staff, respiratory therapists, transportation and laboratory workers, and a prison guard. Eleven of the individuals were known to be HIV-infected. A total of seven have died, including five HIV-infected persons. Of the two deaths in noninfected persons, one was due to a drug overdose and one occurred in an individual undergoing cancer treatment. The skin test conversion rate in previously PPD-negative workers has been 20% to 50%.

In addition to specifying general standards for infection control, including negative pressure rooms, and supplemental approaches, such as HEPA filtration and ultraviolet irradiation, CDC draft guidelines for infection control indicate that the minimal acceptable level of respiratory protection for workers exposed to TB should be a HEPA filter respirator. The Occupational Safety and Health Administration (OSHA) has recently indicated that employers in a variety of health care settings are obligated to establish TB control programs and that the HEPA filter respirators will be considered the minimal acceptable standard of protection. As noted by Dr Tapper, the legal requirement of the use of these devices, which are difficult to wear and are associated with increased cost, has caused much controversy. Their necessity remains unclear, since institutions that had fully implemented earlier CDC guidelines recommending use of a dust-mist particulate respirator have generally reported success in terminating nosocomial transmission of TB infection.

Many other issues concerning health care worker exposure remain unresolved. One is the difficulty in compliance with both current OSHA requirements and elements of the Americans with Disability Act. As related by Dr Tapper, the questions arising in the context of TB exposure are whether an institution can accommodate a worker's handicapping condition if the condition is HIV infection and whether HIV-infected workers can reliably be protected from TB exposures. Other unresolved issues include the reliability of skin testing in monitoring nosocomial transmission, distinguishing between nosocomial- and community-related skin test conversions, and monitoring of exposure in anergic HIV-infected workers. In addition, there is no established prophylactic regimen for HIV-positive or HIV-negative workers exposed to MDR-TB. The utility of the current CDC-recommended combination of pyrazinamide and either ethambutol or a quinolone (ofloxacin or ciprofloxacin) remains largely unproven and in one study has been reported to be poorly tolerated. ■

Diarrhea Associated With HIV Disease

Diarrheal illness in patients with HIV disease was discussed at the New York meeting by Douglas T. Dieterich, MD, from the New York University School of Medicine in New York.

As related by Dr Dieterich, diarrheal illness has been observed to occur in approximately 60% of patients with AIDS. A recent study has shown that such illness has a profound economic and quality of life impact: the effect of chronic diarrhea vs no diarrhea among AIDS patients with CD4+ cell counts <200/μL was a reduction in function, global health, and fatigue quality of life measures, a doubling of annual cost of treatment ($24,567 vs $14,471), a doubling of disability days (131 vs 72), and a doubling of proportion of patients requiring home assistance (66% vs 35%), with all of these differences being statistically significant. Dr Dieterich stressed that while the lower end of the range of proportion of cases in which an etiologic diagnosis can be made is 50%, assiduous and repeated efforts at diagnosis can raise the diagnostic yield to 85%. Approximately 50% of pathogens currently are treatable. With regard to the potential role of HIV in diarrheal illness, Dr Dieterich noted that HIV can be found in rectal and small-bowel biopsies, that the GI tract (mouth and rectum) may be a portal of entry of HIV, and that local infection of GI tissues and mucosal inflammation caused by HIV may contribute to symptoms. He also noted that recent findings suggest that human herpesvirus 6, which is frequently found in the GI tract, may induce CD4 receptors in various tissue cells. However, he maintained that the role of HIV as a primary enteric pathogen remains unclear and emphasized that, although it is tempting to invoke HIV enteropathy when initial testing is unrevealing, it is highly probable that some other pathogen will be found if diagnostic efforts are continued or repeated and that pathogen-specific treatment is of greater benefit to the patient than symptomatic treatment. The approach to evaluation of diarrheal illness in HIV disease recommended by Dr Dieterich is shown in Figure 7.

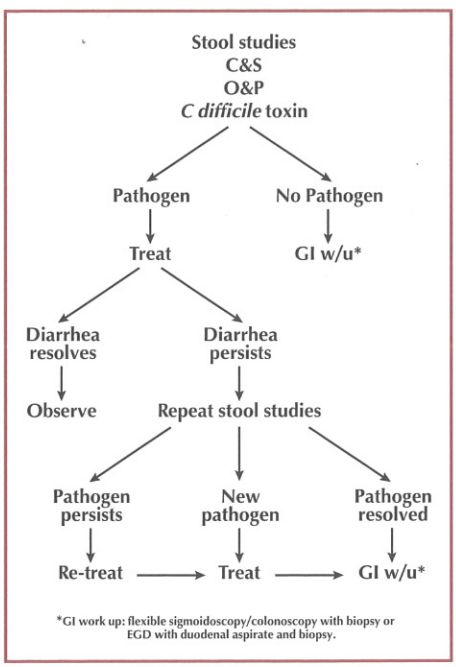

Figure 7. Evaluation of diarrhea in patients with HIV disease. C&S = culture and stain. O&P = ova and parasites. w/u = work-up. EGD = esophagogastroduodenoscopy. Figure courtesy of Douglas T. Dieterich, MD.

