



Maine AIDS Care

AIDS Consultation Service Maine Medical Center Winter 94-95

Prophylaxis of Opportunistic Infections May Be Our Most Important Intervention - An Update

Until antiviral regimens improve, prophylaxis against pneumocystis and other opportunistic infections remains our most effective intervention in HIV disease. Use of trimethoprim-sulfa for pneumocystis prevention has clearly prolonged survival of AIDS patients. However, as pneumocystis pneumonia has decreased in incidence, other opportunistic infections have become more troublesome. Therefore, the role of prophylaxis against disseminated mycobacterium avium complex (MAC), toxoplasmosis, CMV disease, and fungal infections is receiving careful scrutiny.

For patients with CD4 Counts <200, trimethoprim sulfa is the drug of choice for primary prophylaxis against pneumocystis pneumonia. It is the most effective choice, least costly, and has the additional benefit of preventing toxoplasmosis encephalitis. The majority of patients with an initial drug rash or fever from trimethoprim-sulfa may be successfully rechallenged, or desensitized. Alternatives such as dapsone and aerosol pentamidine are less effective than trimethoprim-sulfa, and pentamidine is more costly.

Rifabutin has been approved for prevention of disseminated MAC in patients with CD4 counts <100. Most clinicians believe that MAC prophylaxis is best begun at CD4 Counts of 50 or less. Several recent studies now document the effectiveness of clarithromycin for MAC

prophylaxis. Some clinicians recommend routine blood cultures for MAC to rule out dissemination before starting prophylaxis. Both rifabutin and clarithromycin appear to lower the incidence of bacteremia due to MAC by 50%. No impact on overall survival has yet been demonstrated, but a recent "quality of life" analysis supports prophylaxis for MAC.

For seropositive patients, toxoplasmosis encephalitis can be prevented with either trimethoprim-sulfa or dapsone combined with pyrimethamine. Prophylaxis is usually recommended at CD4 counts <200.

The possible role of fluconazole for prophylaxis of cryptococcal meningitis is controversial. This infection is less common than other OI's mentioned above, and therefore the role of prophylaxis is less clear.

Finally, with the release of oral gancyclovir, prevention of CMV retinitis (and other disseminated CMV disease) may be possible in the near future. Preliminary results suggest an effectiveness of 50% with oral gancyclovir prophylaxis of CMV retinitis. However oral gancyclovir is not yet approved for primary prophylaxis.

Current recommendations for prophylaxis of opportunistic infections are summarized in the enclosed insert.

FDA Approves Oral Gancyclovir

As of January 1995, the FDA has approved the use of oral gancyclovir for maintenance therapy of CMV retinitis. In several pilot studies, oral gancyclovir (1gm po tid) appeared equally effective with IV regimens for the prevention of relapse of CMV retinitis once the infection has been controlled. Side effects (granulocytopenia, nausea) are less frequent than with the IV forms. Although preliminary information suggests oral gancyclovir may be effective for primary prophylaxis of CMV retinitis, the drug has not yet received FDA approval for this indication. Recommendations regarding its possible use will depend on the final results of several studies now in progress.

Another new development in the treatment of CMV retinitis is the use of intraocular implants of a plastic membrane that releases gancyclovir. Initial studies are promising. A research trial at New England Eye Center (617)636-4604 is currently evaluating this option.

**AIDS Treatment
Information Hotline
1-(800)-871-2701**

Recognition of Clinical Syndromes Associated with Opportunistic Infections

Although the manifestations of many opportunistic infections in persons with HIV are variable, there are specific clinical syndromes that are often caused by particular opportunistic infections. With continued improvement in treatment, it is often possible to suppress these infections with an associated improvement in the person's well being. In general, the level of the CD4 cell count is a key predictor of the likelihood of some of these infections. Most of the serious opportunistic infections are rarely seen when CD4 counts are greater than 100. Some common clinical scenarios are outlined below according to these CD4 count benchmarks.

CD4 Count <200

Chronic Cough

Persistence of a dry cough for greater than 2 weeks in a person with a CD4 count <200 should raise the suspicion of pneumocystis pneumonia. Although viral respiratory infections are a more common cause, persistence of cough, particularly if accompanied by a sense of breathlessness, is the typical presentation of pneumocystis pneumonia. Although trimethoprim sulfa prophylaxis is very effective, PCP still occurs, and is a particular concern in patients on less effective prophylactic regimens. Other considerations include tuberculosis, viral and bacterial pneumonias.

Chest x-rays may detect mixed alveolar interstitial infiltrates characteristic of PCP, but may be negative early in the disease. Diagnosis of PCP usually requires detection of organisms by immuno-fluorescence or silver stain of individual sputum or bronchoscopic washings. Less severe cases of PCP may be treated as outpatients on oral regimens as noted on the insert page.

