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Treatment and Prophylaxis of *Pneumocystis carinii* Pneumonia in AIDS Patients

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Summary

Pneumocystis carinii pneumonia (PCP) is seen in people with a defect in cell-mediated immunity. Today the most common cause for this is the Acquired Immunodeficiency Syndrome (AIDS). There have been some remarkable advances recently in the development of new drug regimens to combat this otherwise fatal infection. Although cotrimoxazole (trimethoprim-sulfamethoxazole) is still the drug of first choice it cannot be tolerated by a significant proportion of patients, and therapies such as pentamidine (pentamidine-isethionate) [intravenous or nebulised], dapsone-trimethoprim, eflornithine (DFMO; difluoromethylornithine), trimetrexate, and clindamycin-primaquine are finding therapeutic niches. The major advantage in these other agents is not improved efficacy but different toxicity profiles, enabling therapy to be most appropriately tailored to individual patients' conditions. Although the majority of patients should now survive an attack of PCP, relapses will occur if prophylaxis is not used. There is also the capacity to predict accurately which patients are at risk for this pneumonia and prevent it through the use of chemoprophylaxis. These advances in the treatment and prevention of PCP, together with anti-retroviral therapy, mean that this is an area of AIDS management that has resulted in improved long term survival.

Pneumocystis carinii is a low grade pathogen that causes an insidious pneumonitis in people with immune defects – especially those with defects in cell-mediated immunity, e.g. malnourished infants, organ transplant recipients and patients on immunosuppressive chemotherapy.

Since the commencement of the AIDS pandemic (Masur et al. 1981) there has been an exponential increase in the incidence of *Pneumocystis carinii* pneumonia (PCP) in the Western world. Currently PCP accounts for 60% of initial AIDS diagnosis and approximately 85% of AIDS patients will develop this form of pneumonia during the course of their illness (Kovacs & Masur 1989).

PCP is suspected on the basis of the clinical symptoms of cough, night sweats and increasing dyspnoea, with chest x-ray changes of diffuse interstitial shadowing, and low arterial oxygen pressure (paO₂) in a person in a high risk group. The diagnosis can only be confirmed by the microscopic detection of typical pneumocysts in alveolar tissue or bronchial secretions.

1. Treatment

Since the emergence of AIDS there have been considerable changes in the treatment of PCP. In the 1950s pentamidine administered intramuscularly was the treatment of choice. However, the high incidence of sterile abscess formation at the site of injection and the finding that hypotension and cardiac arrhythmias are not encountered more often with intravenous administration led to a preference for slow intravenous infusions (Mallory et al.

1987).

In the 1960s the development of cotrimoxazole (trimethoprim-sulfamethoxazole) changed treatment strategies. It appeared to be as effective as pentamidine but was associated with a much lower incidence of adverse drug reactions. Cotrimoxazole therefore replaced pentamidine as the treatment of choice (Hughes et al. 1978).

With the rapid increase in the number of cases of PCP related to AIDS in the early 1980s it became apparent that there is a higher incidence of adverse drug reactions with cotrimoxazole in these patients than in the non-AIDS groups (approaching 100% in some studies) [Jaffe et al. 1983]. Most investigators now feel that cotrimoxazole has no advantage over pentamidine as a first-line treatment for PCP in AIDS patients. Recently a number of other regimens have been advocated by various centres as efficacious against *P. carinii* (table I; figs 1 and 2). These include pentamidine (pentamidine isethionate) administered as an aerosol, oral dapsone-trimethoprim, eflornithine (DFMO; difluoromethylornithine), trimetrexate and calcium folinate (folinic acid), and clindamycin plus primaquine. Although all regimens show reasonable effectiveness, a range of toxicities is often encountered. The major features of each regimen are discussed briefly below.

