NONTUBERCULOUS MYCOBACTERIAL DISEASE

IN THE NINETIES

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I. Background

A. Introduction

In the early 1800's Koch was the first to describe the role of the tubercle bacillus in human disease. Within a decade other varieties of mycobacteria were described and named according to their source of isolation, such as bovine, avian, reptilian, and piscine. From 1885 until the 1930's these organisms were increasingly isolated from human material; but it was not until the 1950's that the concept of human mycobacterosis attributable to mycobacteria other than tuberculosis was established (1). In 1959 Runyon provided the first classification of "recently recognized pathogens that lacked accepted names" and stated the "diseases they produce are sadly anonymous" (2). From these early days until the present, diseases produced by these organisms have variously been labeled anonymous mycobacteria, atypical mycobacteria, mycobacteria-other than tuberculous (MOTT) and environmental, opportunistic and nontuberculous mycobacteria. For the purpose of this review I shall use the designation nontuberculous mycobacterial disease (NTMD) to include all human disease produced by mycobacteria other than mycobacterium tuberculosis, mycobacterium bovis or mycobacterium leprae.

B. Runyon Classification

In the contemporary mycobacteriology laboratory biochemical and molecular biologic techniques have rendered Runyon's classification techniques obsolete for the positive identification of many NTM. It is nevertheless useful to the clinician to be familiar with this scheme for classifying species that cause human disease (3). Until modern laboratory methods such as radiometric isolation and identification by genetic probes are in common use for all mycobacterial species, a knowledge of the Runyon classification can be useful for presumptive identification.

Runyon's initial classification scheme listed in Table 1 was based upon pigment production, rate of bacterial growth and growth characteristics of the organisms (2).

TABLE 1

Runyon Classification of Nontuberculous Mycobacteria

	Rate of Growth	Pigment	Colonies
Group I Photochromogens	21-28d	White, yellow	Smooth, rough
Group II Scotochromogens	10-14d	Yellow, red	Smooth
Group III Nonphotochromogens	21-28d	Tan, none	Small, smooth, round
Group IV Rapid growers	4-5d	Tan, none	Rough, smooth, cords

Group I known as photochromogens grow best on egg media of the Lowenstein-Jensen type. Growth is apparent in from 21-28 days and the colonies demonstrate little or no pigment in the dark but change to yellow when exposed to the light. Most colonies appear smooth but rough strains have also been described.

Group II known as scotochromogens are cultured on the same media with colonies apparent in from 10-14 days. The initial growth in the dark is predominately yellow to orange but changes to red when exposed to light. Scotochromogen colonies are predominately smooth in appearance.

Group III known as nonchromogens are similar to Group I and are apparent in 21-28 days. Unlike Group I, however, pigment production is poor with a white to beige color that does not change when exposed to light. Colonies are small, smooth and round in appearance.

Group IV known as rapid growers have coloring identical to the nonphotochromogens but attain full growth in only 3-5 days after inoculation. Colonies may be smooth or rough in appearance with a tendency to cord formation.

Biochemical differences and optimal growth temperatures further separate these organism within these four groups (3). Using this classification organisms known to cause human disease in immunocompetent or immunocompromised hosts are listed in Table 2 (4-6).

TABLE 2

Nontuberculous Mycobacteria Causing Human Disease Grouped by the Runyon Classification

Species	Primary Disease
Group I: Photochromogens	
M. kansasii	Pulmonary, disseminated
M. simiae	Pulmonary, disseminated
M. marinum	Cutaneous
Group II: Scotochromogens	
M. scrofulaceum	Lymph node, pulmonary, disseminated
M. xenopi	Pulmonary, disseminated
M. szulgai	Pulmonary, disseminated
M. gordonae	Disseminated, nosocomial
Group III: Nonchromogens	
M. avium-intracellulare (MAC)	Lymph node, pulmonary, disseminated
M. malmoense	Pulmonary, disseminated
M. ulcerans	Cutaneous
M. hemophilum	Cutaneous, soft tissue, disseminated
M. genavense	Lymph node, disseminated
Group IV: Rapid Growers	
M. fortuitum-chelonae (MFC)	Cutaneous, soft tissue, nosocomial

Although the Runyon classifications are somewhat obsolete for the modern mycobacteriology laboratory, it is a useful schema for the clinician to rapidly associate the prototype bacteria with the resultant primary clinical disease. Thus, Runyon Group I or the photochromogens are typified by M. kansasii that most often produces pulmonary disease in immunocompetent adults and a disseminated disease in immunocompromised persons. Group II or the scotochromogens are typified by M. scrofulaceum that is primarily a lymph node infection limited almost entirely to immunocompetent children. Dissemination of M. scrofulaceum occurs in immunocompromised adults and children. Group III or the nonchromogens are typified by the most common adult pathogen the M. avium-intracellulare complex (MAC). MAC infection results in pulmonary, lymph node or disseminated disease depending on the immune status of the host. Group IV or the rapid growers are typified by the M. fortuitum-chelonae complex (MFC) that was initially described as primarily a cutaneous or soft tissue disease in immunocompetent adults. Recent reports however have emphasized its increasing occurrence as a nosocomially infection. Dissemination of MFC is similar to the other NTM and predominately occurs in the immunocompromised host (7, 8).

C. Epidemiology

Most of the nontuberculous mycobacteria are ubiquitous and have been isolated from water, soil, dust, domestic and wild animals, milk and food (3, 7, 9-11). Although frequent environmental contaminants, only certain nontuberculous mycobacterial species are associated with human disease. The reservoirs of these medically important mycobacteria are listed in Table 3 (12).

TABLE 3

Reservoirs of Nontuberculous Mycobacteria in Human Disease

Mycobacterium	Group	Reservoir
M. avium complex	III	Water, soil, animals
M. kansasii	I	Water, animals
M. fortuitum complex	IV	Water, soil, animals
M. scrofulaceum	II	Water, soil, food

The mycobacterium avian complex (MAC) (Group III) causes the highest incidence of human disease. It has been shown that these organisms can be aerosolized in significant numbers particularly above bodies of water. The property of ready aerosolization strongly suggests that inhalation is the route of human infection in the immunocompetent adult with pulmonary disease (13). The gastrointestinal tract is the site of colonization in the immunocompromised host and ingestion of contaminated water is the likely source of infection in this clinical setting. Mycobacterium kansasii (Group I) causes the second highest incidence of human disease and it is least likely to be recovered from non-human sources. It has been recovered on rare occasions from water and animals, but recent evidence suggests that water may be the natural reservoir (11). The mycobacterium fortuitum-chelonae complex (MFC) (Group IV) produces the third highest incidence of human disease and is truly ubiquitous and will survive deprivation and extremes of temperature. These organisms are readily recovered from soil and animals but a majority of infections have also been traced to a water reservoir. Organisms have been isolated from tap water, municipal water supplies, contaminated biologicals, aquariums, water to cool cardioplegic solutions, peritoneal dialysate, wash solutions for bronchoscope decontamination and gentian violet solutions (5). Since most infections are acquired by inoculation after accidental trauma, surgery or injection, these organisms are the most frequent cause of nosocomial infection. Mycobacterium scrofulaceum (Group II) is the least likely of the nontuberculous mycobacteria to cause human disease. It has also been isolated from specimens,

reagents, standing water, and raw milk (3, 7). Isolation from post operative tonsillar specimens may account for the striking prevalence of lymph node disease in children. Mycobacterium marinum (Group I) inhabits water and marine organisms. Infection in humans often follows minor skin trauma in swimming pools, aquariums or natural bodies of water. Infection can also follow trauma from fish spines or nips by crustaceans. Thus, water would seem to be the most important vector in almost all nontuberculous mycobacterial infections that result in human disease.

There has been no firm evidence of human to human transmission of NTM disease although family groupings have occasionally occurred. Patients with infections caused by these organisms do not require isolation although prevention of water contamination particularly in immunocompromised patients may well become important following further investigation.

D. Prevalence

1. Prior to AIDS Epidemic

Although prevalence and distribution of tuberculosis has been closely scrutinized for years, the prevalence of NTMD has remained imprecise. Since NTMD is not a reportable disease and since these organisms may simply colonize the tissues their isolation from body secretions is not diagnostic of human infection. Nevertheless, prior to the AIDS epidemic Good presented the results of two national surveys conducted by the Centers for Disease Control (CDC) (4, 14). These surveys were performed in 1979 and 1980 and the results are summarized in Table 4.

