Nontuberculous Mycobacterial Disease in Northern Australia: A Case Series and Review of the Literature

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We performed a retrospective/prospective review of all cases of disease due to nontuberculous mycobacteria (NTM) reported in the Northern Territory, Australia, during the period 1989–1997. Fifty-eight cases were reported, with an average yearly incidence of 3.9 cases per 100,000 persons. The number increased significantly for the second half of the study period (39 vs. 19 cases; $P < .02$). The yearly incidence of pulmonary *Mycobacterium avium/Mycobacterium intracellulare* complex (MAC) disease not associated with human immunodeficiency virus (HIV) infection was 2.1 cases per 100,000 population. MAC was the most common isolate (78%) and pulmonary disease the most frequent clinical presentation (62%). Disease due to NTM or MAC was not found more commonly in rural areas. Significant risks for non–HIV-associated pulmonary MAC disease included male sex (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.0–4.5) and age >50 years (OR, 26.5; 95% CI, 10.9–67.3), but aboriginal people appeared underrepresented (OR, 0.77; 95% CI, 0.30–1.87). *Mycobacterium tuberculosis* was almost 5 times more likely than NTM to be the cause of non–HIV-associated mycobacterial pulmonary disease (153 vs. 32 cases; OR, 4.79; 95% CI, 3.22–7.14). Mycobacterial lymphadenitis in aboriginal children was more likely to be tuberculous than nontuberculous (OR, 6.5; 95% CI, 1.4–41.7), but not in nonaboriginal children (OR, 1.0). With treatment, 66% of the cases of non–HIV-associated pulmonary MAC disease had favorable outcomes, and 7% of patients had progressive fatal disease. Outcomes of therapy for lymphadenitis and skin/soft-tissue disease were excellent, but those of HIV-associated disseminated MAC disease were poor.

Mycobacteria distinct from *Mycobacterium tuberculosis* complex *(M. tuberculosis, Mycobacterium bovis,* and *Mycobacterium africanum)* and *Mycobacterium leprae* have been recognized since late in the last century, but only since the 1950s have they been well recognized as a cause of human disease. They have been referred to by various names but here will be collectively called nontuberculous mycobacteria (NTM), in accordance with the nomenclature of the American Thoracic Society [1].

Recent reports have shown that disease caused by NTM is on the rise, and in many developed countries NTM account for an increasing proportion of mycobacterial disease. In addition, the distribution of the various NTM is not uniform and appears to be geographically or environmentally dependent, but this remains poorly defined.

The Northern Territory of Australia is a sparsely populated region of contrasting climates: the "top-end" (northernmost) region is tropical, with a monsoonal, hot summer and a dry, warm winter, whereas the central region is semiarid desert. The Northern Territory combines contrasting populations, with the majority living in an urban setting and the rest living in small towns or remote, isolated communities, often with poor resources. There is a large aboriginal population, among whom morbidity and mortality from many infectious diseases are higher than among the nonaboriginal population [2].

Recognizing the increasing significance of disease due to NTM worldwide and in our unique environment, we initiated a study to assess the burden of such disease in our region. Disease caused by NTM is notifiable in the Northern Territory, and almost all cases are referred for diagnosis and management through a central tuberculosis/chest clinic system as part of the Centre for Disease Control.

The aims of our study were (1) to assess the disease incidence, the mycobacterial species involved, the clinical conditions they caused, and to describe their geographical variations; (2) to determine the patients' demographic characteristics and risk factors; (3) to assess outcomes of commonly used investigations in the diagnosis of disease; (4) to determine disease treatments, their outcomes, and their side effects; and (5) to compare incidence and demographics with those of tuberculosis in our region.

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Methods

All incident cases of disease due to NTM reported to the registry of the Centre for Disease Control, in Darwin, during the period of 1989–1997 were included for retrospective/prospective review. Both inpatient and outpatient medical records and relevant radiological data were analyzed.

To assess for any geographical variations, we considered the Northern Territory as 2 parts: the northern half (the top-end region) and the southern half (the center region). The city of Darwin was considered the only urban area (estimated population, 88,084), and the rest was collectively classified as rural (total estimated population, 79,543). Population data were obtained from the Northern Territory Bureau of Statistics.

NTM-associated cases were included in our study if they fulfilled the following criteria. Disease was considered pulmonary if it met the criteria established in 1990 by the American Thoracic Society for nontuberculous pulmonary disease [3]. These criteria, in brief, are as follows: (1) $\geqslant$2 sputum specimens (or 1 sputum and 1 bronchial-washing specimen) that are smear-positive for acid-fast bacilli (AFB) or that yield moderate to heavy growth in culture, and (2) exclusion of other reasonable causes of the disease process. Alternatively, the following may be diagnostic: (1) a tissue biopsy specimen that yields NTM in culture and has consistent histopathologic features or (2) a tissue biopsy specimen that is culture-negative but contains granulomas or AFB, when 2 previously obtained sputum/bronchial-washing specimens have been culture-positive.

Disease was classified as follows: as disseminated, if the causative species was isolated from >1 clinical site or from blood or bone marrow; as lymphadenitis, if culture of a biopsy specimen or swab of a clinically pathological lymph node yielded an NTM; or as skin/soft-tissue disease, if culture of a swab or biopsy specimen of a lesion involving skin, subcutaneous tissue, muscle, or synovium yielded NTM.

Tuberculosis cases were those fitting the Northern Territory notifiable diseases case definition; that is, (1) cases culture-positive for *M. tuberculosis* complex and (2) cases in which specimens were AFB smear–positive and/or histologically and/or clinically consistent, and in which there was response to specific antituberculosis treatment that was reviewed and accepted by the Northern Territory Tuberculosis Unit.

