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***M. avium*, the Modern Epidemic**

by James L. Cook M. D.

In recent months, considerable attention has been focused on the resurgence of tuberculosis across the United States. This problem has been highlighted by several outbreaks of infections due to drug-resistant organisms. But another epidemic of mycobacterial disease has received much less recognition — an apparent increase in illnesses resulting from infection with the nontuberculous mycobacteria, *Mycobacterium avium* and *Mycobacterium intracellulare*, naturally drug-resistant mycobacteria commonly grouped together under the name *M. avium* complex.

Because reporting of disease due to nontuberculous mycobacteria is not required under public health regulations, reliable current incidence data are unavailable. But as a leading referral center for mycobacterial diseases, National Jewish has been seeing what appears to be an increase in the numbers of patients with *M. avium* complex infections, as have the pulmonary and infectious disease specialists throughout the nation with whom we consult.

It is important to note the following:

***M. avium* complex . . .
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1. An apparent upsurge in pulmonary disease due to *M. avium* complex is occurring among non-HIV-infected individuals *in addition to* the widespread infections with these agents among individuals with human immunodeficiency virus infection.
2. *M. avium* complex infection is not often considered in the initial differential diagnosis in patients who clinically appear to have tuberculosis.
3. Contrary to its conventional image as a colonizing microbe in the immunocompetent patient, *M. avium* complex is frequently associated with substantial morbidity and may be associated with increased mortality, and therefore merits vigilant treatment.

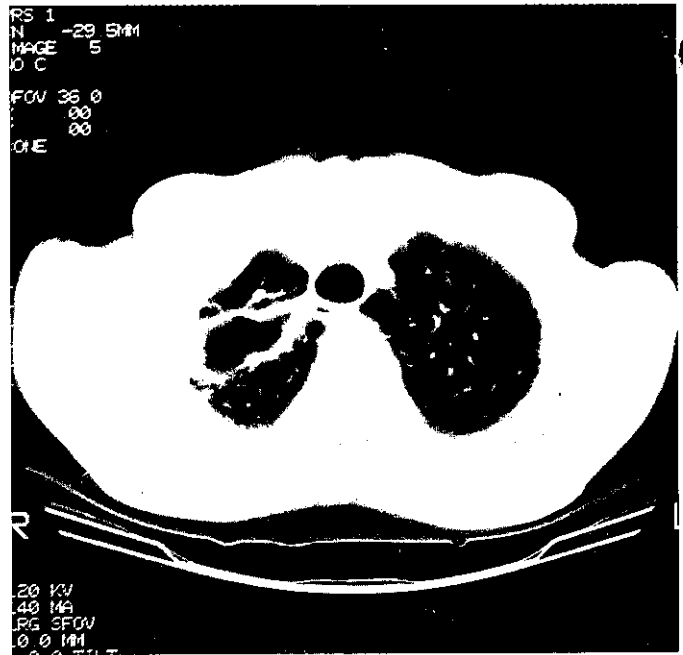
Considering these observations, a general update on this medical problem may be useful.

Clinical features and epidemiology

Disease due to *M. avium* complex presents in two general forms:

- pulmonary disease or localized lymphadenitis in the immunocompetent individual and
- disseminated infection in the immunocompromised patient.

The common symptoms and signs of pulmonary infection include cough, production of purulent sputum, hemoptysis, weight loss, fever and night sweats — a presentation that is indistinguishable from that of tuberculosis. Chest radiographs usually reveal underlying lung disease which appears to predispose to colonization and subsequent infection with these mycobacteria. The first published case reports from the 1940s and 50s, and most subsequent ones, have described the typical patient as an elderly white male with a history of chronic obstructive pulmonary disease, previous TB, bronchiectasis, pneumoconiosis, chronic



X-ray and CT scan of elderly man with cavitory mycobacterium avium disease.

aspiration pneumonia, bronchogenic carcinoma, or gastrectomy. Chest films may show one or more pulmonary cavities or a solitary pulmonary nodule without cavitation (Rosenzweig DY, Schlueter DP. Spectrum of clinical disease in pulmonary infection with *Mycobacterium avium-intracellulare*. Rev Inf Dis 1981; 3: 1046-51).

Extrapulmonary disease due to *M. avium* complex can range from benign, self-limited cervical lymphadenitis in children to widely disseminated infection in immunocompromised individuals. The most common clinical presentation of disseminated infection is persistent fever, with or without night sweats, accompanied by weight loss. Other signs and symptoms may include bone pain, anemia, hepatomegaly, splenomegaly and nodular skin lesions.

Many patients with disseminated disease have abnormalities of cell-mediated immunity. Disseminated *M. avium* complex infection makes a significant contribution to both morbidity and mortality in as many as 24 percent of AIDS patients (Horsburgh CR. *Mycobacterium avium* complex in the acquired immune deficiency syndrome.