TABLE 4

Prevalence of Mycobacterial Isolates
in the United States 1979 to 1980
(n=33,000)

Organism	Percent
M. tuberculosis	66
Nontuberculous	33
MAC	61
MFC	19
M. kansasii	10
Other NTM	10

Of approximately 33,000 isolates, two-thirds were M. tuberculosis and one-third were NTM. Within the group of NTM, M. avium complex accounted for 61%, M. fortiutum complex 19%, M.

kansasii for 10% and other NTM accounted for the remaining 10%. This study helped define the prevalence of isolation of NTM but could not define disease prevalence. A follow-up study of 5,000 patients from whom NTM were isolated attempted to classify the patients as to either colonization or infection (15). Overall, 38% of cases were judged to represent disease and 62% colonization. The estimated rate of disease varied among the different species with 75% of M. kansasii isolates, 47% of MAC isolates and 18% of MFC isolates assessed to represent true infection. Applying these estimates of disease rates to the previous surveillance survey the authors were able to estimate the prevalence of NTMD to be 1.8/100,000 population prior to the AIDS epidemic (4, 14).

2. Subsequent to the AIDS Epidemic

There is now mounting evidence that the prevalence of NTMD is increasing both in the AIDS and non-AIDS population (16, 17). It is estimated that between 24,000-39,000 cases of AIDS-related M. avium complex infection occurred in the first decade of the AIDS epidemic (17). Interestingly, in some hospitals the overall number of NTM infections now exceeds that of tuberculosis (18). The reported prevalence of MAC among AIDS patients has varied from 17-28% but the disease has been diagnosed at autopsy in 50-56% (19-21). These findings suggest that MAC disease may remain undiagnosed presumably because its presence is obscured by its unusual presentation or by the presence of other life-threatening infections. Serotyping of MAC isolates from AIDS patients revealed a larger proportion of strains of serotypes 4, 6 and 8 than is seen in among environmental MAC isolates (22). Additionally all isolates from AIDS patients contain plasmids a phenomena seen in only 33% of environmental isolates (23). The implications of these findings in terms of source of infection, modes of transmission, or pathogenicity and virulence remains to be determined.

Other NTM isolated from AIDS patients with disease include M. scrofulaceum, M. kansasii, M. szulgai, M. asiaticum, M. xenopi, M. flavescens, MFC, M. gordonae, M. malmoense and M. genavense (24). Several of these organisms (i.e., M. gordonae, M. flavescens) have heretofore been considered nonpathogenic and thus saprophytic when isolated from clinical specimens. Therefore all nontuberculous mycobacterial isolates should be regarded as potential pathogens in immunocompromised persons (25).

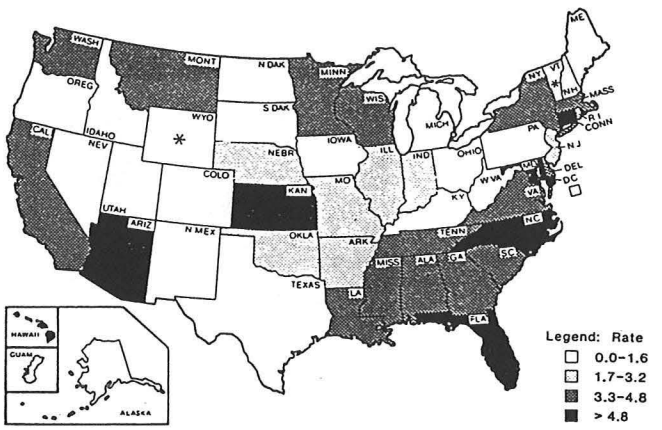
E. Geography

Prior to the AIDS epidemic regional differences in the United States in number and species of isolates of various NTM were well appreciated. Although not indicative of disease, a realization of these geographic differences may suggest to the clinician a suspicion of etiology of disease particularly in the immunocompetent host. As shown in Figure 1 the isolation rates

of MAC per 100,000 population in 1980 varies among the 48 reporting states and territories (4).

Figure 1

Isolation Rate MAC per 100,000 Population



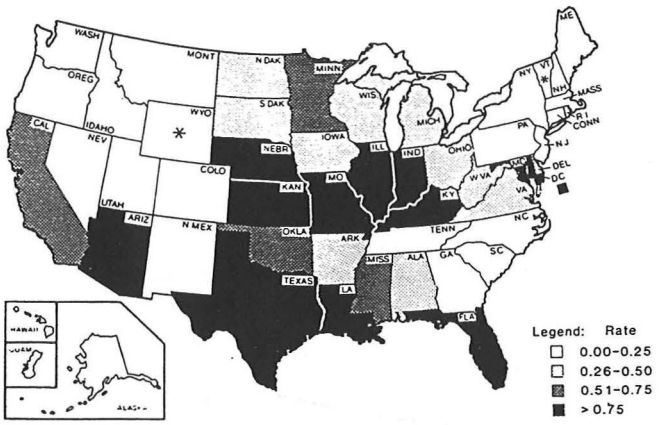
Good, R.C., et al: J. Infect. Dis. 146:829-833, 1982.

MAC rates are highest in the states bordering the Atlantic Ocean and Gulf of Mexico and in several states bordering Canada. Surprisingly, the isolation rate in Kansas (6.8 cases/100,000 population) was exceeded only by the rates in Hawaii (10.9), Connecticut (8.9) and Florida (8.4). Even more surprising to me was the rate for Georgia (3.3-4.8) the home of the Battey Sanitarium where MAC was originally known as the Battey bacillus.

As shown in Figure 2 the isolation rates of M. kansasii per 100,000 population has a different geographic distribution than MAC.

FIGURE 2

Isolation Rate M. kansasii per 100,000 Population



Good, R.C., et al: J. Infect. Dis. 146:829-833, 1982.

The highest isolation rates for M. kansasii are clustered in the central United States and form an inverted T by extending to include Florida to the east and California to the west.

Employing skin test verification, the authors were able to demonstrate that a true difference existed in geographic distribution and infection rate for MAC and M. kansasii in the United States.

No other species of NTM has been surveyed.

F. Differential between Contamination, Colonization and Disease

Isolation of a single colony of M. tuberculosis is clinically significant. This is not true of the NTM because as has been shown these organisms are normal constituents of the environment and may contribute to laboratory contamination. NTM also have a propensity to colonize the airway without producing true infection. Airway colonization is particularly frequent in cystic fibrosis and in chronic obstructive pulmonary disease most likely attributable to impaired mucociliary clearance.

For these reasons the ATS has recommended the diagnostic criteria for pulmonary disease caused by the NTM that are listed in Table 5 (7).

TABLE 5

Diagnostic Criteria for Pulmonary Disease Caused by NTM

I. Cavitary Infiltrate
   1. Exclusion of other disease.
   2. Two sputa or bronchial wash specimens that are AFB^+ with moderate to heavy growth on culture.

II. Noncavitary Infiltrate
   1. Exclusion of other disease.
   2. Two sputa or bronchial wash specimens that are AFB^+ with moderate to heavy growth on culture.

III. Cavitary or noncavitary infiltrate
   1. Lung biopsy with granulomatous inflammation.
   2. Positive culture of lung biopsy or at least two positive sputa cultures.

The diagnosis of pulmonary disease caused by NTM is usually not difficult and rarely requires an invasive procedure. Other reasonable causes of disease are first excluded by appropriate laboratory techniques. A clinical diagnosis of NTMD may then be made when a cavitary radiographic infiltrate is present and when two AFB positive sputa specimens result in a moderate to heavy growth of a NTM species. Bronchial washings are considered to be more sensitive than expectorated sputum but are less specific. Ninety percent of pulmonary disease caused by M. kansasii and up to 75% of pulmonary disease caused by the MAC have cavitary infiltrates and thus are easily diagnosed by these criteria (26).

In the presence of noncavitary radiographic infiltrates other reasonable disease is first excluded. A NTM pulmonary disease may again be diagnosed when two AFB positive sputa or bronchial wash specimens result in a moderate to heavy growth of a NTM species. The ATS has also recommended two weeks of bronchial hygiene or specific chemotherapy to evaluate clearance but notes that this recommendation has not been scientifically investigated. In the absence of data it would seem unreasonable to follow this recommendation in the current medical climate.

In the presence of cavitary or noncavitary radiographic infiltrates when sputum specimens are nondiagnostic a lung biopsy (either transbronchial or open) is recommended. Disease is present if the specimen is positive for granulomatous inflammation or is culture positive for a NTM species.

A variety of skin test reagents have been prepared from various species of NTM, however, they are generally unavailable and lack standardization. These include PPD-A, PPD-B, PPD-F, PPD-G, and PPD-Y from M. avium, M. intracellulare, M. fortuitum, M. scrofulaceum, and M. kansasii respectively. Cross-reactivity among these reagents due to shared antigens has limited their use to epidemiologic studies and they are not clinically useful in the diagnosis of NTM pulmonary disease (27, 28).

