

Tuberculosis Management

The management of tuberculosis was discussed at the Atlanta meeting by Michael L. Tapper, MD, from Lenox Hill Hospital, New York, New York.

Between the mid-1980s and 1992, the number of reported tuberculosis (TB) cases in the US exceeded the projected case number by more than 50,000. The highest case rates and the largest increase in case rates over this period have been in black and hispanic individuals largely between the ages of 30 and 45 years (Figure 6). As observed by Dr Tapper, the increase in cases associated with the convergence of the HIV-infected and *Mycobacterium tuberculosis* (MTB)-infected populations in part reflects the failure of public health systems to adequately control TB, with this being particularly true in the large urban centers in which the disease is now epidemic. He intimated that preliminary epidemiologic data for 1993 are likely to reveal a decrease in case rates in association with recognition of this problem and reinvigorated public health measures, including directly observed therapy (DOT) at some locales. However, he also warned that abatement of vigilance in this regard would lead to resurgence of cases in epidemic areas and increased incidents in locales that have not yet witnessed significant changes in case rates.

Prevention and diagnosis

Centers for Disease Control and Prevention (CDC) estimates of an HIV-infected population of 1 million and latent MTB infection of approximately 10% in the general population indicate the potential for 100,000 cases of active TB in HIV-infected individuals. As related by Dr Tapper, the

presence of AIDS and HIV infection increases risk for reactivation disease by 170-fold and 113-fold, respectively, over that associated with absence of known reactivation risk factors. He stressed that important objectives of TB management remain (1) prevention of cases through early identification of HIV infection, timely tuberculin skin testing, and timely institution of prophylaxis, and (2) improved detection and prompt treatment of disease. Factors contributing to difficulty in accurate diagnosis include: atypical pulmonary patterns; the high frequency of pulmonary disease caused by such other pathogens as *P. carinii* and cytomegalovirus (CMV); the common presence of such other atypical mycobacteria as *M. avium* complex (MAC); frequent occurrence of TB at extrapulmonary sites, which often constitutes the presenting form of disease; and anergy on skin testing. As noted by Dr Tapper, loss of reactivity to skin testing, which is relied upon heavily in diagnosis, becomes increasingly common with increasing immune suppression. Whereas false-negatives occur in approximately 10% of HIV-infected individuals with CD4+ cell counts $>500/\mu\text{L}$, a proportion similar to that among HIV-negative individuals, they are observed in approximately 80% of those with cell counts $<50/\mu\text{L}$. As related by Dr Tapper, it is important that a high clinical index of suspicion for TB be maintained in HIV-infected patients. He suggested that early identification of active disease can be facilitated by

remembering that it can occur simultaneously with other pulmonary infection, by considering any acid-fast bacilli in respiratory specimens to be MTB until proven otherwise, and by utilizing such rapid laboratory diagnostic methods as fluorescent microscopy and radiometric culture and drug susceptibility testing.

With regard to chemoprophylactic regimens, Dr Tapper stated that HIV-positive individuals who are tuberculin-skin-test positive should receive 1 year of isoniazid (INH) at a dose of 300 mg/d with appropriate monitoring of clinical symptoms and liver function tests. HIV-positive individuals who are anergic, but who are deemed at high-risk for TB exposure in the community or in health care facilities, should also be evaluated for INH chemoprophylaxis. Consideration should be given to administering prophylaxis under direct observation to any individual judged likely to be non-compliant.

Dr Tapper noted that prophylaxis for individuals exposed to drug-resistant MTB is problematic. Rifampin prophylaxis is likely to be effective for persons exposed to INH-resistant, rifampin-sensitive strains of MTB. No data exist to recommend a prophylactic regimen for exposure to INH- and rifampin-resistant TB. In June 1992, the CDC published a decision analysis that offers the option of pyrazinamide (PZA) plus a quinolone or ethambutol for persons exposed to multi-drug-resistant TB (MDR-TB). At least one group has reported a high degree of intolerance to the quinolone (ofloxacin)/PZA regimen.