N Engl J Med, 324:1332-7). In a review of *M. avium* complex disease among non-AIDS patients admitted to National Jewish from 1962 to 1984, 5 percent were found to have disseminated infection. When these cases were examined along with all others reported in the medical literature since 1940, only half of the patients were known to be immunologically compromised (Horsburgh CR, Mason UG, Farhi DC, Iseman MD. Disseminated infection with *Mycobacterium avium-intracellulare*. Medicine 1985; 64:36-48).¹⁷

At National Jewish and elsewhere, there is a growing interest in the 24-46 percent of individuals with pulmonary disease caused by *M. avium* complex who do not exhibit obvious predisposing factors. Many of these patients are apparently normal, healthy women (Prince DS, Peterson DD, Steiner RM. Infection with *Mycobacterium avium* complex in patients without predisposing conditions. N Engl J Med 1989; 321:863-8). Preliminary observations at National Jewish also have revealed an apparent increase in the incidence of pectus excavatum, thoracic scoliosis and mitral-valve prolapse among patients who develop pulmonary *M. avium*

complex disease. This association between morphotype and infection appears to be more common in patients with bilateral mid-lung field (middle lobe and lingular) infiltrates. These findings suggest the hypothesis that some of these patients have underlying multi-system connective tissue disorders that may, in some way, predispose them to colonization and infection with *M. avium* complex.

The apparent increase in the incidence of disease due to *M. avium* complex and the changing epidemiologic picture have raised new questions about the sources of infection as well as pathogen and host factors that may contribute to development of illness. It has long been concluded that organisms of the *M. avium* complex, unlike TB, are usually not transmitted from person to person. In early studies, a high proportion of patients with *M. avium-M. intracellulare* infections were from rural areas, with the highest rates seen in the southeastern United States. Environmental exposure is believed to be the primary source of infection (O'Brien RJ, Geiter LJ, Snyder DE Jr. The epidemiology of nontuberculous mycobacterial diseases in the United States: results

(Heifets LB [ed]. Drug susceptibility in the chemotherapy of mycobacterial infections. CRC Press, 1991). It is our opinion that selection of chemotherapeutic agents can and should be based on quantitative assessment of the degree of susceptibility of mycobacterial isolates in a reference laboratory such as the one at National Jewish.

The following is a brief description of techniques used in the clinical Mycobacteriology Laboratory at National Jewish. Tests performed here range from standard procedures to complicated assays, some of which are available only at this institution. Unprocessed sputum specimens and pure cultures are received from more than 1,200 laboratories, hospitals, physicians' offices and other facilities from every state in the country.

1. Isolation. Conventional smear examination of the concentrated sputum specimen is reported within 48 hours. In addition to conventional isolation procedures using agar medium, the BACTEC rapid isolation procedure is used to detect positive cultures of these usually slow-growing strains of bacteria within one week for most isolates and within five days in some cases. Quantification of the numbers of viable mycobacteria (CFU/ml) is also available; this procedure is most appropriate for blood specimens obtained from patients with disseminated infection. Final results of isolation are reported within three weeks for most isolates.
2. Mycobacterial identification. Rapid Gen-Probe identification usually is reported by Fax or telephone within 72 hours. Conventional methods of speciation for Gen-Probe negative cultures, also available from the lab, require about three weeks.
3. Drug susceptibility procedures. The proportion method of conventional drug suscep-

tibility testing in 7H11 agar plates is not currently recommended for *M. avium* complex isolates, since this technique, which was established and validated for *M. tuberculosis* only, is not sensitive enough to distinguish strains with various patterns of susceptibility. Determination of the minimal inhibitory concentration (MIC) in liquid medium (7H12 broth) provides an improved method for such susceptibility testing. These MIC assays can be done with both conventional and experimental drugs. In fact, it is the consensus of the clinical members of the Division of Infectious Diseases at National Jewish that the use of MIC data should be the standard of practice in designing drug treatment regimens for patients with *M. avium* complex infections (Heifets LB, Iseman MD. Individualized therapy versus standard regimens in the treatment of *Mycobacterium avium* infections. Amer Rev Respir Dis 1991, 144:1-2).

