Update on AIDS

Since AIDS (acquired immunodeficiency syndrome) was last reviewed in this journal in 1987,* promising new antiviral agents have reached an advanced stage of development, and candidate vaccines directed against HIV (human immunodeficiency virus) have now entered into preliminary clinical studies. At the same time, more experience has been gained in the use of zidovudine (formerly azidothymidine, AZT) which, as yet, remains the only antiviral agent with activity against HIV that has been released for general use. Significant progress has also been made in the treatment and prevention of some of the specific life-threatening infections caused either by pathogenic or opportunistic organisms to which immunocompromised patients are particularly vulnerable.

Just as intractable as the scientific challenge posed by the advent of AIDS is the economic challenge of providing the drugs used in its management at a price that will bring them within the reach of everyone in need. The evolution of the pandemic has attained dramatic proportions. As more effective means of prevention and treatment become available, resources must be found to satisfy the need for the resulting products wherever they are required, and this must be achieved in a way that preserves incentive within the pharmaceutical industry for continued research. Failure in this will frustrate any prospect of bringing the disease under effective control. Meanwhile, everyone involved needs to understand the scope and limitations of current therapy and appreciate what remains to be achieved. The following account is concerned both with the treatment of the underlying HIV infection and the management of infections characteristic of AIDS.

HIV infection

Pathological aspects

Although the longer-term outlook remains unknown, infection with the human immunodeficiency virus (HIV) can be compatible with prolonged survival, with or without medical intervention. The latent period may be as short as 2 years or — as current projections indicate — as long as 2 decades. Sooner or later, however, AIDS is the ultimate clinical expression of the disease. Subsequently, virtually every organ system can be affected, either as a result of opportunistic or other infections that supervene as the immune system becomes progressively impaired, or from less clearly understood cytopathic and malignant changes. In infants infected at birth the course of the disease is more rapid. One in four develops AIDS within the first year of life and 80% have signs of the disease within 5 years.

HIV is a retrovirus which is transmitted through sexual contact, inoculation of infected blood or blood products, use of contaminated needles and vertical transmission from mother to offspring. Once in the bloodstream, the virus enters several types of cells including lymphocytes, macrophages, Langerhans cells, and neurones within the central nervous system. The prime targets, however, are a subset of helper/inducer T-lymphocytes and their precursors, which are distinguished phenotypically by the CD4+ epitope expressed on their surface. These loci are receptors in the outer envelope of the viral coat with affinity for glycoproteins and they provide the entry points for the virus to penetrate the cell. Once in the cell, the virus releases RNA which is transcribed by one of its enzymes, reverse transcriptase, into DNA. This, in part, becomes integrated into the cell's chromosome. When activated, this DNA sequence is transcribed back into viral RNA which provides the template on which new virus particles are assembled.

Not until the virus has used the chromosomal apparatus in this way to multiply does it induce lethal cytopathic changes in the host cell. Initially, the CD4+ count in the peripheral blood is maintained within normal limits. Subsequently, the count decreases either progressively or erratically as the viral load within the body increases. The factors that determine the rate of replication are unknown, but there is speculation that mycoplasmas and other opportunistic organisms may influence the process. When the count falls below 200/mm^3 — that is, less than 50% of the lower normal limit — the incidence of serious opportunistic infections rises sharply, apparently as a result of impaired responses of CD4+ cells both to soluble protein antigens and to cell-mediated stimulation.

Clinical aspects

Seroconversion is sometimes signalled by an acute febrile illness that is readily mistaken for acute viral mononucleosis. Malaise, headache, photophobia,

* *WHO Drug Information*, Volume 1, No. 2 (1987).

sore throat, gastrointestinal disturbances, cutaneous eruptions, arthralgia and myalgia are characteristic complaints which, in some cases, are accompanied by transient signs of meningitis, encephalitis or peripheral neuropathy.

Later, before clinical manifestations of AIDS supervene, diffuse lymph node enlargement sometimes accompanied by thrombocytopenia, may occur. The histological picture of follicular lymphoid hyperplasia is distinctive since, whereas other forms of lymphocytes are activated, the paracortical CD4+ cells are depleted. Later, as the immune system is overwhelmed, the follicles involute and the nodes become atrophic. During this phase some patients develop an illness that has become known as AIDS-related complex. Typically, they complain of fevers, night sweats, diarrhoea and muscle pains. They lose weight and non-specific skin rashes may be troublesome. White and red cell counts tend to fall and thrombocytopenic purpura can occur. Oral candidiasis or herpes zoster may supervene, but at this stage opportunistic infections are unlikely to be life-threatening.

Ultimately, AIDS is heralded either by serious opportunistic infections, or — particularly in the case of sexually-active homosexual men — by malignant disease, including lymphomas and, more specifically, by a prolific and virtually pathognomonic form of Kaposi's sarcoma. The syndrome, which was described before the HIV virus had been identified, was used to denote patients immunodeficient from an unknown cause who presented with one of these conditions. The term remains indelible in the public mind but, for scientific purposes, it has been superseded by detailed staging classifications of HIV infection (1, 2) which provide useful criteria for selecting or stratifying patients admitted to clinical trials.

Ninety per cent of HIV-infected patients eventually die from supervening infection. They have increased susceptibility to systemic infections that are prevalent within the population at large as well as to opportunistic infections that develop only in immunodeficient individuals. The former, which are typified by tuberculosis, oral candidiasis and herpes infections tend to occur earlier in the course of the disease than more strictly opportunistic infections such as pneumocystis pneumonia, cryptococcal meningitis, and more variable manifestations of systemic disease attributed to infection with cryptosporidium species, cytomegalovirus, *Mycobacterium avium-intracellulare* and toxoplasmosis. Pending the possibility of reversing the underlying immunological defect, prevention and treatment of these infections provides the most effective means of prolonging and improving the quality of life of patients with HIV infection.

Antiviral therapy

As yet, zidovudine remains the only antiviral agent that has been shown in clinical trials to slow the progression of HIV infection and to prolong survival in patients with AIDS. However, it is myelosuppressive and many patients become refractory to its beneficial effects during prolonged therapy. Alternative agents —notably dideoxyinosine and dideoxycitidine—which appear to have a different profile of toxicity, are currently under evaluation. Each of these compounds is a nucleoside analogue that is converted by cellular thymidine kinase and other intracellular enzymes into an active phosphorylated form that prevents viral DNA synthesis by displacing viral RNA from reverse transcriptase. Zidovudine is incorporated into viral DNA by dose-related competitive blockade of the uptake of thymidine into retroviral DNA. Once in place, zidovudine prevents extension of the chain by precluding further phosphodiester linkages. In patients, this antiviral effect is accompanied by an increase in CD4+ lymphocyte counts and an improvement in immune status.

In vitro, zidovudine in therapeutic concentrations has been shown reversibly to reduce the rate of replication of HIV in human lymphocytes and to attenuate its cytopathic effects on the cells. It is most effective when it is added before or shortly after the lymphocytes are inoculated with the virus and its action slowly diminishes with time. Varying degrees of synergism have been demonstrated in inoculated cultures of various cell lines between zidovudine and other substances with either antiviral or immunomodulating activity, including aciclovir, amphotericin B methyl ester, ditiocarb sodium, foscarnet, granulocyte-macrophage colony-stimulating factor, inosine pranobex and interferons. As yet, none of these combinations has been introduced into routine clinical practice, although there is some evidence that both ditiocarb sodium and inosine pranobex inhibit the progression of HIV infection in a clinical context. More information needs to be obtained on the relevance of various putative surrogate markers before such treatments can be compared efficiently and reliably in a clinical context. The CD4+ count has been most widely used to predict the risk of mortality and neoplasia, but

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immunological variables, including HIV p24 antigen and antibody, beta$_2$ microglobulin, and neopterin may also be of value.

Treatment of AIDS and AIDS-related complex

Early clinical studies of orally-administered zidovudine, 1000 to 1500 mg taken in divided dosage at 4-hour intervals throughout the day, showed that sustained treatment can extend survival in patients who have advanced AIDS-related complex or who have survived at least one episode of pneumocystis pneumonia. Treated patients felt subjectively improved, they gained weight, they had fewer opportunistic infections and, in some cases, AIDS-related dementia and other neurological changes were ameliorated. Kaposi's lesions, in contrast, were largely or completely resistant to treatment, particularly among patients with a previous history of opportunistic infection.

