Epidemiology of human disease caused by *Mycobacterium avium* complex

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**CR HORSBURGH. Epidemiology of human disease caused by *Mycobacterium avium* complex. Can J Infect Dis 1994;5(Suppl B):5B-9B.** *Mycobacterium avium* complex (MAC) is a ubiquitous organism. Human infection with this agent causes one of three clinical syndromes: pulmonary disease in persons whose systemic immunity is intact; cervical lymphadenitis, also a disease of normal hosts; and disseminated disease, usually in persons with advanced human immunodeficiency virus infection. While data are sparse, all three clinical syndromes appear to be increasing in frequency. However, the environmental reservoirs and modes of acquisition of MAC have not been elucidated, and strategies for avoidance of MAC infection remain to be defined.

**Key Words:** AIDS, Human immunodeficiency virus (HIV), *Mycobacterium avium* complex (MAC), Pulmonary disease

*Mycobacterium avium* complex (MAC) is a ubiquitous organism, having been recovered from many environmental sources, including water (1-5), birds (6-8), pigs (6-9), cattle (6-8), cow’s milk (10-12) and soil (13). The environmental reservoirs and modes of acquisition of disease-causing strains have not been elucidated. Three distinct clinical syndromes are produced by this agent: pulmonary disease in persons whose systemic immunity is intact; cervical lymphadenitis, also a disease of normal hosts; and disseminated disease, usually in persons with advanced human immunodeficiency virus (HIV) infection (Table 1). This article discusses the epidemiology and clinical presentation of these three syndromes.

**MAC PULMONARY DISEASE**

Pulmonary disease caused by MAC is similar in presentation to tuberculosis. Patients may have localized infiltrates, cavitation, or solitary or multiple pulmonary nodules (14-19); hilar adenopathy alone is uncommon.
Patients are usually febrile, with sputum that contains mycobacteria, by culture if not by smear. Weight loss is less common, but may occur in cases where the disease has remained untreated for a prolonged period of time or been refractory to therapy. Among persons with MAC pulmonary disease, isolates of the M. avium group are similar in number to those of the Mycobacterium avium intracellulare group (20). No clinical differences distinguish the two groups.

MAC pulmonary disease is seen worldwide, with relatively equal frequency. In the United States (21) and Japan (22), there are approximately 1.3 cases per 100,000 persons. In Switzerland, there are 0.9 cases per 100,000 persons (23). Although systematic surveillance for MAC pulmonary disease is not performed, the disease appears to be increasing in frequency as tuberculosis declines; it is unclear to what extent increased reporting may have contributed to these apparent increases. Reports from Pennsylvania (18), Massachusetts (24), Canada (25), Sweden (26) and Switzerland (23) appear to indicate an increasing frequency of disease in these areas. In the most recent year for which data are available (1983), it was estimated that approximately 3000 cases of MAC pulmonary disease occur annually in the United States (21).

The disease is uncommon under the age of 45, although some authors feel that there is a distinct subgroup of young women in the 30- to 45-year age group that is particularly susceptible (27). The average age of persons reported to the Centers for Disease Control and Prevention in Atlanta, Georgia, with pulmonary MAC disease was 58 years, and men were the majority of cases (56%) (21). No specific risk factors for MAC pulmonary disease have been identified. Many of the reported cases have been in persons with a history of prior tuberculosis or heavy smoking, giving rise to the hypothesis that impaired pulmonary clearance mechanisms may predispose to this condition. However, many patients have no clear predisposing factor, and controlled studies of risk factors for this disease are needed.

Most patients respond to therapy with antimycobacterial agents (14-19), although there is no agreement on the optimal regimen. Several studies have reported response rates of 75 to 91%. No studies of the effect of disease on survival have been reported.

**MAC CERVICAL LYMPHADENITIS**

MAC may cause isolated lymphadenitis, almost always limited to the cervical area. Patients may be asymptomatic, or may less commonly have systemic illness, with fevers, weight loss and night sweats (28-32). Draining sinus tracts may be seen if incision and drainage has been attempted. Disease is usually unilateral and abnormal chest radiographs are uncommon. MAC cervical adenitis is almost entirely a disease of children, with most cases occurring in those under the age of five years. There is a slight female predominance, and nearly all reported cases are in caucasians (21).

The decline of tuberculosis as a cause of lymphadenitis in the United States has been accompanied by increased recognition of nontuberculous lymphadenitis, but it is unclear if these increases are relative or absolute. The disease has also been reported from Sweden (26), England (33), Canada (34) and Australia (35). Before 1980 most nontuberculous lymphadenitis in the United States was due to Mycobacterium scrofulaceum (28,29), but in more recent reports MAC has been the cause of the majority of disease (21,30-32). In 1983, there were an estimated 300 cases of MAC lymphadenitis in the United States (21). However, this number is certainly a gross underestimate, since many cases of lymphadenitis are not cultured, and of those that are cultured, nearly half are culture-negative despite a histological appearance compatible with a diagnosis of mycobacterial infection and supportive skin test results. Thus, an estimate of 500 cases annually may still be considered conservative.

