

Mycobacterium avium-M. intracellulare Isolates from Patients with or without Acquired Immunodeficiency Syndrome

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Susceptibility testing and serotyping were performed on 57 isolates of *Mycobacterium avium-M. intracellulare* from patients with acquired immunodeficiency syndrome (AIDS) and 75 isolates from patients without AIDS. Susceptibility patterns and serotypes of AIDS isolates were significantly different from those of non-AIDS isolates. These results may partially explain the poor therapeutic response of *M. avium-M. intracellulare* infections in AIDS patients.

Infection with *Mycobacterium avium-M. intracellulare* is seen in up to 50% of patients with acquired immunodeficiency syndrome (AIDS) (1). Patients with *M. avium-M. intracellulare* infection and AIDS respond less well to antimycobacterial chemotherapy than do patients with pulmonary or disseminated *M. avium-M. intracellulare* infections without AIDS (7, 8; C. R. Horsburgh, U. G. Mason, L. B. Heifets, K. Southwick, J. LaBrecque, and M. D. Iseman, Am. Rev. Respir. Dis., in press). This poor response to chemotherapy is in part due to the severe immunosuppression seen in these patients (2). However, AIDS patients with disease due to *M. tuberculosis* often respond to chemotherapy (12). An additional factor contributing to the poor response of AIDS patients to chemotherapy for *M. avium-M. intracellulare* infections might be that AIDS patients are infected with *M. avium-M. intracellulare* strains which are more virulent, less susceptible to antimycobacterial agents, or both than are isolates from patients without AIDS. To investigate these latter possibilities, we performed a prospective analysis of in vitro susceptibility testing and serotyping of *M. avium-M. intracellulare* isolates from AIDS patients with disseminated infection and compared them retrospectively with isolates of *M. avium-M. intracellulare* from patients with pulmonary *M. avium-M. intracellulare* infection without AIDS.

***M. avium-M. intracellulare* isolates.** All *M. avium-M. intracellulare* isolates from patients with AIDS, as defined by the Centers for Disease Control, Atlanta, Ga., seen at the participating medical centers from July 1984 to June 1985 were collected. Isolates were from blood or bone marrow or were sputum or stool isolates of patients who had evidence of invasive disease at deep-tissue sites. *M. avium-M. intracellulare* isolates from 75 patients with pulmonary infection but without AIDS were collected from patients seen at National Jewish Hospital, Denver, Colo., between 1976 and 1982. The clinical characteristics of these patients are described elsewhere (Horsburgh et al., in press).

In vitro susceptibility testing. In vitro susceptibility testing was performed on 7H11 agar, and isolates were deemed susceptible when a greater than 99% reduction in the number of colonies was observed on the antimicrobial plate when

compared with the control plate as previously described (10).

Serotyping. Isolates were serotyped, as described by McClatchy, by using type-specific antisera (11). When the results of serotyping with antisera were inconclusive, isolates were further evaluated with thin-layer chromatography by the method of Brennan et al. (3).

Statistics. Results were compared by chi-squared analysis.

A total of 57 *M. avium-M. intracellulare* isolates from patients with AIDS were collected during the study period. Of the patients, 23 were from New York, 15 were from Colorado, 8 were from the District of Columbia, 3 were from Washington, 3 were from Virginia, and 1 each were from Pennsylvania, California, and Indiana. Non-AIDS isolates were from the following states (number of isolates): Arizona, nine; California, seven; Colorado, five; Illinois, five; Pennsylvania, four; New York, three; Michigan, three; Washington, three; Alabama, three; Minnesota, three; Texas, three; and 16 other states with one or two each. Identification of *M. avium-M. intracellulare* was confirmed in the mycobacteriology laboratory of the National Jewish Center for Immunology and Respiratory Medicine by standard criteria.

Results of in vitro susceptibility testing of the 57 isolates from patients with AIDS and the 75 isolates from patients without AIDS are shown in Table 1. Isolates from patients with AIDS were significantly less susceptible to kanamycin and rifampin and more susceptible to ethionamide and cycloserine. There were no significant differences in susceptibility testing between isolates of AIDS patients from New York City and those of AIDS patients from elsewhere.

The results of serotyping of *M. avium-M. intracellulare* isolates from patients with or without AIDS are shown in Table 2. Patients with AIDS were significantly more likely to have an isolate identified as serotype 4 than were patients without AIDS. When isolates were analyzed by geographic origin, AIDS patients from New York City were more likely to have serotype 4 isolates than were AIDS patients from elsewhere ($P < 0.01$).

Discussion. We report here the results of a prospective survey of in vitro susceptibility testing and serotyping of *M. avium-M. intracellulare* isolates from patients with AIDS. These isolates were collected from four locations: New York, N.Y.; Bethesda, Md.; Denver, Colo.; and Seattle,

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TABLE 1. Percentage of *M. avium-M. intracellulare* isolates susceptible to antimycobacterial agents in vitro

Drug (concn [$\mu\text{g/ml}$])	% Susceptible isolates from:			
	Non-AIDS patients (n = 75)	Non-New York AIDS patients (n = 34)	New York AIDS patients (n = 23)	All AIDS patients (n = 57)
Isoniazid (1.0)	0	3	0	2
Streptomycin (10)	5	6	0	3
Kanamycin (12)	16	6	0	3 ^a
Capreomycin (20)	0	6	0	3
Ethambutol (15)	32	26	40	32
p-Aminosalicylic acid (8)	0	6	0	3
Ethionamide (15)	42	77	80	78 ^b
Cycloserine (60)	66	94	95	95 ^b
Rifampin (10)	60	26	28	27 ^b
Clofazimine (1.0)	77	83	95	88
Ansamycin (2.0)		89	95	92
Ansamycin (0.5)		26	30	28

^a Significantly different from non-AIDS isolates ($P < 0.02$).