However, it became apparent that the beneficial effects of this treatment were compromised in two important respects. Many patients were intolerant of zidovudine at these dosages and others began to relapse after some six months of sustained therapy. Myelosuppression — which may reflect a high affinity between zidovudine and DNA polymerase in myeloid stem cells — and a dose-dependent chronic myopathy often forced withdrawal of treatment or a reduction in dosage within a few weeks. The most severely ill patients with greatly reduced CD4+ counts were most vulnerable to severe neutropenia and, overall, some 30 per cent of treated patients required blood transfusion.

More recently, evidence has been presented that the dose of zidovudine can be lowered to 500 – 600 mg daily without apparent loss of efficacy and with substantial reduction in toxicity. There are indications that this dosage schedule is most beneficial and better tolerated in younger patients who are relatively fit at the outset but, as yet, there is no certainty that it ameliorates neurological dysfunction. Use of a low maintenance dose has already been endorsed by the United States Food and Drug Administration, but not, as yet, by some European regulatory authorities. It is generally agreed, however, that to avoid a transient increase in HIV antigen levels at the outset of treatment, the higher dose should be used initially.

Suppressive treatment in HIV-positive individuals

Interest is currently focused on the potential of suppressive lower-dose therapy in HIV-positive patients with few or no symptoms. Preliminary evidence suggests that low-dose zidovudine can slow the rate of progression to AIDS in addition to averting the risk of myopathy and reducing the incidence of myelosuppression. However, as yet, no asymptomatic subjects have been followed for more than 2 years. Long-term studies currently in progress will need to be completed before it is known how long suppressive therapy at this dosage remains effective, what effect — if any — it may have on survival, and whether it engenders significant toxicity or accelerates the emergence of viral resistance. While these uncertainties prevail many commentators consider it unwarranted to encourage widespread use of zidovudine among symptom-free patients.

Prophylactic use

Zidovudine, administered immediately after exposure, is claimed to suppress retroviral infections in animals. In view of this, the practice has developed in many health care institutions to offer staff a prophylactic course of zidovudine — typically, 250 mg four times daily for 6 weeks — immediately after they sustain a puncture wound from a potentially contaminated needle. Victims of rape are also sometimes offered this option. However, cases of failed prophylaxis are already on record. Moreover, since the rate of seroconversion following needle injury has been estimated to be less than 0.5%, a definitive assessment of the degree of any protection that may be provided will need to be based on a considerable body of experience. In the present uncertainty, prophylaxis should be offered only when the patient has been informed of the risk of infection, the rationale of administering zidovudine, and the state of knowledge on the short- and long-term toxicity of the drug.

Use in children

Relatively little experience has as yet been gained in the use of zidovudine in children, but it has been used prophylactically in neonates born to infected mothers, and to treat children clinically infected as a result of vertical transmission, blood transfusion or administration of contaminated factor VIII or other blood products. As yet, the optimal dosage, route and frequency have not been determined. The regimens used have been roughly proportionate to those recommended for adults and the same problems have been encountered with adverse effects and dose-related toxicity.

Potential developments in treatment

It has been reported that zidovudine-resistant strains of HIV have thus far remained susceptible *in vitro* to dideoxycytidine and dideoxyinosine, which differ from zidovudine in their adverse effects and, in particular,

seem less likely to induce myelosuppression. Should they become generally available, they will offer scope for combined or sequential treatment regimens that may inhibit the development of resistance and enable dosage requirements of each of the constituents to be reduced. Meanwhile, adjunctive use of granulocyte-macrophage colony-stimulating factor and erythropoietin is being explored as a means of reducing bone marrow suppression and lessening current dependence upon transfusions among vulnerable patients, while zidovudine in combination with interferon alfa is being assessed in the treatment of Kaposi's lesions.

ZIDOVUDINE

Group: antiviral agent
capsules 100 mg
paediatric syrup 50 mg/5 ml
concentrate for intravenous infusion: 10 mg/ml

General information

Zidovudine is a thymidine analogue which is phosphorylated in the body to an active form which inhibits intracellular replication of HIV by serving as a competitive antagonist of reverse transcriptase, an enzyme specific to this retrovirus. It does not cure HIV infection, but it reduces the rate of progression of AIDS to an extent that can usefully prolong survival.

In the absence of fatty foods or of diffuse gastrointestinal pathology it is rapidly absorbed when given by mouth. Substantial amounts are metabolized during the first pass through the liver to a glucuronide that has no antiviral activity. Zidovudine is not highly protein bound and it penetrates readily into the central nervous system. It is excreted in the urine partly unchanged but largely as the glucuronide which is eliminated both by glomerular filtration and active secretion into the renal tubules. It has a short half-life of 1 to 1.5 hours. In order to sustain the viral inhibitory concentration of 1 µmol/l in the plasma throughout the day, the daily therapeutic requirement needs to be taken in divided doses at 4-hour intervals. As a means of reducing dosage, initial studies indicate that probenecid reduces the rate of excretion of zidovudine. However, the possible toxicity of probenecid given long-term to HIV-infected patients is as yet unknown.
Zidovudine enters HIV-infected T-lymphocytes both by diffusion and through an active transport mechanism serving nucleosides. Within the cellular cytoplasm it is enzymatically phosphorylated to a form that acts as a substrate for, and an inhibitor of, viral reverse transcriptase. Its myelosuppressive effects may result from interference with the intracellular phosphorylating mechanism and consequent depletion of the essential nucleoside deoxythymidine triphosphate.

Clinical information

Uses

Management of patients with serious manifestations of AIDS or AIDS-related complex.

In settings that must still be regarded as essentially exploratory, zidovudine has more recently been used with a view to:

- suppressing or reducing impairment of immune function in patients with asymptomatic HIV infection.
- protecting health workers and others accidentally exposed to risk of HIV infection.

Dosage and administration

Treatment

Adults: Induction should be accomplished with a dose of 200 mg every 4 hours for 4 weeks. Lower doses (100 mg every 4 hours) administered subsequently have been claimed to be equally effective and less likely to induce toxic effects, particularly in patients with advanced disease.

Children: 180 mg/m^2 of body surface area (maximum 200 mg) every 6 hours. Because of prolonged presence of maternal antibody, confirmatory tests of infection including p24 antigen or viral culture are recommended before beginning zidovudine therapy in children aged less than 15 months.

The objective is to maintain the plasma drug concentration between 0.6 and 1.0 µmol/l. This requires frequent, regular dosing which is ideally achieved in very young children by continuous intravenous infusion, a technique which is practicable only when an indwelling intravenous catheter can be inserted and when portable infusion pumps suitable for home use are available.

These regimens temporarily reduce the incidence of serious opportunistic infections and the rate of decrease in the CD4+ lymphocyte cell count. Pre-existing thrombocytopenia may also be reduced. Zidovudine, by itself, appears to have little, if any, effect on the progression of Kaposi's lesions, but promising responses have been obtained when it has been given in low dosage together with interferon alfa (5 to 10 million IU daily).

Suppressive therapy in asymptomatic patients

Relatively low doses (500 to 600 mg daily for adults) are currently under investigation in asymptomatic patients with a view to preventing or delaying progression to AIDS. As yet, the optimal time to start zidovudine therapy is unknown. Preliminary reports of the development of resistant strains of HIV during prolonged therapy and of increased numbers of opportunistic infections in patients treated for more than one year, suggest that prolonged monotherapy may not constitute a satisfactory approach to treatment.

Prophylaxis in patients accidentally exposed to risk

Dosages ranging between 1200 and 1500 mg daily have been administered empirically for periods of 1 to 6 weeks. Every effort must be made to institute therapy as soon as possible after exposure.

Contraindications

Known hypersensitivity to zidovudine.

Zidovudine should not be administered to patients with a neutrophil count lower than 7500/mm^3 or a haemoglobin concentration less than 7.5 g/100 ml. Should readings fall below these threshold values during treatment, therapy should be suspended until they are exceeded and then restarted at half the previous dosage. After 2–4 weeks the dose may be gradually increased to the initial level.

Precautions

Patients must always understand that use of zidovudine does not reduce the risk of transmission of the disease.

Capsules should always be taken with liberal amounts of water. Night-time doses, in particular, have sometimes induced oesophageal ulceration.

Accumulation sufficient to induce toxicity may occur in patients with renal or hepatic impairment.