Risk factors were recorded if they met the following definitions: chronic lung disease (CLD), if clinical and radiological findings were consistent or confirmatory findings of respiratory-function tests were available; alcoholism, if >60 g (men) or >40 g (women) of alcohol was consumed daily; and smoking, if exposure was >10 packet-years. A previous history of tuberculosis involved isolation of *M. tuberculosis* >6 months before the NTM.

Initial cultures were performed at the microbiology laboratories of the Royal Darwin and Alice Springs hospitals and Queensland Medical Laboratories (Brisbane and Pathcentre, Perth). Formal testing for identification and antimicrobial susceptibility was performed at the Victorian Infectious Diseases Reference Laboratories, Melbourne; the Institute of Medical and Veterinary Science, Adelaide; the Queensland State Reference Laboratory, Brisbane; and the Western Australian State Reference Laboratory, Perth.

Outcomes of treatment were defined as follows. (1) For a patient with pulmonary disease, a favorable outcome was defined as $\geqslant$2 of the following findings: clinical improvement, radiological improvement, or clearance of the mycobacterial isolate from 3 consecutive sputum specimens (sustained for at least 6 months). For patients with disease other than pulmonary, a favorable outcome was defined on as complete clinical or radiological resolution. (2) Relapse was defined as isolation of the same mycobacterial species from 2 cultures, with recurrence of clinical or radiological disease, following a favorable outcome at the cessation of treatment. (3) Failure was defined as continuing deterioration of clinical or radiological findings and nonclearance of NTM by 6 months of treatment. (4) Default occurred when a patient withdrew from therapy before the prescribed treatment end point or when the outcome at 1 year after treatment was not evaluated.

Data were collected and analyzed with Epi Info software, version 6 (Centers for Disease Control and Prevention, Atlanta). Statistical significance was determined by means of the χ^2 test for 2×2 tables for each of the categorical variables.

Results

Epidemiology. There were 58 cases of disease due to NTM reported during the study period; the yearly incidence rate ranged from 1.8 to 7.5 cases per 100,000 population, and averaged 3.9 per 100,000 (table 1). The number increased significantly when the second half of the study period was compared to the first (39 vs. 19 cases; $P < .02$). This difference remained significant when HIV-infected patients ($n = 15$) were excluded. The average yearly incidence of non–HIV-associated disease due to NTM was 2.8 cases per 100,000 population. In comparison, there was a downward trend in the number of tuberculosis cases reported in the Northern Territory over the same period, from 40 cases per 100,000 population in 1989 to 17 per 100,000 in 1997, with only 1 case associated with HIV. Thus, NTM accounted for an increasing percentage of total mycobacterial disease notifications, from 9% in 1989 to 31% in 1997.

The average yearly incidence of non–HIV-associated pulmonary disease due to NTM was 2.1 cases per 100,000 population. Similar to the increase in the total number of cases, there was a significant increase in the number of non–HIV-

Table 1. Incidence rates (per 100,000 population) of disease due to nontuberculous mycobacteria in the Northern Territory of Australia, 1989–1997.

	Incidence rate (% of cases)		
Year	Total	Non–HIV-associated	HIV-associated
1989	3.7	3.1	0.6
1990	3.1	3.1	0.0
1991	1.8	0.6	1.2
1992	3.0	0.6	2.4
1993	1.8	1.2	0.6
1994	2.9	2.9	0.0
1995	7.5	5.7	1.7
1996	2.8	2.8	0.0
1997	5.7	4.4	1.7

Table 2. Frequency of nontuberculous mycobacteria (NTM) species causing disease in the Northern Territory of Australia, 1989–1997.

NTM species	No. of disease-causing isolates recovered
M. avium–M. intracellular complex	45
M. fortuitum	5
M. abscessus	2
M. haemophilum	2
M. scrofulaceum	2
M. gordonae	1
M. simiae	1
M. terrae	1

NOTE. There were 59 isolates from 58 cases.

associated pulmonary cases during the second half of the study period (22 vs. 10 cases; $P < .05$).

The total number of NTM isolates was 59, and in 1 case, isolates of 2 species were recovered. The most common isolate was MAC (45 isolates); isolates of only 7 other species were recovered (table 2).

Regional analysis of disease-causing isolates showed MAC in all regions; however, *Mycobacterium gordonae, Mycobacterium scrofulaceum, Mycobacterium simiae, Mycobacterium terrae,* and *M. fortuitum* were found only in the tropical top-end region. Apart from 1 *M. abscessus* isolate, the isolates from the center region were all MAC. All skin/soft-tissue and nodal cases were in the top-end region. There was no significant difference in the likelihood of developing disease due to NTM in rural versus urban regions (OR, 0.96; 95% CI, 0.56–1.66). This was also true for all MAC disease (OR, 0.89; 95% CI, 0.47–1.65) and non–HIV-associated pulmonary MAC disease (OR, 1.57; 95% CI, 0.71–3.49).

Table 3 shows the distribution of clinical disease. MAC accounted for 33 (92%) of pulmonary disease cases; 2 other cases were due to *M. scrofulaceum* and 1 to *M. simiae. M. tuberculosis* was almost 5 times more likely than other species to be the pathogen in culture-confirmed cases of non–HIV-associated mycobacterial pulmonary disease in the Northern Territory over the period of our study (153 vs. 32 cases; OR, 4.79; 95% CI, 3.22–7.14).