As stated by Dr Dieterich, the potential microbiologic causes of diarrhea are manifold. Bacterial causes include MAC, MTB, *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, and entero-adherent *Escherichia coli*. The *E coli*, which appear to adhere to colonic mucosa and which are similar to strains that have been found to infect children, have been described as pathogens only within the last year. They reside primarily in the right colon, and diagnosis requires electron microscopy of biopsy tissue. According to Dr Dieterich, the organisms are sensitive to ciprofloxacin, which many patients receive as empiric therapy for diarrhea. Parasitic causes include *Cryptosporidium*, *Isospora*, *Entamoeba histolytica*, *Giardia*, *Microsporidia*, and *Cyclospora*. Viral causes include CMV, herpes simplex virus, adenovirus, astrovirus, picobirnavirus, and calicivirus; the more recently identified viruses are difficult to isolate and have not as yet been found to respond to any known treatment. Although fungi generally are rare causes of diarrhea, *Histoplasma* has been found to cause GI symptoms in a significant proportion of patients in *Histoplasma*-endemic areas. Dr Dieterich noted that such illness can also be observed outside of endemic areas; among patients in New York City, he has observed a number of cases of *Histoplasma* colitis presenting as diarrhea with an unknown primary site of histoplasmosis.

Cryptosporidiosis

GI symptoms of cryptosporidiosis include profuse, watery diarrhea, malabsorption and weight loss, flatulence, abdominal pain, nausea and vomiting, and absence of fever. A notable exception to the usual finding of absence of fever are cases in

which infection of the biliary tree results in cholangitis with bacterial superinfection. Currently, there is no completely effective therapy for cryptosporidiosis, with more than 100 agents having been examined for potential use. Agents evaluated in recent investigations include macrolide/azalide agents, benzoacetonitrile derivatives, and the antiamebic aminoglycoside paromomycin. A study of IV and oral spiramycin by Dr Dieterich and colleagues failed to show activity of the agent. Another group has found some activity of oral azithromycin and currently is evaluating IV azithromycin, having noted that patients who achieved meaningful blood drug levels tended to respond better to treatment. Clarithromycin has not shown activity in in vitro models of infection. With regard to the benzoacetonitrile derivatives, a recent small-scale placebo-controlled trial of diclazuril by Dr Dieterich and colleagues revealed a low response rate and general failure to achieve blood drug levels. Subsequent evaluation of letrazuril, which is better absorbed than diclazuril, in placebo-controlled ACTG 192 has also suggested small beneficial effect. There has been one report of the combination of letrazuril and paromomycin resulting in successful treatment. Anecdotal reports suggest that high-dose paromomycin (1500 to 3000 mg/d in divided doses) may exhibit some activity, and the agent is currently being evaluated in an ACTG trial. Little effect has been observed with such other approaches as treatment with transfer factor, hyperimmune bovine colostrum, or interleukin-2.

Dr Dieterich stated that in addition to continuing efforts at development or identification of effective agents, future efforts are likely to focus on combinations of agents that show at least some activity. With regard to reports that antiretroviral treatment is of benefit in treatment of cryptosporidiosis, Dr Dieterich stated that the observations are likely explained by an effect of such treatment in increasing CD4+ cell counts, with it having been observed that patients with cryptosporidiosis with counts >150/μL tend to spontaneously resolve infection, whereas infection generally is progressive in those with lower counts.

In cryptosporidiosis cases, as in all other cases of chronic diarrhea that are not amenable or do not respond to specific treatment, supportive therapy is essential. Initial options among antimotility agents include loperamide and lomotil; opiates can be tried, including morphine, methadone, paregoric, and deodorized tincture of opium, and, finally, use of the synthetic somatostatin octreotide can be attempted. Enteral feedings and total parenteral nutrition are important components of supportive treatment.