The frequency of anaemia and neutropenia resulting from bone marrow suppression has been considerably reduced by the introduction of lower dosage schedules. Suppression sufficient to warrant transfusion, dosage reduction or drug withdrawal has been estimated to occur in only some 3% of asymptomatic patients receiving 500 mg zidovudine daily. Regular monitoring of the blood count should be sustained, however, for as long as treatment is continued. Patients with conditions that reduce the bone marrow reserve, and particularly disseminated *Mycobacterium avium-intracellulare* infections, are at particular risk of haemotoxicity. Vitamin B_{12} deficiency has also been identified as a risk factor for myelosup-pression, but the administration of supplements has not been found to offer therapeutic advantage. Preliminary results suggest that recombinant human erythropoietin may reduce the risk of myelosuppression among patients with reduced levels of endogenous erythropoietin.

Chronic myopathy is a well-recognized complication of HIV infection. Its incidence has increased with the introduction of zidovudine and it is estimated to have developed in as many as 20% of patients who received high doses of the drug for one year or more. Monitoring of plasma lactate dehydrogenase has provided warning of the need to discontinue treatment before clinical signs of myopathy develop, but the risk seems to be remote with the lower-dosage regimens.

Use in pregnancy and during lactation

Sufficient data are not as yet available to establish safety on the basis of clinical experience. No teratogenic or embryopathic potential has been demonstrated in animal studies but it has shown mutagenic activity in some *in vitro* models. Since the HIV virus can pass the placental barrier in the early phases of gestation, and because it is present in cervical secretions, protective therapy has been recommended throughout pregnancy in women found to be infected. Case histories have been presented to indicate that zidovudine administered throughout pregnancy is tolerated reasonably well by both the mother and the infant. However, further information is needed on the fetal toxicity of zidovudine and on its efficacy in protecting against the vertical transmission of HIV.

It is not known whether zidovudine is excreted in breast milk. It is currently recommended in some highly developed countries that lactating mothers receiving zidovudine should not breast-feed. It would be premature to promulgate this advice in developing countries where bottle feeding is associated with a high risk of infection, until more information is available on any possible risk of zidovudine toxicity or transmission of HIV resulting from breast-feeding.

Drug interactions

Concurrent use of antimicrobials and other drugs that have a myelosuppressive or nephrotoxic effect should be avoided whenever this is practicable. These include folate antagonists (including pyrimethamine, sulfadoxine, trimethoprim/sulfamethoxazole), amphotericin B, dapsone, doxorubicin, flucytosine, ganciclovir, ribavirin, vincristine and vinblastine.

Concurrent administration of methadone, used in the treatment of addiction to narcotic drugs, may also increase the risk of zidovudine myelotoxicity.

The use of interferon alfa in combination with zidovudine might also be expected to increase the risk of myelotoxicity. Such potentiation has not been evident, however, with low-dose zidovudine regimens, and trials of combinations of the two drugs are now in progress with a view to enhancing efficacy and perhaps delaying the development of zidovudine resistance.

Compounds that compete with zidovudine as a substrate for hepatic glucuronidation should also be administered with caution. These include morphine, nonsteroidal anti-inflammatory agents and paracetamol. Prolonged use of paracetamol, in particular, can raise plasma zidovudine concentrations to an extent that might induce dose-related toxicity. However, concurrent administration of probenecid, which is also metabolized in this way and which also decreases the renal excretion of zidovudine, is being investigated as a possible means of reducing current dosage requirements.

Adverse effects

In addition to the effects described above under precautions, headache, nausea, insomnia, and myalgia have been reported more frequently among patients receiving zidovudine than among controls. Other, less common but more serious reported events include myopathy, peripheral neuropathy, and seizures.

Hypersensitivity to zidovudine has occasionally been reported which, in some cases, has responded to attempts at desensitization.

Macrocytic anaemia, which is generally mild and distinct from the potentially severe and more frequent myelosuppressive changes, sometimes appears within a few weeks of starting therapy.

Vaginal tumours, including carcinomas, have been demonstrated in rodents that have received zidovudine over long periods in amounts comparable to the high-dose clinical regimen. The relevance of these findings to patients remains uncertain.

Overdosage

No data are available on the consequences of acute overdosage. Patients with evidence of toxicity should be given supportive care.

Storage

Capsules should be stored in tightly-closed containers, protected from light.

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Associated infections

Infectious diseases constitute the immediate cause of death in 90 per cent of patients with advanced HIV infection. Some are caused by common pathogenic microbes, but many are opportunistic, meaning that they are caused by normally avirulent members of the commensal flora. Knowledge of these is incomplete and new forms of opportunistic infection attributed to previously unrecognized and uncharacterized microbes are still being discovered.

The incidence and spectrum of these infections is different in important respects from those associated with other immunosuppressive disorders. Whereas all immunocompromised patients are vulnerable to toxoplasma encephalitis, oral candidiasis and pulmonary tuberculosis, many opportunistic diseases including *Pneumocystis carinii* pneumonia and systemic infections due to *Cryptococcus neoformans,* cytomegalovirus, *M. avium-intracellulare* and *Cryptosporidia* have, thus far, occurred almost exclusively in HIV-infected persons. The pattern of infection also varies between developed and developing countries. In some African countries as many as 50%of patients with AIDS also have active tuberculosis. In contrast, pneumocystis pneumonia is less frequent in these countries, apparently because many patients die before their immune defences are severely attenuated.

Limited information from controlled clinical studies suggests that regular administration of zidovudine reduces the incidence of opportunistic infections in patients with AIDS. It may also accelerate the rate of response to specific therapy. However, this benefit may be time-limited, since there are indications that these effects begin to wane among patients who have received zidovudine for more than a year. Moreover, since both zidovudine and some of the antimicrobials used to treat opportunistic infections are myelosuppressive, the blood count must be monitored with particular care during combined therapy. Since withdrawal of zidovudine may accelerate the rate of HIV replication, reduction of dosage is often preferable to temporary discontinuation.

This account describes the typical clinical course of the more common infections. However, atypical presentations are frequent, disseminated disease is common, and two or more infections often occur concurrently.

Respiratory disease

From an early stage, HIV-infected patients are unduly vulnerable to common pathogens of the respiratory tract including influenza viruses, pneumococci, *Haemophilus influenzae* and legionella. As immunological function continues to deteriorate, they also become susceptible to tuberculosis, atypical mycobacteria and systemic mycoses. Ultimately, as the underlying disease advances, pneumocystis pneumonia becomes the main cause of death.

Pneumocystis pneumonia

Pneumocystis carinii is a protozoan that normally exists in the lungs as a commensal. Before the AIDS pandemic, it was rarely implicated as a human pathogen. However, more than 80 per cent of patients with AIDS experience at least one episode of pneumocystis pneumonia and it is the most frequent initial manifestation of the syndrome. Rapid multiplication of the organisms in small cystic foci in the alveolar septal walls throughout the lungs rapidly induces an irreversible fibrotic reaction. Despite earlier diagnosis of the disease and important advances in treatment and prophylactic management, it still causes more deaths than any other opportunistic infection.

The first signs of the disease often develop insidiously and are easily missed. Patients known to be at risk should be urged to report increasing shortness of breath or cough promptly. Chest X-rays sometimes reveal extensive infiltration, nodules or cavities, but at first presentation they may be misleadingly normal. Whenever practicable, attempts should be made to identify the organism which may be demonstrable in specially prepared sputum smears or in washings obtained during bronchoalveolar lavage.

Treatment

Oral or intravenous trimethoprim/sulfamethoxazole or intravenous infusions of pentamidine isetionate are often effective when administered at an early stage. Signs of improvement may not be evident for 7–10 days and treatment needs to be maintained, whenever possible, for at least 3 weeks. Both pentamidine and trimethoprim/sulfamethoxazole are associated with a particularly high incidence of toxic effects in AIDS patients and the latter, like zidovudine, is myelosuppressive.

When no improvement is evident after 10 days it is justifiable either to switch to the other drug or even to administer both concurrently. Additional candidate drugs are currently under assessment. Limited, but promising experience has recently been gained with eflornithine, a trypanosomicide that inhibits ornithine metabolism, and trimetrexate, a lipid-soluble analogue of methotrexate, which is a potent inhibitor of pneumocystis dihydrofolate reductase.

The first few days of antimicrobial treatment are critical since the degradation of many dead parasites exacerbates the pre-existing inflammatory process and aggravates hypoxia. However, immediate mortality can be substantially reduced if corticosteroids — either oral prednisolone or, when necessary, intravenous methylprednisolone — are administered as soon as antimicrobial therapy is started to patients with an arterial oxygen tension of less than 70 mm Hg. Oral prednisolone at a dose of 40 mg twice daily for 5 days, followed by 40 mg daily for 5 days, and then 20

mg daily for ten days has not demonstrably increased the vulnerability of patients to other opportunistic infections, with the possible exception of candidiasis and herpes simplex.

