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Disease Due to *Mycobacterium avium-intracellulare*

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Mycobacterium avium and *M intracellulare* are presently grouped together as the *M avium-intracellulare* complex. These closely related organisms belong to Runyon's group III nonchromogenic mycobacteria. The *M avium-intracellulare* organisms are increasingly significant pathogens in North America. Unlike *M kansasii*, the other most prominent nontuberculous Mycobacterium associated with human disease, infections with *M avium-intracellulare* are generally highly resistant to treatment. The reservoirs and routes of transmission are uncertain. The cause of this apparent rise in the rate of infection is obscure. Unlike tuberculosis, *M avium-intracellulare* is not usually transmitted from person to person and therefore is not perceived as an important public health problem. Criteria for a firm diagnosis of pulmonary disease (vs colonization) are questioned. Chemotherapy for the disease has been based on empiricism, and no controlled observations have been made to ascertain the value of single agents or combined therapy in the treatment of this disease. Surgery for pulmonary disease has been employed with variable indications and no control groups for comparison. The increasing incidence of disease due to *M avium-intracellulare* among victims of acquired immunodeficiency syndrome (AIDS) has heightened concern. Thus, we are confronted with a burgeoning medical problem and no ideal studies from which scientifically defensible, statistically significant conclusions can be drawn. Hence, we provide the following sets of observations and recommendations in the hope that they will be useful in contemporary practice.

Epidemiology

Although disease due to *M avium* in animals was described a century ago and clinical descriptions of disease due to *M avium-intracellulare* in man began appearing approximately 30 years ago, there are still significant gaps in our understanding of the epidemiology of this disease. As the incidence of tuberculosis in the United States has declined, disease due to *M avium-intracellulare* has assumed relatively greater importance, and in some areas of the country, such disease is as common as tuberculosis, yet there are no consistent data available on the incidence and prevalence of the disease. This is because nontuberculous mycobacterial disease is not among the reportable diseases in most states and because it is often difficult to distinguish the disease state from the carrier state on the basis of laboratory data alone. Disease due to *M avium-intracellulare* is seldom reported as an underlying cause of death, and thus studies of data on mortality are not helpful.

There is little information available on the routes of infection and pathogenesis of human disease due to *M avium-intracellulare*. The relationship between disease in animals and disease in man is not well understood. It is believed that man-to-man and animal-to-man transmission of infection is not common. Therefore, the key to a better understanding of the epidemiology lies in studies of the ecology of these organisms and in investigations of clusters of human disease, including environmental studies and serotyping of isolates of *M avium-intracellulare*. The availability of a specific diagnostic test for infections with *M avium-intracellulare* (*eg*, antigen for cutaneous testing) would also be valuable, although attempts to find a specific antigen for any mycobacterial disease have not been rewarding.

Disease in Man

One of the first reports of pulmonary disease due to *M avium-intracellulare* is attributed to Feldman et al,[1] who in 1943 described a patient who closely resembled what has become the textbook picture of this disease. In their classic report in 1954 proposing a scheme for classification of nontuberculous mycobacterial disease, Timpe and Runyon[2] reported three patients with pulmonary disease due to *M avium-intracellulare*. During the next several years, large series of patients with such pulmonary disease were reported from tuberculosis hospitals in Georgia and Florida,[3,4] suggesting a relatively high prevalence of disease in the Southeast. A survey of state health departments in 1960 showed that there were also foci of disease due to *M avium-intracellulare* in Texas, southern California, the Pacific Northwest, and the North Central states.[5]

These and subsequent reports[6,7] indicated that most of the patients with pulmonary disease due to *M avium-intracellulare* were white men who were on the average older than patients with tuberculosis. A large number of patients had underlying chronic pulmonary disease such as chronic obstructive pulmonary disease (COPD), bronchiectasis, previous tuberculo-

sis, or silicosis. A large proportion of patients were from rural areas, in contrast to patients with tuberculosis, who were more likely to have lived in urban areas.[8] Other than patients with industrial pneumoconiosis, there was no association of occupational pulmonary disease due to *M avium-intracellulare*.[9] Spread to close contacts of patients with *M avium-intracellulare* was not reported. Response to antituberculosis chemotherapy was often poor, although the disease was very slowly progressive and uncommonly was the sole cause of death.

In addition to pulmonary disease, *M avium-intracellulare* has been found to be a relatively common cause of nontuberculous mycobacterial disease involving lymph nodes and bone. Wolinsky,[10] in a comprehensive review of nontuberculous mycobacterial disease, summarized the medical literature for disease due to *M avium-intracellulare* reported through 1979. Until recently, disseminated disease due to *M avium-intracellulare* was rarely recognized, having been reported in a small number of patients with conditions associated with impaired immunity; however, soon after the initial reports of AIDS, several series of patients with AIDS who had disseminated disease due to *M avium-intracellulare* were reported,[11,12] suggesting that this infection was commonly associated with this condition. In southern California, disseminated disease due to *M avium-intracellulare* was found at postmortem examination in eight of the first nine patients dying at a large university hospital.[12] This infection has also been commonly found in patients with AIDS in New York City and was diagnosed in 17 (48 percent) of 35 patients seen at the National Institutes of Health.[13]

Epidemiologic Studies and Surveys in the United States

A series of studies conducted by the Public Health Service has suggested that infection by *M avium-intracellulare* resulting in reactivity to mycobacterial antigens on cutaneous testing may be quite common. Palmer,[14] analyzing data on sensitivity to tuberculin among nursing students throughout the United States, found that a low level of reactivity to purified protein derivative of tuberculin (PPD) was especially common in residents of the southeastern United States. As there was no association of this low level of reactivity with exposure to tuberculosis, Palmer[14] suggested that this phenomenon may have been caused by infection with a nonpathogenic organism antigenically related to *M tuberculosis*.