New York City epidemic

The contribution of public health system failures to the upsurge in TB is underscored by experience with the disease in central Harlem, New York City. As noted by Dr Tapper, TB rates in this area have long been several orders of magnitude greater than the national average, as well as markedly higher than citywide rates. After a period of marked decline from 1970 rates, case rates began to increase in the late 1970s, with a dramatic rise occurring over the next decade. According to Dr Tapper, the increase was facilitated by the deterioration of the public health infrastructure in New York City, including withdrawal of funds from TB treatment programs and the inability to access patients to begin and complete treatment. In a recent study reported by Brudney et al of more than 200 consecutive TB inpatients of an area hospital, 79% of whom were male and who had a mean age of 42.5 years, it was found that 53% were alcoholic, 45% homeless, 23% unstably housed, and 82% unemployed,

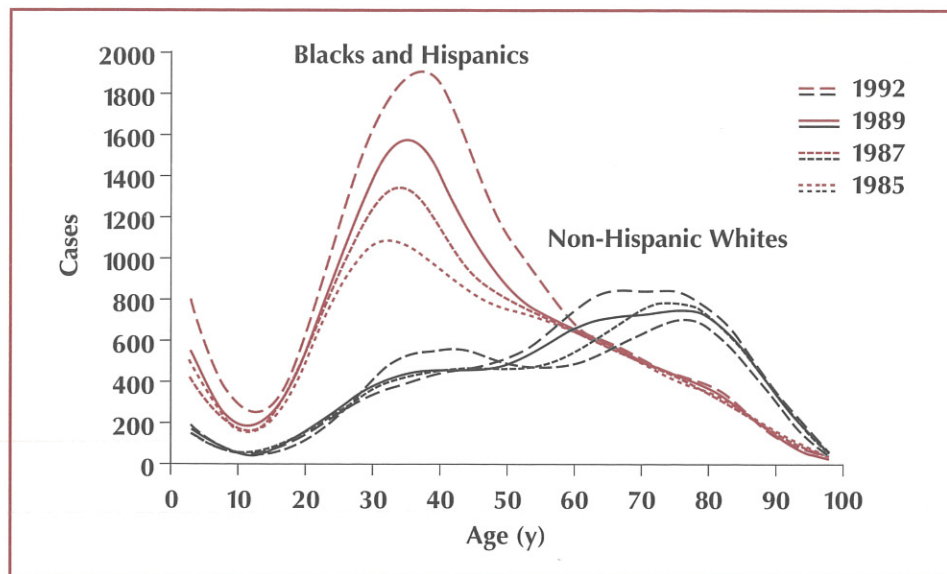


Figure 6. Number of TB cases by age among black or hispanic patients and among non-hispanic white patients in 1985, 1987, 1989, and 1992. Data are from CDC, Division of TB Elimination.

with 40% having advanced HIV disease. Of more than 175 discharged on TB treatment, 4% were cured, 6% remained on treatment, and 1% had died of HIV disease at the time of the report; the remaining 89% were noncompliant, with 56% having no follow-up treatment, 28% having <3 months of treatment, and 6% having ≥3 months of treatment. The high rate of incomplete treatment provides an explanation for the continuing community outbreak and hospital outbreaks, as well as the emergence of drug-resistant MTB.

On a model presented by Dr Tapper, increased numbers of patients with active disease represent increased sources of

Table 5. CDC draft guidelines for initial treatment of TB among children and adults

TB without HIV infection

Option 1

Administer daily INH, RIF, and PZA for 8 weeks followed by 16 weeks of INH and RIF daily or 2–3 times/week¹ in areas where the INH resistance rate is not documented to be less than 4%. EMB or SM should be added to the initial regimen until susceptibility to INH and RIF is demonstrated. Continue treatment for at least 6 months and 3 months beyond culture conversion. Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.

Option 2

Administer daily INH, RIF, PZA, and SM or EMB for 2 weeks followed by 2 times/week¹ administration of the same drugs for 6 weeks (by DOT³), and subsequently, with 2 times/week administration of INH and RIF for 16 weeks (by DOT). Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.

Option 3

Treat by DOT, 3 times/week¹ with INH, RIF, PZA, and EMB or SM for 6 months.² Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.

TB with HIV infection

Options 1, 2, or 3 can be used, but treatment regimens should continue for a total of 9 months and at 6 months beyond culture conversion.

¹All regimens administered 2 times/week or 3 times/week should be monitored by DOT for the duration of therapy.

²The strongest evidence from clinical trials is the effectiveness of all four drugs administered for the full 6 months. There is weaker evidence that SM can be discontinued after 4 months if the isolate is susceptible to all drugs. The evidence for stopping PZA before the end of 6 months is equivocal for the 3 times/week regimen, and there is no evidence on the effectiveness of this regimen with EMB for less than the full 6 months.

³DOT—Directly observed therapy.

Adapted from: CDC MMWR 1993;42:1–8.

MTB infection; in the context of HIV infection, both morbidity and transmission of TB are amplified by (1) a high rate of reactivation disease among latently infected individuals who become HIV-infected and (2) by a high rate of active disease in previously MTB-naïve HIV-infected individuals following acute MTB exposure and infection in association with severe immune deficiency, with the latter problem being particularly apparent in congregate settings. Dr Tapper also stated that he is inclined to the opinion that HIV-infected individuals are more likely to become infected following exposure.