CNS Symptoms

Many patients with low CD4 counts experience mild memory disturbance, sometimes coupled with mild ataxia or motor impairments. In most cases, these symptoms are due to HIV encephalopathy. However, CNS opportunistic infections such as cryptococcal meningitis, CNS toxoplasmosis, or neurosyphilis are other considerations. Cryptococcal meningitis is often indolent with headaches and gradual mental status decline. CNS toxoplasmosis often causes focal neurologic symptoms or seizures, but may present without non-specific CNS changes. Neurosyphilis, which can occur within a few years of treated primary syphilis in HIV+ patients, can cause a variety of CNS symptoms. Rarely, patients may develop progressive

multifocal leukoencephalopathy which, as its name suggests, typically presents with a history of focal neurologic deficits that occur in a stuttering course.

The usual diagnostic approach requires CT or MRI scans of the brain (the latter is more sensitive for the detection of the mass lesions of toxoplasmosis). CNS toxoplasmosis is unlikely in patients who are seronegative for toxoplasma antibodies. However, if mass lesions are detected, an empiric trial of treatment for toxoplasmosis encephalitis is often attempted. Toxoplasmosis usually responds clinically within 2 weeks. If no response is evident, brain biopsy is usually done to obtain a specific diagnosis. Diffuse white matter involvement with cortical atrophy is usually indicative of HIV encephalopathy, while multifocal white matter lesions may suggest progressive multifocal leukoencephalopathy.

If imaging studies are negative, a lumbar puncture is indicated to rule out cryptococcal meningitis (with cryptococcal antigen and culture), neurosyphilis (CSF VDRL), and other inflammatory CNS processes.

Effective treatment may suppress CNS toxoplasmosis, cryptococcus, or syphilis. Some patients with HIV encephalopathy may have transient improvement with a change or increase in antiretroviral regimens. However, no effective treatment exists for HIV encephalopathy or progressive multifocal leukoencephalopathy.

CD4 Count <100

Fever and Wasting Syndrome

Recurrent fever, night sweats, and weight loss may be due to endstage HIV disease alone, but may also signify opportunistic infections such as disseminated mycobacterial infection or lymphoma.

Disseminated mycobacterium infection has an incidence of 30% in patients with CD4 count <50, and often presents with nonspecific systemic symptoms as noted above, sometimes accompanied by diarrhea and anemia. Mycobacterium avium organisms are ubiquitous in the environment, and have been shown to be occasionally acquired from hospital tapwater as well. Diagnosis is usually made by blood culture (specified for mycobacteria), or less frequently by culture of other sites or biopsies (bone marrow, lymph node, colon, etc.). Once diagnosed, symptoms of disseminated MAC can often be suppressed with antibiotic regimens (see insert).

Chronic Diarrhea

Chronic diarrhea may represent HIV enteropathy, but may also be due to enteric bacterial pathogens (ie. salmonella, campylobacter, etc.) or disseminated mycobacterial avium infection involving the colon. Cryptosporidium, a water-borne parasite, can cause voluminous watery diarrhea, as can other similar parasites such as microsporidia. CMV infection of the colon may also cause diarrhea, often associated with painful abdominal cramping. The workup of persistent diarrhea includes stool examinations for enteric bacteria, and ova and parasite exams. The latter should include special procedures for the detection of cryptosporidia. As many of these patients are on chronic antibiotic therapy for OI prophylaxis, a stool for c. difficile toxin is often appropriate as well. Blood cultures for MAC are usually indicated.