The most comprehensive study which presented indirect evidence on the prevalence and the geographic distribution of infection due to *M avium-intracellulare* was the Navy Recruit Program.[15] In this survey, conducted between 1950 and 1962, over 270,000 white male recruits, age 17 to 21 years, and lifelong single-county residents received intradermal injections of reference-standard PPD (PPD-S) and PPD derived from Battey bacilli (PPD-B; the Boone strain of *M avium-intracellulare*). The overall rate of reaction to PPD-B (*ie,* reaction greater than or equal to 4 mm of induration) was approximately 33 percent, but there was considerable geographic variability by state, with rates ranging from 10 to 80 percent. The highest rates were seen in the southeastern United States, and throughout the country, rates were higher in rural than in urban areas. The difference in geographic distribution of rates of reaction to PPD-B and PPD-S suggested that reactivity to PPD-B was independent of infection by *M tuberculosis*. It should be noted that PPD-B was not biostandardized, as was PPD-S, and that the criterion for a "positive" reaction to PPD-B was chosen arbitrarily. Furthermore, infection by nontuberculous mycobacteria other than *M avium-intracellulare (eg, M scrofulaceum)* may result in reactivity to PPD-B. Nonetheless, these data are valuable in the study of the distribution of infection due to *M avium-intracellulare*.

In an attempt to better define the prevalence and distribution of nontuberculous mycobacterial disease, the Center for Disease Control in 1979 and 1980 requested that all state laboratories report mycobacterial isolates of potentially pathogenic significance.[16,17] In 1980, reports were received from 49 of the 54 laboratories surveyed. Of 32,723 isolates of pathogenic mycobacteria reported, 21,286 (65 percent) were *M tuberculosis*. The next most common species reported in 1980 was *M avium-intracellulare;* there were 6,979 isolates, representing 21 percent of all mycobacterial pathogens and 61 percent of all pathogenic nontuberculous mycobacteria reported. The rate of isolation of *M avium-intracellulare* of 3.2/100,000 was approximately one-third that for *M tuberculosis* and varied by state, with the highest rates clustering in southeastern states along the Gulf Coast and in the North Central and Pacific regions. The highest rates were in Hawaii (10.8), Connecticut (8.9), Florida (8.4), and Kansas (6.8). In Wisconsin, Kansas, Minnesota, Nebraska, Montana, and Hawaii, the number of isolates of *M avium-intracellulare* exceeded that of *M tuberculosis*.

Using the estimate that approximately 30 percent of patients with isolates of *M avium-intracellulare* actually have disease,[18] these data from the survey would suggest that over 2,000 persons in the United States had disease due to *M avium-intracellulare* in 1980, *ie,* an incidence of approximately 1/100,000.

Disease in Animals

Avian mycobacteriosis was first described in England in the late 19th century and came to be recognized as an important cause of disease in poultry

flocks.[19] Distribution of disease due to *M avium* in poultry is worldwide but is especially prominent in northern temperate zones. In the United States, disease due to *M avium-intracellulare* in poultry has been a serious economic problem, with the prevalence highest in the North Central states where rates of infection of 50 percent and more have been found. The recent decrease in avian tuberculosis has been attributed to changing patterns in poultry husbandry. Organisms of *M avium-intracellulare* are excreted in the feces of infected birds and have been found to persist in the soil for long periods of time. Thus, eradication of the organisms from the infected flocks may be quite difficult. Although it has been shown that serotypes 1, 2, and 3 of *M avium* are relatively more common among human isolates in areas where poultry farming is prevalent,[20] the reservoir of infection with *M avium-intracellulare* in birds is not believed to be an important source of infection for man.

Of greater economic consequence is infection with *M avium-intracellulare* in swine, which is the most common cause of swine mycobacteriosis.[21] Disease due to *M avium-intracellulare* in swine has been described worldwide, with distribution approximately that seen for infection in poultry. Decreased levels of infection in the flocks has led to a decrease in infection in swine, suggesting that the most common source of swine infection is disease in poultry.

Disease due to *M avium-intracellulare* also has been described in a variety of other animals, including nonhuman primates. In monkeys, *M avium-intracellulare* causes an enteric disease with prominent gastrointestinal symptoms.[22] A report by Holmberg et al[23] of 42 cases of disease due to *M avium-intracellulare* in a monkey colony over a nine-year period indicated that continued animal-to-animal spread of disease was not important, as five different serotypes of *M avium-intracellulare* were isolated from the monkeys. The clinical description of this disease in monkeys, including immunologic studies, suggests that the disease is similar to the disseminated disease due to *M avium-intracellulare* which has been described in patients with AIDS.[11,12]

Although some early reports suggested that the primary source of disease due to *M avium-intracellulare* in man was animal infection,[24] Schaefer's[25] studies showing the serotypic divergence of human and animal isolates of *M avium-intracellulare* indicated that this disease in animals was not of great importance to human disease. These findings have been substantiated by more recent work and have led investigators to postulate that environmental organisms of *M avium-intracellulare* are the most important source of disease and infection in man.

