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PATRONES CLINICOPATOLÓGICOS DE LAS INFECCIONES CUTÁNEAS POR MICOBACTERIAS ATÍPICAS

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A Laura, la meva sort

A Laura i Emma, el millor que he ajudat a fer

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ARTÍCULOS PUBLICADOS

1. Bartralot R, Pujol RM, García-Patos V, Sitjàs D, Martín-Casabona N, Coll P, Alomar A, Castells A. **Cutaneous infections due to nontuberculous mycobacteria: histopathological review of 28 cases. Comparative study between lesions observed in immunosuppressed patients and normal hosts.**
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2. Bartralot R, García-Patos V, Sitjàs D, Rodríguez-Cano L, Mollet J, Martín-Casabona N, Coll P, Castells A, Pujol RM. **Clinical patterns of cutaneous nontuberculous mycobacterial infections.**
   Br J Dermatol 2005; 152: 727-734.

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Artículo: American Thoracic Society. Medical section of the American Lung Association. **Diagnosis and Treatment of Disease Caused by Nontuberculous Mycobacteria.**
Am J Respir Crit Care Med 1997; 156: S1–S25.

RESUMEN

Introducción: Las infecciones cutáneas por micobacterias atípicas tienen lugar por inoculación externa, extensión a la piel desde una infección profunda o por diseminación hematógena de una infección sistémica. La mayoría de infecciones cutáneas por estos microorganismos aparecen en forma de cuadros inespecíficos. Sólo existen dos infecciones que se consideran específicas de especie: el granuloma de los acuarios o de las piscinas, debido a *Mycobacterium marinum*; y la úlcera de Buruli, causada por *Mycobacterium ulcerans*.

Objetivo: Definir patrones clínicos y patológicos de las infecciones cutáneas por micobacterias atípicas.

Métodos: A través del estudio de 51 pacientes con infecciones por micobacterias atípicas, se analizaron sus características clínicas e histológicas. Se compararon los resultados entre los pacientes inmunocompetentes e inmunodeprimidos, así como con la bibliografía publicada mediante una búsqueda en *Medline*. En el grupo de inmunodeprimidos se distinguieron 2 subgrupos: infección cutánea aislada e infección diseminada con afectación cutánea.

Resultados: En los pacientes inmunodeprimidos el número de lesiones fue significativamente mayor. Asimismo, en este grupo se hallaron con mayor frecuencia abscesos y úlceras como lesiones elementales. Las especies responsables en inmunocompetentes fueron distintas de las halladas en los inmunodeprimidos. Se definieron varios patrones de infección cutánea: lesiones con distribución linfocutánea o esporotricoide, lesiones no linfocutáneas en zonas con traumatismo previo, foliculitis y forunculosis en las extremidades inferiores y lesiones generalizadas en las extremidades en pacientes inmunodeprimidos. En pacientes con infección diseminada, se observaron 2 patrones adicionales: lesiones localizadas y lesiones cutáneo-mucosas generalizadas.

Conclusiones: Las manifestaciones cutáneas de las infecciones por micobacterias atípicas pueden agruparse, de acuerdo con criterios como el tipo de lesiones cutáneas y el estado inmunitario de los pacientes, en patrones bastante uniformes.

INTRODUCCIÓN

Las micobacterias atípicas (MA) son consideradas microorganismos oportunistas que provocan infecciones a través de fuentes ambientales y no se ha demostrado la transmisión de persona a persona. Las características clínicas de estas infecciones pueden ser similares a las causadas por *Mycobacterium tuberculosis* aunque, con frecuencia, adoptan patrones clínicos diferentes y suelen ser resistentes a los fármacos tuberculostáticos convencionales. Se han identificado más de 100 especies de MA, 60 de las cuales son consideradas patógenas potenciales para el hombre. Las condiciones para el aislamiento e identificación de algunas MA son diferentes de las requeridas por *M. tuberculosis*, sobre todo en lo que respecta a la temperatura de incubación y al enriquecimiento de los medios de cultivo con determinados nutrientes. Sin embargo, gracias al perfeccionamiento de las técnicas de cultivo y al desarrollo de la biología molecular, periódicamente se describen nuevas especies y las MA se aislan e identifican cada vez con mayor frecuencia. Clásicamente, las especies de MA suelen clasificarse en base a las características de pigmentación de las colonias, a la temperatura óptima de crecimiento y a la rapidez de crecimiento (clasificación de Runyon[1], tabla 1).

TABLA 1. Clasificación de las micobacterias atípicas (Runyon, 1959)

Grupo I. Fotocromógenos (producen pigmento cuando se exponen a la luz)	
	M. kansasii
	M. marinum
	M. simiae
Grupo II. Escotocromógenos (producen pigmento con y sin luz)	
	M. scrofulaceum
	M. szulgai
Grupo III. No cromógenos (no producen pigmento)	
	M. avium-intracellulare
	M. ulcerans
	M. haemophilum
Grupo IV. Micobacterias de crecimiento rápido	
	M. fortuitum
	M. chelonae
	M. abscessus

Algunos tratados prefieren guiarse por la rapidez de crecimiento como criterio principal, distinguiendo MA de crecimiento rápido, lento e intermedio (tabla 2)[2].

TABLA 2. Clasificación de las micobacterias atípicas (Mandell *et al*, Priciples and Practice of Infectious Diseases 6th ed, 2005).

1. Micobacterias de crecimiento rápido.

- No pigmentadas:
  * *M. fortuitum* complex:
    ● Grupo de *M. fortuitum:*
    M. fortuitum, M. peregrinum, M. mucogenicum, M. senegalense, M. septicum, M. mageritense, M. porcinum, M. houstonense, M. bonickei, M. neworleansense.

    ● Grupo de *M. chelonae/abscessus:*
    M. chelonae, M. abscessus, M. immunogenicum.

  * Grupo de *M. smegmatis:*
    M. smegmatis, M. wolinskyi, M. goodii.

- Pigmentadas: *M. flavescens, M. vaccae, M. phlei, M. aurum, M. neoaurum, M. thermoresistible, M. elephantis, M. novocastrense.*

2. Micobacterias de crecimiento lento

- Especies habituales: *M. avium* complex, *M. kansasii, M. xenopi, M. simiae* complex, *M. szulgai, M. malmoense, M. scrofulaceum, M. terrae/nonchromogenicum* complex, *M. asiaticum, M. haemophilum, M. paratuberculosis, M. genavense.*

- Descripción reciente:
  * Pigmentadas: *M. celatum, M. interjectum, M. lentiflavum, M. tusciae, M. palustre, M. conspicuum, M. heckeshornense, M. bohemicum.*
  * No pigmentadas: *M. triplex, M. branderi, M. shottsii.*

3. Micobacterias de crecimiento intermedio: *M. marinum, M. gordonae.*

La relevancia del aislamiento en cultivo de una MA a partir de una muestra biológica debe evaluarse en base a las características clínicas, histológicas y microbiológicas de cada caso particular. Algunas especies son habitualmente patógenas, mientras que otras con frecuencia pueden ser contaminantes de la muestra[3]. En caso de duda suele recurrirse a los llamados "criterios de patogenicidad", que incluyen criterios microbiológicos, clínicos e histopatológicos (última revisión de la *American Thoracic Society*[4]).

La mayoría de las infecciones por MA se incluyen dentro de 4 grandes síndromes: enfermedad pulmonar, linfadenitis, infección diseminada e infecciones de la piel y los tejidos blandos[4]. A estos 4 procesos sindrómicos se han añadido como síndromes independientes las infecciones de tendones, articulaciones y huesos, así como las infecciones relacionadas con catéteres[2].

Las infecciones cutáneas incluyen dos enfermedades que se consideran específicas de especie: el granuloma de los acuarios o de las piscinas, debido a *Mycobacterium marinum*; y la úlcera de Buruli, causada por *Mycobacterium ulcerans*. El resto de infecciones cutáneas se consideran cuadros inespecíficos provocados sobre todo por MA de crecimiento rápido (*M. fortuitum, M. chelonae* y *M. abscessus*). La gran variabilidad en la distribución geográfica de las MA y de sus cepas más patógenas suele también contribuir a esta escasa especificidad clínica y a la aparición de pequeños brotes epidémicos en áreas geográficas concretas.

El hallazgo histopatológico característico de las infecciones cutáneas por MA es el infiltrado inflamatorio dérmico mixto con granulomas y abscesos (con frecuencia formando granulomas supurativos). Sin embargo, es posible encontrar otros patrones histológicos, en relación con el estado inmunológico del paciente y el tiempo de evolución de las lesiones. Así, se ha descrito la presencia de granulomas tuberculoides, sarcoideos y en empalizada; abscesos, infiltrados ricos en células histiocitarias, paniculitis, inflamación crónica inespecífica y foliculitis[5, 6]. En aquellos casos con una clínica sugestiva, la demostración de bacilos ácido-alcohol resistentes (BAAR) mediante tinciones específicas (Ziehl-Neelsen, Kinyoun, auramina-rodamina) es de gran valor diagnóstico.

La incidencia de las infecciones por MA ha aumentado en los últimos 20 años, coincidiendo con una disminución de la prevalencia de la tuberculosis, la epidemia del síndrome de inmunodeficiencia adquirida (SIDA) y el uso de fármacos inmunosupresores. En estudios de cohorte se ha evaluado que las infecciones por MA representan un 15% del total de los aislamientos de BAAR, mientras que el 85% restante corresponde a *M. tuberculosis*[7]. En España, donde la incidencia y prevalencia de tuberculosis es más elevada que en otros países desarrollados, la incidencia de infecciones por MA representa un 0.64-2.29% de todas las infecciones por micobacterias[8, 9].

JUSTIFICACIÓN Y OBJETIVOS

- Justificación.

No existen estudios clinicopatológicos dirigidos a caracterizar los patrones clínicos de presentación de las infecciones cutáneas por MA, en relación tanto a las características clínicas de las lesiones (lesiones elementales, extensión y distribución) como a su presentación histológica, el estado inmunitario del paciente y la especie de MA implicada. En las revisiones sobre infecciones sobre MA se habla de “clínica compatible” e “histología compatible” como criterios de patogenicidad en casos de dificultad de aislamiento e identificación de la MA causante.

Desde un punto de vista práctico, suelen plantearse algunos problemas en el diagnóstico de las infecciones cutáneas por MA:

a) La dificultad de aislar e identificar las MA de las lesiones cutáneas puede motivar la toma repetida de muestras. No existen trabajos previos que definan las formas de presentación de las infecciones cutáneas por MA en las que apoyar la sospecha clínica.

b) Algunas especies de MA precisan requerimientos de crecimiento y aislamiento especiales, que con frecuencia no se hallan incorporadas a la rutina de algunos laboratorios de microbiología. Sólo se realizan cuando hay una “sospecha clínica fundada”, aunque no se han definido previamente dichos criterios.

c) Si bien existen técnicas de biología molecular que permiten realizar un diagnóstico rápido de las especies de MA implicadas en un proceso infeccioso, al tratarse de técnicas de elevado coste, deben basarse en una sospecha fundada (habitualmente criterios clínicos o histológicos así como guías clínicas, protocolos o publicaciones acreditadas). Sin embargo, éstos no existen en el caso de las infecciones cutáneas por MA.

- <u>Objetivos</u>.

1. Principal.

   Identificación de patrones de presentación de las infecciones cutáneas por MA en los que sustentar un diagnóstico de sospecha:

   - Con unas características clínicas lo suficientemente uniformes para incluir los distintos casos en cada patrón.
   - Con patrones histológicos uniformes para cada patrón clínico.
   - Con características similares en grupos de pacientes con sustratos inmunológicos distintos (inmunodeprimidos o inmunocompetentes).
   - Con uniformidad en las especies responsables de cada patrón, de forma que sean específicas para un patrón o, por lo menos, que existan unas especies habitualmente asociadas con una forma de presentación.

2. Secundario.

   Diseño de los distintos patrones de presentación de las infecciones cutáneas por MA de manera que:

   - Sean reproducibles en la práctica diaria, esto es, que se ajusten a situaciones reales.
   - Supongan un instrumento de trabajo o una guía clínica útil para elevar el índice de sospecha de estas infecciones, ya sea por su aspecto clínico, su aspecto histológico o ambos (correlación clinicopatológica).
   - Den seguridad al clínico a la hora de tomar decisiones difíciles como la repetición de tomas de muestras.
   - Orienten, una vez sospechada la infección por MA, sobre las especies probablemente implicadas. Este hecho es clave a la hora de informar al microbiólogo en el caso de sospecha de infección por una especie de MA con requerimientos especiales de cultivo ya que, si no hay

sospecha ni información previas, puede ocurrir que en el laboratorio no se hagan de rutina las técnicas destinadas a favorecer el crecimiento de las especies de aislamiento más difícil (correlación clínica, patológica y microbiológica).

- La existencia de una guía clínica o publicación suficientemente acreditadas permite avalar una sospecha clínica en el caso que sea necesario el estudio mediante técnicas de biología molecular.

PACIENTES, MATERIALES Y MÉTODOS

Esta tesis se basa en el estudio retrospectivo de las infecciones cutáneas por MA diagnosticadas en los servicios de Dermatología de los Hospitales Vall d´Hebron (Barcelona), Hospital de la Santa Creu i Sant Pau (Barcelona), Hospital del Mar (Barcelona), Hospital Josep Trueta (Girona) y Hospital de Palamós (Girona) durante el periodo 1983-2003.

Los criterios de inclusión en el estudio fueron: historias clínicas de pacientes diagnosticados como “infección cutánea por MA” o “infección diseminada por MA con afectación cutánea”, con una especie de MA aislada en cultivo de una biopsia cutánea, de exudado de una fístula o del material de aspiración con aguja fina de un absceso. Las MA fueron identificadas en los servicios de Microbiología de los Hospitales Vall d´Hebron (Barcelona), Hospital de la Santa Creu i Sant Pau (Barcelona), Hospital del Mar (Barcelona) y Hospital Josep Trueta (Girona) mediante métodos estándar[10]. Todos los casos cumplían los criterios de patogenicidad[4].

Los datos analizados fueron:

- Tipo de lesiones elementales (nódulos, pápulas, pústulas, abscesos, úlceras, placas, celulitis y fístulas).
- Número de lesiones (1 a 5, más de 5).
- Localización de las lesiones (extremidades superiores, extremidades inferiores, tronco, cabeza y cuello).
- Extensión de la afectación cutánea, definida como:
  a/ Localizada, cuando se afectaba una sola área corporal (una extremidad, p.ej.). Dentro de las lesiones localizadas, se definieron dos patrones de distribución: linfocutáneo (esporotricoide) y no linfocutáneo.
  b/ Generalizada, si se afectaba más de un área corporal.
- Extensión de la afectación extracutánea, definida como:
  a/ Infección profunda localizada, en presencia de tenosinovitis, artritis u osteomielitis en relación directa con las lesiones cutáneas.

b/ Infección diseminada, ante la existencia de afectación visceral, infección en sangre o médula ósea o infección profunda (huesos o articulaciones) sin relación con las lesiones cutáneas.

- Enfermedades asociadas.
- Fuentes de infección (traumatismos, procedimientos medico-quirúrgicos o diseminación desde un foco interno).
- Tiempo de evolución hasta el diagnóstico.

En función del estado inmunitario, se definieron 2 grupos de pacientes:

- Grupo I, que incluía a los pacientes inmunocompetentes (IC).
- Grupo II, incluyendo a los pacientes inmunodeprimidos (ID).

El grupo II se subdividió asimismo en 2 subgrupos:

● subgrupo IIA, que incluía ID con infección cutánea sin afectación interna.

● subgrupo IIB, incluyendo ID que presentaban manifestaciones cutáneas de una infección diseminada.

Los criterios de inmunosupresión incluían: un tratamiento con corticoides por vía oral o parenteral a dosis equivalente de 0,5 a 1 mg por Kg de prednisona, u otros fármacos inmunosupresores, por un periodo superior a 6 meses en el momento del inicio de los síntomas; síndrome de inmunodeficiencia adquirida (SIDA) con recuento de linfocitos CD4 inferior a 400 células por mm^3; y quemaduras de 2º o 3er grado con afectación de más del 40% de la superficie corporal.

Se revisaron las muestras de biopsia, tanto las tinciones estándar (hematoxilina-eosina) como las tinciones específicas para BAAR (Ziehl-Neelsen y Kinyoun).

Se definieron varios patrones histopatológicos de presentación de las infecciones cutáneas por MA y se recogió el patrón predominante y la presencia de uno o más de ellos:

- Infiltrado inflamatorio mixto con granulomas y abscesos.
- Granulomas tuberculoides.
- Granulomas supurativos.
- Granulomas sarcoideos.
- Granulomas en empalizada.
- Abscesos.
- Infiltrado de células histiocitarias.
- Paniculitis.
- Inflamación crónica inespecífica.
- Foliculitis.

Análisis estadístico

Los análisis estadísticos se realizaron con la prueba de chi-cuadrado o de forma alternativa con la prueba exacta de Fisher.

Búsqueda en *Medline*

Se realizó una búsqueda mediante *Medline* de las infecciones cutáneas y diseminadas por MA. Las palabras clave empleadas fueron las de las especies de MA, cruzadas con “cutaneous” y “disseminated”, p.ej. “*Mycobacterium marinum* and cutaneous”, “*marinum* and cutaneous”, “*Mycobacterium marinum* and disseminated” y “*marinum* and disseminated”. El mismo procedimiento se repitió con las especies de MA más relevantes en patología humana (*M. ulcerans, M. marinum, M. chelonae, M. abscessus, M. fortuitum*, *M. avium* complex, *M. kansasii, M. haemophilum, M. gordonae, M. scrofulaceum, M. simiae, M. szulgai, M. malmoense, M. terrae, M. xenopi*, *M. flavescens* y *M. genavense*). Las publicaciones de cada especie se clasificaron según el estado inmunitario, la presencia de afectación interna y la distribución de las lesiones cutáneas (localizada o generalizada).

RESULTADOS

Datos epidemiológicos

Se recogieron 51 pacientes con infecciones por MA confirmadas mediante cultivo durante el periodo 1983-2003, en 5 hospitales de Cataluña, con una población de referencia de 1.500.000 habitantes. La incidencia de la afectación cutánea en las infecciones por MA se estimó en 0.17 casos por 100.000 habitantes y año.

Se estudiaron 51 pacientes, 31 mujeres y 20 hombres con edades comprendidas entre 2 y 75 años (media 38). Veintinueve pacientes (14 mujeres y 15 hombres) pertenecían al grupo I (inmunocompetentes) y 22 pacientes (5 hombres y 17 mujeres) al grupo II (inmunodeprimidos).

Datos microbiológicos

Las especies responsables se especifican en la tabla 3.

TABLA 3. Especies de MA aisladas en el presente estudio (n=51).

	IC/Grupo I n=29	ID/Grupo II n=22	
		Subgrupo IIA n=15	Subgrupo IIB n=7
M. marinum	21 (41%)	1 (2%)	0
M. chelonae	3 (6%)	6 (12%)	0
M. abscessus	1 (2%)	6 (12%)	0
M. fortuitum	2 (4%)	1 (2%)	0
M. kansasii	0	0	4 (8%)
M. avium complex	0	0	2 (4%)
M. simiae	0	0	1 (2%)
M. gordonae	1 (2%)	0	0
M. terrae	1 (2%)	0	0
M. xenopi	0	1 (2%)	0

IC: inmunocompetentes; ID: inmunodeprimidos; subgrupo IIA: ID sin afectación extracutánea; subgrupo IIB: ID con afectación interna. Porcentajes calculados respecto al total de pacientes (n=51).

Datos clínicos

El retraso en el diagnóstico (definido como el tiempo transcurrido entre la primera consulta por las lesiones cutáneas y el aislamiento de la MA) osciló entre los 10 días y los 18 años en el grupo I y entre 7 días y 9 meses (media 3.2 meses) en el grupo II. En 10 casos (20%) fue necesario tomar más de una muestra (hasta 3 muestras en un caso) para conseguir un cultivo positivo para MA (6 casos del grupo I y 4 del grupo II).

Las características clínicas y las fuentes de infección están detalladas en la tabla 4:

TABLA 4. Características clínicas.

