Probably cytomegalovirus has occasionally caused or contributed to pneumonitis in patients with AIDS, where inclusion bodies are identified in biopsy material. Most authorities treat cytomegalovirus pneumonitis in patients with AIDS by a process of exclusion—in other words, where cytomegalovirus is the only agent identified and where no other pathogen is found. Ganciclovir is the treatment of choice and is administered intravenously by short infusion in a dose of 7·5–15 mg/kg a day for 21 days.[45] Maintenance treatment is then required indefinitely to prevent relapse. As the drug has to be given intravenously this may lead to problems with venous access. Ganciclovir is myelotoxic.

Non-specific interstitial pneumonitis and lymphocytic interstitial pneumonitis

Lymphocytic interstitial pneumonitis is most frequently seen in children with AIDS and non-specific interstitial pneumonitis is being increasingly recognised in adults. So far no effective treatment has been described, though anecdotal reports of cases of response to corticosteroids have appeared. Steroids in patients with AIDS, however, carry the hazard of increasing the incidence of opportunist infections by accentuating immunosuppression.[46 47]

Kaposi sarcoma

Extensive intrathoracic Kaposi sarcoma has been well described; it may affect pulmonary parenchyma, pleura, hilar and mediastinal lymph nodes, and pericardium as well as producing the endobronchial lesions seen at bronchoscopy.[48-50] When appreciable pleuropulmonary disease is present there are nearly always extensive lesions at other sites (skin, gut, lymph node). Extensive pleural or parenchymal sarcoma results in respiratory failure, whereas extensive endobronchial sarcoma may produce airflow obstruction. Troublesome recurrent pleural effusions related to Kaposi sarcoma are often successfully treated by bleomycin pleurodesis. In late and severe cases Kaposi sarcoma may produce severe pulmonary disease, which will then warrant treatment in its own right once concomitant infection has been excluded or treated. Several cytotoxic agents have been used (singly) for palliative treatment, including etoposide, vincristine and vinblastine.[52] Combination chemotherapy for more aggressive disease with doxorubicin (Adriamycin), bleomycin, and vincristine may

be expected to produce a partial response in 50–70% of cases.[53] Alternatively, α interferon has been used, but it has a high incidence of side effects.[54]

Conclusions

Pneumocystis carinii is the most important cause of pneumonitis in patients with AIDS in Europe and North America. The first line treatment of choice is still co-trimoxazole or pentamidine. Other effective treatments are available, though further controlled comparative studies of their efficacy are required. The response to treatment for pneumocystis pneumonia is excellent, with the mortality in first episodes now little more than 5% in most centres. Other common treatable causes of pneumonitis in patients with AIDS are "ordinary" bacterial infections and tuberculosis, where the results of treatment should also be excellent. The value of treatment for *Mycobacterium avium-intracellulare* and cytomegalovirus infections when these are associated with AIDS pneumonitis is less certain.

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