Distribution in Nature and Sources of Infection

Organisms of *M avium-intracellulare* have been found in a variety of environmental sources; Songer[26] has recently summarized the literature on this subject. Early work demonstrated the ability of these organisms to survive in the soil for prolonged periods of time. Kubica et al[27] found strains of *M avium-intracellulare* in 5 percent of the samples of soil from Georgia and postulated that transmission to animal and man may occur, with water as an intermediate vehicle. Reznikov and Dawson[28] in Australia found organisms of *M avium-intracellulare* in samples of soil and have shown a correlation between the prevalence of isolates from the soil and the frequency of isolates from the samples of sputum from patients with pulmonary disease, suggesting that environmental organisms are the primary source of infection in man. These workers had earlier demonstrated strains of *M avium-intracellulare* in house dust and had shown some correlation between the serotypes in house dust and those found in patients with disease.[29] Wolinsky and Rynearson,[30] in examining samples of soil for mycobacteria, found a higher prevalence of organisms of *M avium-intracellulare* from samples in Georgia than from more northern states.

Goslee and Wolinsky[31] have isolated *M avium-intracellulare* from a variety of samples of water in Ohio. Gruft et al[32] have postulated that the distribution of sensitivity to PPD-B and PPD-G on cutaneous tests in the United States found in the Naval Recruit Study could be explained by airborne transmission of aerosols containing organisms of *M avium-intracellulare* which were generated from marine sources along the South Atlantic coast. Subsequently, in a series of studies in the eastern United States, Gruft et al[33] isolated strains of *M avium-intracellulare* from approximately 25 percent of the samples of water tested. The prevalence of isolates was highest along the South Carolina-Georgia coast, especially in brackish waters of low salinity. The demonstration of *M avium-intracellulare* in aerosols and drain water suggests that aerosolization of these organisms from natural sources in water may be a major source of infection for man. More recently, these investigators have shown that *M avium-intracellulare* may be concentrated and preferentially aerosolized from water,[34] lending further support to this hypothesis.

Workers in South Africa found a number of isolates of *M avium-intracellulare* from dust, soil, dried plants, and bedding and have postulated that environmental organisms are the source of the majority of human infections.[35] Meissner and Anz, in a review of extensive studies of *M avium-intracellulare* in man, animals, and the environment in West Germany, have shown a relatively high prevalence of human disease from sero-

types of *M avium*, with a decrease over time.[20] They postulated that the primary source of strains of *M avium* involved in human disease is birds, with wild fowl serving to spread infection. They present data suggesting that cattle and swine are not important hosts for disease in man. Their work with environmental samples suggests that soil and water may serve as the major sources of strains of *M intracellulare* associated with human infections.

Conclusions

There is much yet to be learned about the epidemiology of *M avium-intracellulare*. Further work is needed to define the prevalence and the incidence of disease due to *M avium-intracellulare*. A major step in this direction would be to formalize reporting of such disease through health department networks, as is done for *M tuberculosis*. Promulgation of a standardized definition of disease for reporting purposes would enhance the value of the data on surveillance. While recent work suggests that *M avium-intracellulare* in water may be an important source of infection in the southeastern United States, expansion of these studies to other parts of the country where this disease is common will expand our knowledge in this area. Companion studies of samples of soil and other environmental sources are also important. As noted previously, serotyping of isolates from man, animals, and the environment will help to define the sources of infecting organisms and the exact relationship between animal and human disease. Especially valuable would be intensive studies in areas where the prevalence of disease due to *M avium-intracellulare* has been found to be increasing.

Diagnostic Methods

When organisms of the *M avium-intracellulare* complex are isolated from the sputum, one must determine whether this represents casual isolation from environmental contamination, transient or long-term colonization of the respiratory tract, or invasive pulmonary disease. The diagnosis of pulmonary disease is confounded by the fact that both the diseased *and* colonized states are commonly associated with underlying pulmonary disease with preexisting bullae, cavities, cysts, or bronchiectasis and the fact that organisms of *M avium-intracellulare* occasionally may be found even in the respiratory secretions of normal people.

Clinical Criteria

Symptoms and signs, radiographic images, and a period of observation of adequate duration make up the data base. The symptoms and signs are nonspecific, consisting of cough, production of sputum, hemoptysis, fatigue, loss of weight, fever, and night sweats. The chest x-ray film usually shows evidence of an underlying pulmonary disease which predisposes to colonization with mycobacteria and may furnish a suitable environment for the establishment of invasive pulmonary infection. The most common of these pulmonary conditions are chronic bronchitis and emphysema, healed tuberculosis or fungal disease, bronchiectasis, silicosis, and fibrobullous apical disease. There may be one or more relatively thin-walled cavities which can be difficult to differentiate from the preexisting pulmonary condition. Occasionally, there may be infiltrative pulmonary disease resembling typical tuberculosis or a solitary pulmonary nodule without cavitation. Uncommonly, the disease may occur *de novo* in patients who have no apparent preexisting pulmonary disorder.