1.1 Cotrimoxazole

In high doses (trimethoprim 15 to 20 mg/kg/day, sulfamethoxazole 75 to 100 mg/kg/day) cotrimoxazole has been shown to be effective in the

Table I. Antipneumocystis agents and their current usage

Drug	PCP treatment			PCP prophylaxis
	mild	moderate	severe	
Cotrimoxazole	Oral	IV	IV	Oral
Pentamidine	Neb	Neb + IV	Neb + IV	Neb
Dapsone + TMP	Oral	Oral		Oral
Clindamycin + primaquine	Oral	IV + oral	IV + oral	Oral
Eflornithine		IV	IV	
Trimetrexate + calcium folinate			IV	
Pyrimethamine + sulfadoxine				Oral

Abbreviations: TMP = trimethoprim; IV = intravenous; Neb = nebuliser.

treatment of PCP, and is commonly used as first-line therapy either intravenously or orally. The duration of treatment is 14 to 21 days, depending on the severity of the episode.

Adverse reactions are common with cotrimoxazole, necessitating drug withdrawal in up to 50% of patients (Wharton et al. 1986). The major adverse effects include nausea and vomiting, rash, fever, bone marrow suppression (in 20 to 50% of patients), Stevens-Johnson syndrome (rare) and hepatotoxicity. Some centres prefer intravenous administration rather than oral in the belief that there may be less nausea. It is becoming quite clear that a number of the toxicities associated with cotrimoxazole, such as nausea or haematological toxicity, are dose related and that monitoring drug

concentrations and dose reductions may reduce toxicity (Sattler et al. 1988). For many centres, however, monitoring drug levels is not possible and as newer regimens appear to be as effective many physicians readily change to alternative therapy. Besides changing drugs, many physicians are trying to decrease cotrimoxazole toxicity by either starting treatment with lower doses (960 mg/day trimethoprim, 4800 mg/day sulfamethoxazole) or decreasing treatment courses from 21 to 14 days. Some centres are able to maintain certain patients on cotrimoxazole throughout a full treatment course by 'treating through' any hypersensitivity reactions that occur or by desensitising the patient to the drug (Finegold 1986); however, most doctors are reluctant to do this.