Microsporidiosis

Typical symptoms of microsporidiosis are identical to those of cryptosporidiosis, with the exception that the former is not associated with the severe nausea and vomiting characteristic of the latter and that patients with microsporidiosis may have preserved appetite in apparent association with a relatively reduced tendency of infection to affect the upper GI tract; microsporidiosis may also be associated with fever in cases of cholangitis with bacterial superinfection. According to Dr Dieterich, the prevalence of this relatively recently discovered disease has been reported at 15% to 50% in patients with no other identifiable cause of diarrhea. Diagnosis is best made by electron microscopy of small bowel biopsy; stool tests are still being developed and are as yet unreliable. Albendazole is a promising agent for treatment of microsporidiosis; currently three double-blind placebo-controlled trials of the agent, including ACTG 207, are under way or about to begin. In an uncontrolled study recently reported by Dr Dieterich and colleagues, 29 homosexual men with a mean CD4+ cell count of 21/μL, mean time since AIDS diagnosis of 24 months, mean of seven bowel movements per day for 12 months, and mean weight loss of 17% of normal body weight who were infected with *Enterocytozoon bieneusi* were administered oral albendazole at dosages of 400 to 1600 mg bid. With treatment response assessed as good, partial, or poor for >50%, >25%, and <25% reduction in diarrhea, 50% of patients exhibited a good response and an additional 35% exhibited partial response. Experience of Dr Dieterich and colleagues with albendazole in patients with disseminated *Septata intestinalis*, the other microsporidial species thus far implicated in disease, has shown that this species is very sensitive to the agent, with patients invariably improving within 10 days of treatment; in Dr Dieterich's experience, this organism accounts for only approximately 10% of microsporidiosis cases.

Cyclospora

Cyclospora is another recently described pathogen that has been found to produce devastating diarrhea in AIDS patients. It closely resembles *Cryptosporidium*, and also results in positive acid-fast testing. It can be distinguished from *Cryptosporidium* on the basis of a distinctively shaped nucleus. Although there is no known proven treatment as yet, patients able to tolerate trimethoprim-sulfamethoxazole appear to respond to treatment with the agent.

CMV

Biopsy remains the sole method for definitive diagnosis of CMV GI infection. Cases of upper GI and lower GI infection appear to occur with similar frequency; CMV hepatitis is rare in AIDS patients compared with its incidence in transplant patients. In stressing the need to persevere in arriving at an etiologic diagnosis and the need to consider presence of multiple pathogens, Dr Dieterich recounted a case in which the finding of *C difficile* pseudomembranous colitis, which often is not present alone in AIDS patients, prompted him to biopsy tissue beneath the membranes, which subsequently revealed the presence of CMV, *Cryptosporidium*, and MAC.

As related by Dr Dieterich, CMV GI disease can be successfully treated. A placebo-controlled trial in patients with CMV colitis conducted by Dr Dieterich and colleagues showed that IV ganciclovir was associated with significant effects in treatment response (20/32 vs 11/30), clearance of viral culture (5/25 vs 17/26 positive), weight change, and incidence of extracolonic CMV disease (4 vs 7) during the 14-day study; Dr Dieterich stated that virtually all treated patients exhibited improvement and that although no significant improvement in diarrhea score was observed over the 14 days, all treated patients actually improved in this regard. He stressed that an important finding was that five of the placebo patients (compared with none of the ganciclovir patients) developed CMV retinitis during the 14 days, and urged that any patient suspected of CMV GI infection be referred for ophthalmologic examination. In a more recent study, Dr Dieterich and colleagues found that IV foscarnet treatment in patients with CMV GI infection failing ganciclovir treatment was associated with clinical and pathologic response in eight of ten patients with colonic disease and clinical response in six of nine and pathologic response in six of eight patients with esophageal disease (overall clinical and pathologic response rates of 74% and 67%, respectively), with the median survival in these patients being 5 months. In other recently reported experience, Dr Dieterich and colleagues made the surprising finding that nine of 10 patients failing both ganciclovir and foscarnet alone subsequently responded to combination treatment; the overall median survival in these patients after the start of

combination treatment was 175 days, with median survival among the five who died being 190 days and that among the five survivors being 166 days at last analysis. In a recent pilot/pharmacokinetics study, Dr Dieterich and colleagues found that twice daily foscarnet 90 mg/kg IV was associated with pathologic and endoscopic improvement in 90% of patients with CMV GI disease, with full resolution of symptoms occurring in 80% of patients and partial resolution occurring in 10%. Dr Dieterich noted that confirmation of such findings could have a financial impact, since the 90 mg/kg bid regimen can be administered at home, whereas the 60 mg/kg tid regimen must be administered in the hospital; he also related that the former regimen has been reported to be effective in treatment of CMV retinitis in European experience.

The role of maintenance therapy for CMV GI disease after initial treatment remains unclear. In a study scheduled to begin soon, patients with upper or lower CMV GI disease will receive foscarnet 90 mg/kg IV bid for 4 weeks followed by randomization to maintenance treatment or no maintenance treatment. In an ACTG study that is currently under way, a pharmacokinetic analysis of oral ganciclovir maintenance treatment is to be performed in patients with CMV colitis after 3 weeks of ganciclovir-induction therapy. ■

Developments in CMV Disease Treatment

Developments in CMV disease treatment were discussed at the Boston meeting by W. Lawrence Drew, MD, PhD, from the Mt Zion Medical Center of the University of California at San Francisco.