A period of observation is required in most cases to determine the stability of the disease or the rate of advancement if the disease is progressive and to rule out other causes of pulmonary infection. During this period the physician should make every effort to gather the facts from the past and especially to acquire all of the available previous chest x-ray films and bacteriologic reports. Therapeutic decisions will depend upon the stability or instability of the pulmonary process as determined by clinical judgment, serial bacteriologic studies, and evolution of the chest roentgenograms. In the less common situation where repeatedly positive sputum cultures for *M avium-intracellulare* are found in the setting of severe acute symptoms and a documented new cavitary lesion without other identifiable cause, the diagnosis of disease may be made and therapy initiated without further observation.

Laboratory Criteria

Repeated examinations of the sputum or other respiratory secretions are absolutely necessary. In the usual case of invasive disease, the sputum will contain large numbers of bacilli, yielding a heavy growth in cultures. The smears of sputum stained for acid-fast bacilli are usually positive but may be less reliable than in tuberculosis, probably because the organisms of *M avium-intracellulare* are smaller than most other mycobacteria and thus are more difficult to recognize. Serial specimens may show a great variability in the numbers of acid-fast bacilli seen despite the fact that the cultures are all highly positive. Except for the situation of obvious disease needing immediate treatment mentioned in the preceding paragraph, a series of several initial positive cultures should alert the clinician to *repeat* the bacteriologic studies after an aggressive course of bronchial hygiene (cessation of smoking, bronchodilator therapy for those with reversible obstruction, antibiotics for those with purulent secretions, and chest physiotherapy when appropriate). The

continued presence of the *M avium-intracellulare* organisms after at least two weeks of this treatment is evidence of invasive disease rather than mere colonization; however, the documentation of a progressively declining colony count should encourage the further use of these measures in hope of achieving sputum conversion without the use of chemotherapy.[36]

Special Considerations

1. From *excisional or biopsy material of solid pulmonary lesions,* one should have a compatible histologic picture in addition to a positive culture. Although only one positive culture of tissue is required, it would be desirable to test repeated specimens of sputum, including postbronchoscopic material when diagnosis is sought by transbronchial biopsy.

2. In *patients with AIDS,* diagnosis of mycobacterial disease may be made by the demonstration of acid-fast bacilli from biopsy of tissue. In a series of 149 patients with confirmed or suspected disease due to *M avium-intracellulare* for whom ansamycin was requested from the Center for Disease Control, the specimens most commonly yielding mycobacteria on culture or microscopic examination were the bone marrow (54 percent) and sputum/pulmonary tissue (46 percent), followed by blood (23 percent), lymph node tissue (14 percent), gastrointestinal tract (14 percent), and liver (14 percent). Histologically, a marked granulomatous response is not usually seen. There are either poorly formed or absent granulomas, and sheets of foamy macrophages laden with acid-fast bacilli are commonly found.

Depending upon racial, geographic, and socioeconomic factors, it appears as though either *M avium-intracellulare* or *M tuberculosis* may be the predominant pathogens among victims of AIDS. Among inner-city heroin addicts or Haitian immigrants, *M tuberculosis* may be more prevalent, while among white, middle-class homosexuals, *M avium-intracellulare* is clearly more common. In AIDS or pre-AIDS patients with evidence of mycobacterial infection, the worst situation (disease due to *M avium-intracellulare*) should be presumed and vigorous treatment initiated. Because *M avium-intracellulare* is common in patients with AIDS and because early treatment may reduce morbidity and possibly delay mortality, all patients with AIDS who have symptoms suggestive of disseminated *M avium-intracellulare* should be screened with cultures of blood, smears and cultures of stool, and biopsy and culture of bone marrow. Those with respiratory signs and symptoms should have a smear and culture of sputum and be considered for bronchoscopy. Patients with diarrhea and malabsorption and negative smears of stool for acid-fast bacilli might well undergo a small-bowel biopsy.[12] Any tissue obtained should be cultured for acid-fast bacilli. Because involvement of bone marrow and bacteremia due to *M avium-intracellulare* have been found in relatively asymptomatic patients, periodic screening of asymptomatic patients with AIDS for bacillemia due to *M avium-intracellulare* may be considered. Improved techniques for isolation of *M avium-intracellulare* from blood, including the use of radiometric methods, may facilitate early diagnosis.[37]

3. *Lymph node disease* due to *M avium-intracellulare* is best diagnosed and treated by excision of the involved nodes. Such lymph node disease occurs most commonly in young children; however, recently cases have been noted in victims of AIDS, usually associated with disseminated disease. Under these circumstances a single culture will suffice for diagnosis, provided there is no reason to suspect contamination in the laboratory. Acid-fast stains of these materials may or may not be positive.

4. *Cutaneous tests* and *serologic tests* generally are not useful in diagnosis. An exception to this may be lymph node disease in young children; pediatric practitioners have contended that dual cutaneous testing of children with cervical lymphadenitis using PPD-T (*M tuberculosis* antigen) *vs* PPD-B (the homologous antigen for *M avium-intracellulare*) is useful in distinguishing the type of mycobacterial infection; however, because properly standardized antigens for cutaneous testing are not marketed in the United States nor are they presently available through the Center for Disease Control, this is at present a moot question.

