Current Report—HIV

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Prophylaxis against *Pneumocystis carinii* Pneumonia

Pneumocystis carinii pneumonia (PCP) is the most treatable serious illness in the AIDS patient. Standard therapies for an acute episode of *P. carinii* pneumonia[1] are 2- to 3-week courses of either trimethoprim-sulfamethoxazole (TMP-SMX) 15 mg TMP and 75 mg SMX per kg per day in three divided intravenous or oral doses, or pentamidine isethionate 4 mg/kg/day intravenously. Dapsone 100 mg orally once daily plus trimethoprim 15 mg/kg/day orally in 3 to 4 divided doses also appears effective. Aerosolized pentamidine is not reliably effective for treatment of acute episodes of *P. carinii* pneumonia.

Prophylaxis to prevent PCP is now widely employed. Which patients should receive prophylaxis against PCP? What agents are thought to be effective? When should prophylaxis be started? To evaluate these questions, it is helpful to divide prophylaxis into *primary prophylaxis* and *secondary prophylaxis*.

Primary prophylaxis is to prevent or delay an initial episode of PCP. The most promising agents are trimethoprim-sulfamethoxazole,[2] dapsone,[3] and aerosolized pentamidine.[4-6] All are reported to be effective, although interpretation of published data is difficult as studies to date are of small patient groups or are in the form of abstracts. No comparative studies of these agents, either alone or in conjunction with zidovudine (AZT), are available at present. All appear to be well tolerated in patients who are relatively well, but for TMP-SMX and dapsone, drug toxicity increases as patients become more ill. TMP-SMX is usually given as 1 double strength tablet twice daily. Toxicities include severe rashes, fevers, neutropenia, and hepatitis. Dapsone dosage is 25 mg four times daily. Toxicities include rash, fever, methemoglobinemia, and hepatitis. TMP-SMX and dapsone each cost less than $30 per month. Inhaled pentamidine is now the most common prophylactic agent used, both alone and in conjunction with zidovudine. Toxicity is minimal, even for patients who are quite ill. Side effects include cough, bronchospasm (which can be pretreated with bronchodilators), and metallic taste in the mouth. Treatment with inhaled pentamidine does not prevent systemic (bone, spleen, kidney, etc.) pneumocystosis, whereas TMP-SMX may. The Food and Drug Administration has approved inhaled pentamidine under a Treatment IND (investigational new drug) in a dose of 300 mg once monthly via a Respigard II™ nebulizer.[4] Other dosing schedules that have shown efficacy include 60 mg biweekly via a Fisoneb™ nebulizer[5] and 300 mg monthly via a Mallinckrodt™ nebulizer.[6] The cost is $200 to $450 per month.

When should primary prophylaxis in the HIV-infected patient be initiated? We must keep in mind that the latent period between infection and clinical AIDS appears to be 8 to 10 years.[7] During this time, CD4 (T helper) lymphocytes gradually decrease. AIDS rarely occurs in patients with more than 0.400×10^9 (400/μL) CD4 lymphocytes/L. When CD4 counts fall lower than 0.200×10^9 (200/μL), there is a high risk of PCP in the near future. Most episodes of PCP occur with CD4 counts well below 0.200×10^9/L. Therefore, it seems appropriate to initiate some form of primary prophylaxis at CD4 counts near 0.200×10^9/L. It is noteworthy that studies of HIV-infected patients with less than 0.200×10^9 CD4 lymphocytes/L and who have not had PCP have failed to reveal the presence of *P. carinii* on bronchoscopy.[8] This finding brings into question why prolonged courses of prophylaxis initiated well before CD4 counts fall to 0.200×10^9 would be helpful. Above all, the physician and patient should discuss the alternatives and make a case-by-case decision on the timing and choice of prophylaxis while studies to evaluate these issues continue.

Secondary prophylaxis is to prevent or delay subsequent episodes of PCP after successful therapy of acute *P. carinii* pneumonia. Most studies indicate that TMP-SMX is excessively toxic in patients

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who have already had an episode of PCP. Pentamidine by aerosol appears to be effective and minimally toxic. Inhaled pentamidine is presently the treatment of choice for secondary prophylaxis and should be offered to all patients who have recovered from acute PCP.

References

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Diagnosis and Treatment of Syphilis in HIV-Infected Patients

The diagnosis of syphilis in patients with normal immune responses has been relatively straightforward because of the sensitivity of nontreponemal screening tests (VDRL, RPR) and the specificity of treponemal confirmatory tests (FTA-ABS, MHA-TP). Treatment regimens have remained unchanged for many years. Recently, however, concern has been raised about both the accuracy of serologic tests for syphilis and the adequacy of standard syphilis therapies, especially in the HIV-coinfected patient.[1-3]

Most HIV-infected patients have normal serologic responses to *Treponema pallidum*. However, the altered immune responses characteristic of HIV infection have resulted in both false-positive nontreponemal tests and, more importantly, false-negative tests in some patients with asymptomatic and symptomatic HIV infections. Particularly striking are a few cases of biopsy-confirmed secondary syphilis with negative syphilis serologies. Therefore, patients with negative serologic tests but clinical findings suggestive of primary and secondary syphilis should have special tests performed, including dark-field microscopy and fluorescent antibody staining of lesion exudate and examination of stained biopsy tissue.

Subclinical infection of the central nervous system (CNS) occurs in about 40 percent of patients with early syphilis. The Centers for Disease Control position is that standard treatment of early syphilis with one injection of 2.4 million international units (mIU) of benzathine penicillin G is adequate. However, considerable disagreement exists, and many authorities believe this regimen is not reliably effective in eradicating CNS infection because of its inadequate CNS penetration. Regimens known to have adequate CNS penetration include 10 days of either aqueous procaine penicillin G, 2.4 mIU intramuscularly once daily, along with probenecid, 500 mg orally 4 times daily, *or* aqueous crystalline penicillin G, 2 to 4 mIU intravenously every 4 hours (12 to 24 mIU daily). Whether 2 or 3 weekly doses of benzathine penicillin G are effective has not been determined.

Treatment of latent syphilis should be preceded by cerebrospinal fluid (CSF) examination whenever possible. Evidence of neurosyphilis (leukocytes greater than 5×10^6/L [5 leukocytes/mm^3], CSF protein greater than 0.40 g/L, or reactive CSF-VDRL) should prompt therapy for neurosyphilis with aqueous penicillin G as above. When no CSF abnormalities are present, the diagnosis remains somewhat in doubt, because normal CSF cell counts, protein levels, and negative syphilis serologies may occur in patients with neurosyphilis. In HIV-coinfected patients, treatment is controversial. Therapy with a regimen known to have adequate CNS penetration is most reliable in eradicating possible infection.