	Grupo I n=29	Grupo II n=22	
		Subgrupo IIA n=15	Subgrupo IIB n=7
TIPO DE LESIÓN			
nódulos	20	11	4
pápulas	3	4	0
pústulas	2	0	0
abscesos	2	5	2
úlceras	0	2	1
placas	5	4	0
celulitis	3	0	1
fístulas	1	0	0
NÚMERO DE LESIONES			
1 – 5 lesiones	24	5	5
> 5 lesiones	5	10	2
PATRÓN DE DISTRIBUCIÓN			
Localizado	26	5	5
Linfocutáneo	13	1	0
No linfocutáneo	11	3	5
Infección profunda	2	1	0
Generalizado	3	10	2
FUENTES DE INFECCIÓN			
Traumatismo acuático	22	1	0
Traumatismo no acuático	5	2	0
Cirugía	1	2	0
Foco interno	0	0	7
Desconocido	1	10	0

Las pápulas y los nódulos fueron las lesiones elementales más comunes. Los abscesos se observaron con mayor frecuencia en ID con respecto a los IC (p: 0.029). Se encontraron úlceras en 3 ID. En 7 casos del grupo I (24%) y 9 del grupo II (41%) había más de un tipo de lesión elemental. Aunque no se consideran una lesión elemental, las placas y nódulos inflamatorios con múltiples fístulas supurativas o “en espumadera” (figura 1), se observaron en 1 paciente IC y en 8 ID, todos ellos con infecciones por micobacterias de crecimiento rápido (MCR), que en nuestro estudio estaban representadas por las especies *M. chelonae, M. abscessus* y *M. fortuitum*.

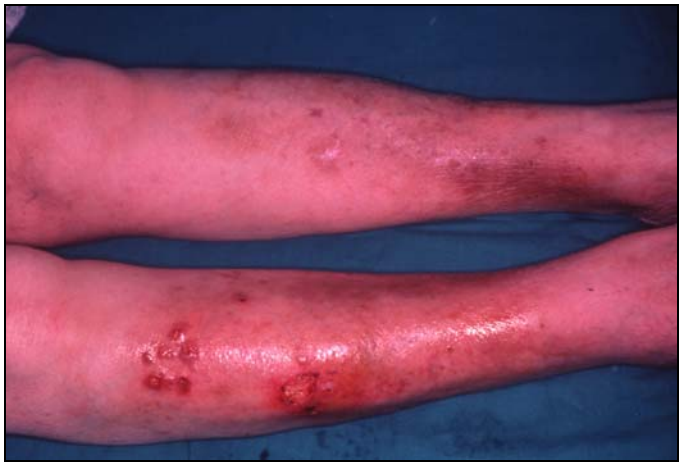


Figura 1. Nódulos, úlceras y placas supurativas en las piernas de una paciente con dermatomiositis en tratamiento corticoideo. Infección por M. abscessus.

El número de lesiones fue significativamente menor en los pacientes del grupo I (P> 0.005). En el grupo II, 10 de los 15 pacientes del subgrupo IIA tenían lesiones múltiples, mientras 5 de los 7 casos del subgrupo IIB tenían lesiones únicas.

Encontramos lesiones localizadas en 36 casos, 26 de los cuales (72%) correspondían a IC y 10 (28%) a ID. La diseminación linfocutánea o esporotricoide (figura 2) de las lesiones se observó en 13 IC y en 1 ID, todos ellos causados por *M. marinum* (tabla 4).

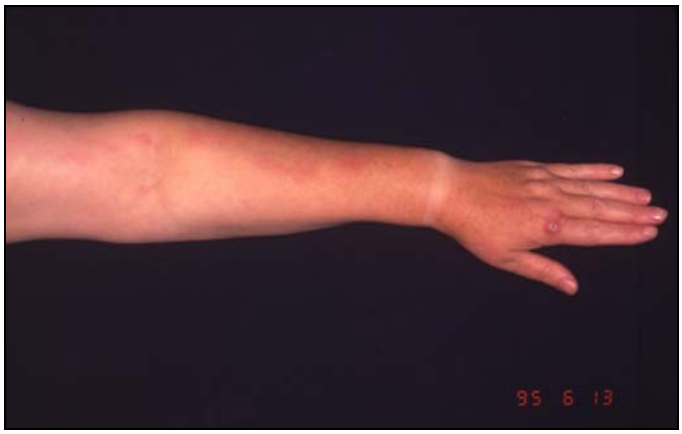
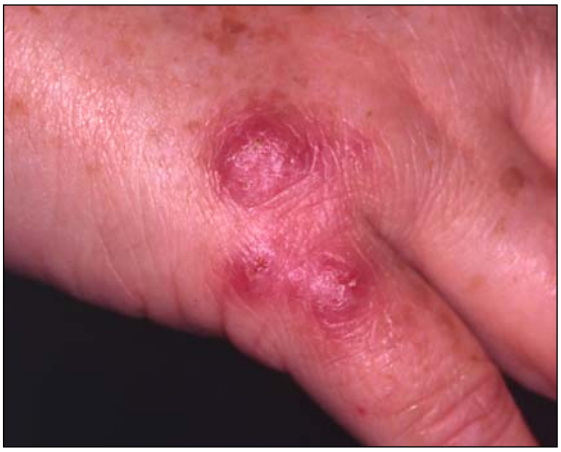


Figura 2. Pápula en dorso de mano acompañada de linfangitis y nódulos en la extermidad superior (síndrome linfocutáneo o patrón esporotricoide). Infección por M. marinum.

Las lesiones no linfocutáneas se detectaron en 11 casos del grupo I (8 *M. marinum* [figura 3], 2 *M. chelonae* y 1 *M. fortuitum*), en 3 pacientes del subgrupo IIA (1 *M. chelonae*, 1 *M. abscessus* y 1 *M. xenopi*) y en 5 casos del subgrupo IIB (2 *M. kansasii* [figura 4], 2 *M. avium* complex y 1 *M. simiae*).

Figura 3. Pápulas agrupadas en zona de traumatismo. Infección por M. marinum.



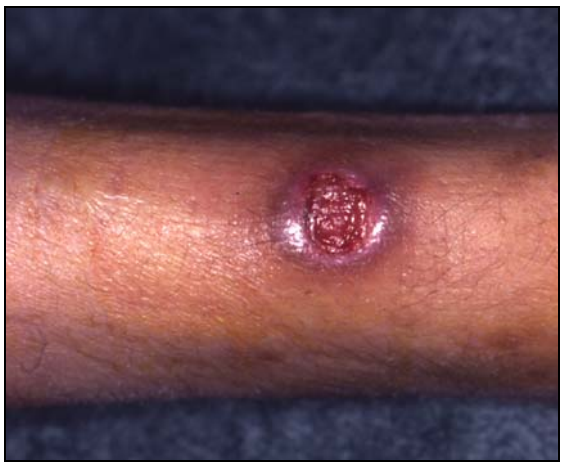


Figura 4. Nódulo ulcerado en paciente con SIDA e infección diseminada por M. kansasii.

Se diagnosticó una infección profunda en 3 pacientes con lesiones no linfocutáneas: una fístula desde una osteomielitis subyacente por *M. fortuitum*; y 2 casos de lesiones cutáneas en los dedos con una osteomielitis subyacente causadas por *M. terrae* (figura 5) y *M. chelonae*, respectivamente.

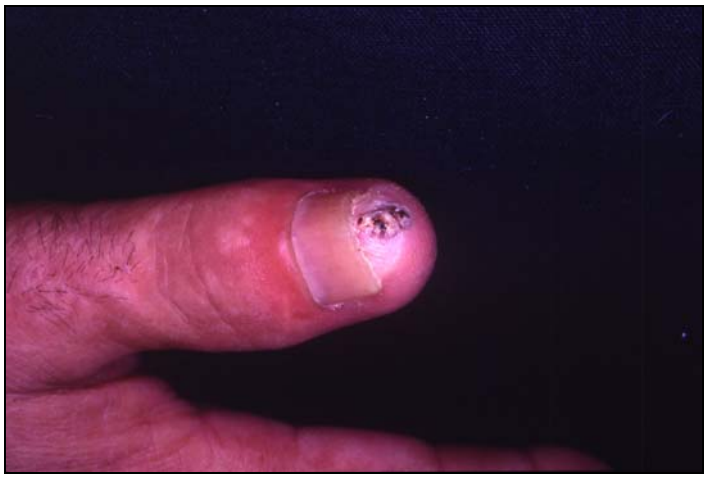


Figura 5. Úlcera en zona de traumatismo punzante. Infección por M. terrae.

Se hallaron lesiones cutáneas generalizadas en 15 pacientes. Tres de ellos eran IC con infecciones por *M. chelonae* (figura 6), *M. abscessus* y *M. gordonae*, respectivamente.

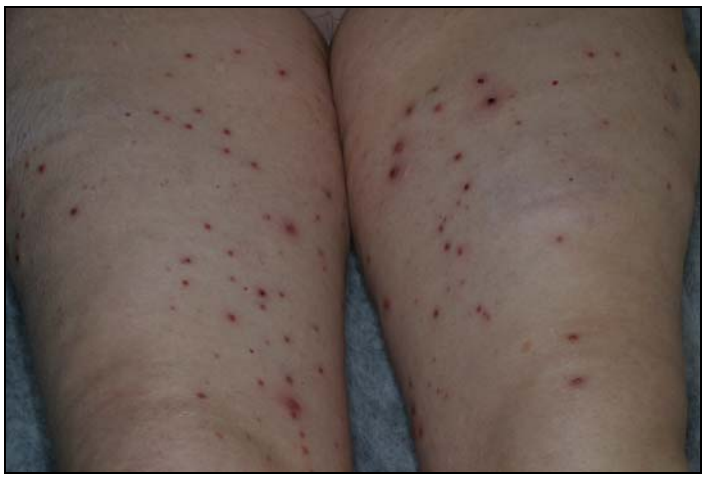
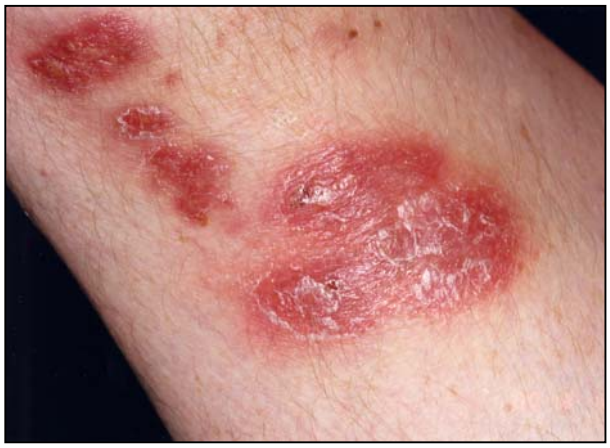


Figura 6. Foliculitis en extremidades inferiores. Infección por M. chelonae.

Los 12 restantes eran ID, 10 del subgrupo IIA (*M. chelonae* [4 casos] [figura 7], *M. abscessus* [5 casos] y *M. fortuitum* [1 caso]), y 2 casos del subgrupo IIB, ambos debidos a *M. kansasii* (figura 8).

Figura 7. Nódulos y placas inflamatorias en paciente con artritis reumatoide en tratamiento inmunosupresor. Infección por M. chelonae.



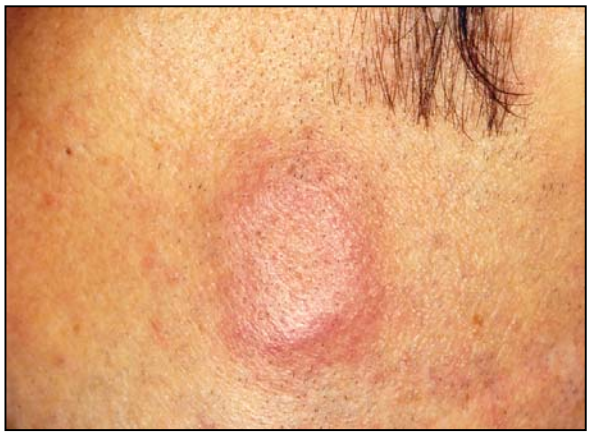


Figura 8. Nódulo facial en paciente con lesiones múltiples e infección diseminada por M. kansasii.

La fuente de infección se pudo identificar en 28 de los 29 pacientes del grupo I y en 5 de los 22 casos del grupo II (todos ellos del subgrupo IIA). El traumatismo en un ambiente acuático fue reconocido por 23 pacientes (21 *M. marinum* y 1 *M. chelonae* del grupo I y 1 *M. marinum* del grupo II); diecinueve casos estaban relacionados con acuarios, 3 lo estaban con piscinas (uno de los cuales era el causado por *M. chelonae*) y el paciente restante había sufrido una herida punzante reparando una tubería. El traumatismo sin relación con el agua se encontró en 7 casos. Cinco pacientes pertenecían al grupo I: dos infecciones por *M. chelonae* tras la depilación de las piernas; una infección por *M. abscessus* tras múltiples pinchazos con cactus; una infección por *M. fortuitum* tras una inyección intramuscular y 1 infección por *M. terrae* tras una herida punzante con una grapa metálica. Los 2 pacientes restantes eran del grupo II, y presentaban infecciones por *M. chelonae* después del arañazo de un gato y por *M. fortuitum* en un granjero tras pequeños traumatismos en las extremidades inferiores. Una intervención quirúrgica precedió a las lesiones en sólo 1 paciente IC, que había sufrido la amputación traumática de una pierna tras un accidente y desarrolló una osteomielitis por *M. fortuitum* y una fístula cutánea en el muñón, así como en 2 ID, con infecciones por *M. chelonae* tras cirugía abdominal

por una enfermedad de Crohn y por *M. xenopi* tras quemaduras extensas tratadas con injertos cutáneos.

Las enfermedades asociadas en los pacientes del grupo II, así como su relación con las especies responsables y la distribución de las lesiones están detalladas en la tabla 5. De los 15 pacientes del subgrupo IIA, 14 tomaban corticoides u otros inmunosupresores y el restante había sufrido quemaduras de 2º y 3er grado en el 90% de la superficie corporal; el subgrupo IIB incluía 7 pacientes con infección diseminada por MA. Seis de ellos tenían SIDA con recuentos de linfocitos CD4 por debajo de 100 células por mm^3 y el restante tenía una sarcoidosis en tratamiento inmunosupresor. La afectación visceral (pulmonar en 6 pacientes y del sistema nervioso central en 1 caso) precedió en todos los casos a las lesiones cutáneas.

TABLA 5. Enfermedades asociadas, especies y distribución de las lesiones en pacientes inmunodeprimidos (Grupo II).

Especies	Enf. asociada[1] (nº de casos)	Localizada	Cutánea generalizada	Infección visceral
M. chelonae	Trasplante renal (4)		4	No
	Artritis reumatoide (1)		1	No
	Enf. Crohn[2] (1)	1		No
M. abscessus	Asma (2)	1	1	No
	Dermatomiositis (2)		2	No
	Artritis reumatoide (1)		1	No
	Lupus eritematoso (1)		1	No
M. fortuitum	Panarteritis nodosa (1)		1	No
M. marinum	Lupus eritematoso (1)	1		No
M. xenopi	Quemaduras (1)	1		No
M. avium complex	SIDA (2)	2		Sí (2)
M. kansasii	SIDA (3)	1	2	Sí (3)
	Sarcoidosis (1)	1		Sí
M. simiae	SIDA (1)	1		Sí

[1]Enfermedad asociada. [2]Enfermedad de Crohn.

Los patrones clínicos de distribución observados en nuestros pacientes se detallan en la tabla 6. Las lesiones relacionadas con un ambiente acuático con o sin diseminación linfocutánea estaban causadas principalmente por *M. marinum* y sólo se afectaba un área del cuerpo; las lesiones sin relación directa con el agua que afectaban un área corporal, estaban frecuentemente causadas por MCR en los pacientes del grupo I y el subgrupo IIA, pero en el subgrupo IIB las especies causantes eran distintas; en IC se hallaron lesiones postraumáticas en varias áreas del cuerpo, mientras que los ID no recordaban una herida o traumatismo previo. Además, las especies causantes eran diferentes en el subgrupo IIA (MCR) de las del subgrupo IIB (*M. kansasii*).

TABLA 6. Distribución, fuente de infección y especie responsable en relación con el estado inmunológico.

DISTRIBUCIÓN	FUENTE DE INFECCIÓN	ESPECIES Y ESTADO INMUNOLÓGICO		
		Grupo I	Subrupo IIA	Subrupo IIB
UN ÁREA CORPORAL	Linfocutánea – Acuática	13 *M. marinum*	1 *M. marinum*	-
	Linfocutánea – No acuática	-	-	-
	No Linfocutánea – Acuática	8 *M. marinum* 1 *M. chelonae*	-	-
	No Linfocutánea – No acuática	2 *M. fortuitum* 1 *M. chelonae* 1 *M. terrae*	2 *M. chelonae* 1 *M. abscessus* 1 *M. xenopi*	2 *M. kansasii* 2 *M. avium* 1 *M. simiae*
VARIAS ÁREAS CORPORALES	Postraumática	1 *M. abscessus* 1 *M. chelonae*	-	-
	No postraumática	1 *M. gordonae*	4 *M. chelonae* 5 *M. abscessus* 1 *M. fortuitum*	2 *M. kansasii*

Hallazgos histológicos

Se estudiaron 40 biopsias cutáneas de 38 pacientes (de un paciente se revisaron 3 biopsias). En 20 de ellos (39%) se objetivó un infiltrado inflamatorio de características mixtas con granulomas y abscesos. La presencia de granulomas se evidenció en el 86% de los pacientes IC y en el 55% de los ID. En contraste, sólo en el 45% de las biopsias obtenidas de pacientes IC se observó la formación de abscesos, mientras que un 83% de los ID los presentaban. Había signos de paniculitis en sólo el 14% de los IC, y hasta en el 72% de los ID. Detectamos un infiltrado histiocitario difuso en 4 pacientes del subgrupo IIB.

En un paciente IC con infección por *M. chelonae* la biopsia evidenció una foliculitis aguda. La presencia de cambios epidérmicos (acantosis, hiperqueratosis e hiperplasia pseudoepiteliomatosa) era evidente en 19 de 22 biopsias de los IC (86%), todos ellos con infección por *M. marinum*. Las tinciones para BAAR fueron positivas en un 21% de IC y en un 72% de ID.

Búsqueda en Medline

Los resultados se detallan en la tabla 7. No se distingue entre casos aislados y series de pacientes. Sin embargo, sólo existen publicaciones con series de pacientes para las especies más prevalentes: *M. ulcerans, M. marinum, M. chelonae, M. abscessus, M. fortuitum*, *M. avium* complex y *M. kansasii*.

TABLA 7. Referencias de *Medline*, especies de MA, distribución de las lesiones cutáneas y estado inmunológico.

Sin afectación interna	**IC**[1]	Nº REF[2]	**ID**[3]	NºREF[2]
LOCALIZADA	*M. ulcerans*	> 50	*M. marinum*	> 50
	M. marinum	> 50	MCR[4]	> 50
	MCR[4]	> 50	*M. scrofulaceum*	2
	M. kansasii	6	*M. kansasii*	1
	M. scrofulaceum	2		
CUTÁNEA GENERALIZADA	MCR[4]	11	MCR[4]	9
	M. marinum	1	*M. marinum*	5
	M. avium	1	*M. haemophilum*	1
			M. scrofulaceum	1
Con afectación interna				
LOCALIZADA	?		*M. kansasii*	1
			M. avium	1
			MCR[4]	1
			M. simiae	1
CUTÁNEA GENERALIZADA	*M. avium*	4	MCR[4]	25
	M. kansasii	1	*M. avium*	18
			M. kansasii	10
			M. haemophilum	9
			M. gordonae	7
			M. marinum	6
			M. scrofulaceum	5
			M. simiae	2
			M. szulgai	2
			M. flavescens	2
			M. malmoense	1
			M. terrae	1
			M. xenopi	1

IC[1]: Inmunocompetentes. NºREF[2]: Número de referencias. **ID**[3]: Inmunodeprimidos. MCR[4]: Micobacterias de crecimiento rápido.

Tratamiento y evolución

La modalidad de tratamiento, su duración y la evolución se resumen en las tablas 8 (inmunocompetentes) y 9 (inmunodeprimidos). Además del antibiótico, se realizó tratamiento quirúrgico en 9 casos, 5 de 29 pacientes IC (17 %) y en 4 de los 22 ID (18 %). En un paciente ID fue necesario amputar la falange distal del quinto dedo de una mano debido a la infección profunda y la falta de respuesta al tratamiento antibiótico. En este caso, la fuente de infección fue presumiblemente el arañazo de un gato. En 4 pacientes ID la evolución fue desfavorable presentando un *exitus* y en 3 de ellos la muerte se consideró en relación con una infección diseminada por MA e inmunosupresión por SIDA.