Treatment Regimens for Opportunistic Infections

<i>Opportunistic Infection</i>	<i>Admin.</i>	<i>Treatment Regimen</i>	<i>Comments</i>
<u><i>Pneumocystis Pneumonia</i></u>	PO	Trimethoprim-Sulfa (15-mg/kg/d trimethoprim - give as divided dose qid)	Preferred treatment regimen
	PO	Trimethoprim (15 mg/kg/d) - Dapsone (100mg po qd)	Alternative for sulfa-allergic patient Check G6PD status.
	PO	Atovaquone (750 mg po tid)	Costly. Bioavailability resists proper distribution.
	IV	Trimethoprim-sulfa	Same dose as po regimen
	IV	Pentamidine (4mg/kg/d/iv or im)	
	IV	Trimetrexate	See package insert for dose recomm.
	IV	Clindamycin (600mg IV q 6hr or 300mg po qid) & primaquine (15mg base po/day x2 days)	
		Use steroids also if PO 2 < 70.	Prednisone 40 mg po bid x5 days then 20 mg/d for duration of treatment.
Adjunctive:			
<u><i>Disseminated Mycobacterium Avium Complex</i></u>		Clarithromycin (500-1000 mg po bid) - Usually in combination with ethambutol (15mg/kg/d) with or without rifabutin. (Other agents to consider include cefazolin, ciprofloxacin, amikacin)	Indefinite duration
<u><i>CMV Retinitis/Colitis</i></u>	IV	Gancyclovir (5mg/kg IV bid) or foscarnet (60mg/iv q8hs or 90mg/kg/IV q12 hrs)	2 week induction regimens
	IV / PO	Maintenance with gancyclovir (5mg/kg/iv/qd) or foscarnet (90-120mg/kg/d) or Gancyclovir oral (1gram po tid)	Major toxicities of Gancyclovir: Bone Marrow Suppression Major toxicities of Foscarnet: Electrolyte Imbalance Hypocalcemia Renal failure Seizures
<u><i>Cryptococcal Meningitis</i></u>	IV	Amphotericin B (0.4-0.8 mg/kg/d) - Flucytosine (100-150 mg/kg/d divided qid)	Initial treatment
	PO	Fluconazole (400 mg/d)	Maintenance with fluconazole usually preferred
<i>Toxoplasmosis</i>		Pyrimethamine (100-200mg loading dose, then 50-100 mg/d po x6 wks) and folic acid (10mg/d/po) plus Sulfadiazine (4g/d po x6 wks)	Acute management. Chronic suppression is also required at modified doses.
<i>Cryptosporidia</i>		No treatments of proven effectiveness	Of possible benefit: Paromomycin

The information contained in this insert is current as of March 1995.

Regimens for Primary Prophylaxis Against Opportunistic Infections

Opportunistic Infection	Regimens	Comments
<i>Pneumocystis</i> (CD4 <200) 1) any patient with a past history of <i>pneumocystis</i> 2) more than 2 weeks wasting disease or thrush	Trimethoprim-sulfa (one DS/d or one DS 3x/wk)	Most effective (>95%) and least costly regimen. Rechallenge often successful if drug has been stopped for skin rash.
	Dapsone (50-100 mg/day) pyrimethamine (25-50mg/d)	Less effective. 30% reaction in sulfa intolerant patients.
	Aerosol pentamidine (300mg/month)	Less effective. costly.
Disseminated MAC (CD4 <50)	Rifabutin (300mg/day)	50% effective. Watch drug interactions with fluconazole and other meds.
	Clarithromycin (500 mg/bid)	Similar effectiveness to rifabutin.
Toxoplasmosis (if seropositive)	Trimethoprim-sulfa (one DS / day)	
	Dapsone-pyrimethamine (as above)	
CMV - disseminated (CD4 <50)	None yet approved	Acyclovir - ineffective
		? Oral Gancyclovir (not yet approved for primary prophylaxis)
Cryptococcal meningitis		!!! Fluconazole (Not approved for prophylaxis) Cost-effectiveness is unclear. May increase fluconazole resistance.

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Medication Costs for OI Prophylaxis

Drug Name	Trade Name	Dosage	Price Per Month	*Access Information
Acyclovir	Zovirax	800mg qd	\$156.00 - 198.00	PA 1-800-722-9294
TMP-SMZ	Bactrim DS	1 tab 3x/week	\$6.20 - 9.80	
Clarithromycin	Blaxin	500mg bid	\$173.00 - 206.00	Info 1-800-688-9118
Dapsone	Dapsone	100mg qd	\$6.30 - 9.80	
Rifabutin	Mycobutin	150mg bid	\$210.00 - 228.00	PA 1-800-795-9759
Fluconazole	Diflucan	100mg qd	\$204.00 - 224.00	PA 1-800-869-9979

Price information gathered from Pharmacies (?) in Portland, S. Portland, Scarborough, & Gray.

*PA = Patient Assistance Programs

If these measures are unrevealing, lower and upper GI endoscopy with biopsy may be necessary for a definite diagnosis. Treatable diseases that can be diagnosed only by biopsy include CMV colitis and MAC infection of the GI tract.

Visual Disturbance

CMV retinitis is a sight threatening infection that can be suppressed with antiviral therapy. It often presents with localized visual blurring. Fundoscopic exam may reveal characteristic white exudates with hemorrhage in a perivascular distribution. As lesions often begin in the periphery of the retina, slit lamp examination with pupil dilation may be necessary to make the diagnosis. Although toxoplasmosis may also cause a retinitis, it is usually associated with vitreitis as well. Herpes zoster can cause a necrotizing retinitis that is poorly responsive to antiviral therapy. Other infections that may rarely affect the eyes of patients with HIV include pneumocystis choroiditis, fungal and bacterial endophthalmitis, and optic neuritis due to syphilis.