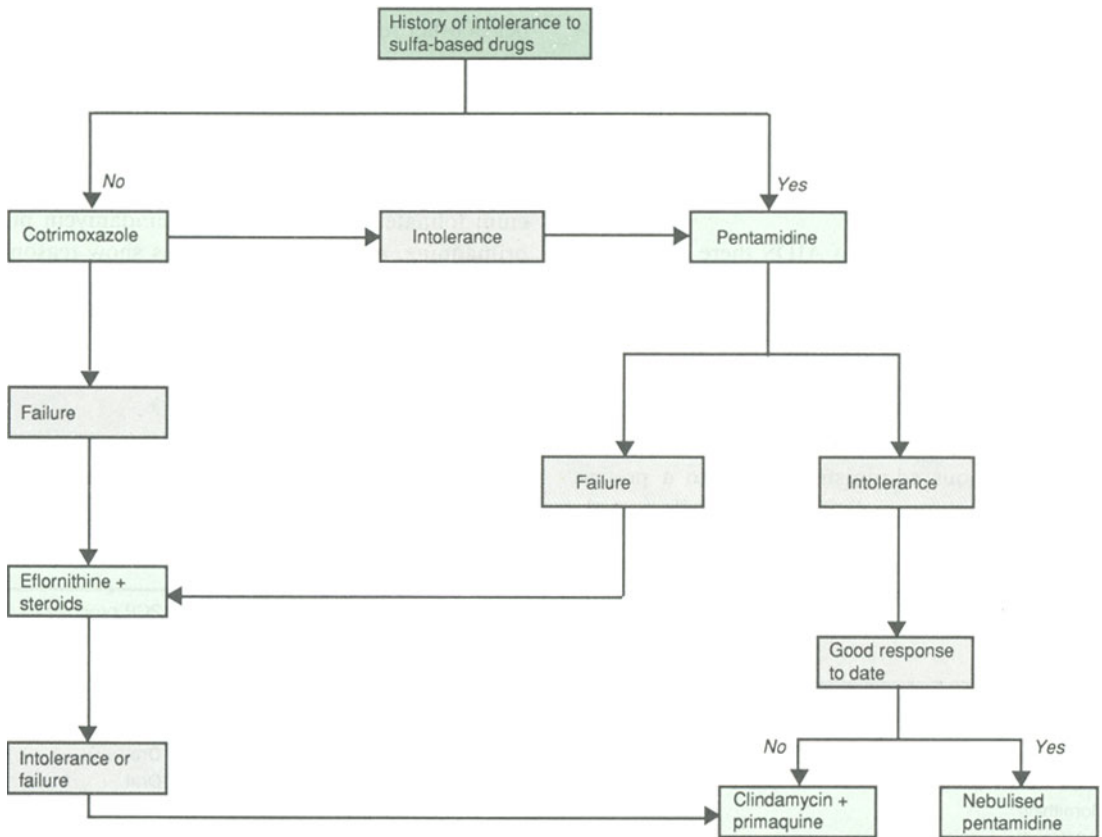


Fig. 1. Inpatient treatment of PCP (moderate to severe infection). If PaO₂ drops to < 8.0 kPa at any stage introduce prednisolone orally or an equivalent dose of methylprednisolone if parenteral treatment necessary. Treatment is for 14 to 21 days, depending on severity of infection and response to treatment.

1.2 Pentamidine

Pentamidine at a dosage of 4 mg/kg (approximately 300mg), administered as a slow intravenous infusion, is an effective treatment for PCP. Response rates are approximately 80%, depending on the severity of the episode. Unfortunately, the effectiveness of pentamidine is limited by a high incidence of adverse reactions, up to 50% of patients in some studies (Wharton et al. 1986).

The most common drug reactions include renal dysfunction, hypotension and dysglycaemia (Goa & Campoli-Richards 1987). Renal impairment appears to be a dose-related effect and is more likely to occur if patients have been treated with pentamidine in the past, have pre-existing renal impairment or are given a prolonged course of treatment.

Hypotension often occurs as the drug is being infused and can usually be countered by slowing the infusion rate (Mallory et al. 1987). Dysglycaemias occur as a result of direct toxicity to the β islet cells of the pancreas and may result in long term diabetes (Waskin et al. 1988). Although these toxicities are potentially life-threatening, close monitoring of blood pressure and serum biochemistry can detect abnormalities early, usually before the patient becomes symptomatic.

The high incidence of toxicity associated with parenteral pentamidine has led to modification of the standard regimen (4 mg/kg/day intravenously for 21 days) in an attempt to diminish these adverse effects. One such modification has been to administer the drug as an aerosol directly to the lungs (Monk & Benfield 1990). Although initial