Chemotherapy

The effectiveness of chemotherapy for disease due to *M avium-intracellulare* is limited by resistance to drugs. Studies of such resistance employing antituberculosis chemotherapeutic agents in the concentrations used for *M tuberculosis* testing reveal a low frequency of susceptibility to the drugs. Nearly all strains are resistant to the majority of drugs.

Observations of patients with disease due to *M avium-intracellulare* showing favorable responses to chemotherapy employing a number of drugs to which the cultures of *M avium-intracellulare* were totally resistant when tested singly has raised the question of additive or synergistic activity among combined drugs. Interesting patterns of favorable interactions of drugs among large numbers of pathogenic strains of *M avium-intracellulare* have been reported. Common features of two studies were the positive interactions between rifampin and ethambutol, between rifampin and ethionamide, and among ethambutol, ethionamide, and kanamycin or streptomycin; striking in a negative sense was the relatively low activity of isoniazid in these testing systems.[38-40] On the other hand, another group reported no synergistic response on testing with multiple drugs among 75 strains of *M*

avium-intracellulare recovered from their patients.[40] While *in vitro* studies of apparent synergism may be of considerable interest, their applicability is limited in that they are usually beyond the capability of standard mycobacterial laboratories, and there is yet no clinical evidence linking such *in vitro* phenomena to the outcome of therapy in patients.

The fear of selecting resistant strains of *M avium-intracellulare* has made some clinicians reluctant to employ simpler, less toxic regimens against disease due to *M avium-intracellulare;* however, if drug resistance of *M avium-intracellulare* occurs by exclusion of drugs rather than selective overgrowth of drug-resistant variants, one might initiate three-drug therapy (such as isoniazid, rifampin, and ethambutol) in patients without inordinate risk of squandering whatever potential benefit these drugs afford. A report of an ultimate lower rate of favorable response among patients previously treated with simpler regimens than those originally treated with five-drug therapy (53 percent vs 75 percent) could reflect either increased drug resistance after therapy or simply selection for referral to that institution of those patients initially infected with more resistant organisms.[41] Overall, we do not believe that the difference in outcome is sufficiently compelling at this time to mandate initial five-drug therapy for all patients with newly diagnosed disease due to *M avium-intracellulare*.

Treatment of Pulmonary Disease

There are a number of important considerations in the treatment of pulmonary disease due to *M avium-intracellulare*. These include whom and when to treat, which drugs to employ, how long to treat, how to assess the response to therapy, and when or if surgical resection should be employed.

The simplest of pulmonary disease due to *M avium-intracellulare* is the patient with the well-circumscribed solitary pulmonary nodule which is resected for diagnosis and demonstrates granuloma with *M avium-intracellulare* on culture. Assuming no other gross radiographic abnormalities and normal immune status, it is our opinion that no additional chemotherapy need be administered.[42]

In some less extensive cases in which the diagnosis cannot be firmly established (noncavitary infiltrates; inconsistent results from cultures; few or no symptoms), efforts at bronchial hygiene, observation, and follow-up are indicated. Chemotherapy would be indicated later if progressive disease becomes manifest.

The most practical chemotherapy of the typical moderate case (moderately advanced radiographic status; moderate and stable respiratory symptoms) employs the standard antituberculosis drugs (isoniazid, ethambutol, and rifampin) for an 18-month to 24-month period plus streptomycin during the first two to three months. Five-drug or six-drug regimens typically entail more drug-induced toxic effects, side effects, and noncompliance; such organisms are more expensive due to the prolonged hospitalization required to initiate the poorly tolerated regimens and the actual costs of the drugs as well. Thus, they appear unsuitable as the initial therapy in such cases. Successful results should occur with three-drug or four-drug regimens in 40 to 60 percent of such cases using isoniazid, rifampin, ethambutol, and streptomycin; over half of the remainder will be left with a chronically active but stable disease, judged by long-term follow-up, even after treatment is stopped. Resectional surgery is an option if such patients are good risks with localized disease.

The intensive approach using five to six drugs should be reserved for those cases with serious illness (marginal pulmonary reserve status, far advanced radiographic status, or clearly advancing disease during observation on chemotherapy). Up to 80 percent initial response has been achieved with these regimens; however, relapse has been a common problem limiting ultimate success. The choice of drugs has been empirical. In addition to the first-line drugs (isoniazid, rifampin, ethambutol, and streptomycin), ethionamide, cycloserine, and kanamycin have been the most commonly employed agents. As noted previously, the role of testing for susceptibility in selecting drugs is uncertain; however, general practice has entailed selection of agents to which there is sensitivity *in vitro* and the use of agents not previously employed in that patient.

Treatment of Extrapulmonary Disease

Extrapulmonary disease due to *M avium-intracellulare* has a variety of manifestations ranging from benign, self-limited cervical lymphadenitis in children to overwhelming disseminated disease in immunocompromised patients. Between these extremes lies a variety of intermediate disorders including localized soft-tissue infections, isolated osteomyelitis or arthritis, and multifocal osteomyelitis. As might be expected, management of these diverse problems varies greatly.