Disseminated Skin Lesions

New onset of papular or indurative skin lesions may follow dissemination of bacteria (mycobacterium avium), fungi (cryptococcus, histoplasmosis), and virus (CMV). Exposure to cats may lead to bacillary angiomatous, a variant of cat scratch disease seen in AIDS patients, that is characterized by multiple erythematous papules or angiomas. At times, bacillary angiomatous can be confused with Kaposi's sarcoma. The distinction between these two conditions is critical, as bacillary infections can be cured with antibiotic treatment. More commonly, papular eruptions are due to xerosis, eosinophilic folliculitis, or other AIDS-related skin ailments. Skin biopsy often reveals the diagnosis of disease in these patients, and silver staining should be requested when bacillary angiomatosis is a consideration.

Maine Bureau of Health Issues Guidelines for Prevention of Cryptosporidiosis Infection

Cryptosporidiosis in normal hosts is a self limited enteric illness caused by a protozoan parasite. It is usually transmitted by ingestion of contaminated water. In persons with HIV disease, cryptosporidiosis can become a life threatening infection for which no standard therapy exists. Since the 1993 outbreak of cryptosporidiosis in the Milwaukee water supply, attention has been focused on the safety of public water supplies with regard to cryptosporidiosis and other enteric parasites. Although no standard method for assessing risk in local water supplies has yet been agreed upon, a national survey of public water systems is planned. At the present time, there is no evidence that public water supplies pose a significant risk of cryptosporidia exposure in Maine. However, the Maine Bureau of Health has issued the following suggestions for prevention of exposure to this parasite:

- do not drink water directly from rivers or lakes or other surface water sources
- swimming in freshwater or even chlorinated pools (the organism is resistant to chlorine), is a possible risk
- in the event of a local outbreak of infection, boiling water for 1 minute will eliminate risk
- avoid unpasteurized milk or other unpasteurized dairy products

AIDS Consultation Service to Participate in Trial of Experimental Protease Inhibitor

Protease inhibitors show promise as antiretroviral agents, with much higher in vitro potency against HIV than currently available medications. In collaboration with the Community Research Initiative of Boston, the ACS will participate in a trial of a protease inhibitor developed by Abbott Laboratories (ABT-538). The initial trial will be open for patients who have not previously received AZT, and will compare AZT plus ABT-538 with AZT plus placebo. A second trial will offer ABT-538 or placebo to patients with CD4 counts <100, provided they have previously been on antiretroviral treatment for 9 months. We hope this will be the first of several clinical trials of this regimen in Maine. Inquiries regarding this study can be made to the AIDS Consultation Service at 1-800-871-2701.

Other on-going clinical trials at AIDS Consultation Service include the experimental non-nucleoside RT-inhibitor, Delavirdine, with either AZT, DDI, or a triple combination regimen.

AIDS Consultation Service Offers Information FAX Service

The AIDS Consultation Service at Maine Medical Center has initiated an information fax service to distribute bulletins on HIV care, updated CDC recommendation, and other information useful in the care of persons with HIV. If you would like to receive this information free of charge, contact Kathy Anderson at the AIDS Consultation Service at (207)871-2099 or fax your name, address, and fax number to (207)871-6116. If you do not have a fax machine and wish to obtain this information through the mail, please forward your name and address to Kathy Anderson, AIDS Consultation Service, 22 Bramhall Street, Portland Maine 04102-3175.

*World AIDS Cases 2,500,000**

US AIDS Cases 434,397¹

US AIDS Deaths 220,871²

Maine AIDS Cases 592

Maine AIDS Deaths 291

Maine Data as of December 31, 1994

** Estimated*

¹ Reported through 1/6/95 by CDC

² Total US deaths reported through 12/31/93 by CDC

Upcoming HIV/AIDS Education

- 03/07/95 "HIV Update for the Emergency Room"
Winter Emergency Medicine Symposium at Sunday River Bethel Maine
Robert P. Smith, M.D.
- 03/28/95 "Update on Management of HIV+ Patients"
Grand Rounds, Kennebec Valley Medical Center, Augusta, Maine 04330
Robert P. Smith, M.D.
- 04/25/95 "Living with HIV: Client/Provider Perspectives"
Eastern Nursing Research Society 7th Annual Scientific Sessions
Sheraton Tara Hotel, So. Portland, Me.
Sandra T. Putnam, RN,MSN,FNP
- 05/02/95 "HIV in the Office Practice"
Family Medicine Symposium at the Sonesta Hotel, Portland Maine
Robert P. Smith, M.D.
- 05/02/95 "HIV Update"
Goodall Hospital, Sanford Maine
Sandra Putnam, RN,MSN,FNP
- 05/03/95 "Early Treatment of the HIV Positive Patient"
Ambulatory Care Coalition Teleconference
- 05/03/95 "HIV/AIDS: Moving from Fear and Discrimination to Empowerment"
Holiday Inn By the Bay, Portland Maine
USM's Dept of Cont. Ed. for Health Professionals (207)780-5951

If you are providing an HIV/AIDS related educational session, please let us know at (207)871-2099

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