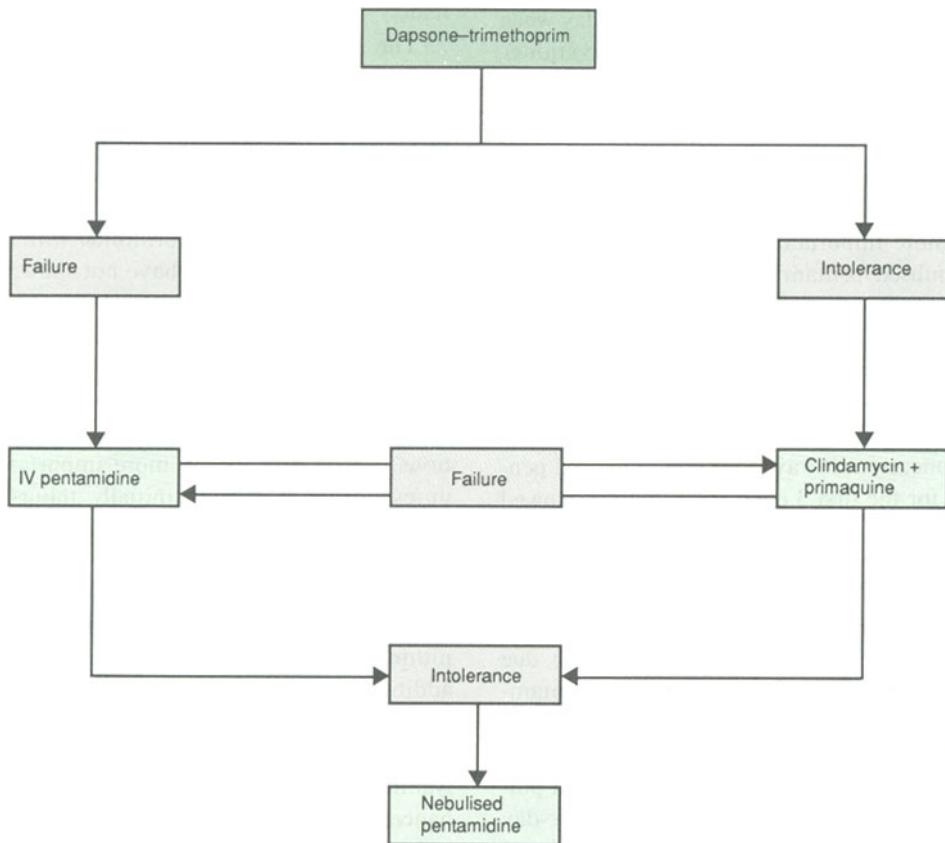


Fig. 2. Outpatient treatment of PCP (normal PaO₂, minimal changes in chest x-ray); IV = intravenous.

pilot studies using this regimen showed promising results (Montgomery et al. 1987), later comparative studies of intravenous versus nebulised pentamidine showed an unacceptably high failure rate (Conte et al. 1990; Soo Hoo et al. 1990). The disadvantage with using nebulised pentamidine for treatment is that even the most efficient delivery system can only carry aerosolised drug to those parts of the lung with adequate ventilation. If patients are having difficulty in getting enough oxygen into their alveolar spaces then it is highly unlikely that they will be able to get adequate amounts of drug to the alveoli as well. We therefore would not use this method in patients who are hypoxic or whose chest x-rays show any marked degree of interstitial shadowing.

One disadvantage with the nebulised route is that patients are more intolerant to the presence of high concentrations of pentamidine every day when they are acutely unwell (personal observations). Unlike prophylactic therapy, where wide margins of error can be tolerated (in terms of amount of drug deposited in the alveoli), with treatment courses the unknown variables of drug concentration, droplet size, flow rates and nebuliser types become more important. Despite these disadvantages nebulised pentamidine may be suitable for the treatment of patients with mild pneumonia (normal resting arterial blood gases, minimal changes on x-ray), intolerance to sulfa-based drugs or those keen to be treated as outpatients.

One modified regimen that has been tried consists of concurrent intravenous and nebulised pentamidine for the first 3 days of treatment followed by alternate-day intravenous administration until the course is complete. The rationale behind such an approach is that it takes 3 to 5 days of intravenous therapy before adequate lung tissue concentrations are achieved (Donnelly et al. 1988), due to the strong protein binding properties of pentamidine; therefore, the use of aerosol delivery should rapidly elevate lung concentrations into the therapeutic range (Debs et al. 1987). Once initial pulmonary loading has been achieved, alternate-day intravenous administration should prevent accumulation of pentamidine (Conte et al. 1990), and

hence result in less toxicity. We have found that since the introduction of this new regimen there has been a significant reduction in pentamidine-related reactions with no loss of efficacy.

1.3 Eflornithine

Eflornithine is a decarboxylase enzyme inhibitor which interferes with polyamine synthesis (important for cell growth) [Sjoerdsma & Schechter 1984]. We have shown this drug to be an effective salvage treatment in patients who fail to respond to conventional therapy (Smith et al. 1990a). It is administered as a continuous intravenous infusion at a dose of 400 mg/kg for 14 days. An oral formulation is available but it is not well absorbed and causes diarrhoea. Response rates are approximately 60% when used as salvage therapy.

The major toxicity with eflornithine is related to bone marrow suppression (occurring in up to 40% of patients). Other adverse reactions are phlebitis at the injection site and alopecia. Although an effective second-line agent in patients with a poor prognosis, studies nearing completion in our unit comparing eflornithine with cotrimoxazole as a first-line agent have not shown comparable efficacy (Smith et al. 1990b). There are 3 possible explanations for eflornithine being less effective when used as primary therapy rather than salvage therapy. Firstly, eflornithine has no activity against possible secondary bacterial chest infections, which may play a more important role in unresponsive PCP than initially thought. When patients are switched to eflornithine because of apparent failure of primary therapy they are usually also treated with antibacterial and antituberculosis agents. Secondly, the polyamine inhibition of eflornithine in tissue cultures can be bypassed by the addition of exogenous polyamines (Cushion et al. 1985). It is possible that in very ill patients in an increased catabolic state, who have exhausted polyamine supplies, the effects of eflornithine are enhanced. Finally, in animal models of trypanosomiasis there is pronounced synergism between eflornithine and other anti-protozoal agents (Bac-

chi & McCann 1987); such may also be true for human PCP.

