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Authors

Kelly, Kristen M
Yousefi, Shokooh
Carandang, Gloria
et al.

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Mycobacterial Disease in the AIDS Patient

Kristen Cesario, M.D.
Shookooh Yousefi, Ph.D.
Gloria Carandang, B.S.
Thomas Cesario, M.D.

Mycobacteria have been known since the nineteenth century to be pathogenic for humans. Thus Koch first described the tubercle bacillus in 1882. Before the turn of the century, atypical variants had also been appreciated that were associated with disease in animals. Over time a greater appreciation of these organisms and their means of spread led to better attempts at control and treatment of these agents. With the introduction into society of the human immune deficiency virus (HIV), however, the natural mechanisms by which the body controls the organisms were significantly impaired in HIV-infected patients and atypical forms of mycobacterial disease became prevalent. These organisms have now become one of the most significant threats to these individuals and on occasion may require some form of surgical intervention.

CLASSIFICATION

In Table 7.1 are listed most of the important mycobacteria encountered in the HIV-infected patient. All in all, the genus *Mycobacterium* contains about 50 species. The most common infections seen in HIV-infected patients are those asso-

TABLE 7.1. Mycobacteria Commonly Found in HIV-infected Patients

Strict pathogens	*M. avium*
M. tuberculosis	*M. intracellulare*
M. bovis	*M. fortuitum*
M. leprae	*M. chelonae*
Other mycobacteria	Usually saprophytic agents
M. kansasii	*M. gordonae*
M. xenopi	*M. smegmatis*

ciated with *Mycobacterium avium intracellulare* complex (MAI) and *Mycobacterium tuberculosis*. This chapter will concentrate primarily on these organisms. The MAI complex itself is composed of 28 seroagglutination types,[1] although *M. avium* and *M. intracellulare* are distinct genera. Mycobacteria can be easily grown on conventional media such as Lowenstein-Jensen or Middlebrook 7H-10. They may also be identified using radiolabeled broth such as that employed in the BACTEC system.[2]

EPIDEMIOLOGY

It is generally assumed that atypical mycobacteria and especially MAI are environmentally acquired.[3] Wolinsky and Rynearson[4] were able to isolate nontuberculous mycobacteria (NTM) from 82% of soil samples in the eastern United States, and mycobacteria in the MAI complex have been identified in birds[5] and animals.[6] Falkinham et al.[7] have found that nontuberculous mycobacteria such as MAI are often found in fresh and brackish waters such as estuaries and rivers along the southeastern coast of the U.S. *M. kansasii*[8] and *M. xenopi*[9] have been found in specimens from water supplies and tap water, and MAI has been identified in the hot water system of a hospital.[10] The potential, however, for human-to-human transmission of nontuberculous mycobacteria is very low.[3] Table 7.2 reviews the important epidemiological features of MAI infections in

TABLE 7.2. Epidemiologic Features of *Mycobacterium avium intracellulare* in AIDS Patients

Environmentally acquired, probably from soil or water sources
Can be found in hot water supplies of hospitals
No clear evidence of human-to-human spread
Currently found in disseminated form in 15% to 24% of AIDS patients
More common in younger patients
No significant difference between racial groups as regards acquisition of the infection
Seen most commonly in individuals with CD4 counts below 100 cells/mm^3

AIDS patients. In contrast, *M. tuberculosis* is classically spread human to human by the respiratory route with the risk of infection being related to the frequency and density of TB bacilli in the air of the environment.[11]

Previously thought of as a relatively unusual infection of the respiratory tract primarily in patients with chronic lung diseases or as an occasional cause of lymphadenitis in children,[1] nontuberculous mycobacteria began to significantly increase in incidence along with the AIDS epidemic.[12] Disseminated forms of the disease were particularly common. Through the first six years of the epidemic, the percentage of reported AIDS cases with disseminated nontuberculous mycobacteria infection remained stable at 5.5%.[12] The vast majority of these infections (96%) were caused by MAI. It was found that disseminated nontuberculous mycobacterial disease in the population of AIDS patients was seen less commonly in Hispanics, declined with age, was equally common in both sexes, and was seen with equal frequency in persons who had acquired HIV infection by different routes.[12] What was found important, however, was the level of CD4 cell count at the time the dissemination was manifest. Usually, disseminated infection, at least with MAI complex, occurred in patients with less than 60 CD4 cells/mm^3 [13] late in the course of the HIV infection and after a diagnosis of AIDS had been established. Nightingale et al.[14] have shown a direct correlation between CD4 counts and the frequency of bacteremia with MAI.