TABLA 8. Tratamiento y evolución en pacientes inmunocompetentes.

CULTIVO	Nº CASOS	TRATAMIENTO	DURACIÓN	EVOLUCIÓN
M. marinum	1	Rifampicina, eritromicina, tetraciclina	Desconocido	Resolución
M. marinum	1	Claritromicina, ofloxacino, rifampicina	4 meses	Resolución
M. marinum	1	Rifampicina, doxiciclina	3 meses	Resolución
M. marinum	8	Minociclina	1,5 – 6 meses (media 4,4)	Resolución
M. marinum	8	Minociclina y claritromicina	3 – 8 meses (media 5,7)	Resolución
M. marinum	1	Cirugía	-	Resolución
M. marinum	1	Minociclina, azitromicina	6 meses	Resolución
M. chelonae	1	Doxiciclina, roxitromicina, cirugía	2,5 meses	Resolución
M. chelonae	1	Cirugía	-	Resolución
M. chelonae	1	Eritromicina	2,5 meses	Resolución
M. abscessus	1	Eritromicina, amikacina	6 meses	Resolución
M. fortuitum	1	Isoniazida, rifampicina, etambutol, pirazinamida	6 meses	Resolución
M. fortuitum	1	Trimetoprim-sulfametoxazol, cirugía	3 meses	Resolución
M. gordonae	1	Trimetoprim-sulfametoxazol	5 meses	Resolución
M. terrae	1	Rifampicina, etambutol, cirugía	6 meses	Resolución

TABLA 9. Tratamiento y evolución en pacientes inmunodeprimidos.

CULTIVO	Nº CASOS	ENFERMEDAD DE BASE	TRATAMIENTO	DURACIÓN	EVOLUCIÓN
M. chelonae	1	Trasplante renal	Eritromicina, amikacina, cirugía	1,5 meses	Resolución
M. chelonae	1	Enfermedad de Crohn	Eritromicina, amikacina, cirugía	3,5 meses	Resolución
M. chelonae	1	Trasplante renal	Doxiciclina, trimetoprim-sulfametoxazol, cirugía	8 meses	Resolución
M. chelonae	1	Trasplante renal	Claritromicina	5 meses	Resolución
M. chelonae	1	Trasplante renal	Rifampicina, claritromicina, ofloxacino	12 meses	Resolución
M. chelonae	1	Artritis reumatoide	Cefpodoxime	1 mes	Exitus
M. abscessus	1	Asma	Minociclina, trimetoprim-sulfametoxazol	2 meses	Resolución
M. abscessus	1	Asma	Cefoxitina	1 mes	Resolución
M. abscessus	1	Dermatomiositis	Trimetoprim-sulfametoxazol	7 meses	Resolución
M. abscessus	1	Dermatomiositis	Rifampicina, claritromicina, ofloxacino	6 meses	Resolución
M. abscessus	1	Artritis reumatoide	Claritromicina, ciprofloxacino	6 meses	Resolución
M. abscessus	1	Lupus eritematoso	Isoniazida, rifampicina, etambutol, claritromicina	6 meses	Resolución
M. fortuitum	1	Panarteritis nodosa	Rifampicina, claritromicina	6 meses	Resolución
M. kansasii	2	Sarcoidosis	Isoniazida, rifampicina, etambutol	12 meses	Desconocido
M. kansasii	1	SIDA	Azitromicina, cloxacilina	1 mes	Exitus
M. kansasii	1	SIDA	Isoniazida, etambutol, ofloxacino	6 meses	Desconocido
M. avium complex	2	SIDA	Desconocido	Desconocido	Exitus
M. simiae	1	SIDA	Isoniazida, rifampicina, etambutol, pirazinamida	18 meses	Exitus
M. marinum	1	Lupus eritematoso	Rifampicina, etambutol	9 meses	Resolución
M. xenopi	1	Quemaduras	Cirugía	-	Resolución

DISCUSIÓN

Existen pocas publicaciones que hayan intentado caracterizar las manifestaciones cutáneas de las infecciones por MA. El trabajo más extenso se debe a Ingram *et al* [11] quienes, en una revisión de infecciones de piel y tejidos blandos por *M. chelonae*, proponen 3 patrones clínicos: a) lesiones cutáneas diseminadas en pacientes ID; b) celulitis o abscesos en IC en relación con traumatismos e incidentalmente asociados con tenosinovitis u osteomielitis subyacente; y c) infecciones locales en portadores crónicos de catéteres.

Aunque en los dos trabajos en los que se apoya esta tesis no aportamos ningún caso de infección por *M. ulcerans*, no debemos olvidar que representa la tercera causa mundial de infección por micobacterias tras *M. tuberculosis* y *M. leprae*[3]. Aunque en nuestro medio no sea una enfermedad habitual, el diagnóstico temprano es esencial para tratar adecuadamente la infección, ya que la respuesta a los antibióticos es escasa o nula. Además, la infección por *M. ulcerans* (o úlcera de Buruli) es probablemente la infección por MA con características epidemiológicas, clínicas e histológicas mejor definidas, distintas del resto de infecciones por MA. Se ha descrito la afectación visceral excepcionalmente en pacientes con SIDA[12], con anemia de células falciformes[13] e incluso en sujetos IC[14].

De acuerdo con este estudio, se pueden definir varios patrones clínicos en las infecciones por MA, especificando en cada uno las especies causantes más representativas. Las lesiones cutáneas pueden presentarse de forma exclusiva en la piel o en el contexto de una infección diseminada. En ambos grupos, las lesiones cutáneas pueden ser localizadas o generalizadas (tabla10).

TABLA 10. Patrones clínicos de infecciones cutáneas por MA.

ESTADO GENERAL Y DISTRIBUCIÓN	**PATRONES CLÍNICOS Y ESPECIES ASOCIADAS**	
Sin afectación interna		
LOCALIZADA	I.	Infección por *M. ulcerans* (Úlcera de Buruli).
	IIa.	Lesiones esporotricoides, origen acuático (*M. marinum*, MCR[1] y *M. kansasii*).
	IIb.	Lesiones esporotricoides, origen no acuático (MCR[1], *M. kansasii* y *M. avium* complex).
	IIIa.	Lesiones no linfocutáneas, origen acuático (*M. marinum*, MCR[1] y *M. kansasii*).
	IIIb.	Lesiones no linfocutáneas, origen no acuático, postquirúrgicas, por catéteres (MCR[1]).
CUTÁNEA GENERALIZADA	IV.	Foliculitis y/o forunculosis después de depilación u origen acuático (MCR[1]).
	V.	Lesiones en extremidades en pacientes con tratamiento inmunosupresor (MCR[1]).
Con afectación interna		
LOCALIZADA	VI.	Lesiones aisladas en pacientes inmunodeprimidos (*M. kansasii, M. avium* complex, MCR[1] y *M. simiae*).
CUTÁNEA GENERALIZADA	VII.	Lesiones cutáneas y mucosas e infección diseminada en pacientes con inmunosupresión congénita (déficit de citocinas de tipo 1) o adquirida (*M. kansasii, M. avium* complex, *M. haemophilum,* MCR[1], *M. simiae, M. gordonae, M. marinum, M. scrofulaceum, M. szulgai, M. malmoense, M. terrae, M. xenopi, M. smegmatis* y *M. flavescens*).

MCR[1]: Micobacterias de crecimiento rápido.

En los pacientes con infecciones localizadas, pueden definirse 2 patrones: un patrón linfocutáneo o esporotricoide (patrón II), en el que aparecen nódulos en las zonas donde ha existido un traumatismo previo, pudiendo desarrollar lesiones satélites periféricas (figura 3) y posteriormente diseminación linfática regional, generalmente de la extremidad superior (figura 2); en segundo lugar, un patrón no linfocutáneo (patrón III), caracterizado por nódulos o abscesos limitados a la zona previamente traumatizada (figura 5). Ambos patrones pueden estar relacionados con una fuente de infección acuática (patrones IIa y IIIa). Sin embargo, dado que la mayoría de especies patogénicas de MA pueden aislarse del agua corriente y de los suministros hospitalarios de agua, es difícil implicar o descartar una fuente de infección en relación con el agua en casos aislados, ya que para ello se requieren técnicas de diagnóstico molecular como la reacción en cadena de la polimerasa (PCR)[15] que demuestren la similitud genotípica de la especie causante de la infección con la especie aislada en el entorno.

M. marinum es la causa más frecuente de las infecciones localizadas de origen acuático, tanto de las linfocutáneas como de las no linfocutáneas. Aunque no hay gran diferencia entre los casos observados en IC e ID[16], las infecciones por *M. marinum* en estos últimos conllevan un mayor riesgo tanto de extenderse hacia estructuras profundas, afectando tendones y huesos, como de ocasionar lesiones esporotricoides, lesiones cutáneas generalizadas[17] o incluso afectación interna[18]. Histológicamente, se suele hallar una inflamación dérmica mixta con granulomas y abscesos (figura 9), típicamente acompañada de cambios epidérmicos[6] (figura 10).

Figura 9. Patrón mixto con granulomas y abscesos dérmicos (H-E x 400). M. marinum.

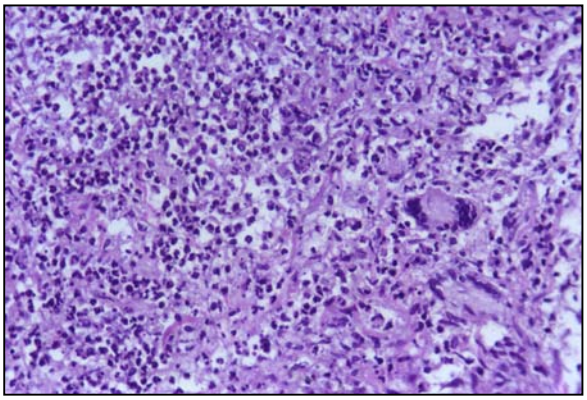
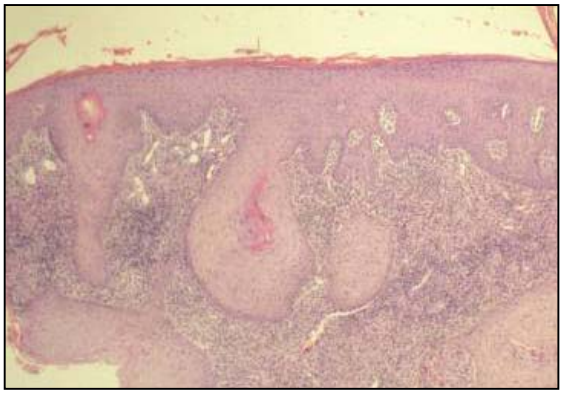


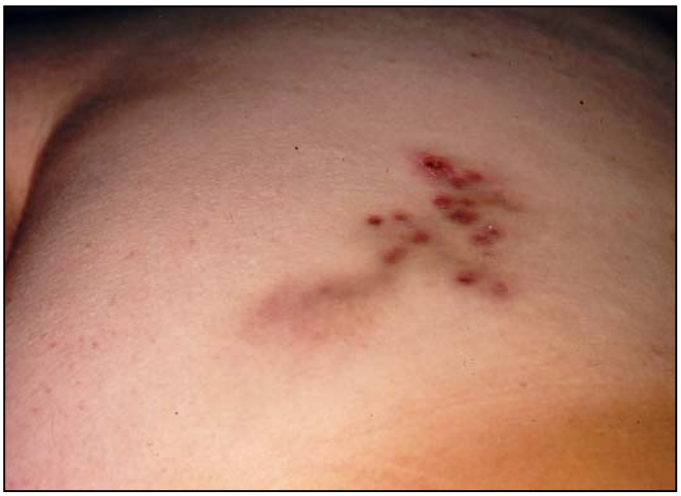
Figura 10. Hiperplasia epidérmica pseudoepiteliomatosa e infiltrado dérmico linfohistiocitario (H-E x 40). M. marinum.



Sin embargo, cuando la fuente de infección está en relación con el agua pero no con acuarios de peces tropicales ni piscinas, se debe sospechar la presencia de otras MA distintas de *M. marinum* (*M. chelonae, M. abscessus, M. fortuitum, M. kansasii, M. scrofulaceum, M. gordonae, M. avium* complex y *M. flavescens*). Además, *M. tuberculosis* y una gran variedad de microorganismos (*Sporothrix schenckii* y otros hongos, varias especies de *Nocardia, Francisella tularensis, Staphylococcus aureus, Streptococcus pyogenes,* varias especies de *Leishmania, Herpes simplex* y el virus vacunal) se han descrito como posibles causas de lesiones linfocutáneas, relacionadas o no con el agua[19].

Las infecciones localizadas y no linfocutáneas que no tienen relación directa con un ambiente acuático están habitualmente causadas por MCR. Una historia detallada suele revelar el antecedente de heridas accidentales, actos médicos como intervenciones quirúrgicas, colocación de catéteres o inyecciones (figura 11), así como tratamientos cosméticos médicos y paramédicos[20, 21].

Figura 11. Infección localizada por M. fortuitum secundaria a inyección intramuscular.



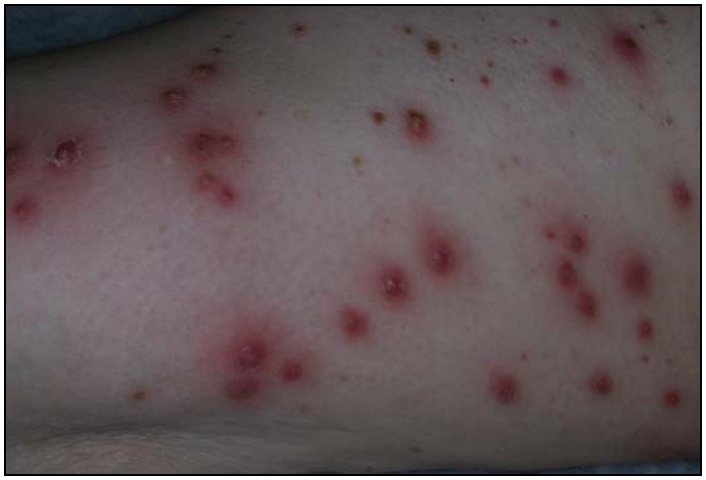
Además de casos aislados, se han publicado brotes de infecciones debidos a la contaminación de instrumental médico y paramédico[22]. En algunos estudios se ha podido demostrar que la fuente de infección era el agua corriente o el agua del depósito del hospital[15]. Así pues, aunque consideremos que el ambiente acuático no

tiene una relación directa con la adquisición de la infección, siempre debemos descartar el agua como el principal reservorio de la MA.

La extensión en profundidad de la infección cutánea, en forma de tenosinovitis u osteomielitis, es más probable si existe el antecedente de una herida punzante, si se han inyectado corticoides intralesionales erróneamente para tratar las lesiones cutáneas y, evidentemente, en ID[23]. Además, a partir de una infección inicialmente profunda puede haber afectación cutánea secundaria en forma de abscesos, úlceras o fístulas. Por este motivo, en dichas circunstancias y si no hay respuesta al tratamiento, deben realizarse exploraciones complementarias de imagen (radiografía, tomografía axial computerizada, gammagrafía ósea, resonancia magnética nuclear) para descartar la afectación de tendones y huesos subyacentes.

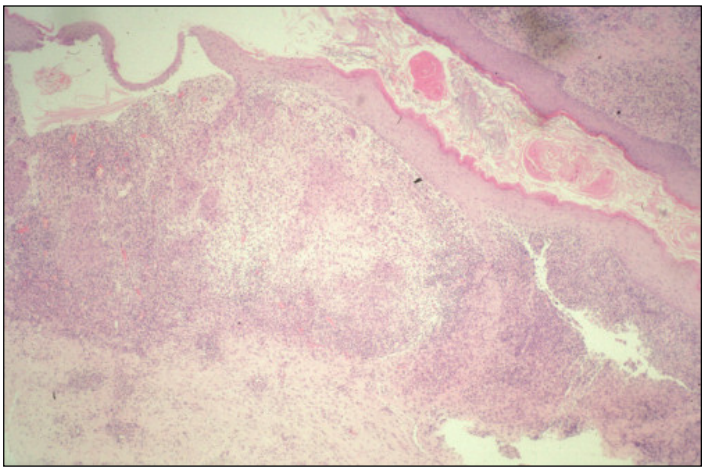
Las lesiones cutáneas generalizadas pueden presentarse sin afectación sistémica. En estos pacientes, casi siempre se aisla una MCR como responsable (tablas 6 y 7). Podemos distinguir 2 patrones de presentación, uno en IC (patrón IV) y el otro en ID (patrón V). En los IC (patrón IV) se suele diagnosticar una foliculitis o forunculosis relacionada con la depilación con cera o por afeitado [24], salones de pedicura[25] o inmersión en agua estancada[26]. Se han descrito tanto casos aislados como pequeños brotes epidémicos[27]. Típicamente, los cultivos bacterianos son negativos y los pacientes no responden al tratamiento con penicilinas. Nuestro estudio incluye 2 de dichos casos, ambos causados por MCR (figura 12).

Figura 12. Foliculitis en extremidades inferiores por M. chelonae.



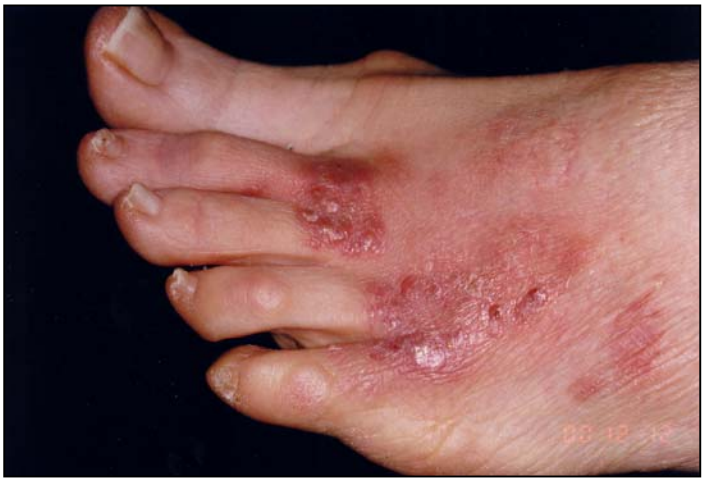
Histológicamente, lo más frecuente es hallar una foliculitis aguda, pero también se ha descrito la presencia de granulomas perifoliculares[6, 27](figura 13).

Figura 13. Inflamación granulomatosa perifolicular (H-E x 40).
Infección por M. chelonae.



Por su parte, los ID (habitualmente pacientes que reciben corticoides u otros inmunosupresores por trasplantes o enfermedades crónicas) presentan una erupción de nódulos, abscesos, úlceras y, típicamente, placas y nódulos inflamatorios con múltiples pústulas o fístulas supurativas (“en espumadera”) en las extremidades inferiores y las nalgas (patrón V, figuras 1, 7 y 14).

Figura 14. Placas inflamatorias con pústulas en paciente
con artritis reumatoide en tratamiento inmunosupresor.
Infección por M. chelonae.



En la mayoría de casos no existe un traumatismo previo que explique las lesiones, por lo que no está claro si aparecen por múltiples puntos de inoculación, autoinoculación o incluso por diseminación hematógena[28]. En nuestro estudio todos los casos de este patrón estaban provocados por MCR. Sólo un paciente ID presentaba una osteomielitis subyacente a una lesión cutánea. En el estudio histológico es habitual encontrar granulomas sarcoideos o supurativos (figura 15). Las tinciones específicas suelen revelar la presencia de múltiples BAAR[6] (figura 16). El pronóstico de estas infecciones es bueno[11] aunque, al tratarse de ID, existe el riesgo de infecciones profundas y de diseminación sistémica.

Figura 15. Granuloma supurativo (H-E x 100) Infección por M. abscessus.