All cases of disseminated disease were due to MAC, with the exception of 1 case due to *M. fortuitum* and *M. abscessus.* Among cases of skin/soft-tissue disease, 4 (44%) were due to *M. fortuitum*, 2 each were due to *M. haemophilum* and MAC, and 1 was due to *M. terrae.* All cases of NTM lymphadenitis involved patients aged 0–9 years; these cases were due to MAC (2 cases), *M. fortuitum* (1), and *M. gordonae* (1). Over the period of the study the most commonly reported mycobacterial cause of lymphadenitis in Northern Territory children (aged <15) was *M. tuberculosis* (15 of 19 cases), and aboriginal children were >6 times more likely to have tuberculous lymphadenitis (13 cases) than nontuberculous lymphadenitis (2 cases; OR, 6.5; 95% CI, 1.4–41.7). However, there was no such difference for nonaboriginal children (OR, 1.0), among whom there were 2 reported cases of each type.

Age at notification was influenced by the site of disease (figure 1). The mean age in cases of pulmonary non–HIV-associated disease was 57 years, and it was higher for nonaboriginal than for aboriginal people (58 vs. 52 years). The OR for developing disease due to NTM for persons aged ⩾50 years (vs. <50 years) was 6.9 (95% CI, 4.0–12.0). In addition, the OR for developing non–HIV-associated pulmonary disease for persons aged ⩾50 years (vs. <50 years) was 26.5 (95% CI, 10.9–67.3).

Males accounted for 41 and females for 17 cases of NTM disease, corresponding to average incidence rates per year of 5.2 per 100,000 for males and 2.3 per 100,000 for females (OR [males vs. females], 2.2; 95% CI, 1.2–4.0). Such findings were similar for non–HIV-associated pulmonary disease (OR, 2.1; 95% CI, 1.0–4.5). Australia-born people accounted for 49 (85%) of the cases. Of the 9 cases involving people born overseas, the mean duration of residence in Australia was 25 years (range, 1–60 years). Of those born in Australia, 12 were aboriginal. Overall, 63% of cases occurred in nonaboriginal Australia-born people, 21% in aboriginal people, and 16% in people born overseas; in comparison, cases of tuberculosis over the study period occurred in 12% of nonaboriginal Australia-born people, in 62% of aboriginal people, and in 26% of people born overseas (figure 2). The risk of developing disease due to NTM was similar for aboriginal and nonaboriginal people (OR, 0.72; 95% CI, 0.36–1.40) and was similar when only non–HIV-associated pulmonary disease cases were analyzed (OR, 0.77; 95% CI, 0.30–1.87).

Risk factors. The most common risk factors associated with disease due to NTM were smoking (66%), CLD (42%), HIV infection (26%), and alcoholism (20%). Less often noted were immunosuppressive therapy (10%), malignancy (6%), connective tissue disease (6%), previous *M. tuberculosis* infection (4%), leprosy (4%), and diabetes (2%). All cases involving lymphadenitis had no risk factors.

For non–HIV-associated pulmonary disease, the associations of smoking (81%), CLD (69%), and alcoholism (31%) remained high. Six cases (19%) were associated with immunosuppressive therapy (table 4), including 3 in which the patients were receiving methotrexate. In 2 cases smoking was the only risk factor.

Of the 53 cases of disease due to NTM and 31 of non–HIV-associated pulmonary disease, 1 each involved a patient with diabetes, although ascertainment of diabetes was not complete.

Disseminated disease in comparison with localized disease was significantly associated with HIV infection ($P < .001$). The

Table 3. Clinical distribution of nontuberculous mycobacteria disease in the Northern Territory of Australia, 1989–1997.

Type of disease	No. of non–HIV-associated cases	No. of HIV-associated cases	Total
Pulmonary	32	4	36
Disseminated	1	8	9
Skin/soft-tissue	6	3	9
Lymphadenitis	4	0	4
Total	43	15	58

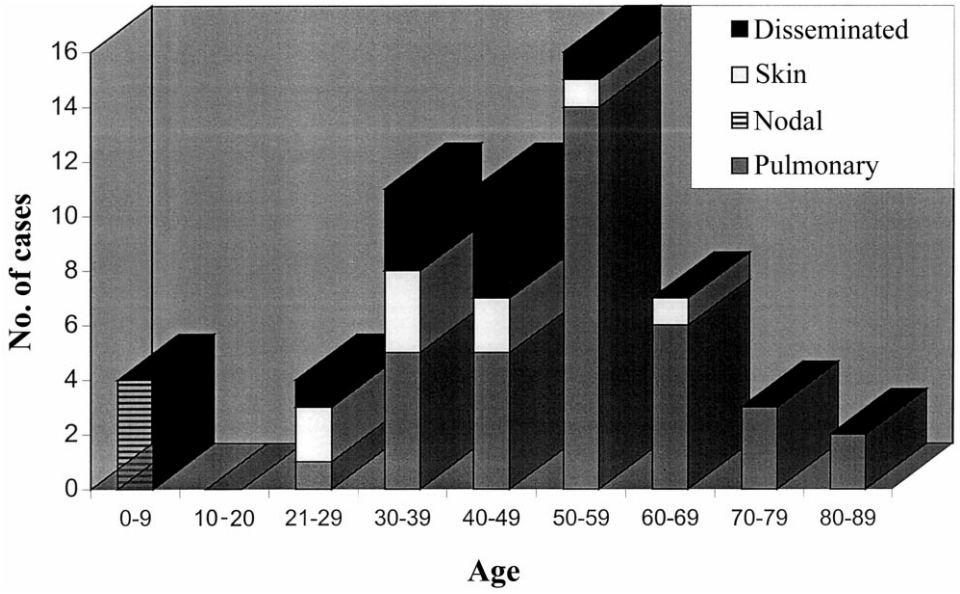

Figure 1. Ages of patients in the Northern Territory of Australia at notification of indicated disease due to nontuberculous mycobacteria

mean CD4 cell count of the HIV-infected patients at diagnosis was 18×10^6/L (range, 6–41×10^6/L). The single case of non–HIV-associated disseminated disease involved diffuse *M. abscessus* and *M. fortuitum* lymphadenitis; it occurred in a 49-year-old aboriginal man with no detectable underlying immune deficiency.