Most of the patients with multifocal or disseminated disease due to *M avium-intracellulare* have discernible abnormalties of cell-mediated immunity. In some instances the defect appears to be a specific abnormality which results in increased vulnerability apparently only to *M avium-intracellulare*. In others, there appears to be a nearly global disruption of cell-mediated immunity; most striking is AIDS. Other conditions associated with disseminated *M avium-intracellulare* are lymphohematogenous malignant neoplasms and immunosuppressive chemotherapy for organ transplantation, solid tumors, or collagen-vascular diseases.

The management of patients with these diverse disorders logically varies with the type of disease. For isolated lymphadenitis in children, it would appear that excision and observation without chemotherapy are suitable. For otherwise healthy subjects with single-site soft-tissue infection, arthritis, or osteomyelitis, a combination of drainage or débridement with three-drug to four-drug chemotherapy appears generally successful;[43] however, for those with multifocal or disseminated disease and obvious disturbances of immunity, a much more aggressive approach to treatment is required. Whenever possible, steps to restore immune capacity should be taken, including reducing immunosuppressive therapy to the minimum. Also, consideration should be given to positive measures to restore immunocompetence including administration of transfer factor, which has appeared to restore host defenses in anecdotal cases of mycobacterial disease with anergy.[44,45] Immunomodulation by indomethacin, which has been shown to restore lymphocytic activity against antigen to *M avium-intracellulare* (PPD-B) *in vitro* in certain patients with unexplained anergy is yet unproven in a clinical study and probably ought not be generally employed at this time.[46]

While there have not been controlled studies examining the efficacy of different chemotherapeutic agents or regimens for disseminated disease due to *M avium-intracellulare*, the generally accepted practice has been to employ regimens of five to six drugs. The most active of the conventional agents appear to be rifampin, ethambutol, ethionamide, cycloserine, kanamycin, and streptomycin; isoniazid has relatively low activity against *M avium-intracellulare*, in contrast to *M tuberculosis*. The most commonly employed agents used to treat disseminated disease due to *M avium-intracellulare* rifampin, ethambutol, isoniazid, ethionamide, cycloserine, and streptomycin.

Recent experience with extrapulmonary disease has suggested that clofazimine, an antileprosy agent, may improve the outcome in patients without AIDS who have multifocal extrapulmonary disease.[47] Clofazimine is a riminophenazine compound with considerable *in vitro* activity against *M avium-intracellulare*.[48] Preliminary studies in patients with pulmonary disease have been equivocal or disappointing.[42] The apparently greater activity of clofazimine in *extrapulmonary* disease may be due to the distribution of the drug within the body; clofazimine is avidly taken up by epithelium, the bone marrow, and the reticuloendothelial system where tissue and intracellular concentrations are very high. This may be contrasted with very low initial levels of the drug that have been noted in the serum and, presumably, in the pulmonary tissue. Side effects and toxic effects of clofazimine are usually due to deposition of the compound in body tissues. Progressive pigmentation of the skin typically develops throughout the course of administration and very gradually clears after treatment. A more significant complication is abdominal pain associated with deposition of the drug in the interstitial epithelium; such symptoms are cumulatively dose-related and usually appear late in treatment. At present, clofazimine is available from the National Jewish Hospital in Denver, Colorado under its Investigational New Drug (IND) permit and from the Food and Drug Administration on application for an "emergency" IND.

Another new agent which has been employed for disseminated *M avium-intracellulare* is ansamycin (LM 427), a spiropiperidyl rifamycin with substantially greater *in vitro* activity against *M avium-intracellulare* than rifampin. Ansamycin was active against 85 percent of a series of strains related to human disease at the Center for Disease Control at a concentration of 2 μg/ml, while rifampin was comparably active against only 5 percent of the strains at the usual testing concentration of 1 μg/ml.[49] Ansamycin is presently regarded as a research drug; due to the pressing morbidity and mortality of disseminated *M avium-intracellulare* among patients with AIDS, ansamycin was released for use in the absence of conventional trials observing clinical toxic effects; however, preliminary observations indicate that it is well tolerated and relatively free of untoward effects. Clinical observations among the approximately 100 patients thus far observed who received ansamycin reveal only uncommon instances of mild elevation of the level of transaminase or thrombocytopenia. The number of patients who have received ansamycin is relatively small, and these patients (largely victims of AIDS) have a multiplicity of other disorders that cloud the clinical picture. Allowing for these uncertainties, it is the impression of one observer that the combination of ansamycin and clofazimine showed clearly the greatest activity against disseminated *M avium-intracellulare*, seemingly more than conventional chemotherapy for *M avium-intracellulare* or the combination of ansamycin and the other antimycobacterial agents without clofazimine (Richard Weisman, Pharm.D., CDC Conference on Ansamycin, Atlanta, September 1983). Ansamycin presently is restricted to use in patients with life-threatening disease due to *M avium-intracellulare* and may be obtained from the Center for Disease Control in Atlanta.

Thus, our current recommendations for disseminated *M avium-intracellulare* in immunocompromised adult patients would include the following: (1) rifampin (600 mg orally per day) if the organism is sensitive to rifampin, *or* ansamycin (150 to 300 mg orally per day) if the organism is resistant to rifampin and sensitive to ansamycin (do not use rifampin and ansamycin simultaneously); (2) clofazimine 100 mg three times per day orally); (3) ethambutol (25 mg/kg orally per day for six

weeks and then 15 mg/kg/day regardless of susceptibility to ethambutol); (4) ethionamide (250 mg orally two to four times daily, depending on the patient's size and tolerance) regardless of susceptibility to ethionamide; (5) streptomycin (15 mg/kg intramuscularly daily, assuming normal renal function, for 60 days); then reduce frequency or dosage for total treatment up to six months; (6) other drugs may be used depending on patterns of susceptibility or intolerance to the previously mentioned medications; and (7) comparable regimens in suitably reduced doses should be employed for children, diminutive adults, or adults with compromised renal fuction.