NTMD of lymph nodes, skin, soft tissue, bones and joints are diagnosed by cultural confirmation of granulomatous inflammation found on biopsy (7, 29).

Diagnosis of disseminated NTMD in non AIDS patients is made by cultural confirmation of organisms from sterile closed sites such as blood, bone marrow or from biopsy of a skin lesion (30).

Diagnosis of disseminated NTMD in AIDS patients is similar to non AIDS patients except that a positive stool culture is more often present. The presence of diarrhea, malabsorption and negative smears for acid fast organisms may require small bowel biopsy for confirmation (25, 31). Histologically granulomas are unusual but sheets of foamy macrophages filled with acid fast organism are present and result in cultural confirmation.

II. Clinical Classification of NTM Causing Human Disease

The number of NTM known to produce disease in immunocompetent and immunocompromised hosts has now grown to approximately 16 species (12). In this AIDS era the number of species involved in human disease will no doubt rise and new species will be identified. As Dr. Yarbrough so elegantly described in his recent Grand Rounds, the average physician would have great difficulty in processing more than seven pieces of information at any given time. That being the case I shall try to describe a clinical classification of the NTM by the clinical syndromes that they produce rather than the grouping of bacterial growth characteristics provided by the Runyon classification.

Table 6 tabulates the clinical syndromes associated with the 16 different species on NTM (5, 6, 12).

TABLE 6

Clinical Syndromes Associated with 16 Species of NTM

Syndrome	Cause	
	Common Species	Less Common Species
Pulmonary Disease	MAC *M. kansasii* M. xenopi	M. szulgai, simiae, scrofulaceum, fortuitum-chelonae malmoense, genavense
Lymph Node	MAC M. scrofulaceum	*M. kansasii*, fortuitum-chelonae
Skin Disease		
Swim pool	M. marinum	-----
Sporotrichoid	M. marinum	M. fortuitum-chelonae, *M. kansasii*
Abscesses, ulcers, sinus tracts	M. fortuitum-chelonae	M. hemophilum
chronic ulcer (Buruli)	M. ulcerans	
Skeletal/bone, joint, tendon	*M. kansasii*, MAC M. fortuitum-chelonae	M. marinum, scrofulaceum
Disseminated Disease	MAC, *M. kansasii*	M. fortuitum-chelonae, scrofulaceum All other NTM

MAC and M. kansasii are primarily pulmonary pathogens in the immunocompetent host but they may also cause occasional cases of lymph node, skin, ulcerative and skeletal disease. MAC is the most common cause of dissemination in the immunocompromised host; however, M. kansasii is also well described. M. xenopi is considered a significant pulmonary pathogen in Southern Ontario where it accounts for 38% of all NTM pulmonary infections. In this geographic area dissemination is not unusual in the immunocompromised host (5, 32). MFC is a rare pulmonary or lymph node pathogen but is a primary cause of traumatic ulcerations, soft tissue abscesses, skeletal, bone, joint and tendon disease. Disseminated disease is less common than MAC and M. kansasii in the immunocompromised host (33). M. scrofulaceum is primarily a lymph node pathogen in children and rarely causes pulmonary, skeletal, or soft tissue disease. Dissemination is rare even in the immunocompromised host (34).

M. marinum can be considered a skin infection with rare involvement of bone joints or soft tissues. Disseminated disease from this NTM remains a reportable case (35).

Thus, the clinical syndromes caused by MAC, M. kansasii, MFC, M. scrofulaceum and M. marinum separate rather nicely into principal organ systems involved. These NTM are by far the most common cause of disease in this area. For this reason it is necessary for the clinician to have a working knowledge of the clinical presentations, treatment and prophylaxis if indicated of these five NTM.

A. MAC (Mycobacterium Avium-Intracellulare Complex)

1. Clinical Disease in Patients Without AIDS

a. Pulmonary Disease

The first case of human pulmonary disease due to MAC was reported in 1943 in a middle aged miner from the Mesabi Iron Range of Minnesota (36). Since that time it has been recognized that pulmonary involvement with MAC may include so called "classic" and "nonclassic" presentations. The differences in these groups of patients are summarized in Table 7 (37, 38, 39-41).

TABLE 7

MAC Pulmonary Disease in Patients Without AIDS (n=85)

	Classic n=64	Nonclassic n=21
Chronic lung disease	64	0
Age (yr)	64 ± 14	66 ± 9.6
Sex (F) (%)	40	81
Caucasian (%)	80	86

As first described "classic" pulmonary disease due to MAC occurred predominately in white middle aged males with pre-existing pulmonary disease. Chronic obstructive pulmonary disease was the most common underlying abnormality but bronchiectasis, active or inactive tuberculosis, a variety of pneumoconiosis and bronchogenic carcinoma have all been reported. Approximately 75% of patients have evidence of radiographic cavitary infiltrates, predominately in the apical posterior segments of the upper lobes. Cavities are usually multiple and measure over 4 cm. Scarring and volume loss are rare occurring

in only 5%. Adenopathy is uncommon (4%) but endobronchial spread may occur in up to 80%. Advanced disease is present in greater than 70% on presentation. These radiographic characteristics of classic pulmonary MAC disease cannot be distinguished from M. tuberculosis (42).

An increasing incidence of "nonclassic" MAC pulmonary disease has been described (16). These patients are predominately older Caucasian women without underlying pulmonary disease who have usually been in good health. They are distinct radiographically from "classic" pulmonary disease. Approximately 70% of radiographs have multiple discrete pulmonary nodules. The nodular disease may be either localized or diffuse with consolidation occurring in 10%, interstitial disease in 10% and isolated cavities in only 2%. Overall, cavitation occurred in 24% (40). Progression of radiographic abnormalities occurs slowly over 2-9 years and advanced disease is uncommon occurring in only 29% on presentation (16, 40, 42a).

High resolution computed tomography has recently been demonstrated to be useful in predicting MAC disease in patients with "nonclassic" pulmonary disease. Patients with bronchiectasis were evaluated with high resolution computed tomography of the chest. Of 100 patients evaluated 24 had multiple nodules that were predominately <5 mm in diameter. Ninety-two percent of this group were female. In 19 of 24 patients the nodules were in the same lobe as the bronchiectasis and 53% had positive cultures for MAC. Of the 76 patients without small nodules 62% were female and only 4% had positive cultures for MAC. In both groups there were also positive fungal and other nontuberculosis mycobacteria cultures. The finding of multiple small nodules in female patients associated with bronchiectasis is by no means specific, but should alert the clinician to consider the diagnosis of MAC pulmonary disease in the immunocompetent host (43).

Clinical symptoms of patients with "classic" and "nonclassic" pulmonary disease are equally indolent (Table 8) (37, 40).

TABLE 8

Clinical Symptoms of Pulmonary Disease with MAC Infections (n=85)

Symptom	Percent
Cough and sputum	86
Fever	14
Weight loss	14
Hemoptysis	14

Productive cough and purulent sputum are the primary symptoms present in 86% of patients. These symptoms are frequently attributed to acute or chronic bronchitis and most patients will receive repeated courses of broad-spectrum antibiotics usually without change in cough or infiltrates. In one study cough was present a mean of 25.6 ± 36.5 weeks before diagnosis. Fever, weight loss and hemoptysis occurred in only 14%. Dyspnea, night sweats and malaise are distinctly uncommon and markers of chronic disease such as anemia and leukocytosis are exceedingly rare (37, 40).

Non-AIDS patients receiving cytotoxic chemotherapy, corticosteroids or allogenic bone marrow, renal or cardiac transplants are also at increased risk for pulmonary MAC disease. Patients in these categories commonly present with atypical clinical and radiographic features that are indistinguishable from patients with AIDS (44).

In most patients with MAC pulmonary disease the diagnosis is made according to the criteria published by the ATS. Only rarely will transbronchial or open lung biopsy be required for diagnosis (7). The more invasive procedures are most often required in patients with a low burden of organisms.

Histopathologic presentations are varied; both caseating and noncaseating granulomatous necrosis are common and may be associated with a granulomatous bronchitis. Ill formed granulomata with histocytic reactions are more commonly reported in immunodeficient patients but are also seen in immunocompetent hosts. Granulomatous vasculitis and nonspecific interstitial pneumonitis with organizing pneumonia may be rarely reported as the only pathologic finding (45).

Treatment of MAC pulmonary disease in non-AIDS patients has been poorly studied compared to patients with AIDS. Moreover, due to the indolence of the disease, parenteral medications, are usually not an option. MAC organisms are resistant *in vitro* to all standard TB drugs with the exception of cycloserine. Several choices for the treatment of MAC pulmonary disease in non-AIDS patients are listed in Table 9 (37, 46, 47).