Nosocomial outbreaks

The numerous nosocomial outbreaks of MDR-TB in largely HIV-infected patients have been characterized by extremely high mortality rates and rapid progression to death. As related by Dr Tapper, factors contributing to these outbreaks include: delayed recognition of TB, with failure to consider the diagnosis in the presence of nonclassical radiographic findings; laboratory delays in specimen processing; delayed recognition of drug resistance; and delayed initiation of effective treatment, resulting in prolonged periods of infectiousness. As noted by Dr Tapper, an analysis by the CDC of patient characteristics in one outbreak showed that 14 (82%) of 17 patients presented with pulmonary and extrapulmonary infection sites, that only 69% had positive first sputum smears (with 94% eventually having positive smears), and that 82% had abnormal admission x-rays. Although infiltrates were common (13 of 14), other typical findings of pulmonary TB such as effusion (2 of 14), adenopathy (4 of 14), and miliary patterns (1 of 14) were largely absent. Another set of factors contributing to outbreaks consists of inadequate isolation procedures, including delayed initiation and inadequate duration of isolation, isolation lapses, inadequate ventilation, and inadequate precautions for cough-inducing procedures.

Treatment guidelines

According to statistics presented by Dr Tapper, initial resistance to at least one drug among TB cases increased from 8.9% nationally during 1982–1986 to 13.4% in 1991. Resistance to both INH and rifampin increased from 0.5% to 3.0% between the two periods. Patients with increased risk for drug-resistant TB include foreign-born persons from areas with high resistance rates (eg, Asia, Africa, and Latin America), residents of US areas with high prevalence of drug resistance, those who have previously been treated with anti-TB drugs,

UPCOMING EVENTS

International Society for Sexually Transmitted Disease Research (ISSTD) Meeting, New Orleans, Louisiana, USA, August 27–30, 1995. David H. Martin, MD, Chairman.

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those with positive bacteriologic findings after 3 months of treatment, and those who are contacts of known drug-resistant cases. The 1993 CDC draft guidelines for initial treatment of TB are shown in Table 5. Four drugs are recommended for use in all areas in which the INH resistance rate is ≥4% or in which the prevalence of INH resistance rate is not known. Recommendations for HIV-infected and HIV-uninfected individuals differ only with regard to the current recommendation that HIV-infected patients should be treated for 9 months and at least 6 months after culture conversion rather than 6 months and at least 3 months after culture conversion. Dr Tapper stated that it is possible that newer recommendations will indicate that adequate treatment can be provided in HIV-infected patients with drug-susceptible TB by a 6-month course of therapy with a four-drug regimen. He stressed that the recent decline in TB rates has been the result of intensive effort on the part of health care workers and largely reflects the success of strict adherence to directly observed therapy (DOT). On current recommendations, all treatment occurring on a twice or thrice weekly basis should be monitored by DOT for the duration of therapy.

Health care worker exposure

Widespread concern regarding exposure of health care workers to TB has also been addressed in CDC draft guidelines. According to statistics from MDR-TB outbreak hospitals related by Dr Tapper, 20 cases of MDR-TB among workers have been documented, and additional cases were seen outside these outbreaks. Cases have included physicians, nurses, dental

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/ μ L 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 symp-

toms. 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.

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

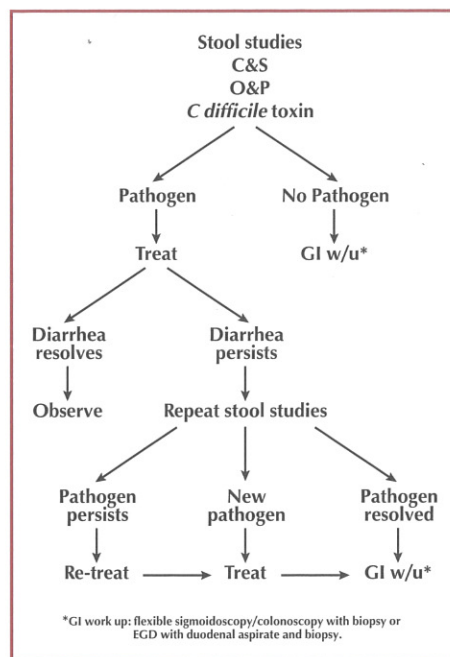


Figure 7. Evaluation of diarrhea in patients with HIV disease. C&S = culture and stain. O&P = ova and parasites. w/u = work-up. EGD = esophago-gastroduodenoscopy. Figure courtesy of Douglas T. Dieterich, MD.