Prophylaxis

Ideally, every patient who has been successfully treated, or who has a CD4+ lymphocyte count of less than 200/mm^3, should receive continuous prophylaxis. Various estimates place the 3-month relapse rate among untreated patients between 10 and 40%, of which about 1 in 5 episodes are fatal.

Until recently, reliance was vested largely in trimethoprim/sulfamethoxazole and pyrimethamine/sulfadoxine but these were poorly tolerated by many patients. Intravenous pentamidine is too toxic to be used prophylactically. However, the development of an aerosol formulation of pentamidine, which is inhaled into the lungs, has eliminated much of the systemic toxicity associated with its use and monthly inhalations have been shown to reduce the risk of re-infection substantially. Unfortunately, widespread use of aerosolized pentamidine has been accompanied by a rise in extrapulmonary *P. carinii* infection. More recently, concern has been expressed that resistance to antimicrobial agents may be emerging in *P. carinii* isolates or that they may be developing virulence factors that enable them to cause disease in the elderly and other new patient populations.

Pulmonary tuberculosis

There are indications of a resurgence of tuberculosis everywhere where AIDS is prevalent and, among patients with advanced HIV infection, the disease causes substantial mortality. The initial signs of the disease may become apparent at any time during the evolution of HIV infection. About half the cases present with extrapulmonary disease and pulmonary lesions are often atypical. Unilateral or bilateral infiltrates in the lower lobes are more common than upper lobe lesions and cavities.

There is no evidence, as yet, of atypical patterns of antibiotic resistance in *M. tuberculosis* isolates from AIDS patients. Limited retrospective data (1) generated in the USA suggest that rates of treatment failure and relapse following standard antituberculous therapy are comparable to those prevailing in the population at large, although the incidence of adverse reactions may be substantially higher. Among patients who comply with the prescribed regimen, conventional therapy results in rapid sterilization of sputum, radiographic improvement, and low rates of relapse. Treatment is usually started with isoniazid, rifampicin and pyrazinamide. To prevent relapse, many clinicians strive to continue treatment indefinitely unless this is precluded by drug toxicity. Studies are also currently in hand to assess the potential of various regimens in primary preventive chemotherapy.

1. WHO Model Prescribing Information. *Drugs Used in Mycobacterial Diseases.* World Health Organization, Geneva, 1991.

Histoplasmosis and coccidioidomycosis

In regions where the causative organisms, *Histoplasma capsulatum* and *Coccidioides immitis*, are endemic, patients with HIV infection are at risk of developing disseminated fungal disease. In otherwise healthy persons such infections are either subclinical or self-limiting within the lungs.

The initial symptoms are often non-specific, but pulmonary involvement characterized by cough, fever, malaise and weight loss — and confirmed by radiological evidence of pulmonary interstitial infiltrates — can be prominent. Nausea, vomiting and diarrhoea are common. Haematogenous dissemination ultimately results in terminal septic shock. Diagnosis is dependent upon demonstration of the organism in bronchoalveolar washings, biopsy material or positive cultures from blood or bone marrow. In severely ill patients, however, initiation of treatment is warranted on the clinical findings and a positive serum antibody test.

Amphotericin B in a total dose of 2 to 3 g has so far provided the only prospect of clinical improvement. To reduce the risk of immediate relapse, ketoconazole or lower dosages of amphotericin B need to be maintained indefinitely.

Neurological disorders

As many as 20% of HIV-infected patients develop neurological complications. Some of these apparently result from a direct encephalitic effect of the HIV virus. Others are due to neoplastic lesions, notably lymphomas. Most, however, result from opportunistic infections. Toxoplasma encephalitis accounts for most focal lesions, while cytomegalovirus and herpes simplex are relatively rarely implicated. Life-threatening meningitis is usually due to *Cryptococcus neoformans* and only very occasionally to coccidioidomycosis or tuberculoma.

Toxoplasmosis

Toxoplasma gondii, a protozoan parasite of mammals, is transmitted when oocysts, excreted by household pets or present in undercooked meat, are ingested. Invasive forms enter the bloodstream to reach the brain, heart and lungs where they form cystic aggregates that remain latent but subject to reactivation throughout the life of the host. In many communities most people have been infected by early adulthood, but otherwise healthy persons do not develop clinically evident disease. In HIV-infected patients, however, toxoplasmosis holds serious implications:

- Primary infection may result in focal necrotizing encephalitis and occasionally retinochoroiditis and pneumonitis as a result of unconstrained multiplication of tachyzoites.

- Reactivation of latent bradyzoites produces focal neurological signs in some 30% of patients with AIDS. Hemiparesis, cognitive disorders, seizures and other signs suggestive of an intracerebral space-occupying lesion tend to develop subacutely over several weeks, and they are sometimes accompanied by symptoms of a diffuse encephalopathy. Fever and headache can be prominent. Meningeal irritation is infrequent. Changes in the cerebrospinal fluid are usually non-specific.

- Congenital transmission can occur either as a consequence of a previously established latent infection or of a new primary infection in the mother. In many instances this induces spontaneous abortion or fetal death. Children born with signs of infection are generally severely ill, often with a potentially fatal syndrome characterized by hydrocephalus, hepatosplenomegaly with jaundice, mental retardation and chorioretinitis. Congenital disease that only becomes apparent later in life is usually less severe, but ocular or neurological impairment is common (1).

Prevention

The risk of transmission can be reduced if meat is adequately cooked and if vegetables and fruit are washed carefully before they are eaten.

Treatment of toxoplasmic encephalitis

A histopathological diagnosis should be established whenever possible since non-infective conditions including lymphoma, Kaposi's sarcoma and multifocal leukoencephalopathy may also cause focal neurological lesions. Serological tests are of limited value and culture of organisms from biopsy material may take several weeks. Often, treatment has to be started empirically, sometimes on the basis of tomograms showing multiple discrete lesions within the brain typically arranged in ring formation.

All HIV-infected patients, including pregnant women, suspected of having active toxoplasmosis should receive pyrimethamine in combination with a sulfonamide (usually sulfadiazine). Both drugs penetrate into the cerebrospinal fluid in therapeutically-active concentrations. Relatively high dosages need to be given, despite the patients' vulnerability to adverse effects and the inability of many of them to tolerate treatment for more than 6 weeks. Leukopenia, thrombocytopenia, fever and rash are common. Calcium folinate, which counteracts the blockade of folate metabolism in mammalian cells without affecting antiprotozoal activity, should be administered every third day to reduce the risk of anaemia. Patients should also remain well hydrated since sulfadiazine is poorly soluble in the urine.

Pyrimethamine has been used alone in patients intolerant of sulfonamides at dosages several times higher than those normally recommended. The incidence of adverse effects at these dosages, and particularly of myelosuppression, has not been fully assessed. Intravenous clindamycin has also been used in these circumstances. However, whereas it is effective in the treatment of chorioretinitis, its value in toxoplasmic encephalitis remains uncertain.

Because of the severity of the condition and the high rate of recurrence, suppressive therapy with lower daily dosages of pyrimethamine and sulfadiazine should be continued indefinitely after successful primary treatment whenever this is feasible.

Cryptococcal meningitis

Cryptococcus neoformans, a yeast-like fungus widely present in soil and, in greater concentrations, in bird excreta, causes disseminated disease in about 5% of persons with advanced HIV infection. It readily spreads from the lungs to the meninges (causing cryptococcomas) — and, less commonly, to the bone marrow, the genitourinary tract and the skin.

The onset of cryptococcal meningitis is generally insidious. Fever and headache are often the only presenting signs. Nausea, vomiting and neck stiff-

1. A discussion of the treatment of congenital toxoplasmosis is contained in WHO Model Prescribing Information. *Drugs Used in Parasitic Diseases*. World Health Organization, Geneva, 1990.

ness may be absent and focal neurological signs are uncommon. Sometimes there are no signs directly referable to the nervous system. Typical extraneural manifestations include skin lesions, pneumonitis and pleural effusion and retinitis. Untreated, the disease runs a slowly progressive and ultimately fatal course. Early diagnosis is usually dependent upon demonstration of cryptococcal antigen in the serum or culture of cryptococci from the cerebrospinal fluid.