1.4 Trimetrexate

Trimetrexate is a potent folic acid antagonist which is taken up by both mammalian and pneumocystis cells. It produces a fatal blockage of folic acid metabolism (Allegra et al. 1987a). Calcium folinate is administered concurrently to 'rescue' mammalian cells from this blockage, as only mammalian cells possess the mechanism to actively transport calcium folinate into the cell. The net result is the selective destruction of pneumocystis cells while leaving the host cells relatively undamaged. This therapy is being investigated as both first-line and salvage treatment.

Results to date are encouraging, with response rates of 66 to 88%, although reports of early relapses (Allegra et al 1987b) and the practical difficulties in administration (the drug must be given by medical staff on a strict 6-hour regimen) will probably mean that this regimen never gains widespread acceptance. As with eflornithine, bone marrow toxicity is the biggest drawback although this usually responds to an increased dose of calcium folinate. Elevation of liver enzymes has also been reported.

Trimetrexate is administered intravenously at a dose of 45 mg/m²/day in 50ml 5% dextrose in water for 21 days and the calcium folinate 20 mg/m² every 6 hours for 24 days, although the 2 agents cannot be infused concurrently in the same intravenous line as precipitation will occur. Currently this regimen is used only as salvage therapy by a few centres.

1.5 Dapsone-Trimethoprim

The combination of dapsone (100 mg/day) and trimethoprim (20 mg/kg/day) has been shown to be of some benefit in the treatment of PCP, with 100% survival reported in one small study (Leoung et al. 1986). However, the incidence of adverse drug reactions was also high, at 95% of patients treated. In another comparative study dapsone-trimetho-

prim was shown to be equal in efficacy to cotrimoxazole but with less toxicity (Medina et al. 1990). The majority of drug reactions were minor (rash, nausea, neutropenia and asymptomatic methaemoglobinaemia). This combination therefore seems an attractive alternative to pentamidine or cotrimoxazole in the treatment of mild to moderate episodes of PCP. It is only available as an oral preparation.

An unusual drug reaction that has been noted with the combination of dapsone-trimethoprim is haemolytic anaemia, especially in patients with glucose-6-dehydrogenase enzyme deficiency (Rashbridge & Scott 1973). This regimen is now commonly used in ambulatory or outpatient treatment of PCP.

1.6 Clindamycin-Primaquine

Clindamycin and primaquine have only recently been used in patients after studies in the rat model of PCP showed this combination to be effective. Initial pilot studies in patients gave response rates of 92 to 100% (Ruf & Pohle 1989; Toma et al. 1989). Although rashes, diarrhoea, nausea and mild methaemoglobinaemia were seen, the regimen was generally well tolerated.

This combination is attractive in that many of the sulfa-based hypersensitivity reactions seen with other regimens do not occur, and the bacterial secondary infections which commonly accompany PCP are treated as well. It is expected that this regimen will gain widespread acceptance as more experience accumulates. Pseudomembranous colitis secondary to *Clostridium difficile* toxin has not been a major problem.

1.7 Corticosteroids

Corticosteroids have been advocated as being of benefit in the prevention of adult respiratory distress syndrome (ARDS)-type deterioration and a number of studies have shown improvement in oxygenation and resolution of clinical features (Bozzette 1990; Gagnon et al. 1990). Steroids certainly have a dramatic effect in some hypoxic

patients, with rapid improvements in PaO₂, clearance of infiltrates on chest x-rays and a resolution of fever. Their ultimate place in the management of PCP, however, is the subject of debate (Kovacs & Masur 1990).