TABLE 9

Treatment Options for MAC
Pulmonary Disease in Non-AIDS Patients

INH/ETB/RIF/Streptomycin
Surgery for localized disease
ETB/RIB/Clarithromycin ± Streptomycin
or
Azithromycin

In the older literature sputa conversion of patients with MAC pulmonary disease correlated with the number of agents administered (40, 47). Therefore, the ATS has recommended that patients be treated with INH 300 mgm/d, Ethambutol 15-25 mgm/kg/d, Rifampin 600 mgm/d and Streptomycin 1 gm twice a week. This regimen has reported the highest sputa conversion rate (80%) and the lowest relapse rate (4%). This four drug regimen has not been proven by comparative trials but has proven efficacious in a large majority of patients. Treatment should continue for 18-24 months or 12 months after initial sputum conversion. If disease is localized to one lobe, surgical resection is recommended as an adjunct to chemotherapy (48, 49). This older regimen did not incorporate the newer antibiotics that have been found to have both in vitro and in vivo activity in AIDS patients with MAC disease. Therefore, a contemporary regimen based on the AIDS literature has recently demonstrated that Ethambutol 15-25 mgm/kg/d plus Rifabutin 300 mgm/d plus either Clarithromycin 1000 mgm/d or Azithromycin 600-1200 mgm/d results in successful treatment. Streptomycin should be considered for the first two-four months in patients with extensive cavitary disease (49a). Ethambutol and Rifabutin are synergistic in vitro and MAC organisms show the greatest in vitro sensitivities to the macrolides.

Treatment should be continued until patients have been cultured negative for 10-12 months. Recommendations for this regimen may change with completion of on going studies of treatment of MAC pulmonary disease.

b. Lymph Node Disease

Granulomatous inflammation accounts for approximately 20% of cases of upper anterior cervical, submandibular, submaxillary and pre-auricular lymphadenopathy in children ages one to five years. Mycobacterial lymphadenitis usually presents as an insidious, painless, unilateral process involving one or more nodes in a regional distribution. Axillary and inguinal nodes are rarely involved and sinus track formation occurs in only 6%.

The etiologies of this granulomatous lymphadenitis is listed in Table 10 (50, 51).

TABLE 10

Etiology of Granulomatous Lymphadenitis
in Children Age One to Five

Mycobacteria	Percent
MAC	60-80
M. scrofulaceum	10-20
M. tuberculosis	10

Granulomatous lymphadenitis in children is most commonly due to MAC occurring in from 60-80% of isolates. M. scrofulaceum is the infecting agent in from 10-20% with M. tuberculosis occurring in only 10%. These findings are in distinct contrast to mycobacterial lymphadenitis in persons older than 12 years where 95% is due to M. tuberculosis with only approximately 3% to MAC.

Fine needle aspiration with a positive culture will only make a diagnosis in 50% of cases (52). Histopathologically the nodes demonstrate caseating granulomatous inflammation and necrosis, epithelial histocytes and occasionally giant cells. When this pathologic presentation is reported, complete surgical excision is the standard of care and is usually curative (53-55). Antimycobacterial therapy is seldom necessary in the treatment of lymphadenitis except in the setting of an immunodeficiency state. However, the impact of the newer macrolides is unknown and in the future effective chemotherapy may obviate lymph node excision.

c. Disseminated Disease in Non-AIDS Patients

Although disseminated MAC disease occurs in immunocompromised patients without HIV infection, it is associated with the same high degree of mortality seen in the AIDS population (56, 57). Therapies that have proven effective in the treatment of MAC disease in HIV infected patients are likewise recommended for immunocompromised hosts without HIV infection.

2. Clinical Disease in AIDS Patients

a. Pulmonary Disease

A minority of AIDS patients may present with a clinical syndrome of focal pulmonary infection due to MAC without dissemination. When focal pulmonary disease occurs it is always difficult to distinguish from M. tuberculosis and any HIV positive patient with unidentified acid fast bacilli in the sputum should receive emperic chemotherapy for M. tuberculosis. Two clinical associations that may be useful in predicting MAC infections are the findings that M. tuberculosis infections are the AIDS defining illness in only 4% of HIV infected persons.

Whereas 92% of MAC pulmonary infections have concurrent or previous AIDS defining illnesses. The additional finding of a lower mean CD_4 lymphocyte count in the MAC infected patients of 60/mm^3 compared to 170/mm^3 in M. tuberculosis infected patients is somewhat less useful. Infections due to M. tuberculosis would be expected at a higher CD_4 lymphocyte count because of the relative virulence of M. tuberculosis when compared with MAC (58).

Clinically symptomatology and physical findings in M. tuberculosis and MAC infection are compared in Table 11.

TABLE 11

Symptoms and Physical Findings of Pulmonary Mycobacterial Infections in HIV Patients

Symptom & Finding	MAC (n=55)	M. tuberculosis (n=39)
Fever (%)	88	91
Mean weight loss (Kg ± SD)	10.5 ± 5.9	11.4 ± 7.2
Cough (%)	70	84
SOB (%)	57	64
Cachexia (%)	56	43
Local lymphadenopathy (%)	9	26
Perianal ulcers (%)	14	0

The symptomatology and physical findings are indistinguishable within the two groups being predominately fever, productive cough, dyspnea, weight loss and cachexia. The only statistically significant differences were the finding of localized lymphadenopathy in 9% of MAC infections and 26% of M. tuberculosis infections and perianal ulcers in 14% of MAC infections and in none of the M. tuberculosis infected patients in this series (58, 59).

Chest roentgenographic finding in patients with AIDS and pulmonary mycobacterial infections have also been contrasted and appear in Table 12.

TABLE 12

Chest Roentgenographic Findings in Pulmonary Mycobacterial Disease in HIV Infected Persons

Finding	MAC (n=28) (%)	M. TB (n=29) (%)
Typical pattern	7 (25)	24 (83)
Alveolar infiltrate	6 (21)	18 (62)
Interstitial infiltrate	14 (50)	14 (48)
Normal CXR	6 (21)	0 (0)

In contrast to immunocompetent adult patients with M. tuberculosis it has recently been appreciated that chest radiographs of AIDS patients are usually more characteristic of the pattern seen in primary tuberculosis rather than reactivation disease. In particular, cavitation and upper lobe infiltrates are uncommon whereas hilar adenopathy, pleural effusion and a miliary pattern are frequent. Several recent studies have suggested that a differentiation of MAC pulmonary disease from tuberculous pulmonary mycobacterial disease may be entertained in HIV infected patients from radiographic findings (58, 59).

In HIV infected patients with tuberculosis 83% have radiographic findings suggesting of mycobacterial disease including cavitation, apical scarring, pleural effusions, hilar adenopathy, miliary pattern and alveolar infiltrates usually not involving the upper lobes. Only 25% of patients with MAC pulmonary infection demonstrate these abnormalities. The only rather consistent radiographic differentiation of MAC infected patients was the finding of a normal chest x-ray in up to 25%, a finding that was not present in any patients in this series with M. tuberculosis infection (58, 59).

MAC pulmonary disease occurs predominately in patients with severely depressed CD_4 lymphocyte counts ($<50/mm^3$). In this setting it is clinically and radiographically indistinguishable from other opportunistic infections including pneumocystis pneumonia. Although not diagnostic of infection, it seems reasonable that the presence of three sputa positive for MAC in AIDS patients would be an indication for treatment. Transbronchial biopsy positive specimens would be confirmatory.

Recommendations for treatment of localized pulmonary MAC infections would be the same as in the immunocompetent host and includes Ethambutol, Rifabutin, Clarithromycin or Azithromycin.

b. Lymph Node Disease

Peripheral lymphadenitis due to MAC also occasionally occurs in patients with HIV infection without

disseminated disease. This lymphadenitis may be associated with overlying cutaneous lesions (60). Gallium scanning has been used to identify nodes for biopsy (61). Diagnosis can be made by the finding of histocytes with negatively stained linear cytoplasmic inclusions termed pseudogaucher cells (62). Histocytes are filled with mycobacteria most often with poor granuloma formation.

Other rather recently recognized Group III nonchromogens that may cause cutaneous disease and lymphadenitis include M. hemophilum and M. genavense. These organisms usually require identification by the State Health Department or the CDC.