More recent information suggests that disseminated MAI infection occurs in 15–24% of patients with AIDS[13] and some autopsy studies have suggested the incidence may be higher.[15,16] While MAI infections constitute the vast majority of nontuberculous mycobacteria infections seen in AIDS patients, other species may also produce disease in this setting but at a lesser frequency.[17]

Mycobacterium tuberculosis infections had experienced a steady decline in case rates from the time national TB reporting was instituted in 1953 through 1984.[11] From 1984 the number of cases rose progressively[18] and increased numbers of persons with extrapulmonary disease were seen. The disease is most common in blacks and Hispanics.[11]

PATHOGENESIS

Acquisition of MAI has generally been presumed to be via the respiratory route; however, recent considerations in the HIV-infected patient have questioned this hypothesis and have suggested that the GI tract may be the portal of entry.[19] It has also been shown that asymptomatic colonization of respiratory secretions and stool frequency precedes MAI bacteremia.[20] Further, it appears likely that MAI in AIDS patients often represents a recent infection.[11]

M. tuberculosis, in contrast, largely results from reactivation of previous infection in patients with AIDS.[21] In the case of both MAI and *M. tuberculosis* infections in HIV patients, altered cellular immunity as assessed by CD4 numbers and functions and by diminished macrophage capabilities results in progressive mycobacterial disease and influences the clinical presentation.[11]

CLINICAL MANIFESTATIONS

The most common presentation of patients with AIDS and disseminated MAI infections is that of unexplained fever and weight loss in the setting of a low ($<100/mm^3$) CD4 count.[15,22,23] Disseminated MAI has also been found to be the most common cause of fever of unknown origin in AIDS patients.[24]

Common symptoms and signs include fever, weight loss, and malaise. Chronic diarrhea, night sweats, and abdominal pain are also frequent. Other less common manifestations include extrahepatic obstruction,[13] endobronchial lesions,[25] skin lesions,[26] arthritis,[27] and endophthalmitis.[28] Anemia to a severe degree is often a part of MAI infection in the setting of AIDS.[29] Chest x-ray findings range from normal[30] to nodular, diffuse, or patchy infiltrates.[11] Abdominal CT scans may show hepatosplenomegaly or large nodes in the retroperitoneal and mesenteric areas.[31]

Regarding *M. tuberculosis* infections in AIDS patients, constitutional symptoms such as fever, night sweats, fatigue, malaise, and weight loss again often dominate the clinical picture.[11] Cough is frequent and extrapulmonary disseminated forms of the disease are more often encountered frequently. TB tends to occur earlier in the course of HIV infection than MAI. Thus, CD4 counts are often higher,[32,33] i.e., >200 mm^3.

Pulmonary involvement infections occur in 70% or more of patients with dual *M. tuberculosis* and HIV infection.[11] Typically hilar and mediastinal nodes with lower lobe diffuse alveolar or linear infiltration are seen radiographically.[34]

Diagnosis

Diagnosis of MAI is established by culture especially of the blood. Stool, sputum, bronchial washings, and bone marrow may also be cultured. The value of a single culture of respiratory secretions, however, may represent colonization only and not dissemination. As indicated above, the organism can be cultured on routine media used for mycobacteria. The BACTEC system which measures the production of C^{14}-labeled CO_2 from substrates specific for mycobacteria is frequently useful. Additionally, I^{125}-labeled DNA probes which detect specific ribosomal RNA in primary culture may be used.[35] This will facilitate diagnosis and provide early identification as to the type of mycobacteria involved. For *M. tuberculosis,* culture of the organism from any site, especially sputum, establishes the diagnosis.

Skin test reactivity for *M. tuberculosis* infection is frequently overlooked as a diagnostic modality. While AIDS patients are frequently anergic, as much as 56% of HIV-infected patients retain skin test reactivity when infected by the tubercle bacillus.[11]

Treatment

MAI organisms are often resistant in vitro to many first-line agents used against the tubercle bacillus. Several of the newer agents however have appeared more

useful in the test tube. The early trials[15,36] resulted in a pessimistic outlook regarding the response to the antimicrobial agents for patients with AIDS and MAI infections; however later studies have provided optimism.

Agins et al.[37] reported on the use of ethambutol, rifampin, clofazimine, and isoniazid and noted that bacteremia cleared on this regimen in five of seven patients and symptoms improved in six.

Hoy et al.[38] evaluated a combination of rifampin, clofazimine, isoniazid, and ethambutol. Mycobacteremia was cleared in 22 of 25 patients and 10 experienced complete resolution of symptoms. The authors attributed their success to a higher dose of rifampin (300 to 500 mg/day) compared to other studies, earlier diagnosis, and synergy between rifampin and ethambutol.