The difficulty in deciding where to use steroids comes from the observations that maximum effectiveness is achieved if steroids are given before profound pulmonary inflammation occurs. It is well recognised that deterioration in lung function occurs in the first 3 days after the initiation of treatment. This is probably due to cytokine stimulation in response to the release of antigenic protein from disrupted *P. carinii* cells. Steroids have proven effectiveness at preventing these effects when initiated concurrently with antipneumocystis therapy.

The role of late or rescue corticosteroid use remains unclear. In clinical practice corticosteroids would be given to those patients with poor prognostic markers on admission to hospital, i.e. PaO₂ of < 8.0 kPa, severe interstitial infiltrates on chest x-ray and elevated lactic dehydrogenase (LDH) levels (> 700 U/L) [Brenner et al. 1987]. There is still debate as to the optimum dosing regimen but current recommendations suggest prednisolone 40mg 2 to 4 times a day for 5 days, followed by 40mg daily for 5 days, then 20 mg/day until the end of treatment (Bozzette et al. 1990; Masur et al. 1990). Worries have been expressed that too long a course could result in further immunosuppression or that other concurrent infections such as herpes, tuberculosis or candidial infections may be more severe and difficult to treat (Sattler 1991). Certainly, refractory oral and oesophageal candidosis is a problem during corticosteroid therapy.

2. Prophylaxis

Although PCP can be treated with a reasonable degree of success, the underlying immune dysfunction that allowed the pneumonia to develop remains. This means that reinfection or relapse is likely.

Patients appear to be most at risk for PCP relapses 6 to 9 month after an initial attack (Golden et al. 1989). Since subsequent episodes carry a

higher mortality than the first attack, prevention of relapses should result in better long term survival in some patients (Rainer et al. 1987).

The choice of agents suitable for PCP prophylaxis includes cotrimoxazole, dapsone, pyrimethamine-sulfadoxine, pentamidine, and clindamycin + primaquine.

2.1 Cotrimoxazole

Cotrimoxazole given daily or 3 times a week has been shown to be effective in preventing PCP in patients without AIDS (Hughes et al. 1987) and more recently in AIDS patients as well (Raviglione et al. 1990; Ruskin & La Riviere 1991). The recommended dose is 5 mg/kg trimethoprim and 25 mg/kg sulfamethoxazole in 2 divided doses as tablets. Although probably the most effective form of prophylaxis, its use is somewhat limited in a number of patients with AIDS due to adverse reactions. The most common is skin rash; nausea is another complaint that patients often find intolerable in a medication that they will need to be on for the rest of their life.

2.2 Dapsone

Dapsone has been shown to be effective in the prevention of PCP at a dose of 50 to 100 mg/day (Kemper et al. 1990). With long term follow-up under 5% of patients had a relapse. Again, adverse reactions are common, the most worrying being haemolytic anaemia and methaemoglobinaemia. Some investigators have suggested that lower doses (50 to 100 mg/week) may give adequate protection (Ogata-Arakaki et al. 1990) but this has not been our experience. When dapsone is given with pyrimethamine it may also protect against cerebral toxoplasmosis (Clolet et al. 1991). Myelosuppression in patients concurrently on zidovudine (azidothymidine) therapy has been seen in some patients, particularly if combined therapy has been given for more than a year.

2.3 Pyrimethamine-Sulfadoxine

The combination of pyrimethamine and sulfadoxine has been reported to have some benefit in preventing PCP despite its lack of success in treat-

ment. It does not appear to be as effective as co-trimoxazole, with a relapse rate following first-episode PCP of about 23% over 6 months (Fischl & Dickinson 1986). It is usually given as 1 or 2 tablets/week and it is likely that its poor efficacy is related to inadequate drug concentrations. Rash and nausea are common side effects. The Stevens-Johnson syndrome, which may occur in up to 4% of patients, is a severe limitation to its use.

2.4 Nebulised Pentamidine

Pentamidine has recently received considerable attention as a potentially beneficial drug for PCP prophylaxis (Corkery et al. 1988; Monk & Benfield 1990; Thomas et al. 1990). Nebulised pentamidine has been used with success by a large number of centres dealing with AIDS patients. The rationale for its use as an aerosol is to deliver the drug specifically to the site of infection and avoid toxicity to other organs. It is theoretically possible to do this with pentamidine for a number of reasons: firstly, it is possible to aerosolise the drug to form droplets that can reach the alveolar spaces; secondly, it adheres strongly to alveolar macrophages and so does not enter the systemic circulation in significant amounts; and, finally, the long half-life of the drug, together with its concentration in the lung, means that long dosing intervals of between 2 and 4 weeks are possible (Conte & Golden 1988; Hirschel et al. 1991; Kronawitter et al. 1991).