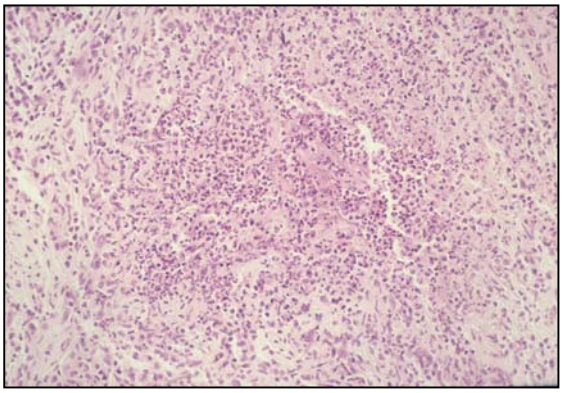
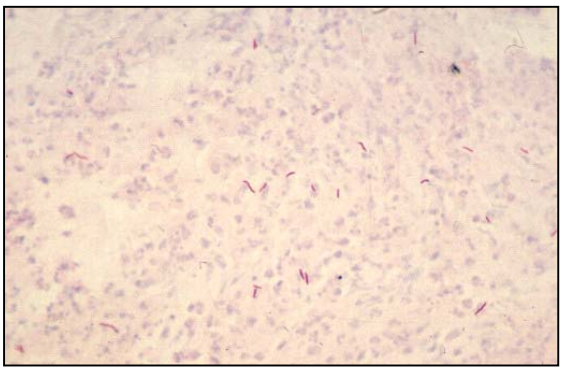


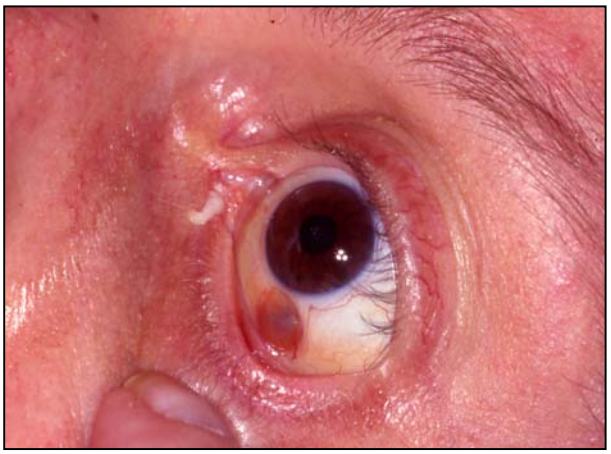
Figura 16. Múltiples BAAR. Infección por M. abscessus (Z-N x 400).



Las infecciones diseminadas por MA ocurren casi siempre en pacientes con intensa inmunosupresión (linfomas y leucemias, inmunodeficiencia celular y SIDA). Las lesiones cutáneas pueden ser localizadas (patrón VI) o generalizadas (patrón VII), aunque las primeras se han descrito raramente[29]. Sin embargo, en nuestro estudio 5 de los 7 pacientes con afectación visceral tenían lesiones localizadas. A diferencia de los IC, los ID presentan lesiones en zonas no expuestas y, además, no se relacionan con traumatismos previos (figura 4). Habitualmente pues, las infecciones diseminadas cursan con afectación cutánea generalizada[30, 31, 32]. En sujetos ID con lesiones cutáneas generalizadas pero sin afectación interna, las lesiones suelen localizarse en las extremidades, mientras que en los pacientes ID con una infección

diseminada suelen afectar también el tronco, la cabeza y las mucosas (tabla 10, figura 17).

Figura 17. Pápula inflamatoria en conjuntiva bulbar.
Infección diseminada por M. kansasii.



La observación de lesiones cutáneo-mucosas (localizadas o generalizadas) en pacientes ID con infecciones diseminadas, suele ocurrir en el contexto de una infección interna sintomática. Sin embargo, es frecuente que el estudio de las lesiones cutáneas permita el aislamiento de la MA responsable y el diagnóstico de la infección extracutánea. Sólo en raras ocasiones las lesiones cutáneo-mucosas (localizadas o generalizadas) son la primera manifestación de una infección diseminada.

Entre las especies de MA que suelen estar implicadas en las infecciones diseminadas, las MCR son las más frecuentes[11], aunque otras especies como *M. kansasii*[31], *M. avium* complex[32] y *M. haemophilum*[33] también son habituales. *M. kansasii* y *M. avium* complex son principalmente patógenos pulmonares. *M. avium* complex también causa infecciones del tubo digestivo. Los pacientes con inmunosupresión grave tienen un elevado riesgo de diseminación hematógena desde los órganos citados hacia la piel, los huesos y las articulaciones, los ganglios linfáticos, el hígado, el bazo y el sistema nervioso central[11, 31]. También es posible la infección diseminada desde un foco primario cutáneo[34]. Las lesiones cutáneas están presentes en más del 75% de las infecciones por *M. haemophilum*. Sin embargo, las

infecciones por esta especie probablemente están infradiagnosticadas debido a sus especiales requerimientos de cultivo[35]. Parece ser que algunas especies tienen mayor tendencia a aislarse en determinadas situaciones de inmunosupresión. Las infecciones por *M. avium* complex, *M. kansasii* y *M. haemophilum* son más frecuentes en el contexto de un SIDA, mientras que las infecciones por MCR son más habituales en pacientes tratados con quimioterapia y después de trasplantes de órganos o de células madre hematopoyéticas[36]. Las biopsias cutáneas de los sujetos ID con infección diseminada no suelen presentar granulomas. Típicamente, se observan abscesos (figura 18), un infiltrado difuso de histiocitos (figura 19) que en ocasiones adoptan un aspecto "espumoso" similar al de la lepra lepromatosa y abundantes BAAR (figura 20)[6].

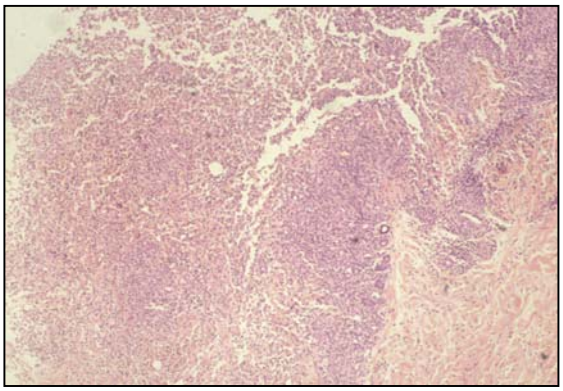


Figura 18. Absceso dérmico y necrosis. Infección por M. avium* complex *(H-E x 100).

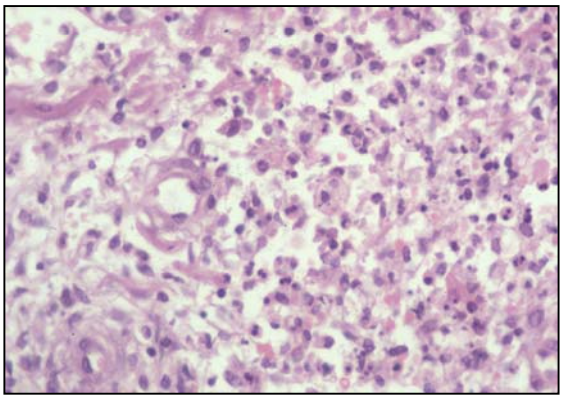


Figura 19. Infiltrado histiocitario difuso con células espumosas. Infección diseminada por M. kansasii (H-E x 400).

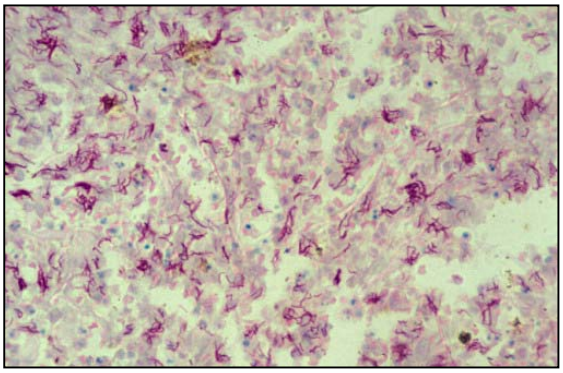


Figura 20. Incontables BAAR, formando agregados (Z-N x 400). M. kansasii.

Independientemente de la especie responsable, las infecciones diseminadas con afectación cutánea tienen en general mal pronóstico, incluso en casos tratados adecuadamente[11, 36]. En nuestro estudio, 3 pacientes con SIDA fallecieron como

consecuencia de una infección diseminada por MA. Se han descrito también casos con un pronóstico menos grave, en relación con un grado de inmunosupresión menos intenso[37].

Ocasionalmente se han descrito infecciones diseminadas en sujetos aparentemente normales, indistinguibles de las observadas en individuos ID[38, 39, 40]. En estos casos debería realizarse un estudio de la respuesta inmunitaria dependiente de los monocitos y del perfil de secreción de citocinas de tipo 1. Esta situación clínica particular suele observarse en niños con mutaciones en los genes que codifican para las citocinas de tipo 1 (interleucina-12 [IL-12]) y sus receptores (receptor del interferón gamma [IFN-γR] y receptor de la interleucina-12 [IL-12R])[41]. Dichas mutaciones producen deficiencias en la activación de los macrófagos, que en los pacientes homocigotos pueden cursar con un déficit completo, dando lugar a infecciones que suelen ser letales, y ocasionalmente a déficit parciales que suelen conllevar un mejor pronóstico[42]. Se han descrito pacientes heterocigotos de estas mutaciones que cursan con infecciones limitadas a la piel, los huesos y los ganglios linfáticos[43]. Todos los casos descritos de defectos genéticos en las citocinas de tipo 1 e infecciones diseminadas por MA con afectación de piel y tejidos blandos, presentaban lesiones cutáneas generalizadas.

En las tablas 8 y 9 se detallan los tratamientos y la evolución de los pacientes incluidos en el estudio. La conclusión más evidente es la diversidad de pautas utilizadas, con la excepción de las infecciones por *M. marinum*, donde existe una cierta uniformidad en el uso de tetraciclinas (minociclina, doxiciclina o tetraciclina base) asociadas en los casos más recientes con macrólidos (claritromicina, eritromicina o azitromicina). En las infecciones por MCR la diversidad de pautas es mayor, tanto en IC como en ID, aunque se tiende a usar las mismas familias de antibióticos: rifampicina, tetraciclinas, macrólidos, quinolonas, sulfamidas y aminoglucósidos. En las infecciones diseminadas se prescriben pautas similares a las de la tuberculosis, con la adición de un macrólido o una quinolona. La explicación a tal disparidad en esta serie parece deberse al prolongado periodo del estudio (20 años); los tratamientos no han sido guiados por antibiogramas previos; los especialistas responsables en cada caso tienden a usar los antibióticos con los que están más familiarizados y en cada hospital las pautas empíricas son distintas.

CONCLUSIONES

1. Las manifestaciones cutáneas de las infecciones por MA pueden agruparse en patrones de presentación bastante característicos y uniformes (tabla 10), de acuerdo con criterios como el tipo de lesiones cutáneas, su estudio histológico, el estado inmunitario del paciente y la especie de MA responsable.

2. La definición de los patrones clínicos e histológicos desarrolla y establece con más claridad lo que se denomina vagamente “clínica compatible” e “histología compatible” en las revisiones sobre infecciones sobre MA y que, sin embargo, se consideran criterios de patogenicidad.

3. El conocimiento de las características clínicas e histológicas (correlación clinicopatológica) de las infecciones cutáneas por MA es clave para llegar al diagnóstico microbiológico de confirmación, ya que un diagnóstico de sospecha correcto permite la toma de muestras en condiciones óptimas y da seguridad a la hora de decidir si es necesario repetir la obtención de muestras, sobre todo en casos de MA difíciles de cultivar.

4. La identificación de un patrón clínico concreto puede incluso ayudar a establecer una sospecha de las especies causantes más probables, aportando una información adicional al microbiólogo que facilite el aislamiento y la identificación de la MA responsable.

5. La existencia de patrones concretos permite que cada caso sea valorado con criterios uniformes y, si forman parte de protocolos, guías clínicas o publicaciones acreditados, deberían ser motivo suficiente para la realización de técnicas especiales, como las de biología molecular.

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Cutaneous infections due to nontuberculous mycobacteria: histopathological review of 28 cases. Comparative study between lesions observed in immunosuppressed patients and normal hosts

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To evaluate the histopathological features observed in patients with cutaneous infections due to nontuberculous mycobacteria (NTM) and to compare the histopathological patterns observed in immunosuppressed patients and normal hosts. Twenty-eight biopsy specimens corresponding to 27 patients with cutaneous infections due to NTM were reviewed. Eighteen biopsies corresponded to normal hosts (14 *Mycobacterium marinum*, 2 *Mycobacterium chelonae*, 1 *Mycobacterium terrae* and 1 *Mycobacterium gordonae*) and 10 biopsy specimens were obtained from 9 immunosuppressed patients (3 *Mycobacterium chelonae*, one of which had two biopsies, 1 *Mycobacterium abscessus*, 2 *Mycobacterium kansasii*, 1 *Mycobacterium marinum*, 1 *Mycobacterium avium* complex and 1 *Mycobacterium simiae*). A panel of histopathological features was evaluated by two independent observers in each biopsy specimen. Epidermal changes (acanthosis, pseudoepitheliomatous hyperplasia, exocytosis) were mainly observed in *M. marinum* infections. In immunosuppressed patients the infiltrate tended to be deeper, involving the subcutaneous tissue (100%) with a more diffuse distribution and constant abscess formation. A marked granulomatous inflammatory reaction was observed in 83% of immunocompetent and in 60% of immunosuppressed patients. In immunosuppressed patients a relationship between the chronic evolution of the disease and granuloma formation was demonstrated. A diffuse infiltrate of histiocytes with occasionally foamy appearance was noted in three biopsy specimens from three patients with AIDS. Acute and chronic panniculitis was detected in 8 biopsy specimens. In one biopsy (*M. chelonae*) an acute suppurative folliculitis was observed. Different histopathological patterns can be noted in biopsy specimens from cutaneous nontuberculous mycobacterial infections. The evolution of the disease and the immunologic status of the host may explain this spectrum of morphological changes. Tuberculoid, palisading and sarcoid-like granulomas, a diffuse infiltrate of histiocytic foamy cells, acute and chronic panniculitis, non-specific chronic inflammation, cutaneous abscesses, suppurative granulomas and necrotizing folliculitis can be detected. Suppurative granulomas are the most characteristic feature in skin biopsy specimens from cutaneous NTM infections. Some

histopathological patterns seem more prevalent in immunosuppressed patients.

Bartralot R, Pujol RM, García-Patos V, Sitjas D, Martin-Casabona N, Coll P, Alomar A, Castells A. Cutaneous infections due to nontuberculous mycobacteria: histopathological review of 28 cases. Comparative study between lesions observed in immunosuppressed patients and normal hosts.
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Nontuberculous mycobacteria (NTM) are an heterogeneous group of acid-fast bacteria that rarely cause cutaneous lesions. Two species, *Mycobacterium ulcerans* and *Mycobacterium marinum* cause well-defined clinicopathological entities known respectively as Buruli ulcer and swimming pool (fish-tank) granuloma. Cutaneous lesions produced by the other mycobacteria are associated with a diversity of non-specific clinical and histopathological appearances.

Different histopathological patterns can be observed in cutaneous NTM infections. A granulomatous inflammatory infiltrate with tuberculoid granuloma formation, sarcoid-like granulomas or rheumatoid-like nodules are frequently present, but dermal or subcutaneous abscesses, a diffuse dermal or subcutaneous histiocytic infiltration, acute or chronic subcutaneous tissue inflammatory infiltrates (panniculitis) or even non-specific chronic inflammation have also been described. These patterns may coexist in biopsy specimens with a variable intensity and distribution.

Histopathological features observed in 28 biopsies from 27 patients with cutaneous infections due to several NTM were evaluated. A comparative study between histopathological findings observed in normal hosts and immunosuppressed patients was performed.

Material and methods

A retrospective study (period 1983–1997) of 28 biopsy specimens from 27 cases (11 men and 16 women) of cutaneous infections due to nontuberculous mycobacteria (NTM) was performed. Data were recorded from several Hospitals from Catalonia (Hospital de la Santa Creu i Sant Pau and Hospital Vall d'Hebron from Barcelona; Hospital de Palamós and Hospital Josep Trueta from Girona). The age of patients ranged from 13 to 75 years old. Nine patients were immunosuppressed (IS) and 18 were normal hosts (NH).

The IS patients were 1 man and 8 women with ages ranging from 22 to 61 years old (mean 40 years old). Three patients were renal transplant recipients under chronic immunosuppressive treatment with oral corticosteroids and cyclosporin A (2 cases) or azathioprine (1 case). Four patients had AIDS and the remaining 2 cases were under chronic oral corticosteroid therapy for systemic lupus erythematosus and asthma.

Isolation from cutaneous biopsies or exudate smears was achieved in standard culture media (Lowenstein-Jensen, Middlebrook 7H11, Bactec^{TM}). Identification of the mycobacterial species was based on standard methods.[1]

Twenty-eight biopsy specimens were available for histopathological evaluation (Table 1). Eighteen biopsies corresponded to patients without underlying immunosuppression (14 *Mycobacterium marinum*, 2 *Mycobacterium chelonae*, 1 *Mycobacterium terrae* and 1 *Mycobacterium gordonae* infections). Ten biopsy specimens corresponding to 4 *Mycobacterium chelonae*, 1 *Mycobacterium abscessus*, 2 *Mycobacterium kansasii*, 1 *Mycobacterium marinum*, 1 *Mycobacterium avium* complex and 1 *Mycobacterium simiae* were obtained from 9 immunosuppressed patients, one of whom had 2 biopsies that grew *M. chelonae*. Demonstration of acid-fast bacilli in histological samples was performed with Ziehl-Neelsen and/or Kinyoun staining.

Although some NTM studied (*M. gordonae*, *M. terrae* and *Mycobacterium simiae)* have only rarely been described as pathogens, our patients fulfilled criteria of pathogenicity as previously described.[2]

Clinically, the lesions corresponded to papules or

Table 1. Nontuberculous mycobacteria: cases studied

	Immunosuppressed	Normal hosts
Total biopsies	10	18
Rapid growers	5 (50%)	2 (12%)
M. chelonae	4 (Renal T.[C, Az, CsA])	2
M. abscessus	1 (Asthma [C])	0
Slow growers	5 (50%)	16 (88%)
M. marinum	1 (SLE [C, Cph.])	14
M. kansasii	2 (AIDS)	0
M. avium complex	1 (AIDS)	0
M. gordonae	0	1
M. terrae	0	1
M. simiae	1 (AIDS)	0

Renal T: Renal Transplant, C: Corticosteroids, Az: Azathioprine, CsA: Cyclosporin A, SLE: systemic lupus erythematosus, Cph: Cyclophosphamide, AIDS: acquired immunodeficiency syndrome.

pustules in 5 cases (4 NH, 1 IS), nodules in 19 (10 NH, 9 IS), abscesses in 2 (1 NH, 1 IS), plaques in 5 (4 NH, 1 IS), ulcers in 1 IS and cellulitis in 3 (2 NH, 1 IS). A linear (sporotrichoid) spread of nodules (4 cases) or plaques (1 case) was noted in 5 *M. marinum* infections. The upper limbs were affected in 12 NH and in 2 IS, whereas the lower limbs were involved in 5 NH and in 7 IS. One IS patient with *M. kansasii* infection presented lesions in the upper and lower limbs. A solitary lesion was observed in 7 patients (4 NH, 3 IS); from 1 to 9 lesions were present in 17 (12 NH, 5 IS) and 10 lesions or more in 3 cases (2 NH, 1 IS).

In order to compare the NH and the IS groups, a panel of histopathological features was evaluated blindly by two independent observers in each biopsy specimen. In cases with discordant findings, biopsy specimens were reexamined by the two observers together in order to come to an agreement.

Table 2. Histopathological features in immunosuppressed patients (IS) and normal hosts (NH)

	IS (10 biopsies)	NH (18 biopsies)
Epidermis		
Acanthosis	3 (30%)	15 (83%)
Pseudoepitheliomatous hyperplasia	2 (20%)	7 (39%)
Exocytosis	0	10 (56%)
Intraepidermal abscesses	1 (10%)	0
Ulceration	0	1 (5.5%)
Dermis and subcutis		
Depth Infiltrate		
PD	1 (10%)	1 (5.5%)
SRD	2 (20%)	5 (28%)
DRD	7 (70%)	13 (72%)
ST	10 (100%)	7 (39%)
Infiltrate distribution		
PS	2 (20%)	10 (56%)
DS	2 (20%)	6 (33%)
PD	4 (40%)	6 (33%)
DD	10 (100%)	11 (61%)
Inflammatory cells		
Giant cells	8 (80%)	13 (72%)
Lymphocytes	6 (60%)	16 (89%)
Histiocytes	9 (90%)	17 (94%)
PMN	10 (100%)	16 (89%)
Plasma cells	2 (20%)	6 (33%)
Granuloma	6 (60%)	15 (83%)
Tuberculoid	0	1 (5.5%)
Sarcoid-like	2 (20%)	10 (56%)
GA-like	0	1 (5.5%)
Palisading	2 (20%)	3 (17%)
Suppurative	5 (50%)	5 (28%)
Other	0	0
Necrosis	4 (40%)	7 (39%)
Dermal necrosis	6 (60%)	9 (50%)
Abscesses	10 (100%)	9 (50%)
Positive staining (Ziehl-Neelsen, Kinyoun)	9 (90%)	2 (11%)

PD: papillary dermis; SRD: superficial reticular dermis; DRD: deep reticular dermis; ST: subcutaneous tissue; PS: perivascular superficial; DS: diffuse superficial; PD perivascular deep; DD: diffuse deep; PMN: polymorphonuclear neutrophils; GA: granuloma annulare.