Investigations. Chest radiographs revealed cavitating pulmonary disease in 72% of HIV-negative cases but none in HIV-positive cases. Non–HIV-associated pulmonary disease involved the upper zones of the lung in 86%, middle zones in 32%, and lower zones in 4% of cases, and the incidence of unilateral versus bilateral disease was similar (54% vs. 46%).

Of the patients with pulmonary disease, 75% had positive AFB smears, regardless of HIV status. Over the same period, among culture-positive cases of pulmonary *M. tuberculosis* disease, the smear-positivity rate was 76% (117 of 153 cases). For cases due to NTM, there was no significant difference in likelihood of smear positivity between cavitating and noncavitating disease.

Treatment and Outcome

Non–HIV-associated pulmonary disease. Twenty-eight of 32 patients were treated for >1 month and had follow-up information available (table 4), and for 19 (68%) of these 28 the outcome was favorable. One patient's favorable treatment outcome followed surgical resection of the involved lung. Treatment failed for 6 patients (21%), of whom 2 (7% of treated patients) died of disease due to NTM despite 20 and 12 months of chemotherapy with regimens that included ethambutol and clarithromycin. Two patients (7%) had a relapse of disease. Both cases involved MAC cavitating disease in smokers with CLD who were receiving immunosuppressive therapy. Treatment involved dual therapy with ethambutol and clarithromycin for 7 and 12 months, respectively, and relapse was detected 2 and 3 months, respectively, following cessation of therapy. The second patient had become sputum-culture-negative 9 months before treatment ended. In comparison, for those who did not have a relapse detected, the mean duration of therapy was 14 months (range, 4–24 months), with a drug regimen averaging a minimum of 3 drugs at any time (range, 2–4 drugs). One patient (4%) defaulted after 13 months of treatment.

Twenty-five patients (86%) were initially treated for *M. tuberculosis* disease for a mean of 1.5 months (range, 1–6 months). There were no sputum conversions achieved during this treatment period. Ten patients (40%) experienced adverse reactions to this regimen, which involved a rash in 7. Twelve patients (41%) experienced side effects with the specific anti-NTM regimens: 5 had rash; 3, gastrointestinal symptoms; 3, musculoskeletal effects; and 1 each, hepatitis, renal dysfunction, visual changes, and blood dyscrasia. If these side effects are combined with the adverse reactions to the antituberculous regimen, then 16 patients (55%) had significant side effects during their treatment. The risk of side effects was significantly higher in cases of cavitating disease than in cases of noncavitating disease (15 of 20 vs. 1 of 9 cases; $P < .01$).

Lymphadenitis. All 4 patients with lymphadenitis underwent surgical excision of the involved lymph node, with no adjunctive chemotherapy. A curative outcome was achieved in all cases, with no relapse detected at a mean follow-up of 4 years (range, 1.5–7 years).

Skin/soft-tissue disease. This was treated with a combination of surgery and chemotherapy in 7 cases and with chemotherapy alone in 1 case. All patients completed treatment,

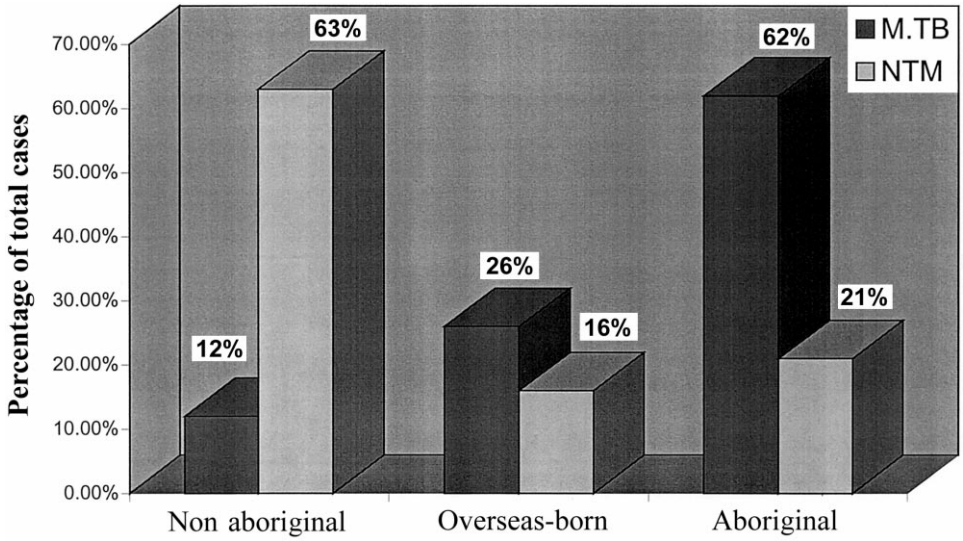

Figure 2. Ethnic background of persons in the Northern Territory of Australia with disease due to nontuberculous mycobacteria *(light bars)* and of those with disease due to *M. tuberculosis (dark bars)*.

with a mean duration of therapy of 5 months (range, 2–6 months). No relapses were detected after a mean follow-up of 10 months (range, 2–39 months).

Disseminated disease. Of the 7 patients with HIV-associated cases for whom follow-up information was available, 6 (86%) died, all within 8 months of diagnosis (mean, 4 months), 5 despite receiving anti-MAC therapy. The only patient receiving adjunctive highly active antiretroviral therapy (HAART) was well during anti-MAC treatment at 12 months after the diagnosis. In the sole patient with a non–HIV-associated case, there was an excellent clinical response following 27 months of treatment, with no detectable residual disease at a 12-month follow-up.