Adverse reactions seen with this form of administration include unpleasant taste (approximately 100%), cough (30%), bronchoconstriction (dose-dependent and reversible with a bronchodilator) [Smith et al. 1988], nausea (5%) and increased saliva production (30%). There have been very few reports of systemic toxicity (Leen & Mandal 1988) and on the whole this method of prophylaxis appears well tolerated.

As with the use of nebulised pentamidine for the treatment of PCP, prophylactic regimens have been developed *ad hoc* by each major centre seeing AIDS patients so that nebuliser equipment, dosage and dosing intervals have varied widely, making direct comparisons difficult. Doses have ranged

from 60 to 600mg of pentamidine, dosing intervals from weekly to monthly administration. There is also wide variation in the types of nebulisers used to deliver the drug. As most commercially available nebulisers were designed for the administration of bronchodilators and thus target the large airways, these have had to have been modified, redesigned (Simonds et al. 1989) or new models developed to give a nebuliser that produces large quantities of aerosol capable of alveolar deposition. Unfortunately, some of the nebulisers in current use do not achieve these criteria, and result in inadequate lung protection and dissatisfaction with this form of therapy.

Although there is considerable debate about which nebuliser to choose (O'Doherty et al. 1988; Smalldone et al. 1988), it is unlikely that one particular brand is clinically significantly better than any other. Both jet and ultrasonic nebulisers, throwaway or reusable, are currently being advocated as the most efficient; however, any nebuliser is appropriate as long as it can consistently deliver enough droplets of adequate size to coat all the alveolar spaces. In practice this means that the majority of droplets should be less than $5\mu\text{m}$ in size, preferably 2 to $3\mu\text{m}$ (Newman 1985; Stahlhofen et al. 1980). Droplets smaller than this may not settle in the lungs but be exhaled; larger droplets will impact in the oropharynx and large airways, increasing adverse effects such as cough and bronchoconstriction and decreasing efficacy.

The efficacy of nebulised pentamidine has been established in several large scale controlled studies, among them one placebo-controlled study from Canada (Montaner et al. 1991), one from France comparing nebulised pentamidine and zidovudine with zidovudine alone (Girard et al. 1989), and one dose-ranging study comparing a large dose of pentamidine (300mg monthly) with a much smaller dose (30mg fortnightly) [Leoung et al. 1990]. However, doubts about its widespread applicability remain.

It is not known whether long term use of nebulised pentamidine will result in interstitial lung damage. A study of 173 patients on long term prophylaxis at our centre showed that there is no de-

terioration in peak expiratory flow rates over time (Smith et al. 1991); however, more extensive studies on lung function are needed. Worries have also been expressed about the failure of this form of prophylaxis to protect against the possibility of disseminated *P. carinii* and about an increasing incidence of pneumothoraces in AIDS patients. Although a number of case reports of disseminated *P. carinii* infection have been published (Northfelt 1989), no comparative studies have been reported against other forms of prophylaxis. Less than 60 cases have been reported in the world literature, most associated with concurrent severe pulmonary infection or in patients with a past history of PCP. It is likely, therefore, that disseminated *P. carinii* infection is very rare.

Similarly, the increase in cases of pneumothoraces (Martinez et al. 1988) seems to be more related to the number of episodes of PCP a patient has had rather than what form of prophylaxis he or she is on. Pneumothoraces are probably caused by the rupture of thin-walled pneumococles which appear during recovery from PCP. As patients live longer following their PCP (Harris 1990) it is likely that more of these events will be seen.

Another major problem with this form of prophylaxis is the considerable expense of the drug, the equipment required for nebulisation and of trained personnel. However, despite these concerns about long term adverse effects and the considerable cost of this form of prophylaxis, it will always be widely used as a considerable number of patients will not be able to tolerate the adverse effects of the other currently available systemic forms of PCP prophylaxis, especially as they all contain a sulfa moiety to which many HIV-positive patients are intolerant.