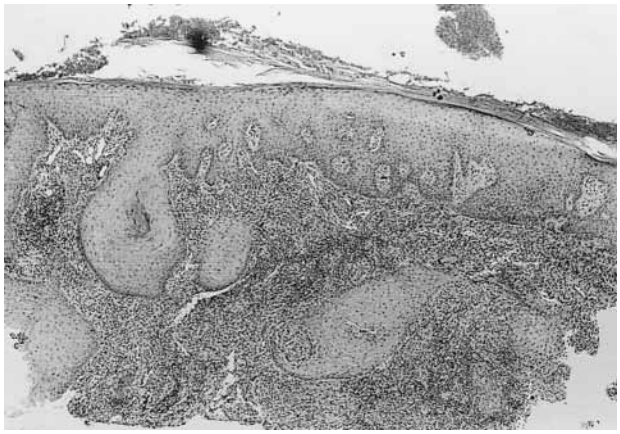

Fig. 1. Pseudoepitheliomatous hyperplasia and granulomatous inflammatory infiltrate in the dermis (*M. marinum*). (H-E×40).

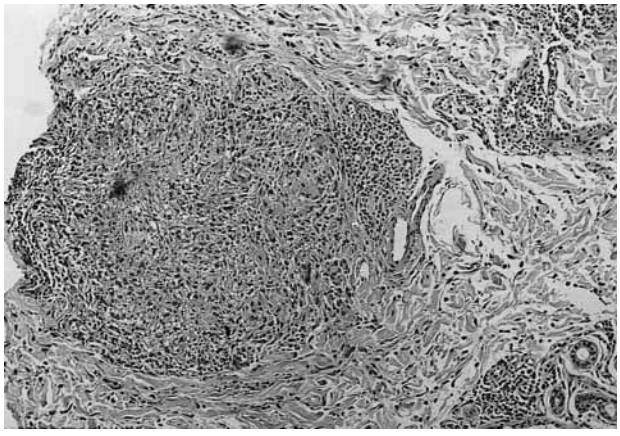

Fig. 2. Granulomatous sarcoid-like inflammatory infiltrate with central necrosis (*M. marinum*). (H-E×100).

Results

The results of histopathological features observed in biopsy specimens from immunosuppressed patients and normal hosts are detailed in Table 2.

Epidermal changes (acanthosis, pseudoepitheliomatous hyperplasia, exocytosis) were mainly observed in biopsies from immunocompetent patients (83%) and specially in *M. marinum* infections (fish-tank granulomas) (50%) (Fig. 1).

In normal hosts, the infiltrate tended to involve the deep reticular dermis and was more frequently noted in a superficial perivascular (56%) and/or in a diffuse deep dermal distribution (61%). In 83% of biopsy specimens obtained from this group of patients, marked granulomatous inflammatory reaction was present (sarcoid-like [10 biopsies] (Fig. 2), tuberculoid [1], palisading [3] (Fig. 3) and suppurative (abscessified) granulomas [5] (Fig. 4)). In one biopsy specimen (*M. chelonae*) from a normal host a necrotizing folliculitis was observed.

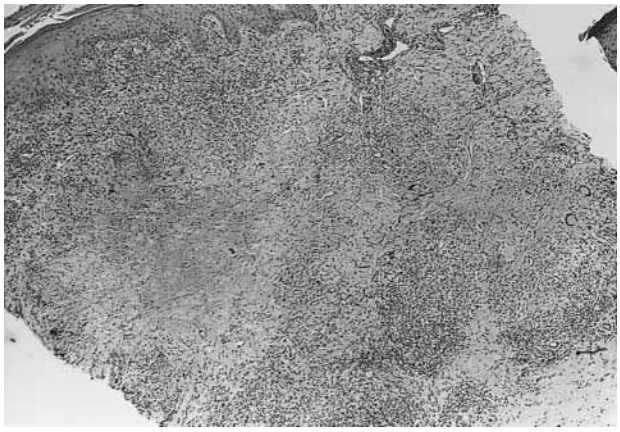

Fig. 3. Extensive dermal necrosis and palisading granulomatous inflammatory infiltrate in mid dermis (*M. chelonae*). (H-E×40).

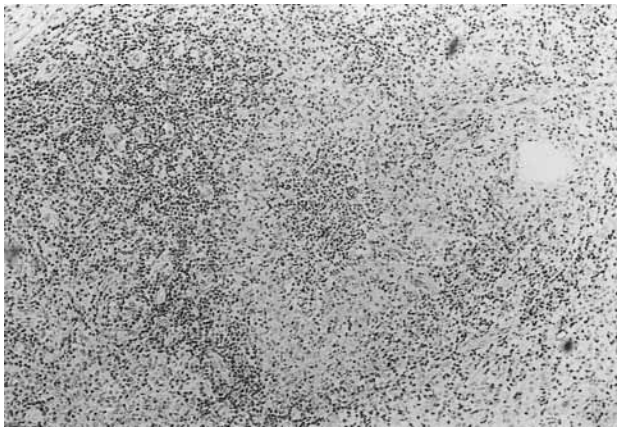

Fig. 4. Suppurative granuloma. Central abscess, histiocytic granulomatous response and peripheral lymphocytic infiltrate (*M. marinum*). (H-E×100).

In immunosuppressed patients the infiltrate tended to be deeper, involving the subcutaneous tissue (100%), with a more diffuse distribution and constant abscess formation (Fig. 5). Granulomatous inflammatory reaction was observed in 60% of patients (sarcoid-like [2], suppurative [5] and palisading [2]). A diffuse deep dermal or subcutaneous infiltrate of histiocytes with occasional foamy appearance was noted in 3 biopsy specimens from patients with AIDS, 2 with *M. kansasii* and 1 with *M. avium* complex infection (Fig. 6).

The presence of abscessified granulomas presenting a central neutrophilic abscess within a histiocytic granuloma, frequently surrounded by a peripheral lymphocytic infiltrate was the most characteristic histopathological pattern in skin biopsies from cutaneous NTM infections. Acute and chronic panniculitis was detected in 8 biopsy specimens. Abscess formation was detected in 50% of biopsies from normal hosts and in all biopsies from immunosuppressed patients. Acid-fast bacillus stain was positive in 9 biopsy specimens from 10 immunosuppressed patients (90%) and only in 2 biopsies (11%) from 18 normal hosts. In 4 IS patients abundant bacilli with clump formation was detected.

In normal hosts, granuloma formation was an almost constant feature and a direct relationship be-

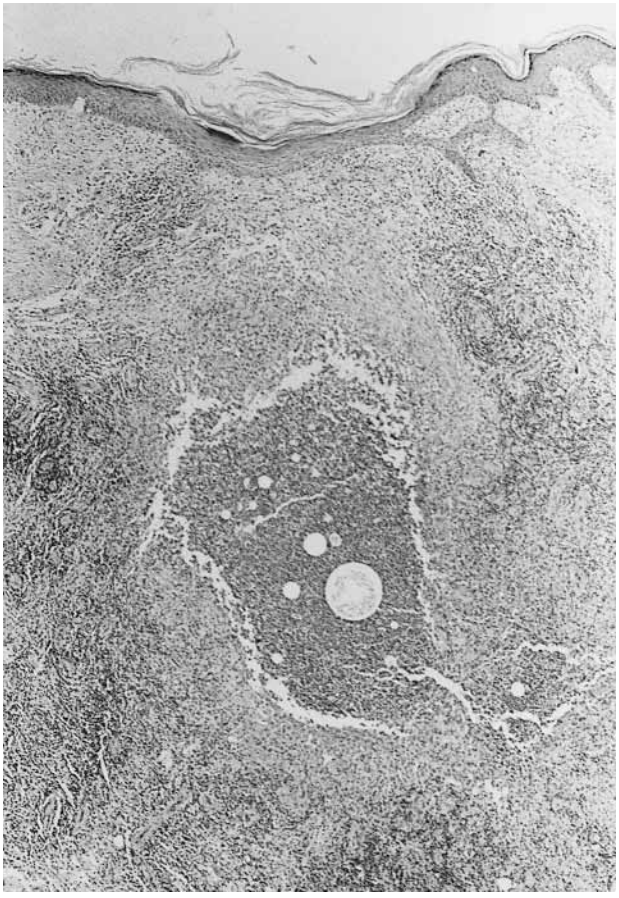

Fig. 5. Abscess formation in mid dermis (*M. chelonae*). (H-E×40).

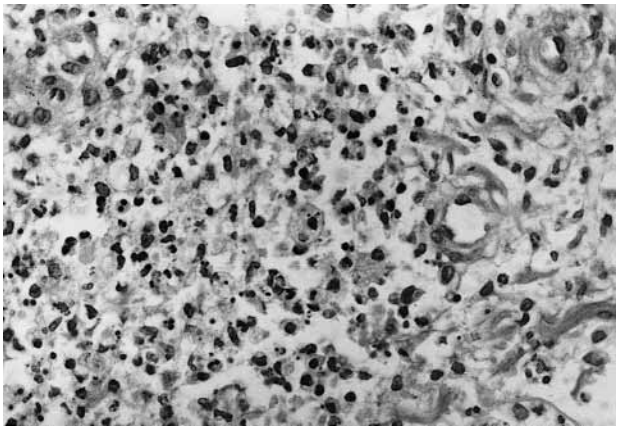

Fig. 6. Foamy diffuse histiocytic infiltrate in deep dermis observed in a patient with AIDS (*M. kansasii*). (H-E×400).

Table 3. Relationship between time of evolution and granuloma formation

Time (*)	Normal hosts (n=18) Granuloma (%)	Immunosuppressed (n=9) Granuloma (%)
<3 months	4/5 (80%)	2/6 (33%)
>3 months	11/13 (85%)	3/3 (100%)

(*) Duration of the cutaneous lesions.

tween the duration of the disease and granuloma formation was not demonstrated. Eighty per cent of biopsy specimens obtained from lesions of less than 3 months of duration exhibited an unequivocal granulomatous inflammatory infiltrate; likewise, this granulomatous response in older lesions (>3 months) was detected in 85% of cases. Conversely, in immunosuppressed patients, early lesions (<3 months of evolution) rarely exhibited granuloma formation (2/6: 33%) whereas in more evolved lesions (>3 months) a chronic granulomatous inflammatory infiltrate was a constant (100%) histopathological finding (Table 3). In one IS patient with *M. chelonae* infection data about time of evolution was not available.

Discussion

Cutaneous NTM infections present variable clinical and histopathological features. The histological changes range from an acute suppurative process to typical granulomatous inflammation[3] and are not species specific; therefore, identical findings can be observed in infections caused by different mycobacteria. The inflammatory response is usually localized in mid and deep dermis extending occasionally to the subcutaneous tissue.

In 1983, Santa Cruz et al.[4] distinguished 7 basic patterns of inflammation (abscesses, well-formed or tuberculoid granulomas, diffuse histiocytic infiltration, panniculitis, nonspecific chronic inflammation, naked or sarcoid granulomas and rheumatoid-like nodules). They pointed out that one or more patterns could be seen in the same biopsy specimen. Street et al.[5] stressed the frequency of lymphohistiocytic infiltrates with granuloma formation in most cases, but only 33% were tuberculoid. Recently, Rodriguez et al.[6] distinguished three main histopathological patterns: granulomatous nodular or diffuse inflammation with mixed granulomas, abscesses with mild granulomatous reaction and deep dermal or subcutaneous granulomatous inflammation with no neutrophilic component.

Granulomas in cutaneous NTM infections are usually poorly formed and some neutrophils may be admixed forming suppurative granulomas. This biphasic inflammatory response, consisting of polymorphonuclear abscesses mixed with granuloma formation and necrosis seems to be the most characteristic histopathological pattern in cutaneous NTM infections.[7] In our series, an additional pattern consisting of an acute necrotizing folliculitis was identified. In only rare instances, folliculitis has previously been reported as a specific cutaneous manifestation of NTM infection.[8,9]

The different histological patterns noted in biopsies from cutaneous NTM infections may be related to the immunologic status of the host. However, as far as we know, no previous comparative studies of cutaneous NTM infections between immunosuppressed patients and normal hosts have been reported.

Several authors have pointed out that the histopathological features of cutaneous NTM infections in immunosuppressed patients tend to be atypical and that granuloma formation may be absent.[10] In our series, some histopathological patterns seem to be more prevalent in immunosuppressed patients. The inflammatory infiltrate tends to involve diffusely deep dermis and subcutaneous tissue. Neutrophilic infiltrates and abscess formation are also constant. Granuloma formation is frequently noted (60%), manifested most frequently as suppurative granulomas (50%), although sarcoid-like (20%) or palisading granulomas (20%) can also be present. The observation of a diffuse foamy histiocytic infiltrate involving the deep dermis and/or subcutaneous tissue, resembling that of lepromatous leprosy, seems to be a pattern observed exclusively in patients with profound immunodeficiency.[11] In normal hosts, the inflammatory infiltrate tends to involve deep dermis and less frequently subcutis (39%). Granuloma formation is an almost constant feature (83%); poorly defined sarcoid-like granulomas were observed in 56% of biopsies, but suppurative granulomas (28%) or palisading granulomas (17%) were also found. Only 1 patient presented well-formed, tuberculoid granulomata.

No histopathological differences were noted between infections caused by different species of NTM. Only epidermal changes (acanthosis, pseudoepitheliomatous hyperplasia) seem to be more frequent in *M. marinum* infections.

The time of evolution may also be an important factor that may influence the histopathological changes observed in cutaneous NTM infections. Controversial results regarding histopathological differences between early and advanced *M. marinum* infections have been reported.[12–16] In our study, granuloma formation was an early histopathological change in cutaneous biopsies from normal hosts. However, the dynamic nature of the disease was more clearly demonstrated in immunosuppressed patients. Significant differences were observed between early lesions, that showed a predominantly neutrophilic or histiocytic response and long-standing lesions, which presented a constant and prominent granulomatous inflammatory reaction.

The demonstration of acid-fast bacilli with specific staining depends on the number of bacilli in the sample studied, which is related mainly with the immunologic status of the host, and that is usually smaller in normal hosts.[17] In a series of 71 *M. abscessus* infections in normal hosts, acid-fast bacilli staining was positive in only 27%.[6] In our study, acid-fast bacilli were demonstrated only in 2 out of 16 biopsies (11%) in NH patients, whereas Ziehl-Neelsen or Kinyoun stains were positive in 9 out of 10 biopsies (90%) from IS patients. Occasionally, in biopsies from severely immunosuppressed patients bacillary clump formation was noted (4 biopsy specimens), although grain formation[18] was not observed.

In conclusion, the observation of a biphasic pattern of polymorphonuclear microabscesses in the dermis and subcutaneous tissue and epithelioid granuloma formation, with or without necrosis, should always raise the possibility of an infection by NTM. Several histopathological features seem more frequent in immunosuppressed patients. The duration of the infection and the immunologic status of the host are the two main parameters that lead to the variability of the clinical and histopathological findings observed in cutaneous NTM infections.

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Clinical patterns of cutaneous nontuberculous mycobacterial infections

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Summary

Background Cutaneous nontuberculous mycobacterial infections result from external inoculation, spread of a deeper infection, or haematogenous spread of a disseminated infection. There are two species-specific infections (fish-tank or swimming-pool granuloma, due to *Mycobacterium marinum*, and Buruli ulcer, caused by *M. ulcerans*). Most infections, however, produce a nonspecific clinical picture.

Objectives To define clinical patterns of cutaneous disease in nontuberculous mycobacterial infections.

Methods Fifty-one patients with cutaneous nontuberculous mycobacterial infections were reviewed. Clinical and histopathological features of normal hosts and immunosuppressed patients were compared. Two subgroups of immunosuppressed patients were distinguished: patients with cutaneous infection and patients with a disseminated infection and cutaneous involvement.

Results In immunosuppressed patients the number of lesions was significantly higher. Abscesses and ulceration were also more frequently observed. Different species were found in normal hosts and immunosuppressed patients. Several clinical patterns of cutaneous infection were defined: lymphocutaneous or sporotrichoid lesions; nonlymphocutaneous lesions at the site of trauma; folliculitis and furunculosis involving the lower extremities; disseminated lesions on the extremities in immunosuppressed patients. Two patterns were observed in patients with a disseminated infection: localized cutaneous lesions and disseminated cutaneous and mucosal lesions.

Conclusions Cutaneous manifestations of nontuberculous mycobacterial infections may be classified according to criteria such as cutaneous lesions and immune status.

Isolates of nontuberculous mycobacteria (NTM) in culture should be evaluated on the basis of clinical, pathological and microbiological features. Some species are frequently found as pathogens, whereas other species are usually contaminants.[1] Specific diagnostic criteria for pathogenicity of NTM have been updated by the American Thoracic Society.[2]

Four clinical syndromes account for most infections by NTM: pulmonary disease, lymphadenitis, disseminated disease and skin or soft tissue infections.[2] The latter include two species-specific disorders caused by *Mycobacterium marinum* (fish-tank or swimming-pool granuloma) and *M. ulcerans* (Buruli ulcer), and several nonspecific clinical pictures caused mainly by rapidly growing mycobacteria (*M. fortuitum*, *M. chelonae* and *M. abscessus*). Nevertheless, there is a great variability in geographical distribution of NTM and their pathogenic strains, thus explaining the appearance of clusters of infections by NTM in some areas.

The incidence of infections by NTM has increased in the last 20 years in relation to the decrease in prevalence of tuberculosis, the AIDS epidemic and the use of immunosuppressive drugs. In large studies, NTM account for 15% of total isolates of acid-fast bacilli (AFB) and the remaining 85% correspond to *M. tuberculosis*.[3] In Spain, the incidence of infections by NTM represents 0·64–2·29% of all mycobacterial infections.[4,5]

Materials and methods

A retrospective study of cutaneous NTM infections diagnosed in the Departments of Dermatology of the Hospital Vall d'Hebron (Barcelona), Hospital Santa Creu i Sant Pau (Barcelona), Hospital del Mar (Barcelona), Hospital Josep Trueta (Girona) and Hospital Palamós (Girona) during the period 1983–2003 was performed.

Inclusion criteria were: clinical charts of patients diagnosed as having 'cutaneous NTM infection' or 'visceral NTM infection with cutaneous involvement', with NTM cultured from skin biopsy specimens, from sinus drainage exudate or from needle aspiration of abscesses. NTM were identified in the Departments of Microbiology using standard methods.[6] All cases fulfilled the criteria of pathogenicity.[2]

Data analysed were: elementary lesions (nodules, papules, pustules, abscesses, ulcers, plaques, cellulitis and draining sinuses), number (solitary, two to five and more than five) and localization (upper limbs, lower limbs, trunk, head and neck). The extent of cutaneous involvement was defined as: (i) localized, when one body area was involved, and (ii) disseminated cutaneous, if more than one body area was affected. In localized lesions, two patterns of distribution were also defined: lymphocutaneous (sporotrichoid) and nonlymphocutaneous. Localized deep involvement was recorded when tenosynovitis, arthritis and/or osteomyelitis were directly related to the cutaneous lesions; the diagnosis of disseminated infection with NTM was established when visceral involvement, infection at the bloodstream level and deep (joint and bone) infection not related to the cutaneous lesions were present. Associated diseases, sources of infection (trauma, medical procedures and dissemination from an internal focus) and time of evolution until diagnosis were recorded.

Two groups were defined regarding their immune status: group I, patients without immunological deficiencies, i.e. normal hosts (NHs); and group II, patients with a demonstrable immunosuppression, i.e. immunosuppressed patients (ISPs). Criteria for immune impairment were: treatment with corticosteroids (prednisone 0·5–1 mg kg^{-1} daily) or other immunosuppressive drugs for longer than 6 months, human immunodeficiency virus infection with CD4 cell count < 400 cells mm^{-3}, and second- or third-degree burns with involvement of $> 40\%$ of total body surface.