Treatment

All patients from whom cryptococci are isolated should be treated, even if they have no signs of infection, because of the high risk of meningitis and disseminated disease. Amphotericin B infused intravenously at a daily dose of 0.5 to 1 mg/kg has, until recently, offered the only prospect of cure. Administration must be maintained for at least 6 weeks and until cultures of cerebrospinal fluid have been negative for 4 weeks. At this dosage the drug may induce chills, fever or renal dysfunction, but premature withdrawal of treatment is rarely necessary. However, failure rates are high and relapses are frequent unless weekly infusions can be maintained indefinitely.

Preliminary results suggest that fluconazole, itraconazole and other orally-active triazole antifungal agents may be comparably effective both in treatment and prophylaxis. The results of one recent study suggest that fluconazole is both similarly effective and better tolerated than amphotericin B.

Ophthalmological complications

The HIV virus itself may occasionally induce retinal haemorrhage and optic neuropathy. In other cases, Kaposi's sarcoma may spread to involve the conjunctivae, the eyelids and the orbit. However, vision is more frequently compromised by infections due to cytomegalovirus and, less frequently, *Toxoplasma gondii* or *Pneumocystis carinii.*

Cytomegalovirus

Asymptomatic cytomegalovirus infections, which are widespread in most communities, are transmitted congenitally, by sexual contact or by blood transfusion. In HIV-infected patients the organism is a cause of retinochoroiditis, enteritis and pneumonitis and it is often present, together with *Mycobacterium avium-intracellulare* and Epstein-Barr virus, in patients in a state of advanced cachexia.

Nearly all cases of chorioretinitis in HIV-infected patients are caused by cytomegalovirus. The visual loss is progressive and irreversible. Flame-shaped intraretinal haemorrhages superimposed on white granular necrotic patches are seen in the fundi.

Parenteral antiviral therapy with ganciclovir usually arrests progression of retinochoroiditis and cytomegalovirus enteritis, but pulmonary infection is often less responsive. Therapy must be sustained if prompt relapse is to be averted but, because ganciclovir is myelosuppressive, this can be impracticable. Foscarnet has been used as an alternative in this situation.

Febrile illness

Unexplained fever occurs frequently in HIV-infected patients. Diagnosis should be directed primarily to identifying pathogens that can be effectively treated, notably *Pneumocystis carinii,* salmonella, cytomegalovirus and *Mycobacterium tuberculosis.*

Mycobacteria

Any of the known pathogenic mycobacteria can induce infections in HIV-infected patients. In North America *Mycobacterium avium-intracellulare* is most commonly implicated, while in Africa, tuberculosis is relatively more common within this population of patients.

Infection due to *M. avium-intracellulare,* which can be isolated from a large proportion of patients with advanced HIV infection, may contribute substantially to the weight loss, inanition, fever and diarrhoea that typify the disease. Acid-fast bacilli may be present in large numbers without inciting a granulomatous reaction and focal lesions can occur in virtually any organ system.

Treatment

M. tuberculosis can usually be differentiated from atypical mycobacteria by skilled examination of sputum smears. However, identification of atypical mycobacteria in clinical isolates does not necessarily establish their clinical relevance. Other pathogens should be sought when the diagnosis remains in doubt. It is important, none the less, to start treatment promptly and to revise it, if necessary, in the light of subsequent microbiological evidence.

M. avium-intracellulare is usually susceptible, *in vitro,* to clofazimine, cycloserine and ethionamide. Clofazimine is generally preferred to treat disseminated disease since it is selectively concentrated in the bone marrow and the reticuloendothelial system. It is often administered in combination with rifampicin.

However, the effect of treatment on morbidity and survival time remains uncertain.

Diarrhoeal disease

Symptoms of colitis or small-bowel watery diarrhoea are common among HIV-infected patients. When they are severe they constitute the most distressing manifestation of the disease. Small bowel diarrhoea can result from extensive Kaposi's lesions and sometimes from the cytopathic effect of the HIV virus. However, most cases result from bacterial, protozoan or helminthic colonization. Some of these organisms, including cryptosporidia, cytomegalovirus, *Mycobacterium avium-intracellulare*, and *Isosporum belli* cause diarrhoea almost exclusively in patients with HIV infection. Others, including *Giardia intestinalis*, *Entamoeba histolytica*, *Helicobacter*, shigella and salmonella commonly cause intestinal disease in homosexual men. In immunosuppressed patients some of these organisms, particularly salmonellae, are liable to cause disseminated disease.

Whenever possible, the cause of the diarrhoea should be established and specific treatment provided. Failing this, management is symptomatic. High caloric and protein intake reduces the degree of muscle wasting. Megestrol (a synthetic progestogen) is sometimes used to stimulate appetite. The use of antidiarrhoeal agents such as codeine phosphate is justified when symptomatic relief is the major consideration. The meperidine analogues, diphenoxylate and loperamide should not be used in ulcerative inflammatory bowel disease or in the management of acute diarrhoea in young children because of the danger of toxic dilatation of the colon.

Cryptosporidiosis

Cryptosporidia, long recognized as pathogenic protozoans in veterinary practice, have recently been identified as an important cause of persistent debilitating watery diarrhoea and weight loss in HIV-infected patients. Transmission, which occurs by the faecal–oral route, is particularly common among homosexual men and where sanitation is inadequate. The small bowel is extensively colonized and invasion of the biliary tree occasionally results in stenosis and cholecystitis. The organisms can be demonstrated in the stools only in iodine-stained wet mounts and acid-fast stained smears.

Spiramycin is of some value, but the outcome is uncertain and gastrointestinal irritation can be severe. Dosages of 1 to 3 g daily have resulted in remission, but treatment may need to be extended for 4 months or more before organisms are cleared from the stools.

Isospora belli

The frequency with which the protozoan, *Isospora belli*, causes diarrhoea in HIV-infected patients varies in different countries. It can be demonstrated in the stools using the techniques developed for cryptosporidia. Most cases are readily treated with trimethoprim/sulfamethoxazole.

Cytomegalovirus

Cytomegalovirus is an uncommon but potentially lethal cause of diarrhoea in HIV-infected patients. Any portion of the intestine may be involved and intense inflammation may result in perforation or substantial haemorrhage. Diagnosis is confirmed by endoscopy and demonstration of inclusion bodies in a biopsy specimen.

Skin eruptions

Most patients with HIV infection develop dermatological conditions at some point in the course of the disease. A pathognomonic, highly proliferative form of Kaposi's sarcoma is often the first clinical manifestation of AIDS. Among the infectious diseases, candidiasis and, to a lesser extent, herpes zoster and herpes simplex have the highest prevalence. Staphylococcal and streptococcal diseases and scabies are also common. Drug-induced eruptions, which are also frequent, can create diagnostic problems.

Oral candidiasis

Candida albicans, a yeast that is a normal commensal in the microbial flora of the skin, the oral cavity and the vagina, commonly causes infection when immunological defences are suppressed by treatment or disease.

Oral candidiasis is frequently the first indication of immune impairment in HIV-infected patients. It is characterized by white sloughs covering areas of superficial ulceration on the gums, palate and tongue that contain many yeast organisms and that are readily detached. In severe cases these lesions extend into the lower pharynx and oesophagus to cause dysphagia, nausea and epigastric pain. Serious haemorrhage and even oesophageal perforation have occurred, but such complications are exceedingly rare.

Treatment

Mild infections confined to the oral cavity are often cleared temporarily by repeatedly painting the mucosal surfaces with a 1% aqueous solution of methylrosanilinium chloride (gentian violet) for several days. More extensive lesions are usually responsive either to the triazole antifungal agents clotrimazole or to nystatin tablets taken 4 times daily and retained in the mouth for as long as possible. Resistant cases may respond to amphotericin B lozenges. Since prompt relapse is almost inevitable, therapy needs to be maintained indefinitely.

Oesophageal candidiasis must be treated systemically. Ketoconazole is effective when oral therapy is practicable. Otherwise, amphotericin B or fluconazole must be administered by intravenous infusion. Fluconazole has also been reported to be effective in the treatment of serious candidal infections in other sites, including the lung, the peritoneum and the urinary tract.

Herpes simplex

Mucosal and cutaneous herpes simplex lesions occur commonly among HIV-infected patients. Disseminated infection has not been reported, but occasional cases of herpes encephalitis, meningitis, oesophagitis and pericarditis have been reported.

Superficial lesions usually respond to oral or parenteral aciclovir but, since the condition recurs within days or weeks of termination of treatment, maintenance therapy must subsequently be continued indefinitely. The emergence of resistance has recently been reported and a call has been made for screening procedures to monitor this trend.