I could find no treatment recommendations for isolated nontuberculous lymphadenitis in HIV infected patients. Excision and drugs effective in pulmonary infections would seem a reasonable choice.

c. Localized GI Disease

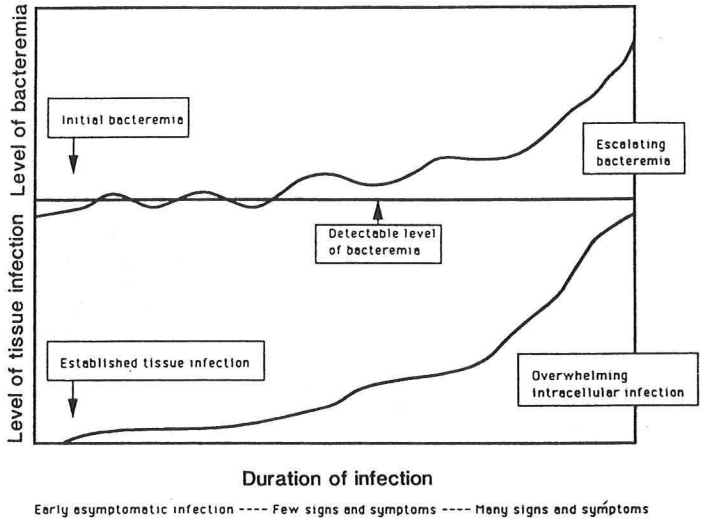
Localized GI disease due to MAC also occurs in the absence of dissemination but is beyond the scope of this presentation.

d. Disseminated MAC Infection in AIDS (DMAC)

Disseminated infection due to MAC remains the most common systemic bacterial infection among AIDS patients in the United States (63). In a prospective study 1,006 HIV infected patients at PMH were followed from the date of diagnosis. The incidence of MAC bacteremia was 21% at one year and 43% at two years. The incidence of MAC bacteremia after the diagnosis of AIDS was 39% among patients with CD_4 lymphocyte counts of $<10/mm^3$, 15% among those with counts of $40-59/mm^3$ and only 3% among those with counts of $100-199/mm^3$ (64). Many studies have now described the natural history and progression of DMAC disease in patients with AIDS. Figure 3 depicts these events (38).

FIGURE 3

Natural History DMAC in AIDS



Environmental exposure occurs most likely from an aqueous source resulting in the gastrointestinal acquisition of MAC organisms. There is then colonization and direct invasion of tissues with increasing mycobacterial replication resulting initially in intermittent bacteremia. At some point a declining host immunity results in continuous bacteremia, overwhelming MAC infection, and death. Symptoms are usually absent during acquisition of infection and the intermittent bacteremic phase and become manifest with continuous bacteremia and worsen with severe systemic disease resulting in a shorter survival interval (38, 63).

A compilation of the most frequently described symptoms, physical finds and laboratory abnormalities are summarized in Table 13 (38, 63, 65-67).

Table 13

Symptoms, Physical Findings, Laboratory Abnormalities in DMAC in AIDS

Finding	Number	Percent
Fever	120	87
Sweats	85	78
Diarrhea	92	47
Abdominal pain	54	35
Nausea/vomiting	31	26
Weight loss	37	38
Lymphadenopathy		
Intraabdominal	54	37
Mediastinal	49	10
Hepatosplenomegaly	38	24
Anemia (<8gms Hgb)	39	85
Elevated alkaline phosphatase	38	53

Symptoms and signs of DMAC have remained relatively consistent among several published series. Two to six weeks of fever, sweats, diarrhea and wasting are the most common presentation. Nausea, vomiting and intractable abdominal pain occur in over one-third and indicate the frequency of gastrointestinal involvement. Physical findings include weight loss and intraabdominal lymphadenopathy and hepatosplenomegaly in up to 40%. Mediastinal adenopathy is rare occurring in 20% or less. Worsening anemia and an elevated alkaline phosphatase out of proportion to hepatic transaminase occurs late when continuous bacteremia has been established. Early intermittent bacteremic infections may be difficult to detect due to lack of symptomatology, physical findings or laboratory abnormalities.

Few studies have correlated specific clinical manifestation of DMAC with prognosis. However, a number of investigations have reported that AIDS patients with DMAC have a shorten survival time. Table 14 summaries data from four retrospective studies that have evaluated the impact of DMAC on the length of the survival period (68-71) (Table 14).

TABLE 14

Survival of AIDS Patients With and Without DMAC

	Median Survival (d)		
	Without DMAC	DMAC Diagnosis	DMAC Treatment
Reference			
68	330	120	240
69	280	139	---
70	275	107	---
71	---	125	310
	avg 295	avg 123	avg 275

The duration of survival of patients without a diagnosis of DMAC was fairly consistent and averaged 295 d or 9.8 mo. Even more consistent was survival time after a diagnosis of DMAC which averaged 123 d or 4.1 mo. Sathe independently demonstrated that worsening anemia was a significant negative predictor of survival in AID patients with DMAC (69). These earlier studies also showed that the treatment of DMAC with regimens that included a macrolide was associated with an average increase of survival to 275 d or 9.2 mo (68, 71).

Bacteremia with the organism found almost exclusively in circulating monocytes occurs in 86-96% of patients with DMAC. Bone marrow, respiratory tract, liver and stool have also been reported positive in up to 50% of patients (38, 63). A single positive blood culture is considered diagnostic of disseminated disease. Colony counts usually range from 101 to 103 CFU/ml of blood but high levels of mycobacteremia with up to 106 CFU/ml are not uncommon. The tissue load of infection may be 102 to 105 times greater than in the blood. While it is not known precisely to what degree the level of bacteremia correlates with clinical infection in tissues, the assessment of changes in the numbers of circulating mycobacteria has evolved as a surrogate marker of therapeutic efficacy (58, 72). Isolation of MAC organisms from bone marrow and liver may precede bacteremia and are diagnostic of disseminated infection (73-75). Isolation of MAC organisms from respiratory secretions or stool is not diagnostic of disseminated disease but has been shown to precede dissemination in a large fraction of patients (74).

Treatment of DMAC disease in AIDS patients is no longer controversial since prospective studies have now shown both clinical and bacteriologic improvement that is associated with increased survival (76, 77). Recommendations for treatment regimens are changing rapidly but current alternatives are listed in Table 15.

TABLE 15

Treatment Regimens for DMAC in AIDS

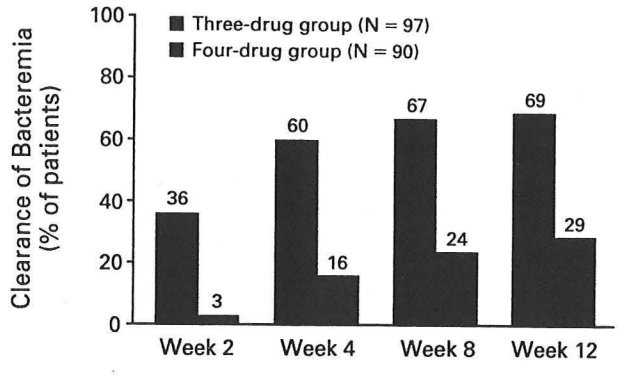
Clarithromycin/Ethambutol/Rifabutin or Azithromycin	
Clarithromycin/Ethambutol or Azithromycin	Clofazimine or Fluroquinolones or Rifabutin or Amikacin

The macrolides are the most active drug used to treat MAC. However, despite initial clinical and bacteriologic improvement in 99% of patients treated with macrolide monotherapy, relapses with resistant strains frequently occurred (78). Thus, several multidrug regimens have been proposed to lower the rate of relapse. An increasingly popular agent to use is Rifabutin (Ansamycin) an effective prophylactic agent for DMAC (79, 80). As monotherapy, Ethambutol moderately reduces the circulating load of MAC bacteria whereas Clofazimine and Rifampin have been ineffective (81).

A recent prospective study has now demonstrated that the combination of Clarithromycin 1000 mgm b.i.d., Ethambutol 15 mgm/kg/d, Rifabutin 300-600 mgm/d (three drug group) is superior to the older recommendation of Rifampin 600 mgm/d, Ethambutol 15 mgm/kg/d, Clofazimine 100 mgm/d and Ciprofloxacin 750 mgm b.i.d. (four drug group). Figure 4 presents the efficacy of the two groups in bacterial clearance.

FIGURE 4

Efficacy of Bacterial Clearance



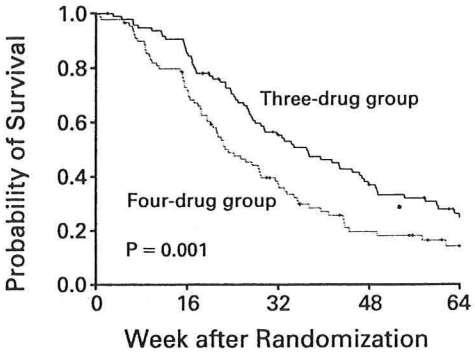
Shafran, et al: N. Engl. J. Med. 335:377-383, 1996.