Chiu et al.[39] used amikacin (7.5 mg/kg given intravenously daily for 4 weeks) plus ciprofloxacin, ethambutol, and rifampin for at least 12 weeks. This drug combination decreased the level of mycobacteremia and decreased symptoms.

Later Kemper et al.[40] utilized an entirely oral regimen of rifampin, ethambutol, clofazimine, and ciprofloxacin and left the use of intravenous amikacin to the discretion of the investigator. These authors also reported that bacteremia and symptomatology were decreased often within 2 weeks of the time these drugs were employed. Colony counts rose rapidly, however, if treatment was discontinued.

Denson et al.[41] used a five-drug combination including amikacin, clofazimine, rifampin, ethambutol, and ciprofloxacin and obtained a favorable response in four patients. De Lalla et al.[42] reported the use of clarithromycin, ciprofloxacin, and amikacin in 12 AIDS patients. These investigators found that mycobacteremia cleared in all 12 patients who were treated with this regimen.

Finally, Young et al.[43] used azithromycin alone in 23 patients for periods up to 30 days. This drug alone was found to reduce bacteremia in 75% of patients treated for 20 days or longer.

From these trials we can obtain presumptive evidence that chemotherapy is beneficial for MAI infections in AIDS patients. It appears that a four-drug oral regimen of ciprofloxacin, clofazimine, ethambutol, and rifampin is beneficial. Clarithromycin or azithromycin can play an added role or possibly be substituted for one of these drugs, especially if the patient becomes intolerant. Amikacin given intravenously is of use in the patient who appears unstable. This duration of therapy is not resolved but it is probable that a drug combination needs to be continuously employed throughout the lifetime of the individual. Table 7.3 outlines the agents used to treat MAI and provides the dosage.

For *M. tuberculosis* most researchers have found that the standard antituberculosis chemotherapy regimens are both safe and effective.[34,44,45] A recommended treatment schedule includes 300 mg/day isoniazid, 600 mg/day rifampin, and 20–30 mg/kg/day of pyrazinamide.[46] The latter is continued for 2 months and the two former agents for either 9 months or 6 months after culture conversion (whichever is longer). Drug susceptibility testing must be employed in all cases, and if drug resistance is found the choice of agents and the duration of therapy must be revised (usually extended to 18–24 months). Recently outbreaks of drug-resistant tuberculosis have been encountered[47,48] in HIV-infected patients and will clearly pose a problem to be followed closely.

TABLE 7.3. Initial Therapy for HIV-infected Adult Patients with *Mycobacterium avium intracellulare* Infection

Drug	*Dose*	*Route*	*Schedule*
Ciprofloxacin	750 mg	Oral	Twice a day
Clofazimine	100 mg	Oral	Every day
Ethambutol	15 mg/kg	Oral	Every day
Rifampin	600 mg	Oral	Every day
Alternative or additional agents			
Clarithromycin	500 mg	Oral	Twice a day
Amikacin	7.5 mg/kg	Intravenous	Every day

PROGNOSIS

It has been debated whether or not MAI infections adversely affect survival in patients with HIV infection. A number of studies, however, have now firmly suggested that such an infection in the setting of HIV does influence life span. Horsburgh et al.[49] compared patients with AIDS alone and patients with AIDS and disseminated *Mycobacterium avium* complex. In a case-controlled study matching features such as CD4 counts, these investigators demonstrated that patients with disseminated MAI had a significantly shorter survival (5.6 ± 1.1 months) than those who did not (10.8 ± 1.3 months). These same authors found treatment eliminated this difference and the survival of treated patients with disseminated MAI was not significantly different from that of AIDS patients without disseminated MAI infection.

Jacobson et al.[50] also verified that disseminated MAI reduced the duration of life span in AIDS patients. Werlikowske et al.[51] retrospectively reviewed the records of patients with AIDS and disseminated *Mycobacterium avium intracellulare* infection. In a multivariate analysis, they suggested patients who were treated for MAI survived longer than those who were not so treated.

As regards, *M. tuberculosis* infection, Small et al.[52] reported that all 60 patients in their study cleared sputum within 1 to 20 weeks from the start of therapy and only three relapsed. One treatment failure occurred in a patient with multiply drug-resistant organisms. Pitchenik et al.[53] prospectively reported on 90 patients with tuberculosis and HIV infection. Of accessible patients, 96% converted their sputum within 3 months and only 19% relapsed but most (9 of 11) of this latter group were noncompliant. In both studies, the majority of patients died during the study but mortality was due mainly to conditions other than the tuberculosis. Only 10% to 20% of the patients experienced adverse drug reactions.