Diagnostics

As related by Dr Drew, advances in CMV diagnostics include wide availability of a novel CMV antigenemia assay, involving staining of peripheral blood samples with tagged monoclonal antibodies, that permits documentation of CMV viremia on a same-day basis. According to Dr Drew the antigen assay is also an effective means of documenting CMV central nervous system (CNS) disease. Although initial experience with the test in Dr Drew's laboratory suggested 60% to 70% accuracy compared with blood culture, continued use in their hands and at other laboratories has shown sensitivity approaching 90% to 100%. Dr Drew stated that the shell vial assay, which can provide results within 24 hours, has proven to also have high accuracy in detecting viremia according to blood culture standards. A particular virtue of the antigen assay is the ability to quantitate viremia. For example, it is possible that a correlation between degree of viral antigenemia and CMV wasting syndrome will be demonstrated. Another diagnostic development, the branched-DNA assay for measuring levels of CMV DNA in the blood, also provides quantitative results. Dr Drew presented an example in which a patient developed CMV retinitis 3 weeks after persistent increased viral DNA levels were initially detected on the assay, followed by levels falling below detection limits at 10 days after initiation of ganciclovir treatment. As related by Dr Drew, the branched-DNA assay may thus prove to be of value in predicting onset of disease, as well as providing a practical method for monitoring patients during treatment—eg, for documenting an antiviral effect and then its dimunition in association with resistance. Similar considerations apply to quantitative PCR techniques that are currently undergoing adaptation for routine clinical use.

Resistance

Studies performed by Dr Drew and colleagues several years ago indicate that CMV isolates resistant to ganciclovir can be isolated in approximately 10% of patients after 3 months of treatment. The majority of cases of resistance are due to mutation in the viral kinase required for initial phosphorylation of ganciclovir. Rare cases are attributable to mutation in cellular DNA polymerase, and double mutations may occasionally occur. As noted by Dr Drew, resistance is manifest by progressive increases in drug 50% effective doses (ED-50s) over time and appears to be the result of selection of preexisting mutants in the viral population. The viral kinase mutations that have been associated with resistance include substitutions at amino acid residues 460 and 595 in the UL97 or protein kinase gene. As stated by Dr Drew, given successful adaptation for routine clinical laboratory use, use of PCR to detect such mutations in clinical isolates may prove valuable in patient management, providing extremely rapid identification or prediction of resistance compared with current culture-based phenotypic assays. He noted that resistant genotypes are identified by PCR only when they constitute at least approximately 10% of the viral population in an individual sample and that this threshold level appears to correlate with initial increases in ED-50s. Thus, it is unlikely that detection of resistant genotypes by PCR would significantly antedate development of phenotypic resistance.

Development of resistance to foscarnet was expected to occur less frequently than ganciclovir resistance, given that foscarnet does not require phosphorylation to its active form. Studies at Dr Drew's laboratory have indicated that whereas all ganciclovir-sensitive CMV strains remain susceptible to foscarnet, approximately half of ganciclovir-resistant strains also exhibit reduced sensitivity to foscarnet. Dr Drew suggested that these isolates may exhibit DNA polymerase resistance mutations or double mutations. According to data from a Studies of the Ocular Complications of AIDS (SOCA) patient group presented by Dr Drew, there was an equivalent increase in the proportion of both ganciclovir-treated and foscarnet-treated patients becoming blood culture-positive over time on treatment after initial conversion to negative culture. This suggests a similar rate of resistance development in patients receiving the two drugs, but definitive interpretation will follow the results of antiviral resistance testing of all isolates. According to Dr Drew, information on the incidence of resistance in SOCA patient isolates and on the relationship of resistance to clinical events in these patients may be available before year end.

Oral ganciclovir

As related by Dr Drew, study of the effects of oral (1 to 3 g/d) and IV (5 mg/kg/d) ganciclovir on CMV titer in semen of infected patients over 28 days has shown that both forms of ganciclovir are associated with decreased titers in the majority of patients. Although the antiviral effect of the oral form is reduced compared with the IV drug, in association with poor bioavailability, the need for an oral agent for use in prophylaxis and maintenance and the documentation of meaningful antiviral activity by the oral agent have prompted performance of a number of trials of oral treatment. According to Dr Drew, preliminary data from a large-scale preventive study are expected by year end and enrollment of a community consortium prevention trial is nearly complete. Maintenance trials include one in which patients were randomized to oral or IV maintenance after IV induction therapy and one in which patients already on IV maintenance were offered the choice of continuing on IV or switching to oral maintenance. Data from