Group II was subdivided into subgroup IIA, including ISPs with a cutaneous infection with NTM, without internal involvement; and subgroup IIB with ISPs presenting cutaneous manifestations from a disseminated infection.

Available cutaneous histopathological specimens [haematoxylin and eosin stain and AFB stains (Ziehl–Neelsen and Kinyoun)] were reviewed. Several histopathological patterns were defined: tuberculoid, suppurative, palisading and sarcoid granulomas, abscesses, histiocytic cell infiltrate, panniculitis, nonspecific inflammation and folliculitis. The predominant pattern and the presence of one or more pattern(s) were recorded.

Statistical analysis

Statistical analyses were performed by χ^2 or alternatively by Fisher's exact test.

Results

Epidemiological data

Culture-confirmed infection with NTM was reported in 51 patients from 1983 to 2003 in five hospitals from Catalonia (Spain) with a reference population of 1·5 million inhabitants. The incidence of infection with NTM was about 0·17 cases per 100 000 inhabitants per year.

Fifty-one patients were studied, 31 females and 20 males, age range 2–75 years (mean 38). Twenty-nine patients (14 females and 15 males) belonged to group I, and 22 patients (five males and 17 females) to group II.

Clinical data

The responsible NTM species are illustrated in Table 1. The diagnostic delay (defined as the time from the first consultation because of cutaneous lesions and the isolation of NTM) ranged from 10 days to 18 years in group I and from 7 days to 9 months (mean 3·2 months) in group II. More than one sample (up to three) was needed in 10 cases (20%) to grow NTM in culture (six cases from group I and four from group II).

The clinical features and the source of infection are illustrated in Table 2: papules and nodules were the most common lesions. Abscesses were more frequently observed in ISPs than in NHs ($P = 0·029$). Ulceration was observed in only three ISPs. More than one type of lesion was observed in seven patients in group I (24%) and in nine in group II (41%). Although not considered an elementary lesion, inflammatory

Table 1 Species of nontuberculous mycobacteria in cutaneous infections

		ISPs/group II (n = 22)	
	NHs/group I (n = 29)	Subgroup IIA (n = 15)	Subgroup IIB (n = 17)
Mycobacterium marinum	21 (41%)	1 (2%)	0
Mycobacterium chelonae	3 (6%)	6 (12%)	0
Mycobacterium abscessus	1 (2%)	6 (12%)	0
Mycobacterium fortuitum	2 (4%)	1 (2%)	0
Mycobacterium kansasii	0	0	4 (8%)
Mycobacterium avium complex	0	0	2 (4%)
Mycobacterium simiae	0	0	1 (2%)
Mycobacterium gordonae	1 (2%)	0	0
Mycobacterium terrae	1 (2%)	0	0
Mycobacterium xenopi	0	1 (2%)	0

NHs, Normal hosts; ISPs, immunosuppressed patients; subgroup IIA, ISPs without extracutaneous involvement; subgroup IIB, ISPs with visceral involvement.

Table 2 Clinical features

		Group II (n = 22)	
	Group I (n = 29)	Subgroup IIA (n = 15)	Subgroup IIB (n = 7)
Type of lesion			
Nodules	20	11	4
Papules	3	4	0
Pustules	2	0	0
Abscesses	2	5	2
Ulcers	0	2	1
Plaques	5	4	0
Cellulitis	3	0	1
Draining sinuses	1	0	0
Number of lesions			
1–5 lesions	24	5	5
> 5 lesions	5	10	2
Pattern of distribution			
Localized	26	5	5
Lymphocutaneous	13	1	0
Nonlymphocutaneous	11	3	5
Deep infection	2	1	0
Disseminated cutaneous	3	10	2
Source of infection			
Aquagenic trauma	22	1	0
Nonaquagenic trauma	5	2	0
Surgical procedure	1	2	0
Internal focus	0	0	7
Unknown	1	10	0

plaques and nodules with punched-out suppurative ulcers inside (Fig. 1) were found in one NH and in eight ISPs, all with infections caused by rapidly growing mycobacteria.

The number of lesions was significantly lower in patients from group I ($P < 0{\cdot}005$). In group II, 10 of 15 patients from subgroup IIA developed multiple lesions, whereas five of seven patients from subgroup IIB had solitary lesions.

Localized lesions were found in 36 cases, 26 of them (72%) corresponding to NHs and 10 (28%) to ISPs. A lymphocutaneous (sporotrichoid) spread of lesions was observed in 13 NHs and in one ISP, all of them caused by *M. marinum* (Table 2). Nonlymphocutaneous lesions were observed in 11 patients from group I (eight *M. marinum*, two *M. chelonae* and one *M. fortuitum*), in three patients from subgroup IIA (one *M. chelonae*, one *M. abscessus* and one *M. xenopi*) and in five patients from subgroup IIB [two *M. kansasii* (Fig. 2), two *M. avium* complex and one *M. simiae*]. Deep infection was seen in three patients with nonlymphocutaneous lesions: a draining sinus from an underlying *M. fortuitum* osteomyelitis; and two cases of cutaneous lesions in fingers with an underlying osteomyelitis due to *M. terrae* (Fig. 3) and *M. chelonae*, respectively.

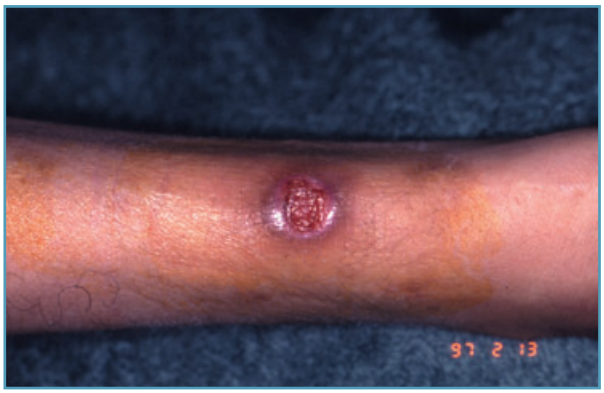

Fig 2. Ulcerated nodule in a severely immunosuppressed AIDS patient with a mycobacterial lung infection. *Mycobacterium kansasii* infection.

Disseminated cutaneous lesions were present in 15 patients. Three of them were NHs with *M. chelonae*, *M. abscessus* and *M. gordonae* infection, respectively. Twelve patients were ISPs, 10 belonging to subgroup IIA [*M. chelonae* (four cases), *M. abscessus* (five cases) and *M. fortuitum* (one case)] and two cases from subgroup IIB, both due to *M. kansasii* (Fig. 4).

The source of infection could be recorded in 28 of 29 patients from group I and in five of 22 patients from group II (all of them from subgroup IIA). Water-related trauma was evoked by 23 patients (21 *M. marinum* and one *M. chelonae* from

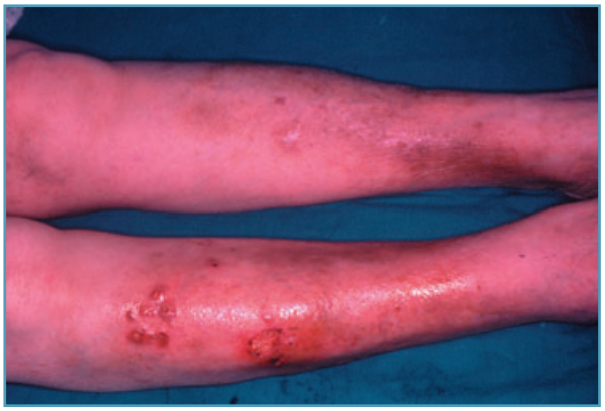

Fig 1. Nodules, ulcers and plaque with punched-out ulcers on the lower legs in a patient with asthma under corticosteroid treament. *Mycobacterium abscessus* infection.

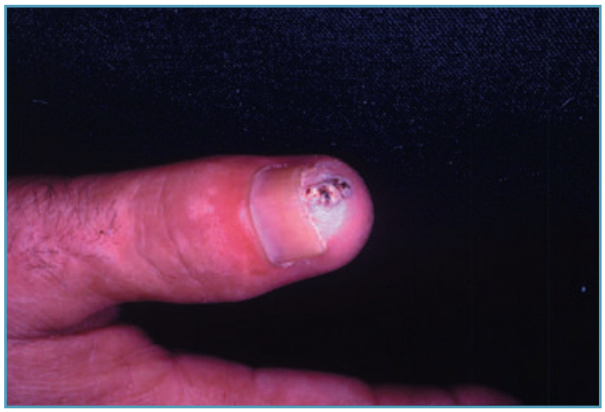

Fig 3. Hyperkeratotic plaque and osteomyelitis after puncture with a metallic staple. *Mycobacterium terrae* infection.

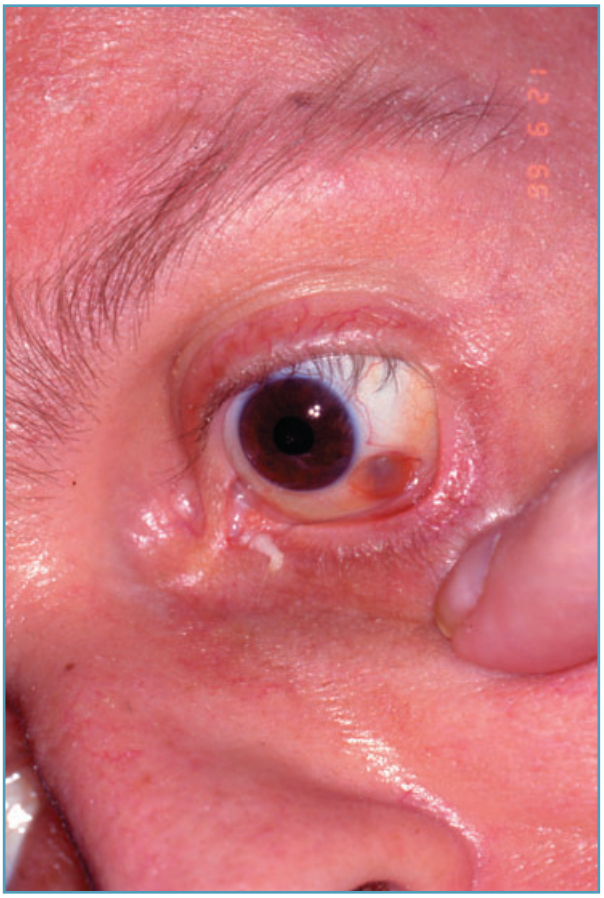

Fig 4. Papule in the conjunctiva in an AIDS patient with disseminated *Mycobacterium kansasii* infection.

group I and one *M. marinum* from group II): 19 cases were related to aquaria, three cases were related to swimming pools (including one *M. chelonae* infection), and the remaining patient suffered a tubing puncture. Nonaquagenic trauma was found in seven cases. Five patients belonged to group I: two *M. chelonae* infections after a wound and after depilation, respectively; one *M. abscessus* infection after puncture with a Mexican cactus; one *M. fortuitum* infection after depilation and one *M. terrae* infection after a puncture with a metallic staple; and two patients from group II, with one *M. chelonae* infection after a cat scratch and one *M. fortuitum* infection in a farmer after a minor trauma. A surgical procedure preceded the infection in one NH (*M. fortuitum*, traumatic amputation of a leg) and in two ISPs (*M. chelonae* infection after abdominal surgery and *M. xenopi* infection after severe and extensive burns treated with skin grafting).

Associated diseases in group II and their relationship with the involved species and the distribution of the lesions are illustrated in Table 3. Of 15 patients of subgroup IIA, 14 were taking corticosteroids and/or other immunosuppressive agents and another had second- and third-degree burns involving 90% of the body surface; subgroup IIB included seven patients with a disseminated infection. Six of them had AIDS with CD4 cell count < 100 cells mm^{-3} and one had sarcoidosis under immunosuppressive therapy. Visceral involvement (pulmonary in six patients and central nervous system infection in one) preceded the cutaneous lesions in all cases.

The clinical pictures observed in our patients are summarized in Table 4. Water-related lesions with or without a lymphocutaneous spread were mainly caused by *M. marinum* and only one body area was involved; nonaquagenic lesions affecting one body area were frequently due to rapidly growing mycobacteria in group I and subgroup IIA, but other species were responsible in subgroup IIB; post-traumatic lesions in several body areas were only found in NHs, whereas ISPs did not evoke a previous trauma. In addition, the responsible species differed between subgroup IIA (rapidly growing mycobacteria) and subgroup IIB (*M. kansasii*).

Histological findings

Forty biopsies from 38 patients were available for evaluation. A mixed granulomatous and suppurative inflammation was found in 20 patients (39%). Granulomas were seen in 86% of

Table 3 Associated diseases, causative species and distribution of lesions in immunosuppressed patients (group II)

Species	Associated disease	Localized	Disseminated cutaneous	Visceral infection
Mycobacterium chelonae	Renal transplant (4)		4	No
	Rheumatoid arthritis (1)		1	No
	Crohn's disease (1)	1		No
Mycobacterium abscessus	Asthma (2)	1	1	No
	Dermatomyositis (2)		2	No
	Rheumatoid arthritis (1)		1	No
	Lupus erythematosus (1)		1	No
Mycobacterium fortuitum	Polyarteritis nodosa (1)		1	No
Mycobacterium marinum	Lupus erythematosus (1)	1		No
Mycobacterium xenopi	Burns (1)	1		No
Mycobacterium avium complex	AIDS (2)	2		Yes (2)
Mycobacterium kansasii	AIDS (3)	1	2	Yes (3)
	Sarcoidosis (1)	1		Yes
Mycobacterium simiae	AIDS (1)	1		Yes

Table 4 Distribution, source of infection and responsible species of *Mycobacterium* in relation to the immunological status

			Species and immunological status		
Distribution		Source	Group I	Subgroup IIA	Subgroup IIB
One body area	Lymphocutaneous	Aquagenic	13 *M. marinum*	1 *M. marinum*	–
		Nonaquagenic	–	–	–
	Nonlymphocutaneous	Aquagenic	8 *M. marinum* 1 *M. chelonae*	–	–
		Nonaquagenic	2 *M. fortuitum* 1 *M. chelonae* 1 *M. terrae*	2 *M. chelonae* 1 *M. abscessus* 1 *M. xenopi*	2 *M. kansasii* 2 *M. avium* 1 *M. simiae*
Several body areas		Post-traumatic	1 *M. abscessus* 1 *M. chelonae*	–	–
		Not post-traumatic	1 *M. gordonae*	4 *M. chelonae* 5 *M. abscessus* 1 *M. fortuitum*	2 *M. kansasii*

NHs and in 55% of ISPs. Abscesses were observed in 45% of NHs and in 83% of ISPs. Panniculitis was seen in 14% of NHs and in 72% of ISPs. A diffuse histiocytic infiltrate was detected in four patients from subgroup IIB. An acute folliculitis was seen in a patient with *M. chelonae* infection. Epidermal changes (acanthosis, hyperkeratosis and pseudoepitheliomatous hyperplasia) were seen in 19 of 22 biopsies from NHs, all with *M. marinum* infection. Positive AFB staining was found in 21% of NHs and in 72% of ISPs.

Discussion

Clinical cutaneous patterns of infections by NTM have rarely been reported. In a review of *M. chelonae*-related soft tissue infections, three patterns were proposed: disseminated cutaneous lesions in ISPs; cellulitis or abscesses in NHs related to trauma and incidentally associated with an underlying bone infection; and long-term catheter-related infections.[7]

Mycobacterium ulcerans infection (Buruli ulcer) is probably the NTM infection with more specific epidemiological, clinical and histopathological features. In our series, however, no cases were observed. Internal involvement has exceptionally been described in AIDS patients,[8] in sickle-cell anaemia[9] and in NHs.[10] It represents the third worldwide cause of mycobacterial infection after *M. tuberculosis* and *M. leprae*.[1]

According to our results, several patterns of skin infections by NTM may be defined. Table 5 shows a proposed classification of these patterns, specifying the most representative species. Cutaneous lesions can be observed either as pure cutaneous forms or along with a disseminated infection. In both groups, lesions may be localized or disseminated.

Table 5 Proposed clinical patterns of non-tuberculous mycobacterial infections

General status and distribution	Proposed clinical patterns and associated species of *Mycobacterium*
No internal involvement	
Localized	I *M. ulcerans* infection (Buruli ulcer)
	IIa Sporotrichoid lesions, aquagenic source (*M. marinum*, RGM, *M. kansasii*)
	IIb Sporotrichoid lesions, nonaquagenic source (RGM, *M. kansasii*, *M. avium* complex)
	IIIa Nonlymphocutaneous, aquagenic source (*M. marinum*, RGM, *M. kansasii*)
	IIIb Nonlymphocutaneous, nonaquagenic, postsurgical, catheter-related (RGM)
Disseminated cutaneous	IV Folliculitis and/or furunculosis after depilation or water-related (RGM)
	V Lesions on lower and/or upper limbs and immunosuppressive drugs (RGM)
Internal involvement	
Localized	VI Solitary lesions in immunosuppressed patients (*M. kansasii*, *M. avium* complex, RGM, *M. simiae*)
Disseminated cutaneous	VII Cutaneous and mucous membrane lesions and disseminated infection in patients with congenital (type-1 cytokine defect) or acquired immunosuppression (*M. kansasii*, *M. avium* complex, *M. haemophilum*, RGM, *M. simiae*, *M. gordonae*, *M. marinum*, *M. scrofulaceum*, *M. szulgai*, *M. malmoense*, *M. terrae*, *M. xenopi*, *M. smegmatis* and *M. flavescens*)

RGM, Rapidly growing mycobacteria

In patients presenting localized infections, two patterns can be defined: a lymphocutaneous or sporotrichoid pattern, in which nodules appearing at sites of previous trauma develop a lymphocutaneous spread, mainly in the upper limbs; and a nonlymphocutaneous infection, characterized by nodules and/or abscesses at the sites of trauma. Both patterns may be related to water exposure. As most pathogenic species of NTM may be isolated from tap water and from hospital water supplies, it is difficult to assure an aquagenic source in isolated cases, especially if polymerase chain reaction-based techniques are not available.[11]

Mycobacterium marinum is the most frequent cause of aquagenic lymphocutaneous and nonlymphocutaneous localized infections. *Mycobacterium marinum* infections are similar in both NHs and ISPs.[12] The latter might have a greater risk for developing deep infections, sporotrichoid lesions, disseminated cutaneous lesions[13] and internal involvement.[14] Histologically, a mixed suppurative and granulomatous inflammatory dermal infiltrate and epidermal changes are usually observed.[15]

Nevertheless, when localized infections are water related but there is no relationship with tropical fishes or swimming pools, other species of NTM should be suspected (*M. chelonae*, *M. abscessus*, *M. fortuitum*, *M. kansasii*, *M. scrofulaceum*, *M. gordonae*, *M. avium* complex and *M. flavescens*). In addition, *M. tuberculosis* and other microorganisms (*Sporothrix schenckii* and other fungi, *Nocardia* species, *Francisella tularensis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Leishmania* species, herpes simplex and cowpox virus) should also be considered as causes of lymphocutaneous syndromes.[16]

Nonlymphocutaneous localized infections that are not water related are mostly caused by rapidly growing mycobacteria. A careful history usually reveals accidental injuries, medical procedures (surgery, injections, catheters) and medical and paramedical cosmetic procedures.[17,18] In addition to isolated cases, outbreaks due to medical and paramedical devices contaminated by hospital or municipal water supplies have also been reported.[19]

A secondary deeper infection such as tenosynovitis or osteomyelitis is more frequent when there is a previous puncture wound, when intralesional corticosteroids have been erroneously used to treat the cutaneous lesions and in ISPs.[20] Moreover, abscesses, ulcers or draining sinuses may also appear from an underlying bone infection. Thus, radiographic study to rule out a bone infection is recommended in these cases and when response to treatment is poor.