Herpes zoster

Herpes zoster often supervenes months or even years before other opportunistic infections. In the later stages of HIV infection disseminated disease can occur.

Transient remission is sometimes induced by high doses of intravenous aciclovir. However, most cases resolve spontaneously and the efficacy of prolonged suppressive treatment has not been established. Treatment is consequently justified only when the disease is debilitating and there is a high risk of serious complications.

ACICLOVIR

Group: antiviral agent
tablet: 200 mg, 400 mg
powder for injection: 500 mg

Aciclovir is a synthetic purine nucleoside analogue with antiviral properties and is derived from guanine. It acts against herpes viruses by disrupting DNA synthesis and inhibiting viral replication. However, herpes simplex virus in immunocompromised patients is often resistant to aciclovir. Absorption from the gastrointestinal tract is variable and incomplete. It is widely distributed in tissues and body fluids and is excreted in the urine primarily unchanged.

Uses

- Treatment of severe primary genital herpes infections.
- Treatment of herpes simplex encephalitis.
- Treatment of disseminated herpes zoster.

Dosage and administration

Powder for injection should be reconstituted with 10–20 ml water for injection immediately before use. It should be administered by slow infusion over a period of one hour to avoid acute impairment of renal function.

Primary genital herpes:
5 mg/kg three times daily for 5 days.
Herpes simplex encephalitis:
10 mg/kg three times daily for 10 days.
Disseminated herpes zoster:
10 mg/kg three times daily for 7 days.

Less severe genital infections respond to oral administration: 200 mg five times daily for 7 days.

Contraindications

- Hypersensitivity.

Precautions

High fluid intake reduces the risk of acute renal impairment.

Use in pregnancy

Aciclovir is mutagenic in animal models. Its use must be determined by the physical state of the mother.

Adverse effects
Headache, nausea and vomiting occur commonly after oral administration.
Transient renal impairment may occur during intravenous therapy, possibly as a result of crystallization in the renal tubules. This usually responds rapidly to dosage reduction or withdrawal of the drug. Acute renal failure has responded to haemodialysis.

Overdosage
Since aciclovir is incompletely absorbed from the gastrointestinal tract, oral overdosage is unlikely to have serious sequelae.

Storage
Ointment and tablets should be stored in tightly closed containers below 25 °C.
Aciclovir for injection should be stored between 2 and 8 °C. After reconstitution the solution is stable for up to 12 hours at 20 °C.

AMPHOTERICIN B
Group: antifungal agent
powder for injection: 50 mg vial
lozenges: 10 mg

A lipophilic polyene antibiotic which is also active against protozoa and certain fungi. Since it is poorly absorbed from the gastrointestinal tract it must be administered parenterally.
It is extensively bound to lipoproteins, but it enters serous cavities and crosses the placental barrier. It is excreted unchanged in the urine over a period of several weeks.

Uses
- Treatment of cryptococcal meningitis and oesophageal candidiasis.

Dosage and administration
Amphotericin B is a highly toxic substance that should be used only under experienced medical supervision. Required dosages should be administered by slow intravenous infusion, when possible via a central venous catheter. An oral dose of 5 mg hydrocortisone sodium succinate taken one hour before infusion may reduce the severity of chills, fever and vomiting.

Infusion fluids should be freshly prepared by dissolving 50 mg in 10 ml of sterile water and making up to 500 ml with 5% glucose to give a final concentration of 100 micrograms/ml. Solutions containing electrolytes or preservatives are incompatible since they promote precipitation.

Cryptococcal meningitis
Daily infusions of 0.5 –1 mg/kg should be administered for at least 6 weeks. Infusions should be continued at weekly intervals indefinitely to prevent relapse.

Oral candidiasis
Lozenges taken 4 times daily after food for 2 weeks should be retained as close to major lesions as possible and allowed to dissolve in the mouth.

Oesophageal candidiasis
A dose of 3 mg/kg should be infused daily for 10–14 days.

Contraindications
- Known hypersensitivity.

Precautions
Close medical supervision is required throughout treatment.
Renal function and serum potassium concentrations should be closely monitored when high doses are administered.
A high fluid intake should be maintained. Potassium supplements may be required to compensate for urinary losses. Dosage must be reduced if renal function deteriorates substantially and particularly if serum creatinine levels rise by over 50%. Infusions of an osmotic diuretic such as mannitol may then be of value.
The blood count should be monitored at regular intervals since bone marrow depression supervenes frequently. Occasionally, blood transfusion is required.

Use in pregnancy
Safe use during pregnancy has not been established. Amphotericin B should be used only when the need of the mother outweighs the risk of harm to the fetus.

Adverse effects
Chills, fever and vomiting are frequent during infusion. Anaphylaxis, flushing, muscle and joint pains, headache and anorexia may also occur. These effects are often most marked in the first days of treatment.
Deterioration of renal function, which may be only partially reversible, must be anticipated.

Progressive normochromic anaemia is indicative of bone-marrow suppression. Selective leukopenia and thrombocytopenia are less common.
Nerve palsies, impaired vision, tinnitus and difficult micturition have also been reported.

Drug interactions
Concomitant administration of other nephrotoxic drugs should be avoided.

Overdosage
Large doses may result in anuria, dysrhythmias, cardiac arrest, hypotension, visual disturbances and convulsions. Treatment is symptomatic. Amphotericin B cannot be removed by haemodialysis.

Storage
Vials should be kept in tightly closed containers, protected from light.

CALCIUM FOLINATE
Group: antidote to folinic acid antagonists
tablet : 15 mg

A metabolically-active, reduced form of folic acid which is rapidly absorbed and extensively metabolized in the liver to other folic acid derivatives.

Uses
- To decrease the haemopoietic toxicity of pyrimethamine and other inhibitors of folic acid metabolism (see page 32).

Dosage and administration
Adults and children: Initially, 3–5 mg orally every third day. Dosage needs to be adjusted in accordance with twice-weekly blood counts.The daily requirement may exceed 15 mg and much higher doses have been administered without untoward effect.

Precautions
The possibility of pernicious anaemia should always be excluded before starting treatment with calcium folinate. Its use obscures the diagnosis by rectifying the characteristic megaloblastic anaemia but it does not prevent the neurological damage.

Use in pregnancy
Calcium folinate should always be used when pyrimethamine and sulfonamides are administered during pregnancy.

Adverse effects
Calcium folinate is generally well tolerated. Rarely, hypersensitivity reactions occur, including urticaria, rash and pruritus.

Storage
Tablets should be stored in tightly closed containers, protected from light.

CODEINE
Group: antidiarrhoeal & analgesic
tablet: 30 mg (phosphate)

Codeine is a semisynthetic methyl derivative of morphine. It is less likely to cause dependence than morphine but, none the less, its supply is controlled under Schedule 1 of the Single Convention on Narcotic Drugs, 1961. It exerts its effect mainly on the central nervous system and by an antimotility effect on the bowel.

It is readily absorbed following oral administration and is metabolized in the liver. The plasma half-life is 2–3 hours and it is excreted in the urine largely as inactive metabolites.

Uses
- Treatment of mild to moderate pain.
- Symptomatic relief of diarrhoea.

Dosage
30–60 mg orally 3 to 4 times daily as necessary.

Contraindications
- Children less than 1 year.
- Exacerbations of bronchial asthma.

Precautions
Prolonged use can result in tolerance. However, the risk of dependence is less than with other opioids.

Use in pregnancy
Codeine should be used during pregnancy only when the need outweighs any possible risk to the fetus. Its use during labour can produce respiratory depression in the infant sufficient to necessitate administration of naloxone, 10 micrograms/kg i.m. upon delivery.

Adverse effects
Dose-related adverse effects include nausea, dizziness and sedation.

Prolonged use can result in intractable constipation and, rarely, in paralytic ileus or toxic megacolon.

Drug interactions
Codeine potentiates the effects of other cerebral depressants.

Overdosage
Serious overdosage is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, and pin-point pupils. Cardiovascular collapse and cardiac arrest are terminal events. Supportive therapy includes mechanically assisted ventilation and administration of pressor drugs and fluids to maintain the circulating blood volume. Naloxone should be administered, as necessary, at 2-minute intervals.

Storage
Codeine tablets should be kept in tightly closed containers.

FLUCONAZOLE
Group: antifungal agent
tablet: 50 mg, 100 mg, 200 mg

Fluconazole is a fungistatic triazole derivative which is particularly effective against *Cryptococcus neoformans.* It is well absorbed and passes readily across the blood–brain barrier into the cerebrospinal fluid. It is slowly eliminated unchanged in the urine.