MAC bacteremia was cleared in 69% of patients in the three drug group and 29% of patients in the four drug group at 12 weeks ($p<0.001$). Eighty-seven percent of the three drug group had blood sterilization by week four as compared to only 54% in the four drug group ($p<0.001$).

Likewise, the Kaplan-Meier survival curves presented in Figure 5 were significantly different.

FIGURE 5

Survival Curves HIV Infected Patients
Treated with Different Drug Regimens



No. of Patients at Risk/No. of Events in Next 16-Week Period					
Three-drug group	14/97	28/82	16/48	9/30	10/15
Four-drug group	25/90	31/63	12/29	3/13	5/6

Shafran, et al: N. Engl. J. Med. 335:377-383, 1996.

The median survival of the patients in the three drug group was 8.6 months, as compared to 5.2 months for the patients in the four drug group ($p<0.001$). The difference in survival continued until 16 months. Dosage of above 300 mgm/d of Rifabutin caused uveitis in 25% which was considered an unexceptably high adverse reaction rate. Rifabutin also reduces serum Clarithromycin concentrations by about half (83). Thus, a dose of 1000 mgm of Clarithromycin b.i.d. is recommended for optimum efficacy but gastrointestinal intolerance may force a reduction to 500 mgm b.i.d. Thus this three drug regimen can now be recommended for initial therapy (82).

Clarithromycin or Azithromycin and Ethambutol should most likely be included in any treatment regimens of DMAC in AIDS patients (84). One or more of the following drugs should be added to the macrolides and Ethambutol for treatment failures. Clofazimine 100 mgm/d, Ciprofloxacin 750 mgm b.i.d., Rifabutin 300 mgm/d and Amikacin 7.5-15 mgm/kg/IV/d have all shown activity. In the future in vitro susceptibility will most likely play a greater role in therapeutic choice (85). Additionally, low dose Dexamethasone 2 mgm/d in addition to macrolide multidrug regimens has shown promise in reducing fever, promoting overall well being and inducing weight gain (86). Further studies are necessary before this adjunct can be recommended.

Prophylaxis of MAC dissemination in patients with AIDS is now well accepted. In cost benefit studies prophylaxis yields significant cost savings by decreasing number of days of hospitalization, red cell transfusions and gram positive infections.

The level of CD_4 lymphocyte count to begin prophylaxis is controversial. A significant increase in dissemination occurs below a count of 50 CD_4/lymphocytes/mm^3; however, most studies have used a level of 100 CD_4 lymphocytes/mm^3 to begin treatment. Rifabutin given 300 mgm/d was first shown to be an effective prophylactic agent and is currently the only drug approved by the FDA for this purpose (79, 87). Prophylaxis should continue for life or until evidence of dissemination. Clarithromycin at a dose of 500 mgm b.i.d. has likewise proven efficacious in a randomized, placebo controlled, double blind study (88). However, in the same edition of the New England Journal of Medicine, Havlir and associates showed that Azithromycin given at a dose of 1200 mgm weekly was superior to daily Rifabutin 300 mgm/d in preventing MAC dissemination in AIDS patients with CD_4 lymphocyte counts of less than 100/mm^3 (89). This once weekly dose of Azithromycin can now be recommended due to its better toleration than daily Clarithromycin and fewer drug/drug interaction than Rifabutin. The combination of Azithromycin and Rifabutin is more efficacious but is limited by tolerability and potential drug interactions (90). Azithromycin is available in 250 mgm capsules and 1000 mgm single dose packets. Although less than the 1200 mgm studied, the single dose packet has the advantage of being the least expensive and best tolerated MAC prophylactic agent.

B. Mycobacterium kansasii

1. Clinical Disease in Patients Without AIDS

a. Pulmonary Disease

In contrast to immunocompetent adults with pulmonary MAC infections, a changing spectrum of M. kansasii pulmonary disease has not been reported (5). The pulmonary disease of M. kansasii is the so called "classic" form. Male to female ratio is 3:1 and underlying obstructive pulmonary disease is most common but there is also a definite association with the pneumoconiosis (90). Patients are greater than 60 years of age and are of a higher socioeconomic group and reside in urban areas. There is no ethnic predilections but smoking and alcoholism have been reported with increased frequency.

Symptoms are more indolent than with tuberculosis with cough reported in 60-100% and fever in 10-36%. Hemoptysis has been reported in 15-40% and is more prominent than with MAC pulmonary disease. Mild constitutional symptoms such as weakness, malaise, night sweats, and weight loss have been reported in up to 50%.

Physical findings are minimal and laboratory abnormalities are nonspecific (91).

Radiographic abnormalities are listed in Table 16.

TABLE 16

Radiographic Manifestations of
M. kansasii Infection
(n=187)

Finding	Percent
Upper lobes	99
Right (apical, posterior)	63
Left (apical-posterior)	41
Cavitation	96
>4 cm	27
Thin wall	33
Endobronchial spread	63
Adenopathy, pleural effusion	rare
Normal CXR	1.6

The radiographic abnormalities of M. kansasii pulmonary disease in immunocompetent hosts has not been reported since the classic description by Christensen and colleagues in 1979 (42). In 187 patients with well documented M. Kansasii infections less than 2% had a normal chest roentgenogram. Upper lobe infiltrates occurred in 99% with a slight prediction for the right upper lobe. As in reactivation tuberculosis the apical and posterior segments are most frequently involved and cavitation occurred in 96%. Endobronchial spread was seen in 63% but adenopathy and pleural effusion were rare. Differentiation from pulmonary disease due to M. tuberculosis is not possible radiographically. Computed tomography has not been studied with M. kansasii infection and cannot be compared to MAC pulmonary infection.

Recommended treatment regimens for M. kansasii pulmonary disease in the immunocompetent host are listed in Table 17.

TABLE 17

Recommended Treatment of M. kansasii
Pulmonary Infections

Isoniazid
Rifampin
Ethambutol

Surgery-no role

Isoniazid
Ethambutol
Sulfamethoxazole

M. kansasii is sensitive in vitro to Rifampin, Ethambutol, Erythromycin, Sulfamethoxazole, Amikacin, and Rifabutin. No randomized controlled trials of comparing one drug regimen with another have been conducted. Recommendations for treatment are based on retrospective studies that have demonstrated 100% sputa conversion and a very low relapse rate (0.8%) when the regimen included Rifampin and Ethambutol. M. kansasii is resistant in vitro to Pyrazinamide with intermediate resistance to Isoniazid. Contemporary drug regimens will no doubt be directed toward these in vitro sensitivities, but the current recommendation continues to be Isoniazid 300 mgm/d, Rifampin 600 mgm/d and Ethambutol 15 mgm/kg/d for 18 months (7). This regimen has proven highly effective in sputa conversion (90%) with a low relapse rate. Surgery is no longer recommended with M. kansasii pulmonary disease.

In patients whose organisms have become resistant to Rifampin as a result of previous treatment, the recommendation is Isoniazid 900 mgm/d, Pridoxine 50 mgm/d, Ethambutol 25 mgm/kg and Sulfamethozole 3 gms/d for 18 to 24 months. This oral therapy has also been combined with daily or five times a week Streptomycin or Amikacin for two to three months. With the advent of the use of the macrolides for MAC pulmonary disease, I would expect that the recommendations for treatment of M. kansasii pulmonary disease will change accordingly.

b. Lymph Node Disease

M. kansasii is a rare cause of cervical or other localized lymphadenitis in the immunocompetent host. Diagnosis and treatment are similar to M. scrofulaceum and MAC and include complete excision without incision and drainage. Role of chemotherapy has not been investigated.

c. Skin Disease

Inoculation of the skin has resulted in sporotrichoid granulomatous lesions. Hyperimmune reactions such as erythema nodosum or multiformae have also been rarely reported (92-94). Treatment of M. kansasii skin disease has not been addressed.

d. Disseminated Disease in Non-AIDS

Dissemination of M. kansasii occurs in patients with far advanced pulmonary disease and in patients who are profoundly immunocompromised (95, 96). Manifestations and treatment are similar to HIV infected patients with M. kansasii dissemination.

2. Clinical Disease in Patient with AIDS

a. Pulmonary Disease

M. kansasii infection unlike MAC infection in AIDS patients may produce pulmonary disease unassociated with dissemination. Two recent reports have addressed this question. In one study of 49 HIV positive patients 65% had M. kansasii isolated only from respiratory secretions and 34% had disseminated disease (97). In an earlier study 89% of HIV infected individuals had only pulmonary isolates and responded well to chemotherapy directed at M. kansasii infection (98).