^b Significantly different from non-AIDS isolates ($P < 0.001$).

Wash. Such isolates are therefore not representative of all AIDS patients but do allow speculation about geographic localization of *M. avium-M. intracellulare* isolates. The 75 control isolates represented *M. avium-M. intracellulare* which caused invasive pulmonary disease in patients without AIDS. These isolates were collected between 1976 and 1982 and thus represented historical rather than concurrent controls. However, all isolates from both AIDS and non-AIDS patients were evaluated in the same microbiologic and serologic laboratories. Moreover, the distribution of serotypes in the patients without AIDS reported here was similar to earlier reports of serotypes causing disease in humans (11), suggesting that there is no large variability over time in pathogenic *M. avium-M. intracellulare* isolates.

Differences between *M. avium-M. intracellulare* isolates from patients with AIDS and those without AIDS may reflect differences in the pathophysiology of infection in these groups. *M. avium-M. intracellulare* infection in patients without AIDS is acquired by the respiratory route (8; Horsburgh et al., in press). On the other hand, several

TABLE 2. Serotypes of *M. avium-M. intracellulare* isolates from patients with or without AIDS^a

Serotype	No. of isolates from:			
	Non-AIDS patients (n = 75)	Non-New York AIDS patients (n = 29)	AIDS patients from New York (n = 23)	All AIDS patients (n = 52)
1	0	4	0	4
4	4	6	14 ^b	21 ^c
7	4	1	0	1
8	8	5	2	7
9	1	2	1	3
14	3	0	0	0
15	5	0	0	0
18	2	1	0	1
19	4	0	0	0
Untypable	16	8	4	12
Other	28	4	2	6

^a Two isolates were typed with two serotypes.

^b Significantly different from non-New York AIDS patients ($P < 0.01$).

^c Significantly different from non-AIDS patients ($P < 0.001$).

researchers have proposed that *M. avium-M. intracellulare* infection in AIDS patients is acquired from the gastrointestinal tract rather than the respiratory tract (1, 5). This different portal of entry may predispose AIDS patients to infection with organisms which are different from those which cause infection in patients without AIDS.

M. avium-M. intracellulare isolates from AIDS patients differed significantly from *M. avium-M. intracellulare* isolates from patients without AIDS. Susceptibility patterns showed that AIDS isolates were significantly more susceptible to ethionamide and cycloserine and less susceptible to kanamycin and rifampin than were isolates from patients without AIDS. The severely impaired immunity of AIDS patients certainly is a major factor in the poor response to antimycobacterial therapy seen in these patients. However, different in vitro susceptibility of *M. avium-M. intracellulare* isolates from AIDS patients may also play a role. Therapy of *M. avium-M. intracellulare* infection is more successful if patients receive drugs to which the pathogenic organisms are susceptible in vitro (Horsburgh et al., in press). However, AIDS patients seldom receive cycloserine or ethionamide (to which their isolates are most often susceptible) because the toxicities of these agents add to the already severe gastrointestinal and neurologic problems of these patients. Isolates from AIDS patients are much less frequently susceptible to rifampin than are isolates from non-AIDS patients, suggesting that this drug may be less effective in patients with AIDS.

We believe that 0.5 μg of ansamycin per ml is the appropriate in vitro concentration for susceptibility testing of disseminated *M. avium-M. intracellulare* isolates, since ansamycin levels in serum do not exceed this value with 300-mg/day oral dosing (4). (The drug is concentrated in lung tissue; a 2- $\mu\text{g/ml}$ concentration may therefore be appropriate when testing isolates from infection limited to the lungs.) *M. avium-M. intracellulare* isolates from AIDS patients were susceptible to 0.5 μg of ansamycin per ml in only 28% of the cases, suggesting that this agent also may be of limited usefulness in therapy of *M. avium-M. intracellulare* infection in AIDS patients.

Kiehn et al. (9), in a report of *M. avium-M. intracellulare* infection in AIDS patients from New York, suggested that these patients were more likely to be infected with *M. avium-M. intracellulare* isolates of serotype 4, a serotype which has been noted to be more virulent than other serotypes in animal models (6). In the present series, the increased incidence of serotype 4 isolates was attributable to isolates from New York. Serotype 4 may represent the most common serotype in the New York environment; alternatively, the increased incidence of this serotype in New York may reflect the presence of a localized outbreak. We found no correlation between serotype and results of in vitro susceptibility testing.

AIDS patients with *M. avium-M. intracellulare* infections thus often receive drugs to which their isolates are not susceptible in vitro and do not receive agents to which their isolates are susceptible. Inadequate therapeutic regimens may therefore be a contributing factor in the poor response of these patients to therapy. Improved response to therapy of *M. avium-M. intracellulare* infections in AIDS patients may require new antimycobacterial agents which possess greater activity against *M. avium-M. intracellulare* in vitro and are better tolerated by these debilitated patients.

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