2.5 Clindamycin-Primaquine

Clindamycin/primaquine has only been used as a prophylactic regimen in a very small number of patients who have responded to this combination as treatment of their PCP (Kay & DuBois 1990). Although data are sparse it appears to be well tolerated and probably effective. A dosing schedule

of clindamycin 150mg 4 times daily and primaquine 26.3 mg/day has been proposed (Kay & DuBois 1990). Further experience in larger numbers of patients is needed before this combination can be widely promoted.

2.6 Patient Selection

With the necessity for prevention of relapses of PCP acknowledged by most doctors, many investigators also feel that it is equally important to prevent first attacks – with primary prophylaxis – as opposed to prevention of subsequent episodes – secondary prophylaxis. Primary prophylaxis has been used in patients with Kaposi's sarcoma, where it was found that preventing PCP resulted in improved survival (Fischl et al. 1988). As it is possible to predict which patients with HIV disease are at high risk for the development of PCP (Phair et al. 1990) these patients should be offered prophylaxis (Centres for Disease Control 1989). This would include patients with Kaposi's sarcoma, other non-PCP opportunistic infections, adults with CD4 counts below 200/mm³ and children with a CD4 of less than 20% (Centres for Disease Control 1991). It would be unnecessary to use prophylaxis in HIV-positive patients with normal or near-normal immune status.

As PCP accounts for 60% of AIDS diagnoses and 85% of AIDS patients will develop it during the course of their disease, the elimination of this infection (whether initial or recurrent) with prophylaxis is now starting to affect morbidity and mortality figures. Survival figures for patients with PCP have improved considerably compared to patients with other opportunistic infections over the past few years (Harris 1990; Lemp et al. 1990). This improvement is undoubtedly due to the effects of both antiretroviral treatment with zidovudine plus the reduction in mortality from PCP with the widespread use of PCP prophylaxis.

3. Conclusions

Considerable advances have been made over the past decade in the treatment of PCP, with a resultant reduction in mortality to below 10% today.

An increasing number of agents are available but all are plagued with major toxicities. Cotrimoxazole, the standard, remains the drug of first choice and is still an effective therapy if patients can tolerate it. Perhaps the most significant advance in this area has been the realisation that survival is improved most not by different treatment regimens, but by early diagnosis and initiation of therapy, with outpatient treatment becoming more common. Side effects are seen with all regimens but are predictable and should never be a cause of major morbidity. Modifications of dosing regimens to prevent drug accumulation will reduce most of these side effects.

As with treatment regimens, there are also an increasing number of prophylactic regimens available to the clinician. HIV-infected patients should be commenced on chemoprophylaxis when there is evidence of marked immunodeficiency (CD4 count < 200/mm³, oral candidiasis or opportunistic infections and tumours). Cotrimoxazole is the most effective agent but is not tolerated long term by up to 50% of patients. Dapsone and nebulised pentamidine are also effective but the optimum dose and dosing frequency remain in doubt. Patients are still prone to other opportunistic infections as their survival is extended, and agents in the future with dual or triple activity against pneumocystis, toxoplasmosis and/or cryptosporidiosis are desired. Dapsone-pyrimethamine and the naphthoquinone 566C80 are already showing early promising results in pneumocystis and toxoplasmosis prophylaxis.

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At present no dosage recommendations for **acrivastine** in the US market have been approved. Consequently, on pages **929** (Dosage and Administration, line 2), **937** (section 5, lines 4 and 5), and **938** (first line, final paragraph) the recommended frequency of administration for acrivastine should be 3 times daily.

In the review of **celiprolol** the following corrections should be made:

Page 955: Table III, in the Kajiyama et al. (1990) study the change in total cholesterol should read ↓ 6.8.

Page 962: Table V, in the Taniguichi et al. (1990) trial the study duration was 2 weeks, and in the Yui et al. (1990) clinical trial exercise tolerance was not reported and C = A should be deleted.

Page 966: The Herrman et al. (1988b) study was published in *Münchener Medizinische Wochenschrift*.