Uses
- Treatment and secondary prevention of cryptococcal meningitis.
- Treatment of oropharyngeal and oesophageal candidiasis, and serious systemic candidal infections, particularly of the urinary tract, the peritoneum and the lungs.

Dosage and administration
Cryptococcal meningitis: Investigational studies indicate that a dose of 400 mg is effective if taken daily for at least 12 weeks after cultures from the cerebrospinal fluid are negative. This should be followed by a suppressive dose of 200 mg daily indefinitely.

Oropharyngeal and oesophageal candidiasis: An initial loading dose of 200 mg is followed by 100 mg daily for 21 days.

Contraindications
- Hypersensitivity to azole derivatives.

Precautions
Dosage should be reduced in accordance with the creatinine clearance rate in patients with renal impairment.

Use in pregnancy
Safe use in pregnancy has not been established. The need for treatment must be determined by the condition of the mother.

Adverse effects
Fluconazole is generally well tolerated. Nausea is the most frequently reported adverse effect. Vomiting, abdominal distension and discomfort are also reported.

Elevation of hepatic enzyme levels, which occur in a small percentage of individuals, are readily reversible in the early stages. Treatment should be discontinued if signs develop that are suggestive of hepatic disease.

Fluconazole should be withdrawn if skin rashes progress during treatment. Exfoliative skin disorders have been reported, but a causal association has not been established.

Overdosage
No experience has been gained with overdosage of fluconazole. Emesis and gastric lavage may be tried in the case of accidental overdosage.

Storage
Tablets should be kept in well-closed containers protected from light.

GANCICLOVIR
Group: antiviral agent
powder for injection: 500 mg in vials

Ganciclovir is an acyclic nucleoside analogue of guanine with antiviral properties. It is used specifically to treat serious cytomegalovirus infections. It is also active against the herpes viruses, but it is too toxic to be of practical value in this regard. It acts by disrupting DNA synthesis and inhibiting viral replication. Following intravenous infusion it readily penetrates into the brain and subretinal fluids. It has a plasma half-life of three to four hours and is excreted primarily in the urine.

Uses
- Cytomegalovirus infections which threaten life or sight.

Dosage
Initially, 5 mg/kg every 12 hours by slow intravenous infusion for 14–21 days. Maintenance treatment: 5 mg/kg daily indefinitely.
Dosage should be adjusted in accordance with the creatinine clearance rate in patients with impaired renal function.

Contraindications
- Hypersensitivity.

Precautions
The blood count should be monitored every two days for the first 14 days. Particular vigilance is required when ganciclovir is administered in combination with other myelosuppressive drugs including zidovudine, pentamidine, or sulfamethoxazole/trimethoprim.

Pregnancy
Because of the urgent need to treat cytomegalovirus infections, ganciclovir should not be withheld during pregnancy.

Adverse effects
The most common severe adverse effects are leukopenias, especially neutropenia and thrombocytopenia as well as anaemia. Fever, rash, abnormal liver function tests, raised blood urea, behavioural changes, psychosis, convulsions and coma sometimes occur.

Storage
Vials should be stored below 25 °C. Infusion solutions may be stored for up to 24 hours at 4 °C.

KETOCONAZOLE
Group: antifungal agent
tablet: 200 mg
oral suspension: 100 mg/5 ml

A synthetic imidazole derivative with fungistatic activity against a wide range of organisms. It is rapidly absorbed from the gastrointestinal tract and is partially metabolized in the liver. It is largely excreted in the faeces via the bile.

Uses
- Oropharyngeal and oesophageal candidiasis.

Dosage
Oropharyngeal candidiasis: 200 mg once daily until remission is obtained.

Oesophageal candidiasis: 200–400 mg daily until remission is obtained. The need for subsequent maintenance doses of 200 mg daily should be considered.

Children >2 years: 3–6 mg/kg daily.

Contraindications
- Hypersensitivity to azole derivatives.
- Impaired hepatic function.
- Chronic alcohol dependence.

Precautions
Liver function should be assessed before, and at monthly intervals throughout treatment.

Use in pregnancy
Ketoconazole is fetotoxic in animals. Its use must be determined by the physical state of the mother.

Adverse effects
Anaphylactic reactions have been reported following the first dose. Hypersensitivity may also present as pruritus, purpura or urticaria.
Nausea, vomiting, abdominal pain, constipation, diarrhoea and transient increases in plasma concentrations of hepatic enzymes are common. Treatment should be withdrawn immediately if there is evidence of more severe hepatocellular damage. Gynaecomastia and menstrual irregularities have also been reported.

Drug interactions
Ketoconazole enhances the anticoagulant effect of coumarin derivatives, and reduces serum concentrations of theophylline. Serum concentrations of phenytoin are influenced unpredictably.
Concurrent administration of rifampicin decreases serum concentrations of ketoconazole.
Absorption is reduced in patients taking histamine-H_2 blocking agents.

Overdosage
Induction of emesis or gastric lavage should be undertaken in the event of overdose.

Storage
Ketoconazole tablets should be kept in well-closed containers.

NYSTATIN
Group: antifungal agent
tablet: 500 000 IU

An antifungal polyene antibiotic derived from *Streptomyces noursei* which is effective against a wide variety of yeast and yeast-like infections.

Uses
- Treatment and prevention of oral candidiasis.

Dosage and administration
One tablet should be sucked four times daily; it should be retained in the mouth for as long as possible.

Contraindications and precautions
- Treatment should be discontinued if symptoms of irritation or sensitization occur.

Use in pregnancy
Safe use in pregnancy has not been established. The need for treatment must be determined by the condition of the mother.

Adverse effects
Mild and transient nausea, vomiting and diarrhoea may occur after oral administration. Irritation occurs rarely after topical application.

Storage
Tablets should be stored in well-closed containers.

PENTAMIDINE
Group: antiprotozoal agent
powder for injection: 300 mg (isetionate)
powder for inhalation (aerosol): 300 mg (isetionate)

A stable diamidine compound with antiprotozoal activity that is administered parenterally because it is absorbed unreliably when taken by mouth. It does not enter the cerebrospinal fluid. Detectable amounts remain in the liver and kidney for many months as a result of selective binding. Excretion occurs mainly in the bile; a small fraction is excreted unchanged in the urine within 24 hours.

Uses
- Treatment and prophylaxis of *Pneumocystis carinii* pneumonia.

Dosage and administration
The powder should be reconstituted with water for injection.

Treatment
Intravenous infusion: 4 mg/kg daily infused over at least 60 minutes on 14 consecutive days.
For patients with severe renal failure, infusions should be administered on alternate days.

Prophylaxis
Intravenous infusion: 4 mg/kg at monthly intervals indefinitely, or
Oral inhalation: 300 mg in 6 ml as a single dose every 4 weeks indefinitely. The nebulizer should provide a particle size of less than 5 microns.

Contraindications
- Known hypersensitivity.
- Severe renal impairment.

Precautions
Because of the risk of hypotension and syncope all patients should remain supine and under observation for at least 30 minutes after each injection.
Blood pressure, blood count, serum creatinine and blood glucose concentrations should be monitored daily throughout treatment. Interruption or discontinuation of treatment may need to be considered should acute deterioration of bone marrow, renal or pancreatic function occur.

Use in pregnancy
Use in pregnancy can induce abortion. However, *Pneumocystis carini* pneumonia must always be treated without delay.

Adverse effects
Mild nephrotoxicity is frequent and usually completely reversible.
Rapid intravenous infusion can induce acute hypotension and syncope.
Pancreatic damage firstly induces hypoglycaemia due to excessive insulin release. Hyperglycaemia due to insulin insufficiency and pancreatitis may occur subsequently.
Other adverse effects include hypocalcaemia, gastrointestinal effects, confusion, hallucinations, cardiac dysrhythmias, local induration and, occasionally, sterile abscess formation. Rarely, thrombocytopenia, leukopenia, abnormal hepatic

function tests and Stevens-Johnson syndrome have been reported.

Storage
Vials of dry powder should be stored below 30 °C. Dilute solutions should be stored between 2 and 8 °C and any unused portion should be discarded within 24 hours of preparation.

PYRIMETHAMINE
Group: antiprotozoal agent
tablet: 25 mg, 50 mg

An inhibitor of folic acid metabolism that acts synergistically with sulfonamides to kill toxoplasma tachyzoites. The high dosages required may also interfere with folic acid metabolism in the host. The plasma half-life following oral administration is about 4 days. Pyrimethamine is partially metabolized in the liver and ultimately excreted in the urine.