Disseminated cutaneous lesions may present without internal involvement. In these patients, rapidly growing mycobacteria are mostly found (Table 5). Two clinical pictures can be distinguished in NHs and in ISPs, respectively. NHs often present with folliculitis and/or furunculosis related to depilation (wax, shaving),[21] pedicure whirlpool baths[22] or immersion in stagnant water.[23] Isolated cases and community outbreaks have been reported.[24] Typically, bacterial cultures are negative and there is no response to penicillins. Our series includes two such cases. Histologically, a suppurative folliculitis is the rule, but granuloma formation has also been described.[15,24] On the other hand, ISPs receiving long-term corticosteroids develop nodules, abscesses and ulcers, and typically, inflammatory plaques and nodules with punched-out suppurative ulcers are found on the lower limbs and buttocks. In most cases the lesions are not related to a previous trauma. It is not clear whether they appear through multiple inoculation sites, self-inoculation or from a haematogenous spread.[25] All cases in our series were caused by rapidly growing mycobacteria and one patient had an underlying bone infection. Histopathologically, sarcoidal or suppurative granulomas are usually found. Ziehl–Neelsen stain reveals numerous AFB.[15] Prognosis was good in our series, as previously reported.[7] Nevertheless, these patients are at risk of deep infections and of internal dissemination.

Disseminated infections by NTM occur in severely immunosuppressed patients (lymphoma and leukaemia, cell-mediated immunodeficiency and AIDS). Cutaneous lesions may be localized or disseminated. Localized lesions have rarely been reported.[26] In our series five of seven patients with visceral involvement had localized lesions. Unlike NHs, ISPs develop lesions in nonexposed sites, with no previous traumatic event. Disseminated infections by NTM usually present with disseminated cutaneous lesions.[27–29] In ISPs with disseminated cutaneous lesions and no internal involvement, only the extremities usually show cutaneous lesions, whereas in a disseminated infection the trunk and the face are also involved. In addition to the skin, the mucous membranes may also be affected (Table 5). In both patterns, when cutaneous lesions appear, patients usually have a known internal infection, but the NTM responsible are frequently isolated from the cutaneous samples. Localized or disseminated cutaneous lesions may also be the first manifestation of a disseminated infection. Thus, a careful evaluation is mandatory in ISPs.

Rapidly growing mycobacteria are often the species responsible for disseminated infections,[7] although other species such as *M. kansasii*,[28] *M. avium* complex[29] and *M. haemophilum*[30] may also be found. *Mycobacterium kansasii* and *M. avium* complex are mainly pulmonary pathogens. *Mycobacterium avium* complex also causes digestive tract infections. Severely immunosuppressed patients have a high risk of haematogenous dissemination to the skin, joints, bones, lymph nodes, liver, spleen and central nervous system.[7,28] A disseminated infection from a primary cutaneous focus has also been reported.[31] Cutaneous lesions are present in more than 75% of *M. haemophilum* infections. However, these infections are probably underdiagnosed because of its special laboratory requirements.[32] Infections due to *M. avium* complex, *M. kansasii* and *M. haemophilum* seem to be more frequent in AIDS patients, whereas rapidly growing mycobacteria seem to be more prevalent in patients treated with chemotherapy and after haematopoietic stem cell or solid organ transplantation.[33] Cutaneous biopsies in ISPs with a disseminated infection typically show abscesses, foamy histiocytes and abundant AFB. Granulomas are usually absent.[15]

Regardless of the species responsible, disseminated infections with cutaneous involvement usually have a poor prognosis, despite an adequate therapy.[7,33] In our series, three AIDS

patients died from infection with NTM. Cases with an intermediate prognosis have also been reported.[34]

A disseminated infection indistinguishable from that seen in ISPs has been described in apparent NHs.[35–37] These patients should undergo a study of the monocyte response and of the type 1 cytokine profile, as increasing reports of disseminated infections by NTM in children with mutations in type 1 cytokine [interleukin (IL)-12] and type 1 cytokine receptor (interferon-γ receptor and IL-12 receptor) genes have been published.[38] Homozygous mutations produce deficiencies of the activation of macrophages. Complete deficiencies run with early and severe infections, whereas partial deficiencies have a better prognosis.[39] Heterozygous patients presenting infections limited to the skin, bone and lymph nodes have also been reported.[40] All cases of type 1 cytokine defect with skin or soft tissue involvement presented disseminated cutaneous lesions.

Physicians should be aware of the different clinical and histopathological features of cutaneous infections with NTM, in order to improve their diagnostic skills.

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American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Diagnosis and Treatment of Disease Caused by Nontuberculous Mycobacteria

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE BOARD OF DIRECTORS, MARCH 1997

SUMMARY

Diagnostic Criteria of Nontuberculous Mycobacterial Lung Disease in HIV-Seropositive and -Seronegative Hosts

The following criteria apply to symptomatic patients with infiltrate, nodular or cavitary disease, or a high resolution computed tomography scan that shows multifocal bronchiectasis and/or multiple small nodules.

A. If three sputum/bronchial wash results are available from the previous 12 mo:
   1. three positive cultures with negative AFB smear results or
   2. two positive cultures and one positive AFB smear

B. If only one bronchial wash is available:
   1. positive culture with a 2+, 3+, or 4+ AFB smear or 2+, 3+, or 4+ growth on solid media

C. If sputum/bronchial wash evaluations are nondiagnostic or another disease cannot be excluded:
   1. transbronchial or lung biopsy yielding a NTM or
   2. biopsy showing mycobacterial histopathologic features (granulomatous inflammation and/or AFB) and one or more sputums or bronchial washings are positive for an NTM even in low numbers

Comments:

These criteria fit best with *M. avium* complex, *M. abscessus*, and *M. kansasii*. Too little is known of other NTM to be certain how applicable these criteria will be.

At least three respiratory samples should be evaluated from each patient. Other reasonable causes for the disease should be excluded. Expert consultation should be sought when diagnostic difficulties are encountered.

KEY LABORATORY FEATURES OF THE NONTUBERCULOUS MYCOBACTERIA

1. *Staining and culture.* Current methods of specimen staining and culture used for *M. tuberculosis* are acceptable for most NTM species. The preferred methodology includes fluorochrome staining and culture in a liquid medium as well as on Middlebrook 7H10 or 7H11 agar. Species for which special growth conditions are needed include those responsible for cutaneous disease, which need lower incubation temperatures, and the relatively fastidious species *M. haemophilum, M. genavense*, and *M. conspicuum*.
2. *Species identification.* Methods of rapid species identification including commercial DNA probes (*M. avium* complex, *M. kansasii, M. gordonae*) and high-pressure liquid chromatography are preferred over the slower traditional biochemical methods.
3. *Susceptibility testing of* M. avium *complex.* Susceptibility testing with rifabutin and the antituberculosis drugs is not recommended. Routine testing against clarithromycin should not be performed, but that test should be performed on isolates from patients who have failed prior macrolide therapy or prophylaxis. Minimal inhibitory concentration (MIC) of > 32 μg/ml is the recommended resistance breakpoint.
4. *Susceptibility testing of* M. kansasii. Routine susceptibility testing of *M. kansasii* should include only rifampin, because currently used resistance breakpoints for isoniazid and streptomycin often give misleading results and methods for the other drugs have not been established.
5. *Susceptibility testing of the rapid growers.* Susceptibility testing of clinically significant rapidly growing mycobacteria (*M. fortuitum, M. abscessus, M. chelonae*) should not be performed with the antituberculosis agents. They should be tested against antibacterial drugs including amikacin, doxycycline, imipenem, the fluorinated quinolones, a sulfonamide, cefoxitin, and clarithromycin.

PROPHYLAXIS AND TREATMENT OF NONTUBERCULOUS MYCOBACTERIA DISEASE

1. *Treatment of* M. kansasii *pulmonary disease.* A regimen of daily isoniazid (300 mg), rifampin (600 mg), and ethambutol (25 mg/kg for 2 mo, then 15 mg/kg) for 18 mo with a minimum of 12 mo culture negativity is recommended for pulmonary disease in adults caused by *M. kansasii*. Clarithromycin or rifabutin will need to be substituted for rifampin in HIV-positive patients who take protease inhibitors.
2. *Treatment of* M. avium *complex pulmonary disease.* A regimen of daily clarithromycin (500 mg twice a day) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (300 mg), and ethambutol (25 mg/kg for 2 mo, then 15 mg/kg) is recommended for therapy of adults not infected with the HIV virus. Streptomycin two to three times per week should be considered for the first 8 wk as tolerated. Patients should be treated until culture-negative on therapy for 1 yr.
3. *Treatment of disseminated* M. avium *complex disease.* Therapy in adults should include daily clarithromycin (500 mg twice a day) or azithromycin (250 to 500 mg), plus ethambutol 15 mg/kg per day. Consideration should be given to the addition of a third drug (preferably rifabutin at a dose of 300 mg/d). Therapy should be continued for life until more data becomes available.

4. *Prophylaxis of disseminated* M. avium *complex disease.* Prophylaxis should be given to adults with AIDS with CD4 counts < 50 cells, especially with a history of a prior opportunistic infection. Rifabutin 300 mg/d, clarithromycin 500 mg twice daily, azithromycin 1,200 mg once weekly, and azithromycin 1,200 mg once weekly plus rifabutin 300 mg daily are all proven effective regimens.
5. *Treatment of nontuberculous mycobacteria cervical lymphadenitis.* Nontuberculous mycobacteria cervical lymphadenitis is still treated primarily by surgical excision alone, with a 95% cure rate. A clarithromycin-containing regimen should be considered for patients with extensive disease or a poor response to surgery.
6. *Treatment of nonpulmonary rapidly growing mycobacteria.* Therapy of nonpulmonary disease caused by *M. fortuitum, M. abscessus,* and *M. chelonae* should include drugs such as amikacin and clarithromycin, based on *in vitro* susceptibility tests.

INTRODUCTION

The continued growth in the number and prevalence of mycobacteria species other than the *Mycobacterium tuberculosis* complex, and recent advances in diagnostic methods and drug therapies for disease caused by these agents, has prompted us to put forth this second, updated diagnostic and therapeutic standard that deals exclusively with the nontuberculous mycobacteria. As in the first statement (1), we refer to these mycobacterial species collectively as the nontuberculous mycobacteria (NTM). The principles of therapy and diagnosis of disease caused by *M. tuberculosis* have been dealt with separately and appear in two ATS statements published most recently in 1990 and 1994 (2, 3). Like the previous NTM statement published in 1990 (1), this statement is designed as a basic guide for professionals involved in the diagnosis and management of disease caused by NTM. Although not all-inclusive, the areas of discussion are referenced in enough detail to allow the reader to assess the scientific basis for ideas and recommendations that are put forth. Included within this statement are revised recommendations for diagnostic criteria that apply primarily to the NTM and updated recommendations of specific therapeutic drug regimens for disease caused by *M. avium* complex and other species of NTM, recognizing the major impact of the newer macrolides and rifabutin, which have become available since 1990. Unless otherwise stated, these drug dosages are for adults. Pediatric doses are described where available.

EPIDEMIOLOGY AND PATHOGENESIS

Sources of Infection

Most NTM organisms have been isolated from water and soil (4–6). The best studied of these has been *M. avium* complex. Extensive environmental studies in the United States have shown that *M. avium* complex grows well in natural waters, particularly in the Southeast (7). *Mycobacterium avium* complex strains with plasmids, possibly associated with virulence, have been shown to be preferentially aerosolized, providing a possible mechanism for airborne acquisition of these organisms (8). Although *M. avium* is an important cause of disease in poultry and swine, serologic studies have suggested that animal-to-human transmission is not important in human infection (9), and recent molecular studies involving IS*901*-IS*902* and IS*1245* have shown that strains infecting humans and animals (especially swine) are different (10, 11). It is now generally accepted that environmental sources, especially natural waters, are the reservoir for most human infections caused by *M. avium* complex. The reservoir of *M. avium* for most patients with disseminated disease has not been identified, but it is assumed to be the same as or similar to that for patients with non-HIV–related *M. avium* complex lung disease. *Mycobacterium avium* complex is present in tap water, and one study of disseminated *M. avium* complex disease in AIDS demonstrated that some cases are likely acquired from hospital tap water (12). Interestingly, there does not appear to be a geographic predilection with disseminated disease in the United States, as there is with skin test reactivity and with chronic lung disease.

Water is also the likely source of infection for numerous other NTM species including *M. marinum, M. kansasii,* nosocomial outbreaks or pseudo-outbreaks due to rapidly growing mycobacteria, *M. xenopi,* and *M. simiae. Mycobacterium marinum* has been commonly associated with salt water, fresh water, fish tanks, and swimming pools (13). *Mycobacterium kansasii* has not been recovered from soil or natural water supplies (5). It has been isolated repeatedly, however, from tap water (14, 15) in the same communities where *M. kansasii* disease exists. Interestingly, it has been shown to survive up to 12 mo in tap water but not in soil

Rapidly growing mycobacteria such as *M. fortuitum, M. chelonae,* and *M. abscessus* can be recovered from soil and natural water supplies, and are the most common NTM associated with nosocomial disease (16–24). Investigations of nosocomial outbreaks or pseudo-outbreaks caused by these species including the use of DNA fingerprinting with pulsed-field gel electrophoresis (25, 26) have demonstrated that tap water (18, 19), ice prepared from tap water (20, 21), processed tap water used for dialysis (22), and distilled water used for preparing solutions such as gentian violet (23, 24) are the usual nosocomial sources of the organisms.

Mycobacterium xenopi is an obligate thermophile that requires temperatures of 28° C or above to grow (4). It has been recovered almost exclusively from hot water and hot water taps within hospitals (15, 27–29), where it has been associated with multiple positive (i.e., probably contaminated) clinical samples and a few cases of clinical pulmonary and soft tissue disease (28–30). These clusters of hospital isolates have been reported from the United States, the United Kingdom, and other areas in Europe. In two studies, the clinical isolates and hospital water isolates have been shown to be identical by DNA fingerprinting (28, 29). It has been speculated that the organism enters the hospital from municipal water mains, then multiplies in the hospital heating tanks where the temperature is 43–45° C, the optimal temperature for growth of this organism (30).

Reports of recovery of *M. simiae* from clinical specimens have been clustered in three geographic areas: Israel (31), Cuba, and the southwestern United States—Texas, Arizona, and New Mexico (32–34). Most recoveries have been single positive specimens that are smear-negative (32, 33) and not associated with clinical disease (33), suggesting environmental contamination as a likely source. For several clusters of isolates, organisms were also recovered from the local tap water (34, M. Yakrus, personal communication, 35), suggesting it as the likely organism source.

Mycobacterium malmoense, which has emerged as a major NTM pathogen in northern Europe, has been recovered from natural waters in Finland (36) and soils in Zaire (37) and Japan (38). The recently recognized pathogen *M. genavense* has not been recovered from soil or water, but it has been recovered from a dog and a variety of pet birds including psittacine birds (39, 40). *Mycobacterium ulcerans* disease occurs in discrete but widely dispersed geographic areas in the watersheds

of tropical rain forests, primarily in Africa, Southeast Asia, Australia, and South and Central America (35).

Much less is known about the environmental epidemiology and sources of infection for the other NTM. A number of NTM species have yet to be recovered from the environment, including *M. ulcerans*, *M. haemophilum*, *M. szulgai*, *M. celatum*, *M. genavense*, and *M. conspicuum*. Despite this, environmental sources of infection are highly likely. Good reviews of environmental studies have been provided by Wolinsky and Rynearson (5), Portaels (35), and Falkinham (41).

Much remains to be understood about the pathogenesis of NTM infection and disease in humans. Epidemiologic studies, skin test surveys, and more recently DNA fingerprinting studies suggest that person-to-person transmission of infection is rare. It is assumed that most persons are infected by environmental NTM. Of the likely sources of infection, airborne NTM may play an important role in respiratory disease, whereas ingestion may be the source of infection for children with NTM cervical lymphadenitis and for most patients with AIDS whose disseminated *M. avium* or *M. genavense* begins as gastrointestinal colonization. Bacteremic spread of the organism in patients with AIDS then involves multiple organ systems, including bone marrow, lymph nodes, liver, and spleen. Direct inoculation with NTM organisms from water or other material is likely the source of infection for patients with soft tissue infections. It is not known whether NTM disease (especially pulmonary disease) develops soon after infection or, like tuberculosis, develops after a period of latency.

Prevalence in Humans

Although first observed soon after Koch's discovery of the tubercle bacillus, NTM were not widely recognized as human pathogens until the 1950s, when several large series of patients with NTM lung disease were reported (42–44). These patients were epidemiologically distinct from patients with tuberculosis, being older, more commonly white, and quite often having underlying chronic lung disease such as bronchiectasis, silicosis, and healed tuberculosis. Positive reactions of 10 mm or more to purified protein derivative (PPD) tuberculin were less common than among tuberculous patients, and family contacts tended to be tuberculin-negative.

As reports of patients with NTM disease increased, it became apparent there was marked geographic variability both in the prevalence of disease and in the mycobacterial species responsible for disease. Most patients in the southeastern United States with NTM lung disease were from rural areas and had isolates of *M. avium* complex, whereas those in the central United States more commonly had disease caused by *M. kansasii* (45).

In addition, patients with NTM disease tended to react more strongly to skin test antigens prepared from the infecting mycobacterial species than to standard PPD-S or PPD-T, antigens prepared from *M. tuberculosis* (46). Skin test surveys using NTM antigens suggested that infection by NTM was common, especially in rural areas and in the Southeast (47).

NTM disease is not reportable in the United States, and reliable estimates of its incidence or prevalence have been limited. Two national surveys in the early 1980s were the first to try to define the extent of NTM infection in the United States. The initial study, based on state laboratory reports from 1979–1980, indicated that NTM comprised approximately one-third of the 32,000 mycobacterial isolates (48). Of these, 61% were *M. avium* complex, 19% were *M. fortuitum* complex, and 10% were *M. kansasii*.

A second surveillance study based on reports from tuberculosis control officers on isolates of NTM recovered between 1981 and 1983 showed higher rates of NTM disease among nonwhites, women, and patients residing in urban areas when compared with the initial study. White males, however, continued to serve as the major diseased population (49). Using combinations of national surveillance data, the prevalence of NTM (pulmonary) disease at that time was estimated to be 1.8 cases per 100,000 population for the entire United States. Of this, *M. avium* complex represented 1.1/100,000.

A more recent Centers for Disease Control (CDC) study from 1991 to 1992 (50) that included results from 33 state laboratories demonstrated a dramatic change in the prevalence of NTM. Despite the increases in isolates of *M. tuberculosis* noted in the United States since 1985, there were now more isolates of *M. avium* complex than *M. tuberculosis*, with the latter representing only 26% of the total mycobacterial isolates. The reasons for this dramatic increase in numbers for NTM is unknown, but better clinical recognition and more culturing for both pulmonary and disseminated disease are felt to play important roles.

One category of people with NTM disease not represented in the two earliest studies but almost certainly represented in the 1993 study were patients with AIDS and disseminated NTM disease. HIV-infected patients were at especially high risk of disease due to NTM. The majority of disease in this population ($>$ 95%) is due to *M. avium* (51). Disseminated *M. avium* infection is the most common bacterial infection in patients with AIDS, occurring in 20 to 40% of all patients in several reported series (52–55). Disease in these patients is highly correlated with severe immunosuppression, with the average CD4 cell count at the time of dissemination in the 25 to 30 range (53–55). Patients with $<$ 100 CD4 cells, not receiving prophylaxis, develop disseminated *M. avium* at the rate of approximately 20% per year (53). The overall incidence of *M. avium* as an initial diagnosis has increased among AIDS patients while other complications of AIDS, such as *Pneumocystis* pneumonia, have decreased (56). Disseminated *M. avium* occurs in similar rates in all geographic regions and various HIV risk groups (57). Localized pulmonary disease in AIDS due to *M. avium* occurs in less than 5% of patients (58).

Other NTM species, including *M. kansasii* (51, 59–61), *M. scrofulaceum* (51), *M. gordonae* (51), *M. haemophilum* (60, 61), *M. genavense* (39), *M. celatum* (62), *M. conspicuum* (63), *M. xenopi* (64), *M. fortuitum* (51, 65), *M. marinum* (66), *M. malmoense* (67), and *M. simiae* (68) have also been described as a cause of pulmonary and/or disseminated NTM disease in AIDS. Some of these, especially *M. haemophilum*, *M. kansasii*, and *M. genavense*, have occurred in localized geographic areas. More than 95% of cases of disseminated disease, however, are due to isolates of *M. avium* (51).