Demographic data of HIV infected patients with M. kansasii pulmonary disease reflect the demographics of the AIDS population as a whole and are not clinically useful. Other clinical features of M. kansasii pulmonary infection are listed in Table 18.

TABLE 18

M. kansasii Pulmonary Infections in HIV
(n=37)

Finding	Percent
Fever	100
Cough	100
Weight loss	72
Sweats	41
Chest pain	30
Hemoptysis	16

HIV infected patients with M. kansasii pulmonary disease exhibit the same symptomatology as immunocompetent patients.

Duration of symptoms of cough, fever, and sweats ranged from two weeks to eight months prior to diagnosis. Pleuritic chest pain occurred in 30% and hemoptysis in 16%. Weight loss in 72% was significantly more common than in immunocompetent persons. Patients were all severely immunosuppressed with a mean CD_4 lymphocyte count of $66/mm^3$ and the AIDS defining illness preceded the diagnosis of pulmonary M. kansasii in all cases. Dissemination was rarely documented in this group of patients.

Radiographic manifestations of M. kansasii pulmonary disease in AIDS patients are listed in Table 19.

TABLE 19

Radiographic Manifestations of M. kansasii Infection in AIDS (n=37)

Finding	Percent
Cavitation	47
>4cm	0
Interstitial infiltrate	47
Alveolar infiltrate	42
Pleural effusion	16

Cavitation occurred in 47% and interstitial infiltrates in 47% thus cavitation is less common and interstitial infiltrates more common than in immunocompetent persons. Cavities are thin walled similar to that seen in M. kansasii pulmonary infections in the normal host. Alveolar infiltrates (42%) had an upper lobe predilection and were associated with small bilateral cavitation. Therefore the finding of multiple small thin walled cavities may be useful in the differential diagnosis of pulmonary infiltrates in HIV infected patients with low CD_4 lymphocyte counts. Pleural effusion occurring in 16% was also distinctly more common than in immunocompetent persons.

The clinical and radiographic features of pulmonary M. kansasii infection had a closer resemblance to M. tuberculosis infection in AIDS infected patients and differed significantly from pulmonary infections with MAC.

Treatment recommendations of M. kansasii pulmonary disease in HIV infected persons is the same as in the immunocompetent host. Treatment results of nine severely immunosuppressed HIV patients with M. kansasii pulmonary disease are given in Table 20.

TABLE 20

Results of Treatment of M. kansasii
Pulmonary Disease in AIDS
(n=9)

Finding	Percent
Clinical resolution	100
Radiographic	100
Sputa conversion	77
Mortality at 13 months	55

Treatment with various combination of Isoniazid, Rifampin, Ethambutol, Streptomycin and Trimethoprim-Sulfamethoxazole has proven efficacious. All patients had resolution of fever, respiratory symptoms and radiographic infiltrates within four weeks. There was also conversion of sputa cultures at nine months. Four patients were judged to have died from unrelated causes and five were alive on publication of the study. Autopsies were performed on three patients treated for M. kansasii pulmonary infection and M. kansasii was not recovered from autopsy specimens. Although the number of patients is insufficient to draw a conclusion, this study indicates that M. kansasii pulmonary disease is different from MAC pulmonary disease in AIDS infected patients and diagnosis of M. kansasii warrants a trial of chemotherapy with expectation of a beneficial outcome.

b. Lymph Node, Soft Tissue and Skin Disease

There are no universal or characteristic manifestations of lymph node, soft tissues or skin disease produced by M. kansasii in HIV positive patients. All usually occur as a manifestation of disseminated disease and are treated accordingly.

c. Disseminated Disease

M. tuberculosis has been reported to disseminate in 26-42% of all HIV infected patients (99). Dissemination rate of M. kansasii is similar occurring in approximately 35%. The majority of these patients will also have far advanced pulmonary disease. Clinical symptomatology is nonspecific except for gastrointestinal symptoms associated with diarrhea (97, 100). The gastrointestinal symptomatology correlates well with the pathologic finding of overwhelming GI tract colonization. Chest radiographs in patients with disseminated disease show less cavitation and interstitial infiltrates and may also be normal. CD_4 lymphocyte counts averaged 24/mm^3 in patients with disseminated disease and 62/mm^3 in patients with localized pulmonary disease (97). Co-existent

disseminated MAC has been present in 35% of patients with disseminated M. kansasii disease.

Response to treatment of disseminated M. kansasii with the usual antituberculous regimen used in local pulmonary disease has been poor. In most series only 10-15% of patients have shown any clinical response and mean survival in chemotherapy treated patients is approximately 8.1 months. I could find no comparable treatment trials to those conducted with disseminated MAC infection and efficacy of treatment remains to be demonstrated (101).

There is in vitro data to suggest that the fluroquinolones and the macrolides (Ofloxacin, Sparfloxacin and Clarithromycin) have activity against M. kansasii but treatment regimens incorporating these agents have not been described (102, 103).

C. Mycobacterium fortuitum/chelonae (MFC)

1. Clinical Disease in Patients With and Without AIDS

a. Pulmonary Disease

The etiologic role of rapidly growing mycobacteria (RGM) in chronic pulmonary disease has only recently been well established. Characteristics on 154 patients who met the ATS guidelines for the diagnosis of nontuberculous mycobacterial pulmonary disease are listed in Table 21 (34, 104).

TABLE 21

Characteristics of Pulmonary Disease with RGM (n=154)

Age (yr)	$\bar{m}$ 58.2
Sex F (%)	65
Caucasian (%)	83
Nonsmoker (%)	66
Associated Pulmonary Disorder (%)	68
Usual symptoms (%)	70

Patients with pulmonary disease due to RGM are predominately middle aged Caucasian, nonsmoking women with associated pulmonary disorders. Associated disorder include previous mycobacterial disease, gastroesophageal disorders (achalsia) with chronic aspiration, bronchiectasis, malignancy and infrequently COPD (105, 106). Thirty-two percent had no associated disorders.

Presenting symptoms were similar to other NTM and included chronic cough and sputa production with low grade fever. Night sweats, weight loss, hemoptysis or dyspnea are uncommon.

Radiographic features of RGM pulmonary disease are listed in Table 22.

TABLE 22

Radiographic Features of RGM Pulmonary Disease

Finding	Percent
Multilobar	77
Upper lobes	88
Cavitation	16
Pleural effusion	rare
Adenopathy	rare
Normal	rare

Infiltrates are described as patchy occurring bilaterally in three or more lobes. Upper lobes are most frequently involved with one or both upper lobes involved in 88%. Cavitation is infrequent (16%) and pleural effusion and adenopathy are rare. Patients with achalasia have dense alveolar infiltrates in recurring areas of aspiration.

The clinical course of MFC pulmonary disease is extremely variable. In the majority of patients the clinical course mimics bronchiectasis with periods of sputum production, cough, infiltrates and resolutions of symptoms and radiographic changes with antibiotics. Elderly female nonsmokers particularly with esophageal disease have a increased incidence of bronchiectasis caused by MFC. Diagnosis may be difficult as the organism may be weakly acid fast and laboratory identification may be imprecise.

Treatment is based on identification of the organism and appropriate sensitivities. Pulmonary disease is caused by M. fortuitum in approximately 16% of cases (104, 107). Recommendations include Amikacin and Cefoxitin intravenously for four to eight weeks followed by oral therapy with Trimethoprime/Sulfamethoxazole and Doxycycline, Ciprofloxacin or Ofloxacin for a total of six months (108-110). Clinical response occurs in greater than 80%.

Unfortunately 80% of pulmonary disease is due to M. chelonae subspecies abscesses which is sensitive only to Amikacin and the macrolides (107). Current recommendation is Clarithromycin 500 mgm orally two times a day for at least six months. If disease is localized, surgical resection is recommended with continuation of macrolide therapy for six months post operatively (111).

b. Primary Cutaneous Disease

Skin and soft tissue infections account for the majority of disease due to MFC. Antecedent trauma is almost always present with injuries from automobile accidents, farm equipment, nails, bullets or even superficial abrasions and hypodermic injections implicated (34, 106). Cutaneous disease occurs in all age groups commonly in the immunocompetent host. Nodular lesions are manifest as a localized cellulitis four to six weeks after injury; progressing to abscess formation with scant serous drainage. Lesions are only mildly tender and fever and systemic manifestations are absent. Gram stain and AFB stain are usually negative but organisms are readily identifiable by culture. Biopsy or incision and drainage may be required for diagnosis. Severe trauma may also result in osteomylitis (34, 106, 112).