Discussion

Incidence. It is difficult to compare our incidence rates for disease due to NTM with those published by others [4–9] because of variations in the study periods, selection criteria, case ascertainment, and patient populations studied. Nevertheless, the average yearly incidence for disease due to NTM in the Northern Territory during the period 1989–1997 (3.9 per 100,000) was higher than published previously from Australia during the period 1959–1968 (2 per 100,000) [5] and from the United States during the period 1981–1983 (1.8 per 100,000) [7]. A recent study in Switzerland [6] of non–HIV-associated disease due to NTM revealed an incidence of 0.5 cases per 100,000 population for the years 1983–1988, compared with the incidence in our population of 2.8 cases per 100,000. For all NTM pulmonary disease, our incidence rate of 2.3 cases per 100,000 population was similar to incidence rates reported in Japan (1.7 per 100,000) [4] for the period 1971–1984 and in Hong Kong (2.0 per 100,000) for 1990 [8]. Finally, the incidence rate for MAC pulmonary disease in our study (2.1 cases per 100,000 population) was greater than the rate reported for the United States during the period 1975–1986 (1.0 per 100,000) [9] and for Japan during the period 1971–1984 (1.3 per 100,000) [4].

The higher incidence of disease due to NTM found in the Northern Territory may be a reflection of the hot, tropical climate of our region, as NTM are reportedly more prevalent in warmer climates. Disease due to NTM is more common in warmer than colder regions of Japan [4], and mycobacterial sensitivity studies in both Australia [10] and the United States [11] indicate increasing exposure to NTM in warmer climates. In addition, NTM have been isolated from the water at higher frequencies in areas where water temperatures are relatively high [12, 13].

The higher rates in the Northern Territory may also be attributed in part to the fact that this was the most recent study. Similar to the epidemiology of disease due to NTM worldwide [6, 14–17], the incidence rates of disease due to NTM in the Northern Territory appear to be increasing. Likewise, there is an increasing percentage of NTM among the total mycobacterial disease-causing isolates worldwide [6, 14–16, 18]. This was also found in the Northern Territory, partly because of the falling incidence of *M. tuberculosis* but also because of the increasing numbers of NTM. The HIV epidemic and increased use of immunosuppressive medications are contributing factors [14, 19], but these alone do not explain this finding. Other possible explanations include the following. (1) There is cross-immunity between mycobacterial species [20], and as a result of reducing exposure to *M. tuberculosis* in our communities, there are more mycobacteria-naive people susceptible to NTM infection [21, 22]. (2) NTM virulence is increasing. (3) Exposure

Table 4. Descriptions of patients in the Northern Territory of Australia with non–HIV-associated pulmonary disease due to nontuberculous mycobacteria (NTM), 1989-1997.

Patient	Age (y), sex	*Mycobacterium* species isolated	Risk factor(s)	Treatment (no. of mo)		Total mo. of treatment	Outcome of treatment[b]
				Initial	Against NTM		
1	65, M	MAC	CLD	INH, Rif, PZA, Eth (2)	INH, Rif, PZA, Eth (9); Rif, PZA, Eth, Y (2)	13	Failure
2	39, F	*M. scrofulaceum*	Smoking, alcoholism	INH, Rif, PZA, Eth (1)	INH, Rif, PZA, Eth (14)	15	Favorable
3	52, M	MAC	CLD, smoking, leprosy	INH, Rif, PZA, Eth (2)	INH, Rif, PZA, Eth (12); Eth, PZA (10)	24	Favorable
4	36, M	MAC	CLD, smoking, alcoholism	INH, Rif, PZA, Eth (5)	INH, Rif, (2)	7	Favorable
5	53, M	MAC	Smoking, alcoholism, leprosy	INH, Rif, PZA, Eth (2)	INH, Rif, PZA, Eth (7)	9	Favorable
6	50, M	*M. scrofulaceum*	CLD, smoking, alcoholism	INH, Rif, PZA, Eth (1)	Eth, Rif, PZA (21)	22	Favorable
7	47, M	MAC	CLD, smoking, alcoholism	INH, Rif, PZA, Eth (1)	INH, Rif, PZA, Eth (12)	13	Defaulted
8	55, M	MAC	Smoking	INH, Rif, PZA, Eth (1)	INH, Rif, PZA, Eth (6)	7	Favorable
9	67, M	MAC	CLD, alcoholism	INH, Rif, PZA, Eth (1)	Declined	1	Defaulted, death
10	65, F	MAC	CLD, smoking	INH, Rif, PZA (1)	INH, Rif, PZA (18)	19	Favorable
11	87, M	*M. simiae*	CLD	INH, Rif, PZA, Eth (2)	INH, Eth, Rib, Cpfx (4); Rib, Eth, Cpfx (6)	12	Favorable
12	59, M	MAC	Smoking, malignancy	INH, Rif, PZA, Eth (1)	INH, Rif, PZA, Eth (4)	6	Favorable
13	58, M	MAC	CLD, smoking, alcoholism, diabetes	NA	NA	NA	Transferred out
14	50, F	MAC	IS therapy	INH, Rif, PZA, Eth (1)	Clm, Eth, Rib (12)	13	Relapse
15	51, F	MAC	CLD, smoking, alcoholism	INH, Rif, PZA (1)	Clm, Eth, Rib (18)	19	Favorable
16	52, F	MAC	Smoking, malignancy, CTD	INH, Rif, PZA, Eth (1)	INH, Rif, PZA, Eth, CMZ (12); Clm, Eth, Rib, Azm (12)	25	Failure
17	50, M	MAC	CLD, smoking	INH, Rif, PZA, Eth (1)	INH, Rif, Eth (9); Clm, Eth, Rib (10)	20	Failure, death
18	65, M	MAC	CLD, smoking, alcoholism	None	Clm, Eth, Rib (1); Clm, Eth (5)	6	Favorable
19	68, F	MAC	CLD	NA	NA	NA	Transferred out
20	72, M	MAC	CLD, smoking	INH, Rif, Eth (1)	INH, Rif, Eth (18)	19	Favorable
21	43, M	MAC	CLD, smoking, IS therapy	INH, Rif, PZA, Eth (2)	R, C (19)[a]	21	Favorable
22	58, M	MAC	CLD, smoking, methotrexate, prior TB	INH, Rif, PZA, Eth (1)	Clm, Eth (7)	8	Relapse
23	52, M	MAC	CLD, smoking, alcoholism	INH, Rif, PZA, Eth (6)	Clm, Eth, Rib (24)	24	Failure
24	74, F	MAC	CLD	INH, Rif, PZA, Eth (2)	Clm, Eth (10)	12	Failure, death
25	84, M	MAC	CLD	None	Clm, Eth, Rib (4)	4	Favorable
26	44, M	MAC	Smoking	INH, Rif, PZA, Eth (3)	Clm, Eth, Rib (6)	9	Favorable
27	41, M	MAC	CLD, smoking	INH, Rif, PZA, Eth (1)	Clm, Eth, Rib (1); Azm, Clof (10)	12	Failure
28	57, M	MAC	Smoking	None	Clm, Eth, Rib (9)	9	Favorable
29	53, F	MAC	CLD, smoking	INH, Rif, PZA (1)	Clm, Eth, Rib, Cpfx (2); Clm, Eth, Rib, Clof (2); Clm, Eth, Rib (10)	15	Favorable
30	72, F	MAC	CLD, smoking	None	Clm, Eth, Rib (1)	1	Defaulted
31	56, F	MAC	Smoking, methotrexate, CTD	INH, Rif, PZA, Eth (1)	Clm, Eth, Rib (1); Clm, Eth (10)	12	Favorable
32	62, F	MAC	CLD, methotrexate, CTD	None	Clm, Eth, Rib (12)	12	Favorable