Treatment

Michael D. Iseman, M.D., Chief of the Mycobacterial Diseases Service in the Division of Infectious Diseases at National Jewish, has been involved with the American Thoracic Society and the Centers for Disease Control in formulating guidelines for the standard treatment of mycobacterial diseases. Initial guidelines were published in 1985 (Iseman MD, Corpe RF, O'Brien RJ, Rosenzweig D, Wolinsky E. Disease due to *Mycobacterium avium-intracellulare*. Chest 1985; 87: Suppl: 139S-149S). Since the publication of these preliminary guidelines, new information has become available on patterns of *M. avium* complex isolate susceptibility to antimycobacterial drugs using both conventional agar susceptible tests and single drug and combined drug MIC determinations (Heifets LB, Iseman MD. Choice of

Treatment for immunocompromised patients should focus on restoration of immune function, if possible, including reduction of immunosuppressive therapy to the minimum required

antimicrobial agents for *M. avium* disease based on quantitative tests of drug susceptibility. N Engl J Med 1990; 323:419-20). Some of the general guidelines for initiation of therapy for patients with *M. avium* complex infections that are used in the Infectious Diseases Division at National Jewish are as follows:

1. For the usual "moderately severe" case of pulmonary infection with *M. avium* complex, initial therapy should consist of three drugs including rifampin, ethambutol and one other antimycobacterial drug that is effective against the isolate as determined by in vitro susceptibility testing. An aminoglycoside antibiotic is usually added for the initial 2-4 months of treatment in these cases. The total duration of therapy for such patients is usually 18-24 months depending on the severity of the disease and on the clinical and bacteriologic status of the patient toward the end of the treatment period.
2. For immunologically intact patients with a solitary pulmonary nodule and with no evidence of other pulmonary disease as evidenced by chest radiograph and by high resolution chest CT scan studies, chemotherapy may not need to be given after resectional surgery. However, the nature of the resection and the detail with which the remainder of the lung is evaluated for evidence of infection must be considered

- carefully in this judgment.
3. For patients with rapidly progressive, highly symptomatic pulmonary infection due to *M. avium* complex, more aggressive initial therapy is indicated using 4-6 antimycobacterial drugs based on the results of *in vitro* susceptibility testing. Once again, these regimens are usually designed to include rifampin, ethambutol, a parenteral aminoglycoside antibiotic and at least two other effective agents.
 4. For patients with relatively ✓

localized pulmonary infections due to *M. avium* complex and with adequate cardiorespiratory reserve, resectional surgery combined with antimycobacterial chemotherapy is likely to offer a better chance for cure than chemotherapy alone due to the refractory nature of many of these mycobacterial infections. Owing to the destructive nature of these infections and the intense fibro-calcific response that is mounted against them, surgical procedures in these patients are often complicated

and should be performed only by thoracic surgeons skilled in the management of such cases.

In addition to the above, treatment for immunocompromised patients should focus on restoration of immune function, if possible, including reduction of immunosuppressive therapy to the minimum required.

At National Jewish, treatment of pulmonary disease due to *M. avium* complex infection also includes a multidisciplinary approach to management of the concomitant lung disorders frequently present in these patients, patient education, and psychosocial support of patients coping with chronic illness.

In the past, among the serious problems encountered in designing rational therapeutic regimens for mycobacterial infections has been the inability to analyze serum drug levels in patients on complex chemotherapeutic regimens. Most assays available and tested for antimycobacterial drug levels have been semi-quantitative bioassays for which only one drug can be given and tested at a time. With the recent development of assays of minimum inhibitory concentrations against mycobacterial isolates, analysis of serum drug levels will become increasingly useful in designing effective treatment regimens.

The Infectious Diseases Pharmacokinetics Laboratory (IDPL) in the Infectious Diseases Division at National Jewish has developed HPLC assays for analysis of serum levels of a variety of antimycobacterial drugs. This resource is available to physicians and institutions treating individuals with *M. avium* complex infections as well as other mycobacterial infections including TB. The IDPL also provides pharmacokinetic patient profiles and performs ongoing research aimed at maximizing efficacy and minimizing toxicity of current and investigational antimycobacterial drugs.

From the "Center Bibliography"

(courtesy of the Medical Library at National Jewish Center for Immunology and Respiratory Medicine.)

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Faculty

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Frontiers in Mycobacteriology: *M. avium*, the Modern Epidemic.

A symposium to review current understanding of the diagnosis, epidemiology, immunology, molecular biology, and treatment of *M. avium* infections, in both AIDS and non-AIDS patient populations. In Vail, CO October 15-19, 1992. Send abstracts for poster session to Dr. J. Cook, Program Chairman, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, Colorado 80206-1997 USA. Abstract deadline is July 24, 1992. For information and registration call (303) 398-1359.

The 35th Annual Pediatric Program sponsored by the Department of Pediatrics, University of Colorado School of Medicine, The Children's Hospital and National Jewish. August 2-6, 1992 in Aspen, CO. For information call 303-861-6945.

This conference is designed to meet the educational needs of practicing pediatricians, family physicians and other primary health care providers. This year's program features sessions devoted to Adolescent Medicine, Office Practice, Allergy/Pulmonology/Immunology and Infectious Disease. National Jewish Faculty, Gary Larsen, M.D., Stanley Szeffler, M.D., Leland Fan, M.D., Donald Leung, M.D., Ph.D. and Erwin Gelfand, M.D. will lecture on Wednesday, August 5, the Allergy/Pulmonology/Immunology day.

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