Uses
- Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis.

Dosage and administration
200 mg in divided doses for 1 day followed by 75–100 mg daily for at least 6 weeks, and then a suppressive dose of 25–50 mg daily.

Pyrimethamine at this dosage must *always* be taken together with sulfadiazine. Daily dosages for the latter are set out on page 33.

Pyrimethamine has been administered alone to patients who are hypersensitive to sulfonamides at dosages some four times greater than those suggested here. However, such regimens are associated with a greater risk of bone-marrow depression.

Contraindications
- Known hypersensitivity.
- Severe hepatic or renal dysfunction.
- Pregnancy during the first trimester.

Precautions
Adults and children should receive calcium folinate (3–5 mg twice weekly) concurrently to prevent folinic acid deficiency resulting from high daily doses of pyrimethamine.

Concomitant administration of drugs that interfere with folic acid metabolism, other than sulfadiazine, should be avoided whenever possible.

Use in pregnancy
Pyrimethamine is normally contraindicated during the first trimester but administration should not be delayed when the mother's health is seriously endangered. It should always be given thereafter to reduce the risk of congenital transmission.

Adverse effects
Anorexia, abdominal cramps, vomiting, ataxia, tremors and seizures have been reported.

At the high dosages required for the treatment of toxoplasmosis, pyrimethamine may induce thrombocytopenia, granulocytopenia and a megaloblastic anaemia due to folinic acid deficiency.

Drug interactions
Various other drugs, including all sulfonamides, trimethoprim and methotrexate, act synergistically with pyrimethamine to inhibit folic acid metabolism. Coadministration (other than planned use of sulfadiazine) should be avoided.

Overdosage
Excessive doses of pyrimethamine are potentially fatal and induce anorexia, vomiting and seizures. Induction of emesis or gastric lavage is of value when undertaken within a few hours of ingestion. Convulsions may be controlled with parenteral diazepam.

Storage
Tablets should be kept in well-closed containers protected from light and moisture.

SULFADIAZINE
Group: antiprotozoal agent
tablet: 500 mg
solution for injection: 250 mg/ml

An inhibitor of folic acid metabolism in bacteria and protozoa that acts synergistically with pyrimethamine. Sulfadiazine is rapidly absorbed from the gastrointestinal tract and widely distributed in the body. The serum half-life is approximately 10–12 hours. After partial acetylation in the liver it is excreted in the urine.

Uses
- Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis.

Dosage
Sulfadiazine is always administered orally or intravenously in combination with pyrimethamine (see page 32).
6–8 g/day in 4 divided doses orally or i.v. for at least 6 weeks followed by a suppressive dose of 2–4 g daily indefinitely.

Contraindications
- Known hypersensitivity.
- Pregnancy during the first trimester.
- Severe hepatic or renal dysfunction.

Precautions
The blood count should be monitored twice weekly throughout therapy to detect signs of bone-marrow depression.
Administration should be discontinued immediately should presumptive signs of hypersensitivity occur, including skin rashes, dark urine and purpura.
Sulfadiazine is less soluble in urine than many other sulfonamides. High output of an alkaline urine must be maintained to avoid crystallization.
Concomitant administration of other drugs that interfere with folic acid metabolism (other than pyrimethamine) should be avoided whenever possible.

Use in pregnancy
Administration of sulfonamides can induce severe hypersensitivity reactions in the mother. Their action in displacing bilirubin from protein-binding sites has given rise to concern based on data derived from premature neonates, that they may promote kernicterus. Although they readily cross the placental barrier there is no conclusive evidence that the fetus is at risk.

Adverse effects
Nausea, vomiting, diarrhoea and headache sometimes occur.
Sulfonamide-induced hypersensitivity reactions can be severe. They include rare life-threatening cutaneous reactions such as erythema multiforme (Stevens–Johnson syndrome) and toxic epidermal necrolysis.
Crystalluria may result in dysuria, renal colic, haematuria and, acute renal obstruction.
Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

Overdosage
Continuous forced diuresis may be beneficial and an alkaline urine should be maintained. Treatment is otherwise symptomatic.

Storage
Tablets should be kept in well-closed containers, protected from light.

SULFAMETHOXAZOLE/ TRIMETHOPRIM
Group: antimicrobial agent
tablet: 100 mg + 20 mg, 400 mg + 80 mg, 800 mg + 160 mg
concentrate for intravenous infusion: 400 mg + 80 mg in 5-ml ampoule
suspension: 200 mg + 40 mg in 5 ml

Both components have antiprotozoal activity. They operate synergistically because they independently inhibit different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible protozoa.

Trimethoprim is absorbed more rapidly and is more widely distributed in tissues than sulfamethoxazole. Both compounds enter the cerebrospinal fluid; they are extensively bound to plasma proteins, and each is excreted largely unchanged in the urine at a rate that gives a plasma half-life of about 10 hours.

Uses
- Treatment and prophylaxis of *Pneumocystis carinii* pneumonia.

Dosage and administration
All dosages are suitable for both adults and children.

Treatment
Oral administration: Sulfamethoxazole 100 mg/kg + trimethoprim 20 mg/kg daily in two to four divided doses for 14–21 days.
Intravenous infusion: Severely ill patients should receive sulfamethoxazole 75 mg/kg + trimethoprim 15 mg/kg daily in four intravenous infusions, each administered in a 5% glucose solution in water over 60 minutes.

Patients who do not improve in 4 days should be transferred to pentamidine. Oral dosage forms should be substituted as soon as they can be ingested.

Suppression
Sulfamethoxazole 25 mg/kg + trimethoprim 5 mg/kg in two divided doses on 3 consecutive days each week for as long as immunosuppression persists.

Contraindications
- Known hypersensitivity.
- Severe hepatic or renal dysfunction.

Precautions
Treatment should be suspended immediately should a rash, or any other manifestation of sulfonamide hypersensitivity occur.
The risk of sulfonamide crystalluria is decreased by maintaining a urinary output of at least 1.5 litres daily. Whenever possible, plasma sulfonamide concentrations should be determined periodically. Peak plasma concentrations should be maintained at about 40 micrograms/ml.
Patients must be advised to seek medical advice should they develop a sore throat or fever during treatment. This advice can be of greater value than routine monitoring of the white cell count.
Elderly patients may be more susceptible to severe adverse reactions, especially blood dyscrasias.
Treatment should not be unnecessarily prolonged.
Supplementary calcium folinate may ameliorate myelosuppressive activity in patients who are already anaemic.

Use in pregnancy
Because the disease is life-threatening, treatment should in no circumstance be delayed.

Adverse effects
Skin rashes, recurrent fever, neutropenia, thrombocytopenia and increases in serum transaminase levels are particularly common. Nausea, vomiting and glossitis also occur frequently.
Trimethoprim sometimes induces a megaloblastic anaemia responsive to calcium folinate.
Sulfonamide-induced hypersensitivity reactions can be severe. They include life-threatening cutaneous reactions such as erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis.
Other reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis.
Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

Drug interactions
Maintenance requirements for sulfonylureas and coumarin anticoagulants are often reduced as a result of their displacement from plasma proteins by sulfamethoxazole.
Concomitant use of other inhibitors of folate metabolism (such as pyrimethamine, methotrexate and certain anticonvulsants) increases the risk of megaloblastic anaemia.

Overdosage
Symptoms of acute overdosage include vomiting, dizziness and confusion followed by visual disturbances, petechiae, purpura and jaundice.
Crystalluria, haematuria and anuria may also occur.

Emesis or gastric lavage may be of value within a few hours of ingestion. Provided urinary output is satisfactory, a high fluid intake should be maintained. Haemodialysis may be of value in eliminating some of the drug. Otherwise, treatment is symptomatic and supportive.

Storage
Tablets, suspension and concentrate for infusion should be stored, protected from light, in well-closed containers.

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The information in this section has been subjected to a preliminary consultative process involving members of the WHO Expert Advisory Panel on Drug Evaluation.

Further views will be canvassed before definitive publication in the Model Prescribing Information series. Comments, which are invited at this stage, should be referred to:
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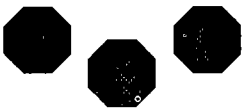

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Drugs used in Mycobacterial Diseases
World Health Organization, Geneva
1991, 40 pages
ISBN 92 4 140103 6 Price: Sw. fr. 9.-
Price in developing countries Sw. fr. 6.30