NOTE. Azm, azithromycin; CLD, chronic lung disease; Clm, clarithromycin; Clof, clofazamine; CMZ, cotrimoxazole; Cpfx, ciprofloxacin; CTD, connective tissue disease; Eth, ethambutol; F, female; INH, isoniazid; IS, immunosuppressive; IT, immunosuppressive therapy; M, male; MAC, *Mycobacterium aviam intracellulare* complex; NA, not available; PZA, pyrazinamide; Rib, rifabutin; Rif, rifampin; TB, tuberculosis; Y, cycloserine.

[a] Underwent surgical resection of involved lung.

[b] See the Methods section for definitions of outcomes of treatment.

to NTM has been increased by changes in human behavior (e.g., aerosolized exposure is increased by taking more showers), and, for unclear reasons, by the increasing number and distribution of NTM in the environment [23]. (4) Because the population is aging, risk factors that promote disease (e.g., CLD) are increasingly prevalent [7]. (5) Increased awareness among clinicians/microbiologists has led to more frequent diagnoses and/or notifications.

Epidemiology. MAC accounted for 78% of all cases of disease due to NTM, which is similar to the 73% reported from Canada [16] and the 62% reported from the United States [7] but greater than the 36% reported from England and Wales

[14]. In non-HIV-infected people, MAC remained the dominant pathogen, accounting for 73% of isolates, compared with 38% of isolates in a study in Switzerland [6]. Although 3 of the above studies all showed significant rates of *M. kansasii* disease (24%–28%) [6, 7, 14], we found none. In addition, among a sample of 485 serial mycobacterial isolates recovered at the Royal Darwin Hospital and identified at the Victorian Infectious Diseases Reference Laboratories from 1990 through 1997, *M. kansasii* was not found (authors' unpublished record review). Because the environmental source of *M. kansasii* is probably water [24], it seems likely that it is uncommon in Northern Territory water supplies.

The regional variation in the NTM species isolated supports the idea that MAC is a hardy and adaptive organism, recovered worldwide [24]. The fact that *M. gordonae, M. scrofulaceum, M. simiae, M. terrae,* and *M. fortuitum* were found only in the top-end region may reflect the reduced availability of suitable natural water supplies and favorable soil conditions in the center region. *M. scrofulaceum* is more common in southern areas of America, which have warmer natural water supplies [12], similar to the tropical top-end region. Although previously it was noted that MAC disease occurred mainly in nonurban areas [21], our findings—and recently those of others [7]—dispute this rural association.

It is not known whether disease due to NTM, especially pulmonary disease, develops soon after infection or, like tuberculosis, can develop after a period of dormancy [1, 25]. Our data concerning people born overseas show that disease occurred in those who had been in Australia for a mean of 25 years, a finding supporting the probability of locally acquired disease and suggesting little dormancy, at least in comparison to the natural history of *M. tuberculosis.*

Risk factors. CLD, smoking, and excessive alcohol consumption [7, 26], as well as HIV infection [24], are well recognized risk factors for disease due to NTM and were commonly associated with it in our study. The finding that 19% of non–HIV-associated pulmonary cases were associated with the use of immunosuppressive therapy highlights the emergence of this group of at-risk patients. Recent reports have also described NTM pulmonary disease in people without predisposing conditions [18, 23], but no similar cases were identified in our study (table 4).