The total duration of chemotherapy in extrapulmonary disease due to *M avium-intracellulare* is difficult to determine. In the series from Arkansas and the National Jewish Hospital, the patients received in the range of 24 to 36 months with multiple drugs; it may be anticipated that toxic effects or side effects will be sufficiently severe to require discontinuation of one or more drugs in most patients.[41] Practically speaking, the greatest efforts in circumventing subjective or minor disturbances should be made with pivotal drugs, namely, ansamycin or rifampin, ethambutol, clofazimine, and ethionamide. Extrapolating from various observations on disease due to *M avium-intracellulare*, we would recommend 24 months of chemotherapy, employing five to six agents (as tolerated) for the first year and an oral regimen consisting of rifampin or ansamycin, ethambutol, and clofazimine in the second year.

The role of surgery is more difficult to determine in extrapulmonary disease due to *M avium-intracellulare*. In general, the principles of surgical management of other osseous or soft-tissue infections should apply to infections due to *M avium-intracellulare;* whenever possible, such closed-space infections should be drained or débrided surgically. Although controlled studies have not yet been conducted on this subject, it would appear advisable to initiate optimal chemotherapeutic coverage before embarking on such surgery. It should be emphasized that surgery compliments but does not obviate the need for chemotherapy; due to the tendency of infections with *M avium-intracellulare* to recur locally or remotely, we believe that a full course of treatment with drugs (approximately 24 months) should be carried out in patients with multifocal disease due to *M avium-intracellulare*, whether or not a defect of immunity is discernible.

Surgery in Pulmonary Disease

Considerable controversy exists regarding the appropriate role for resectional surgery in the management of pulmonary disease due to *M avium-intracellulare*. Clearly, from the previous section on chemotherapy of such disease, it is apparent that medical management alone does not produce optimal results. Two series reporting the outcome of surgery indicate improved long-term outcome (lower rates of persistence of disease or relapse) among patients who receive combined chemotherapy and resectional surgery;[50,51] however, the data from these series must be interpreted with some caution. In these series, careful selection of patients was employed, culling out those with localized, more limited disease and those who by virtue of better cardiopulmonary function and relative freedom from other complicating disorders were more likely to withstand the rigors of surgery. Despite this selection, there was a 7 percent (9/131 patients) perioperative mortality in the series from Battey Hospital.[50] Furthermore, 18 percent (22/122) of the surviving patients had significant postoperative complications, including seven who required subsequent thoracoplasty to control pleural-space problems; however, on the favorable side, among the 122 survivors of surgery, only two patients were noted to die of progressive pulmonary disease attributed to *M avium-intracellulare*. The series from Duke University was smaller, appeared to select more carefully for limited disease, employed more and better preoperative and postoperative chemotherapy, and reported considerably less morbidity and no mortality.[51] Among 33 patients in the Duke study for whom prolonged follow-up data were available (15 months, minimum; 94 months, mean), only two had relapses. Further surgery or chemotherapy returned these two patients to quiescent status.

The disparate findings of morbidity and mortality among these two surgical series may possibly be explained by the following. The series from Battey Hospital commenced earlier than the Duke series; thus, more modern preoperative physiologic evaluation, anesthesia, intraoperative management, postoperative care, and chemotherapy (notably use of rifampin and ethambutol and prolonged preoperative treatment) was employed in the Duke series. Furthermore, early efforts to limit the amount of tissue resected early in the Battey series (segmental or subsegmental resections) very likely resulted in a higher rate of postoperative air leaks. It is our impression that—given contemporary standards of surgery, perioperative care, and chemotherapy—mortality and morbidity, while anticipated, should be lower than the Battey series.

Among the larger series of patients treated primarily with chemotherapy, the results for those patients who underwent adjunctive surgery (largely those for whom medical treatment failed) were somewhat better than from chemotherapy alone.[7,52]

In interpreting these data, it is critical to appreciate the degree to which the patients were selected for surgery. In the Battey series, the 131 patients were

selected from 540 patients (23 percent) seen at Battey Hospital with pulmonary disease due to *M avium-intracellulare* during the period of the study. These 131 patients were younger, had less disease, and had a better prognosis than those treated with drugs alone. In the Duke series the 37 patients were culled from roughly 175 patients (21 percent) (the numbers are inexact because their article refers to 175 patients with "atypical tuberculosis" without identifying species). The obvious major difficulty in interpreting these studies and applying the information to making clinical decisions is whether the surgical groups may have been selecting for surgery those patients more likely to be long-term responders if managed with medication alone. The observation that 25 of 35 patients in the Duke Series experienced sputum conversion (smear and culture negative) with an average of 22 weeks of preoperative chemotherapy raises two questions: Were these patients diseased or merely colonized, and were these patients infected with more susceptible strains of *M avium-intracellulare* and, thus, more likely to respond to chemotherapy? The fact that all of these patients had cavities in the resected specimen confirms the diseased state, but the second question cannot be answered in the absence of a control group.