No risk factors for acquisition of this disease have been identified; however, in Sweden the number of cases increased after discontinuation of bacillus Cal-

### TABLE 1

**Symptoms, signs and laboratory abnormalities that may be observed in disease caused by Mycobacterium avium complex**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Laboratory abnormality</th>
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<tbody>
<tr>
<td>Lymphadenitis</td>
<td>Fever</td>
<td>Lymphadenopathy</td>
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<td></td>
<td></td>
<td>Elevated temperature</td>
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<td>Sinus tract</td>
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<tr>
<td>Pulmonary disease</td>
<td>Fever</td>
<td>Elevated temperature</td>
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<td></td>
<td>Cough</td>
<td>Weight loss</td>
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<td></td>
<td>Dyspnea</td>
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<tr>
<td>Disseminated</td>
<td>Fever</td>
<td>Elevated temperature</td>
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<td></td>
<td>Night sweats</td>
<td>Weight loss</td>
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<td></td>
<td>Diarrhea</td>
<td>Splenomegaly</td>
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<td></td>
<td>Abdominal pain</td>
<td>Hepatomegaly</td>
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*On abdominal computed tomography scan*
mette-Guérin (BCG) vaccination, suggesting a possible protective effect of BCG (26). Most cases of MAC lymphadenitis are treated with surgical excision, and the success rate is high; all reported cases have eventually resolved and deaths have not been reported. Antibiotic therapy is not usually recommended, but has not been extensively investigated.

**DISSEMINATED MAC DISEASE**

Disseminated MAC disease begins as a localized process that progresses rapidly to include numerous organ systems (36). Disease can be acquired through either the gastrointestinal or respiratory tract. In most cases, presenting signs and symptoms are those of the disseminated process, including fevers, night sweats, anemia, weight loss and hepatosplenomegaly. Signs and symptoms specific to the gastrointestinal tract, including abdominal pain, diarrhea and elevated alkaline phosphatase, may also be seen. Pulmonary signs and symptoms, including shortness of breath, sputum production and radiographic abnormalities, are much less common (37). While patients with AIDS have many possible causes for such signs and symptoms, fever, anemia, weight loss, diarrhea and elevated alkaline phosphatase are each significantly associated with disseminated MAC disease (38). The most common clinical presentations are fevers (84% of patients), anemia (hematocrit less than 26%, 76% of patients), night sweats (44% of patients) and weight loss (10% of weight in six months, 40% of patients) (37).

Disseminated MAC disease was extremely rare before 1980 (39). However, the extreme susceptibility of AIDS patients to this disease has led to a marked increase in the number of cases of disseminated MAC (36). Overall, 15 to 24% of AIDS patients acquire disseminated MAC. In 1992, when there were approximately 100,000 AIDS cases, it can be estimated that there were 15,000 to 24,000 cases of disseminated MAC infection. Thus, disseminated MAC infection in persons with AIDS is the most common manifestation of MAC infection.

The greatest risk is associated with severe depression of the CD4+ cell count; disseminated MAC is rarely seen in persons with greater than 100 CD4+ cells/mm$^3$ and the median CD4+ cell count among persons with MAC is 10 cells/mm$^3$ (36). The risk for MAC increases exponentially as the CD4+ count declines (40). The percentage of AIDS patients with disseminated MAC has continued to climb as the AIDS epidemic matures (Figure 1). This is presumed to be the result of an increasing proportion of AIDS patients having the low CD4+ cell levels that put them at risk for MAC.

Among HIV-infected persons, similar risks for MAC are seen when patients are compared by age, race, sex or HIV transmission risk (41). Children with AIDS have a risk for MAC that is similar to that of adults, although children with AIDS whose exposure to HIV occurred through blood or blood products have a higher risk than children with perinatally-acquired HIV infection (42); this is also likely to be a result of lower CD4+ cell levels in those children.

In the United States, there do not appear to be marked geographic differences in the prevalence of disseminated MAC infection. Worldwide, disseminated MAC has been reported with a frequency of 10 to 25% of AIDS patients in England (43), France (44), Germany (45) and Australia (46). Disseminated MAC appears to be less common in developing countries, with prevalence rates of 6% in Mexico (47) and 0% in studies in Uganda (48) and Kenya (49). However, the disease has been reported from the Central African Republic (50), the Caribbean (49) and Brazil (51), although rates are unknown.

Survival of AIDS patients with disseminated MAC is markedly shortened compared with AIDS patients without MAC but with similar CD4+ cell counts and antiretroviral therapy histories (52-54). The median survival after a diagnosis of disseminated MAC in one study was four months, compared with 11 months for AIDS patients without MAC (52). Several studies have suggested that survival is prolonged in persons with MAC who receive antimycobacterial agents (37,52, 55,56), but further studies are needed.

**CONCLUSIONS**

Disease due to MAC has three major clinical manifestations, and all of these appear to be increasing. The reasons for these increases are not clear in all cases, although the increases in disseminated disease in AIDS patients is due in large part to the increasing number of susceptible hosts. A better understanding of the interactions between humans and the environment that lead to MAC disease would help clarify the reasons for these increases. Moreover, the suggestion that BCG or prior mycobacterial exposure may provide protection against MAC (26,49) needs to be further investigated.
REFERENCES

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