It would appear from these studies that the response to antituberculosis therapy in HIV-infected patients is quite good.

TABLE 7.4. Conditions Related to Infection with *Mycobacterium avium intracellulare* in AIDS Patients That Would Merit Surgical Consultation

Conditions where surgery might be possible
Lymph node biopsy
Liver biopsy
Exploration for abdominal mass
Abscess drainage
Persistent cavitary lung disease
Access placement
Infection of the gallbladder
Nonsurgical problems
Endoscopic abnormalities
Differential diagnosis of extrahepatic obstruction
Consultation for persistent abdominal pain

SURGICAL CONSIDERATIONS

Most cases of MAI present with a medical illness and only a minority develop conditions that would merit surgical considerations. Several situations do arise as part of the spectrum of illness associated with MAI that might bring the patient to the attention of the surgeon (Table 7.4).

During those conditions such as persistent abdominal pain where endoscopy might be performed, the operator—either gastroenterologist or surgeon—should be aware of the macroscopic gastrointestinal pathology that MAI might cause. Rene et al.[54] reported that overall 5% of their AIDS patients had gastrointestinal pathology. They described two patients with MAI and enterocolic lesions, one with exudate and one with erythema. Autran et al.[55] and Roth et al.[56] described patients with intestinal lesions suggestive of Whipple's disease but those intestinal alterations were due to MAI. Related to the latter pathology is the fact that severe malabsorption may at least in part be caused by MAI.[57]

Gray and Rabeneck[58] have contributed one of the most extensive descriptions of MAI involvement in the gastrointestinal tract. They reported 35 AIDS patients with infection of the gastrointestinal tract by MAI and noted the duodenum was commonly involved. They particularly described unusual white nodules believed due to MAI. They also reported a case of rectal ulcer associated with MAI infection.

AIDS patients may have diarrhea associated with unusual pathogens such as MAI;[58] they may have abnormal D-xylose studies and entirely normal-appearing gastrointestinal tracts.

Pain may be the result of MAI infection involving abdominal organs including the small bowel.[57] This may require exclusion of surgical disease. The character of the pain has not been well enough described to allow it to be differentiated from other conditions, but at least in the authors' experience the pain while intense is not associated with physical findings suggestive of surgical conditions.

The liver also is frequently involved by MAI infection. Multiple granulomas

may result.[56,59] Elevation of liver enzymes is common under these circumstances[60] and such findings may merit liver biopsy. Tissue obtained may yield the organism on culture establishing the diagnosis if not made by other means. In fact, abnormal liver enzymes may suggest obstructive disease[61] and require differentiation from surgically correctable lesions. Enlarged nodes may also cause extrahepatic biliary tract obstruction.[15]

To complicate matters further, Romano et al.[61] described eight patients with AIDS and right upper quadrant abdominal pain, tenderness, and abnormal liver function studies. All eight patients had thickened gall bladder walls. MAI was recovered from the gall bladder of one of these patients suggesting it could have played a role in the observed changes. Clarification of the exact cause of the pathology in these patients may unfortunately require cholecystectomy.

Lymph node involvement in patients infected with both HIV and MAI is common especially in the abdomen.[31] Nodes can be of such a degree of enlargement that may result in abdominal masses or may obstruct the biliary tree.[15] This may necessitate surgical exploration to establish a diagnosis unless needle biopsy or aspiration under fluoroscopy can be used for the same purpose.

Deziel et al.[62] described 21 major abdominal operations on patients with AIDS, at least four of whom had MAI infection. In three cases, lymph node and liver biopsies were performed and in one case small bowel obstruction was relieved by lysis of adhesions. The role of the MAI if any in the latter was not specified. One additional patient had a pelvic abscess drained which appeared to relate to MAI.

Turning from the gastrointestinal tract to the lung, an unusual cause of cavitary lung disease can be MAI,[63] as well as *M. tuberculosis.* In the case of localized disease caused by multiply resistant organisms, consideration for surgical removal has always been a reasonable possibility, especially if medical therapy failed.[64] With the emergence of resistant mycobacterial strains, this might be a consideration in HIV-infected patients, if they can be stabilized, have a reasonable life expectancy, are compliant, and there is reason to believe the patient will benefit if the localized area were to be removed.

Finally, for MAI, access placement for administration particularly of amikacin can bring the patient to the attention of the surgeon.

For *M. tuberculosis,* few reasons for surgical intervention exist but since the disease is disseminated in AIDS patients there is always the possibility that localized disease could result in a condition requiring surgery. This could again be for the purpose of establishing a diagnosis, providing drainage, relieving osbstructing lesions, or providing access for the administration of intravenous medication.

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