Diabetes is a strong risk factor for the development of other infectious diseases such as melioidosis [27], pneumococcal disease [28], and tuberculosis [29, 30]. Estimates for the prevalence of diabetes in the adult population (aged >19 years) of the Northern Territory are at least 8% for nonaboriginal and 10%–20% for aboriginal people [31]. However, in our study, the incidence of disease due to NTM was not increased among diabetic patients. In addition, there appears to be little previous evidence showing diabetes to be a significant risk factor for disease due to NTM.

Clinical Presentation

Non–HIV-associated pulmonary disease. As seen worldwide [1], pulmonary disease was our most common clinical form of disease due to NTM, accounting for 62% of the total cases and 75% of HIV-negative cases. The commonest NTM pulmonary pathogens worldwide are MAC, *M. kansasii,* and *Mycobacterium xenopi* [15], but their prevalence shows wide geographic variation. Almost all the non–HIV-associated pulmonary disease–causing isolates in our study were MAC (91%), which is a greater proportion than that found by another recent study of non-HIV-infected patients in Switzerland (35%) [6]. Our rate was still higher than those found by other studies that have not excluded cases in HIV-positive patients, in Japan (71%) [4], Hong Kong (54%) [8], and England (3%) [32].

We found no cases involving *M. kansasii* or *M. xenopi.* In areas of America [21], England and Wales [14, 32], Japan [4], and Switzerland [6], *M. kansasii* is common. As in the Northern Territory, little or no pulmonary disease due to *M. kansasii* has been noted in Hong Kong [8], Canada [33], and Sweden [15], where the predominant pathogen was also MAC. *M. xenopi* pulmonary disease has been previously noted to be uncommon in Australia [34] and likewise in neighboring Asia [4, 8], yet reasonably common in Canada [33] and Europe [6, 14].

Rapidly growing mycobacteria, especially *M. abscessus* and *M. fortuitum,* are well described but uncommon (<5%) [4, 6, 14, 33] causes of pulmonary disease, occurring especially in elderly patients without underlying lung disease [35]. We identified no pulmonary cases in our study.

Northern Territory aboriginal people have a greater risk than the nonaboriginal population of acquiring many infectious pulmonary diseases, including tuberculosis [36], melioidosis [27], and cryptococcosis [37], but this greater risk was not found for non–HIV-associated pulmonary disease due to NTM (OR, 0.77; 95% CI, 0.30–1.87). This may reflect the reduced life expectancy of aboriginal people [38], which reduces in the numbers of susceptible people; or if immunity to mycobacteria has a common basis [21, 22], then it may reflect the higher rates of *M. tuberculosis* infection in the aboriginal population [39, 40] may confer some protection against NTM. This theory is supported by findings that BCG vaccination may protect children from localized disease due to NTM [41] and that the incidence of HIV-associated disseminated MAC disease is reduced among patients previously infected with tuberculosis [42] or living in areas where tuberculosis is common [43]. It is also possible that there is underascertainment or underreporting of NTM disease in the remote aboriginal communities. Finally, evidence reported elsewhere [25] does not suggest that ethnicity is a risk factor for disease due to NTM. The absence of increased rates of disease in association with the often overcrowded living conditions in aboriginal communities offers further evidence that person-to-person transmission of NTM is not important.

As found elsewhere [21], we noted that non–HIV-associated NTM pulmonary disease was twice as common among males

than among females, and this is partly explained by higher rates of CLD among both aboriginal [44] and nonaboriginal males. The significantly increased risk of disease in the population aged ⩾50 years was probably due to the increased rates of CLD in the older age groups, and the younger mean age of aboriginal versus nonaboriginal people may reflect increased rates of CLD at a younger age in this population or their reduced life expectancy. These findings are consistent with those of a recent London study, in which non–HIV-associated pulmonary disease was seen most commonly in white men with a mean age of 58 years [33].

Chest radiographic changes in cases of non–HIV-associated pulmonary disease were similar to those seen with tuberculosis, usually involving the upper zones of the lung and almost as commonly bilateral as unilateral. Lesions were cavitating in a high percentage of cases (71%), similar to reports elsewhere [7, 45, 46]. The majority of cases had positive AFB smears (77%), but unlike tuberculosis, not more commonly so in cases of cavitating than in cases of noncavitating disease.

With *M. tuberculosis* more common than NTM as the cause of culture-positive pulmonary disease (OR, 4.79; 95% CI, 3.22–7.14) and necessitating early treatment to prevent transmission, management prior to species-level identification often involves commencement of antituberculous drug therapy, as occurred in 86% of our cases. Advances in early identification via rapid mycobacterial culture techniques and DNA probes will help to reduce the period of uncertainty but will not obviate the need for this early empirical therapy.

Our study confirms that non–HIV-associated MAC pulmonary disease can be a fatally progressive disease despite appropriate treatment. The current recommendation of the American Thoracic Society for initial treatment is to use a regimen including at least 3 drugs: a macrolide (clarithromycin or azithromycin), a rifamycin (rifabutin or rifampin), and ethambutol [1]. In addition, it has been shown in a recent study by Wallace et al. [47] that cessation of therapy (with at least 3 drugs, including clarithromycin) within <10 months of culture negativity can result in early relapse. However, no relapses were detected if therapy was extended to 12 months after the cultures became negative. In our study, the 2 patients who had early relapses had been treated with regimens that involved only 2 drugs (because of side effects) and for <10 months after their sputum cultures became negative. In contrast, those who had not relapsed received treatment with regimens of ⩾3 drugs for an average of 14 months. These results support the recommendations of the American Thoracic Society that treatment be continued until cultures have been negative for 10–12 months [1].