Contemporary surgical practice requires careful preoperative evaluation of the respiratory status of patients prior to pulmonary resectional surgery. In the Battey series, it was stated that ventilatory and arterial blood gas data were used for selection, but the consistency and criteria used for this screening were not stated. In the Duke series, it was noted that 33 of the 37 surgical subjects were heavy smokers, but that no previous pulmonary disease was present (yet four patients had been treated for prior tuberculosis, including one who had undergone left upper lobectomy). In this group the mean forced vital capacity (FVC) was 89 percent of predicted, and the maximum voluntary ventilation (MVV) was 87 percent of predicted; only four patients had a FVC less than 70 percent of predicted, and seven had an MVV less than 70 percent of predicted. Application of these data to prospective selection is somewhat difficult. The patient with normal ventilatory function and gas exchange can clearly withstand even pneumonectomy. It is the patient who has impaired ventilation and gas exchange for whom this decision is critical, both in terms of withstanding surgery and of optimizing control of the underlying disease due to *M avium-intracellulare*, since progressive infection may rapidly lead to respiratory insufficiency. Careful scrutiny must be given to both the ability to withstand the acute surgical event and to the long-term physiologic consequences of resecting the involved pulmonary unit(s).

Underlying the question of the relative merits of chemotherapy and chemotherapeutic surgical management is the issue of the natural history of this disease. What is the natural course of this disorder untreated or poorly controlled? It is impossible to determine this issue because most of the clinical series contain a disproportionate number of patients with advanced disease and because most of the patients suffered from multitudes of other diseases (COPD; diabetes mellitus; silicosis; cancer) or conditions (alcoholism; tobacco abuse). One is left with the strong sense that there are many variants on this disorder, ranging from the stable, solitary pulmonary nodule, to an indolent, slowly advancing infiltrative disease, to a fulminant, progressive cavitary form. On occasion, the clinician has a clear history and a recent series of chest x-ray films which allow him to discern the pattern and pace of progression of the disease. In other settings the clinician is left with the problem of determining whether his patient has a fairly static form or is in transition to a more fulminant form of pulmonary disease due to *M avium-intracellulare*. In the former, one might be disposed to a trial of chemotherapy, while in the latter, one might be pursuaded to employ more aggressive management, including surgery, in an attempt to curtail the disease. Unfortunately, no markers of host competency (immunologic studies) or other risk factors or of the virulence of the organisms (serotype; pattern of drug susceptibility) presently exist to aid with this determination.

Confronted with the limitations and imperfections of available data, we offer the following guidelines for surgery in pulmonary disease due to *M avium-intracellulare*:

1. Resectional surgery results in improved rates of response and lowered rates of relapse in selected patients.

2. Patients should be selected for unilateral cavitary disease, and surgery ought to result in extirpation of all or a clear preponderance of all radiographically visible disease.

3. Patients should be selected for surgery on the basis of adequate cardiopulmonary reserve and relative freedom from serious complicating conditions.

4. Chemotherapy should be administered before surgery, employing three or more agents. The objective of such therapy ought to be to convert the sputum to culture-negative status. If conversion does not occur by 20 weeks of therapy or if by ten weeks there is not a decline in the sputum's bacillary count, surgery should proceed regardless.

5. In the patient who shows prompt clinical, radiographic, and bacteriologic response to chemotherapy, an *optional* course of management would be to continue long-term treatment with drugs. It should be emphasized that data do not allow us to state definitively better outcome with either course (chemotherapy or chemotherapy and surgery) in these patients.

6. Surgery which proceeds along natural fissure planes (lobectomy) should result in fewer postoperative complications.

7. There are no data to determine the duration of postoperative chemotherapy required to prevent relapse. A wide spectrum of opinion exists. Some believe that if there is no minimal residual abnormality, as little as six months is sufficient, while others advocate a total of 24 months regardless of surgery. Agreement was reached that a simplified oral regimen was appropriate once the majority of disease was resected.

8. For the patient with a circumscribed solitary pulmonary nodule which yields *M avium-intracellulare* from the resected specimen, it is our consensus that chemotherapy is probably not indicated.

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National Consensus: Disease Due to *M avium-intracellulare*

1. For the usual, "moderately severe" case of pulmonary disease, initial therapy should consist of isoniazid, rifampin, and ethambutol for 18 to 24 months with streptomycin during the initial two to three months.

2. For patients (immunologically intact) with a solitary pulmonary nodule due to *M avium-intracellulare*, chemotherapy need not be given after resectional surgery.

3. For patients with rapidly progressive, highly symptomatic pulmonary disease, more aggressive initial therapy is indicated employing regimens of five to six drugs, including agents such as ethionamide, cycloserine, or kanamycin (as well as the agents listed previously).

4. For patients with life-threatening disseminated disease due to *M avium-intracellulare*, initial chemotherapy with five or six drugs is indicated. In this setting, ansamycin (LM 427) and clofazimine should be included in the regimen.

5. For patients with localized pulmonary disease and adequate cardiorespiratory reserve, resectional surgery combined with chemotherapy may offer a better outcome than chemotherapy alone.

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