Treatment is adequate debridement followed by Clarithromycin 500 mgm twice a day for six months or up to 12 months if relapse occurs (113).

c. Disseminated Disease

Dissemination of MFC is rare and occurred in only 7% of 125 cases of MFC infection (34). Most cases occur in immunocompromised hosts particularly following renal transplantation, chronic dialysis and in patients on high dose steroid therapy. By contrast disseminated infection with MFC in patients with AIDS is distinctly unusual. Only 10 cases of disseminated MFC infection were found in a survey of 1984 cases of disseminated NTMD in patients with AIDS (114).

Patients present with multiple erythematous subcutaneous nodules that typically involve the exterior surfaces of the arms and legs. Lesions suppurate and drain serous fluid from which organisms can be isolated. Occasionally skin lesions will become invasive developing subcutaneous abscesses that can progress to osteomyelitis (115-118). Unlike localized cutaneous disease produced by MFC there is no preceding trauma and no primary source of infection is evident although blood cultures may be positive.

Treatment is the same as cutaneous disease with Clarithromycin 500 mgm twice a day for six to twelve months. With this regimen 78% of patients with disseminated disease have remained free of disease six months following cessation of therapy (113).

d. Nosocomial Infections

Nosocomial infections are an important clinical manifestation on MFC. These infections may be divided into two groups: postoperative wound infections and infections of

prosthetic devices including indwelling intravenous and intraperitoneal catheters.

The majority of nosocomial infections with MFC are sporadic but epidemics following cardiac bypass surgery and augmentation mammoplasty have been reported (119-123). Cases in the United States have been clustered in Texas and the southern coastal states (124, 125). Contaminated aqueous solutions are the most frequent source of epidemics. MFC can be isolated from tap water and is resistant to disinfection with 2% aqueous formaldehyde and 2% alkaline glutaraldehyde. Sternal wound infection following coronary artery by surgery is the most commonly reported infection but infection of porcine heterograph and mechanical heart values has also occurred.

Minor surgical procedures have also been implicated when chemical methods are used as sterilizing procedures. Scleral abscess, keratitis, granulomatous eye disease and nasolacrimal gland infection have been reported following ophthalmologic procedures (126-128).

Infection of indwelling venous and peritoneal catheters are also well documented (129-133).

Clinical features of postsurgical wound infections due to MFC are similar to those of cutaneous infection. Patients present with erythema, swelling, mild tenderness and serous drainage at the surgical site several weeks to months after the procedure. Acid fast organisms can be demonstrated in the smears of the wound drainage and will grow in cultures planted on routine media at five to seven days.

Patients with MFC prosthetic valve endocarditis are indistinguishable clinically from other forms of the disease with fever, embolic phenomena and heart murmurs. Mortality remains high.

Treatment is surgical debridement, removal of prosthetic devices and other foreign bodies and antibiotic therapy. Antibiotic treatment is identical to other sites of MFC infection.

Clarithromycin 500 mgm twice a day for six months or longer is similar to other MFC infections.

D. Mycobacterium Scrofulaceum

1. Lymph Node Disease

M. scrofulaceum, a scotochromogen, is the second most common cause of NTM lymphadenitis in children under the age of five. The characteristics of this type of lymphadenitis are listed in Table 23 (5, 7).

TABLE 23

M. Scrofulaceum Lymphadenitis in Children

Unilateral	> 90%
Submandibular	> 80%
Local Symptoms	minimal
Systemic Symptoms	rare
CXR	normal
Socioeconomic status	high

Most children with M. scrofulaceum lymphadenitis are between the ages of one and three years and the finding of secondary cases in the household is extremely rare. Lymph nodes are almost always unilateral in the submandibular area. Tonsillar or anterior cervical nodal disease is rare. Symptoms include only a relatively painless enlargement over a period of weeks. Local or systemic symptoms are rare. Chest x-ray is normal and most children are in a relatively high socioeconomic group. Untreated the infections will usually point to the surface, rupture, form a draining sinus and eventually calcify. Pyogenic and tuberculous lymphadenitis are the most important differential diagnoses. Pyogenic nodes are larger, tender with erythema and surrounding edema associated with a febrile response. Tuberculous nodes are usually in the supraclavicular area or in the posterior triangle of the neck and are frequently accompanied by pulmonary disease.

Diagnosis is made by a reasonable suspicion, fine needle aspiration and request for mycobacterial culture (134-136).

Treatment is complete excision of involved nodes and overlying sinus tract. The role of newer macrolide chemotherapy has not been addressed but excision alone is almost always curative and relapses are rare.

2. Disseminated Disease

A review of the English literature from 1966 to 1994 identified only eight cases of disseminated M. scrofulaceum (137). Two cases associated with AIDS, two cases of immunocompetent persons and four cases with severe immunosuppression from other causes. In patients with immunosuppression regardless of etiology skin lesions were present without preceding trauma. Lesions begin as multiple erythematous cutaneous and subcutaneous papules or nodules on the extremities that become keratotic and suppurative and eventually ulcerate (138, 139). Similar skin lesions have been described in AIDS patients with disseminated NTM disease due to MAC, M. kansasii, M. hemophilum, MFC and M. marinum (140-143). Typical cutaneous lesions are followed by the usual debilitating signs previously described in patients with disseminated NMD. Thus, the presence of such lesions in immunosuppressed patients should

alert the clinician to the possibility of disseminated NTM disease.

Treatment regimens for disseminated disease due to M. scrofulaceum have not been addressed. In vitro sensitivities are similar to MAC and initiation of treatment would be with the same agents used to treat disseminated MAC disease in HIV infected patients.

E. Mycobacterium marinum

M. marinum, a photochromogen, primarily produces skin infections in both immunocompetent and immunocompromised hosts. It grows optimally at 32°C and poorly or not at all at temperatures of 37°C or higher. Suspicion of diagnosis is based on an occupational and recreational history which is by necessity lacking in the typical 10-15 minute per patient HMO practice. Swimming pool or seawall abrasion, barnacle scrapes, fish fin punctures or possession of tropical fish tanks are the most useful historical items (36, 144, 145).

Infection occurs after inconsequential trauma and incubations is from two to eight weeks. Initial lesions appear as small papules that enlarge and acquire a blue purple discoloration. Suppuration then occurs and may progress to ulceration. Nodules may appear in the efferent lymphatics and result in a syndrome that resembles cutaneous sporotrichosis. This form is more persistent and does not heal spontaneously (146, 147). Infection of tendon sheaths and periarticular tissue have also been described. Dissemination may occur most commonly in the immunocompromised host.

Diagnosis is made by a high index of suspicion with aspiration or biopsy of the lesion. The laboratory must then be notified that M. Marinum is suspected so that the culture can be incubated at 30-32°C and retained for six weeks. Cultures are positive in 70-80% of cases and are usually associated with a negative AFB stain (5, 36, 144).

The natural history of infection with M. marinum is also variable. Spontaneous remission particularly when trauma is minor is fairly common in an immunocompetent person. However, when ulceration is severe, sporotrichoid lesions appear or cutaneous lesion occurs in an immunocompromised host, chemotherapy is indicated. In vitro susceptibility testing should be performed on all cultures and alteration of drug therapy based on their outcome. Various regimens which have usually included Ethambutol and Rifampin have been successful in a large fraction of patients. However as in other NTM, the macrolide Clarithromycin used as monotherapy has also proven effective. Ethambutol plus Clarithromycin however has a synergistic bactericidal effect in vitro and can now be recommended for initial therapy (148-150). Dosage is imprecise

but the recommendation of 500 mgm twice a day of Clarithromycin and 15-25 mgm/kg/d of Ethambutol would seem reasonable (151).

F. Other Nontuberculous Mycobacteria and clinical syndromes that they most frequently produce

Clinicians need only be aware of the principal syndrome produced by the rare NTM producing human disease. Most have only recently been described in HIV infected patients where all can result in dissemination. Therapy is not known but will most likely be related to the principles of the treatment of MAC since this organism produces the highest incidence of disease and is the most thoroughly investigated (152-158).

Table 24 lists the rare NTM and their principal clinical syndrome.

TABLE 24

Most Common Clinical Syndromes Proceeded by Rare NTM

Pulmonary Disease	M. xenopi, gordonae, simiae, szulgai, malmoense
Lymphatic and Cutaneous Disease	M. ulcerans, terrae, smegnatis, hemophilum
Disseminated Disease	M. hemophilum, genavense

SUMMARY

NTM disease is increasing in the United States both in HIV infected individuals and in immunocompetent hosts. Diagnosis is made by a high index of suspicion based on clinical accumen. A clinical grasp of the diseases produced and the treatment options available should now be a part of the practice of general internal medicine.

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