With the multiple-drug regimens, the risk of side effects is high. This was confirmed by the number of people who experienced significant side effects in our study (52%), similar to the number in other studies [47]. It has been said that antituberculous drugs are well tolerated by patients with MAC disease [1], but that was not our experience: 40% of the patients in our study experienced significant side effects, especially rash, when an antituberculous regimen was begun as initial therapy before the diagnosis of MAC disease.

Lymphadenitis. Among patients aged 0–9 years, the only form of disease due to NTM was lymphadenitis, which is the most common presentation of such disease in children [48]. There were no cases of lymphadenitis in people aged >10 years, although NTM rarely causes lymph node disease outside this age group [15].

Previously, *M. scrofulaceum* was the most commonly isolated cause of NTM lymphadenitis in children [3, 15], responsible for up to 80% of cases. More recently, MAC has been found to be the predominant organism [6, 7, 23, 48], suggesting the numbers of *M. scrofulaceum* in the environment are falling and the numbers of MAC are increasing [24]. Our study findings suggest a changing epidemiology in this area; we found no cases due to *M. scrofulaceum* and 50% due to MAC.

In the southern regions of Australia, mycobacterial lymphadenitis is almost always nontuberculous [49], but in the Northern Territory it is usually due to *M. tuberculosis.* Tuberculous lymphadenitis in Northern Territory aboriginal children was >6 times more common than nontuberculous lymphadenitis and accounted for all cases of mycobacterial lymphadenitis in adults during our study period. Therefore, management of mycobacterial lymphadenitis in Northern Territory adults and aboriginal children should empirically be directed toward tuberculosis until the causative organism has been formally identified [50].

As we required an NTM-positive culture for diagnosis, the number of lymphadenitis cases was likely underreported. In previous studies, 20%–50% of surgical lymph node specimens for which histologic and skin test results were consistent with disease due to NTM have been culture-negative [19, 49].

All our cases were treated successfully with surgical excision alone, an outcome which supports the findings of others that adjunctive chemotherapy is not required [48, 51].

Skin/soft-tissue disease. The rapidly growing mycobacteria *(M. fortuitum, Mycobacterium chelonae,* and *M. abscessus),* along with *Mycobacterium marinum* and *Mycobacterium ulcerans,* are the species of NTM that most commonly cause skin/soft-tissue disease [52]. Four cases were associated with *M. fortuitum,* including 1 involving a dog bite. *M. ulcerans* has been found in southeastern and northeastern parts of Australia [53–55], and occasional cases were reported from the Northern Territory before our study [56, 57]. It was surprising that we found no cases of *M. ulcerans* disease, since it occurs in tropical areas of the world [24], typically near permanent swamps or river systems [58], conditions which abound in the top-end region of the Northern Territory.

M. haemophilum is usually an opportunistic pathogen, causing disease in immunodeficient people, as in our study, in which both patients with *M. haemophilum* disease were infected with HIV. MAC is known to cause soft-tissue infections in immu-

nocompetent people [24], though uncommonly, and infection usually follows an inoculating event such as trauma, surgery, or injection. We had a single case involving an immunocompetent person, who sustained an inoculating thorn injury. The other case was associated with HIV, a coinfection which is well recognized [59].

Treatment for skin/soft-tissue disease usually involves a combination of surgical debridement and/or resection and chemotherapy [1, 60]. The optimal duration of drug therapy is not known, and specific chemotherapy should be directed by results of susceptibility testing of isolates [1]. Good outcomes were achieved in our study with a combination of chemotherapy and surgery, undertaken in all but 1 case, with no relapses at follow-ups done at a minimum of 12 months after treatment. With 1 exception, the relatively short duration of therapy (<6 months) suggests that chemotherapy need not be prolonged.

Disseminated disease. The outcome of disseminated MAC disease was poor prior to the advent of HAART. In our study, even with antimycobacterial therapy, the median survival was only 4 months from notification, a survival similar to that found by other investigators [61, 62]. Similarly, in the HIV Trials Network Study, in which a 3-drug regimen of rifabutin, clarithromycin, and ethambutol was used, the median duration of survival was only 8.6 months [63]. Restoration of immunity with HAART may be the most important factor in treatment [3], as evidenced by the fact that the only patient given HAART was alive and well 12 months after diagnosis.

Conclusions

Disease due to NTM is relatively common in the Northern Territory, and the incidence of disease is increasing. Pulmonary disease is the most common clinical presentation and MAC is the most common pathogen, but there is a spectrum of disease and a variety of disease-causing species. Due to presumed regional variation in environmental NTM, some species causing significant rates of disease elsewhere, including *M. kansasii, M. xenopi, M. ulcerans,* and *Mycobacterium malmoense,* are infrequent or absent in the Northern Territory.

Males and people aged ⩾50 years are at increased risk of disease due to NTM as well as non–HIV-associated NTM pulmonary disease. However, aboriginal people and diabetics are not at increased risk, a finding that reveals important differences between this disease and that caused by *M. tuberculosis* complex. The incidence and pathogenic species of disease due to NTM are influenced by environmental factors; MAC is found in all regions, but *M. gordonae, M. scrofulaceum, M. simiae, M. terrae,* and *M. fortuitum* are found only in the tropical top-end region. In rural and urban regions, however, disease rates are similar.

NTM pulmonary disease most commonly involves the upper zones of the lungs and is usually cavitating; sputum smears are usually AFB positive. In the Northern Territory, mycobacterial lymphadenitis in adults and aboriginal children should be considered tuberculous until proven otherwise.

With appropriate treatment, good outcomes can be achieved in cases of non–HIV-associated disease due to NTM. However, chemotherapeutic regimens for pulmonary disease must be prolonged and involve multiple drugs, and therefore they tend to be associated with a high incidence of side effects.

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