CLINICAL PRESENTATION AND DIAGNOSTIC CRITERIA

Pulmonary Disease

Chronic pulmonary disease is the most common localized clinical manifestation of NTM (41, 69). *Mycobacterium avium* complex, followed by *M. kansasii*, is the most frequent pathogen causing lung disease in the United States. Other pathogens occasionally causing pulmonary disease include *M. abscessus*, *M. fortuitum*, *M. szulgai*, *M. simiae*, *M xenopi*, *M. malmoense*, *M. celatum*, *M. asiaticum*, and *M. shimodii*. *Mycobacterium xenopi* is second to *M. avium* complex as a cause of NTM lung disease in areas of Canada, the United Kingdom, and other areas of Europe, while *M. malmoense* is second to *M. avium* complex in Scandinavia and areas of northern Europe (70). The patients with chronic lung disease due to NTM are generally older adults. Except for patients with cystic fibrosis, chil-

dren rarely develop this form of NTM disease (69). Although some NTM patients have a history of underlying chronic lung disease, not all do. The interpretation of NTM in the sputum of HIV-positive patients presents a particular problem, as these patients are frequently infected with NTM without evidence of pulmonary disease. Such infection may be transient, but it may also reflect disseminated NTM disease or subclinical NTM pulmonary disease. In addition, some NTM species that are generally considered nonpathogenic have been associated with pulmonary disease in the HIV-infected host.

Signs and symptoms of NTM pulmonary disease are variable and nonspecific. They include chronic cough, sputum production, and fatigue. Less commonly, malaise, dyspnea, fever, hemoptysis, and weight loss can also occur, usually with advanced NTM disease. Evaluation is often complicated by the symptoms caused by co-existing lung diseases. These conditions include chronic obstructive airway disease associated with smoking, bronchiectasis, previous mycobacterial diseases, cystic fibrosis, and pneumoconiosis.

There are some differences in the radiographic features of NTM lung disease compared with those produced by *M. tuberculosis* with regard to conventional radiographic studies. Nontuberculous mycobacteria tend to cause thin-walled cavities with less surrounding parenchymal infiltrate, have less bronchogenic but more contiguous spread of disease, and produce more marked involvement of pleura over the involved areas of the lungs. Occasionally, they may produce dense pneumonic disease or a solitary pulmonary nodule without cavitation. Basal pleural disease is not often found, and pleural effusion is rare. Recent studies with high-resolution computed tomography (HRCT) of the chest have shown that up to 90% of patients with mid and lower lung field noncavitary disease with *M. avium* complex have associated multifocal bronchiectasis, with many patients having clusters of small (< 5 mm) nodules in associated areas of the lung (71–74).

There has been a great deal of interest in the availability of species-specific skin test antigens. Unfortunately, many antigens are shared by different mycobacterial species for which there are previously tested NTM skin test antigen preparations, and extensive cross-reactions were observed with PPDs. However, recent studies provide hope for increased specificity of a preparation for *M. avium* complex testing, although it is not yet FDA approved (75). Specific skin test reagents for other NTM infections are not standardized and are neither available nor undergoing clinical trials at this time.

In the absence of specific diagnostic features in the history and physical examination, the chest roentgenogram, and differential skin testing, isolation of the NTM in a culture is essential for diagnosis. However, as these organisms are commonly found in nature, contamination of culture material or transient infection does occur. Thus, a single positive sputum culture, especially with small numbers of organisms, does not always suffice to diagnose NTM disease. Some previous authors suggested that the respiratory tract may be infected with the organism without disease, particularly in patients with chronic respiratory disease (48, 49, 69). This condition was often referred to as "colonization," and was described most often with *M. avium* complex. It was characterized by the presence of noncavitary, stable, and usually minimal radiographic disease in women, and was associated with sporadic excretion of organisms from the respiratory tract. No pathologic studies were done to demonstrate the absence of tissue invasion, and more recent studies with HRCT have shown that these patients often have a combination of multifocal bronchiectasis and nodular parenchymal disease (71–74), with the latter or both now felt to be due to mycobacterial disease. "Colonization" in the true sense (i.e., no tissue invasion) is probably quite rare. In addition, not all patients with this disease have a benign prognosis, a point first emphasized by Prince and colleagues in a landmark 1989 paper (76).

Given these observations, the diagnosis of lung disease caused by NTM is usually not difficult if a combination of clinical, radiographic, and bacteriologic criteria are used. AFB smear, culture results, and clinical status suggest a close correlation among the three. Minimal evaluation should include three or more sputums for AFB and efforts to exclude other confounding disorders such as tuberculosis and lung malignancy. In most patients, a diagnosis can be made without a lung biopsy. Although criteria are based on experience with *M. avium* complex, there is no reason to believe these criteria would not be applicable to other species. The diagnostic criteria are presented in Table 1.

Clinical studies have established the validity of bronchial washings as a culture source for *M. tuberculosis*. Although similar studies have not been done for NTM, bronchial washings are considered to be more sensitive than routine expectorated sputums; however, their relative specificity for clinical disease is unknown. Approximately 90% of patients with disease caused by *M. kansasii* and most patients with disease caused by *M. avium* complex have cavitary infiltrates (77) and can be readily identified. Among patients without cavities, the presence of clinical symptoms and HRCT abnormalities are important adjuncts to defining the presence of NTM disease. Bacteriologic criteria have been best analyzed with cavitary disease for *M. avium* complex and *M. kansasii*, and the HRCT abnormalities, with *M. avium* complex. Although these are reasonable criteria for diagnosing other NTM, their use with other species has not been studied in detail.

In the patient with nondiagnostic cultures and radiographic studies, or concern about the presence of another disease producing radiographic abnormalities, a lung biopsy is often required for diagnosis. If a tissue sample from a transbronchial, percutaneous, or open-lung biopsy yields an NTM organism and shows mycobacterial histopathologic changes (i.e., granulomatous inflammation with or without AFB), this by itself is sufficient to establish the diagnosis of NTM lung disease. If the lung biopsy has a negative culture (something that often happens when transbronchial biopsies are performed because of the small size of the tissue sample) but demonstrates mycobacterial histopathology features (without a history of other granulomatous or mycobacterial disease), NTM lung disease is considered to be present when one or more sputums or bronchial washes are culture-positive for NTM, even if they are negative for AFB on smear and result in light growth on culture.

Lymphadenitis

Infection of the submandibular, submaxillary, cervical, or preauricular lymph nodes in children between 1 and 5 yr old is the most common presentation of NTM lymphadenitis (78–81). It is the most common disease manifestation of NTM in children and, in the absence of HIV infection, rarely affects adults. The disease occurs insidiously, with only rare associated systemic symptoms. The involved lymph nodes are generally unilateral (95%) and not tender. The nodes may enlarge rapidly, and even rupture, with formation of sinus tracts that result in prolonged local drainage. Other nodal groups outside of the head and neck may be involved occasionally (80). There is typically no history of exposure to tuberculosis, screening PPD skin test of family members are usually negative, and the chest radiograph is normal.

TABLE 1

CRITERIA FOR DIAGNOSIS OF NONTUBERCULOUS MYCOBACTERIA PULMONARY DISEASE

Presumed or Confirmed HIV Seronegative Potential Risk Factors		Presumed or Confirmed HIV Seropositive Potential Risk Factors
I. Local immune suppression Alcoholism (*M. avium* complex) Bronchiectasis Cyanotic heart disease Cystic fibrosis Prior mycobacterial disease Pulmonary fibrosis Smoking/chronic obstructive lung disease None	II. General severe immune supression Leukemia Lymphoma Organ transplantation Other immunosuppressive therapy	CD4 count $<$ 200
1. Clinical criteria	a. Same	a. Same
a. Compatible signs/symptoms (cough, fatigue most common; fever, weight loss hemoptysis, dyspnea may be present, particularly in advanced disease) with documented deterioration in clinical status if an underlying condition is present and		
b. Reasonable exclusion of other disease (e.g., tuberculosis, cancer, histoplasmosis) to explain condition, or adequate treatment of other condition with increasing signs/symptoms	b. Same	b. Same
2. Radiographic criteria	a. Same	a. Same
a. Any of the following chest X-ray abnormalities; if baseline films are more than 1 yr old, should be evidence of progression • Infiltrates with or without nodules (persistent $\geq$ 2 mo or progressive) • Cavitation • Nodules alone (multiple)		
b. Any of these HRCT abnormalities • Multiple small nodules • Multifocal bronchiectasis with or without small lung nodules	b. Same	b. Same
3. Bacteriologic criteria	a. Same	a. Same
a. At least three available sputum/bronchial wash samples within 1 yr • Three positive cultures with negative AFB smears or • Two positive cultures and one positive AFB smear or		
b. Single available bronchial wash and inability to obtain sputum samples • Positive culture with 2+, 3+, or 4+ growth or • Positive culture with a 2+, 3+, or 4+ AFB smear or	b. Same except • Culture positive with 1+ or greater growth	b. Same except • Culture positive with 1+ or greater growth (excludes *M. avium* complex)
c. Tissue biopsy • Any growth bronchopulmonary tissue biopsy • Granuloma and/or AFB on lung biopsy with one or more positive cultures from sputum/bronchial wash • Any growth from usually sterile extrapulmonary site	c. Same	c. Same

For a diagnosis of pulmonary disease, all three criteria—(*1*) clinical, (*2*) radiographic, and (*3*) bacteriologic— must be satisfied.

Most children with NTM lymphadenitis will react to skin test antigens prepared from *M. avium* complex, such as PPD-B (79, 82, 83). A 1991 multicenter study of NTM antigens from the CDC that used PPD-B, however, was terminated early, due to a blistering reaction in several of the children (82). More recent studies using a less potent, protein weight–standardized *M. avium* skin-test material called "sensitin" and a dual skin-test technique to determine *M. avium*–dominant versus PPD-dominant reactions have suggested improved specificity with this antigen preparation in study populations with known disease (75). Although these antigens may prove beneficial for future evaluation of cervical lymphadenitis, no commercial NTM skin-test material is currently available for clinical use in the United States, and this procedure is not recommended for diagnosis of NTM. All children in this setting should be tested using PPD tuberculin. Most children tested with intermediate strength (5 tuberculin unit [TU]) PPD tuberculin will have a weakly reactive skin test (5–9 mm) due to cross-reactivity with NTM, but some children may be negative, and as many as one-third will have reactions with 10 mm or more induration (80).

Distinguishing tuberculous from nontuberculous lymphadenitis is key, because the former requires drug therapy and public health tracking, whereas the latter does not. The presumptive diagnosis of NTM lymphadenitis is based on the histopathologic appearance of the lymph node showing caseating granulomata with or without AFB and a negative tuberculin skin test. Failure of the node to yield *M. tuberculosis* provides stronger presumptive evidence for the diagnosis of NTM lymphadenitis.

The utility of fine needle aspiration in obtaining diagnostic material is controversial (84–86). However, granulomata or other compatible cytopathology such as a mixture of degenerating granulocytes, lymphocytes, and epithelioid histiocytes are seen in most cases. A positive culture may be obtained in up to 50% of HIV-seronegative patients and in even higher proportions of HIV-positive patients with tuberculous adenitis.

A definite diagnosis of NTM lymphadenitis is made by recovery of the causative organism from lymph node cultures. A simple diagnostic biopsy or incision and drainage of the involved lymph nodes should be avoided, since most of these

procedures will be followed by fistulae formation with chronic drainage (79). However, even with excised nodes with compatible histopathology, only about 50% will yield positive cultures (79), although the recovery rate may be as high as 82% in some centers (80). Some of these smear-positive, culture-negative cases may be due to fastidious species such as *M. haemophilum* (87) or *M. genavense* (39). Currently, approximately 80% of culture-proven cases of NTM lymphadenitis are due to *M. avium* complex (88). In the United States and Australia the remaining cases are caused by *M. scrofulaceum* (79, 80, 88), while in Scandinavia, the United Kingdom, and other areas of northern Europe, *M. malmoense* has recently emerged as the major pathogen after *M. avium* complex (70, 89, 90). The predominance of *M. avium* complex is a change from 20 years ago, when most geographic areas reported *M. scrofulaceum* as the most common etiologic agent (78, 80). Now in the United States, only about 10% of the culture-proved mycobacterial cervical lymphadenitis in children is due to *M. tuberculosis*; the remainder is due to *M. avium* complex and *M. scrofulaceum* (88). In contrast, in adults more than 90% of the culture-proven mycobacterial lymphadenitis is due to *M. tuberculosis*.

Localized Skin, Soft Tissue, and Skeletal Infection

The NTM species that most commonly cause localized infections of the skin and subcutaneous tissue are *M. fortuitum*, *M. abscessus*, *M. marinum*, and *M. ulcerans* (5). However, virtually all species of NTM have been described as a cause of cutaneous disease (41, 69). Localized drainage or abscess formation at the site of puncture wounds (such as occurs after stepping on a nail), or open traumatic injuries or fractures are most often due to the rapidly growing mycobacterial species *M. fortuitum*, *M. abscessus*, or *M. chelonae* (91). Nosocomial skin and soft-tissue disease caused by these three species is also seen (16–26). These include infections of long-term intravenous or peritoneal catheters (91, 92), postinjection abscesses, or surgical wound infections such as those occurring after augmentation mammoplasty (23, 93) or cardiac-bypass surgery (16, 17, 21, 94). Diagnosis is made by culture of the specific pathogen from drainage material or tissue biopsy.

Mycobacterium marinum is the cause of "swimming pool granuloma" or "fish tank granuloma" (69). The lesions usually appear as papules on an extremity, especially on the elbows, knees, and dorsum of feet and hands, progressing subsequently to shallow ulceration and scar formation. Most lesions are solitary, although occasional "ascending" lesions develop that resemble sporotrichosis. Clinical involvement of regional nodes is uncommon. The organisms may be introduced into the skin through previous abrasions contaminated while cleaning fresh-water fish tanks ("fish tank granuloma") or by scratches or puncture wounds from salt water fish, shrimp, fins, etc. Diagnosis is made from biopsy material, histologic examination, and culture.

Mycobacterium ulcerans causes indolent necrotic lesions of the skin and underlying tissue in Australia and tropical areas of the world (34, 69, 95). It is not endemic in the United States. The lesions occur most commonly in children and young adults and often result in severe deformities of the extremities (95). Drug treatment of the disease has been disappointing; surgical debridement combined with skin grafting is the usual treatment of choice.

Infection of Bursae, Joints, Tendon Sheaths, and Bones

Chronic granulomatous infection caused by NTM may develop in tendon sheaths, bursae, joints, and bones after direct inoculation of the organisms through accidental traumas, surgical incisions, puncture wounds, or injections. *Mycobacterium marinum* (41, 69) and *M. avium* complex (96) are particularly prone to causing tenosynovitis of the hand, although *M. fortuitum*, *M. abscessus*, *M. chelonae*, and *M. kansasii* have also been implicated (41, 69). *Mycobacterium terrae* complex (especially *M. nonchromogenicum*) has also been isolated from synovial tissue of the hand or wrist, and it tends to be associated with a very indolent, chronic type of disease. Occasionally, axial bones and extremities have been infected without apparent trauma and are due presumably to hematogenous infection. After open-heart surgery, osteomyelitis of the sternum caused by *M. abscessus* or *M. fortuitum* has been described, with both epidemic and sporadic disease (16, 17, 21, 94).

Disseminated Disease in Patients without AIDS

Dissemination of NTM in adult patients with immunosuppression but without AIDS (e.g., those with renal or cardiac transplantation, chronic corticosteroid use, leukemia, etc.) has been observed. *Mycobacterium avium* complex (69, 97), *M. kansasii* (98), *M. chelonae* (91, 99–101), *M. scrofulaceum* (69), *M. abscessus* (69), and *M. haemophilum* (60) have all been reported to cause disease in this setting. In general, the disease caused by *M. avium* complex presents as a fever of unknown origin (97), whereas disease caused by *M. kansasii*, *M. chelonae*, *M. abscessus*, and *M. haemophilum* generally presents as multiple subcutaneous nodules or abscesses that drain spontaneously (60, 69, 99–101). The mortality relates directly to the type and severity of underlying disease (101). Lincoln and Gilbert (78) reviewed 12 cases, all fatal, of disseminated NTM disease in children. Most of the children were infected with *M. avium* complex, were less than 3 yr old, and had no apparent underlying disease. A recent review of disseminated *M. avium* complex disease in children noted its occurrence, rarely, in the setting of severe combined immunodeficiency syndrome or chemotherapy for malignancy (102). The isolation of organisms from sterile, closed sites such as bone marrow or blood or from a skin biopsy (in the setting of multiple lesions) is diagnostic of the disease.

Disseminated Disease in Patients with AIDS

Disseminated disease due to NTM in patients with HIV infection usually occurs only in those with very advanced immunosuppression (51–57). Because these patients frequently have other complications, the diagnosis of mycobacterial infection may be confused or delayed. The diagnosis is exceedingly rare in person with $>$ 100 CD4 cells, and it should usually be suspected only in persons with $<$ 50 CD4 cells (53–55). Most patients ($>$ 90%) have prolonged fevers, which may be as high as 103–104° F, frequently accompanied by night sweats. Weight loss is common, and some patients complain of abdominal pain and diarrhea. Physical findings may be only those of advanced HIV disease, although abdominal or retroperitoneal adenopathy and hepatosplenomegaly may be present. Anemia is the most striking laboratory abnormality, with many patients having a hematocrit of $<$ 25%. Alkaline phosphatase is elevated in approximately one-third of patients and may be indicative of hepatic disease due to *M. avium*. Thus, the diagnosis of disseminated *M. avium* should be aggressively pursued in any person with $<$ 50 CD4 cells who has a history of fever, weight loss, anemia, diarrhea, or elevated alkaline phosphatase, especially in one with a history of other opportunistic infections.

The diagnosis of disseminated *M. avium* is most commonly confirmed by isolation of *M. avium* in blood, using any of the culture techniques described in the laboratory section. The bacteremia in *M. avium* is ongoing, and a single culture has a sensitivity of approximately 90%. It is recommended that a single culture be drawn, with repeat cultures only if the first is

negative. Routine blood cultures of asymptomatic patients has a very low yield and is not recommended. In a prospective study of HIV-infected patients with < 50 CD4 cells, approximately 67% of patients with *M. avium* in sputum or stool had disseminated disease within 1 yr, although most did not develop pulmonary disease. However, only one-third of all patients with disseminated disease had a prior positive stool or sputum. Therefore, routine screening of stool or sputum is not indicated, but a positive culture of one of these sites needs to raise concern about future dissemination. Sputums that are smear-positive for AFB in the setting of HIV should always be regarded as tuberculosis until proven otherwise, since *M. tuberculosis* is a common cause of pulmonary disease in HIV-infected patients and is more likely than *M. avium* complex to produce positive AFB smears.

Nontuberculous mycobacteria other than *M. avium* may present as disseminated disease. Disseminated *M. kansasii* is usually associated with pulmonary disease (51, 59). *Mycobacterium genavense* has been isolated from the blood of patients with AIDS and requires extensive laboratory analyses for isolation and identification (39). *Mycobacterium haemophilum* has been associated with infections of the skin, soft tissue, bones, and joints (60, 61). Disseminated disease has rarely been reported with other species, including *M. fortuitum* (51), *M. marinum*, *M. simiae*, *M. scrofulaceum*, *M. celatum*, and *M. malmoense* (41).

LABORATORY METHODS

Digestion, Decontamination, and Staining Procedures

Methods used for digestion and decontamination of clinical samples to recover *M. tuberculosis* have also proved useful for the NTM. In general, however, NTM are more susceptible to killing by NaOH, and for this reason, care must be taken not to exceed the recommended concentration and time guidelines. Because of the frequent presence of bronchiectasis in patients with *M. avium* complex and *M. abscessus* lung disease, *Pseudomonas aeruginosa* overgrowth in specimens from these patients is a more frequent problem than with tuberculosis. Growth of *P. aeruginosa* can be minimized by processing the specimens with the conventional *N*-acetyl-L-cysteine–sodium hydroxide (NALC-NaOH) solution followed by 5% oxalic acid, a procedure that should be considered when one or more specimens are contaminated in this setting (103).

Staining and microscopy of the NTM also follows the guidelines used for *M. tuberculosis*. Both conventional basic fuchsin method (Kinyoun stain) and the fluorochrome method (auramine stain) are effective in recognizing NTM in clinical material, with the fluorochrome method being preferred (104). The appearance of NTM by microscopy is generally indistinguishable from *M. tuberculosis*.

Culture Techniques for Nontuberculous Mycobacteria

The principles and practices of culturing *M. tuberculosis* were updated in 1993 by the CDC (104), with these methods having proved very effective for NTM species. At least three respiratory (sputum) cultures should be used for the initial evaluation. Cultures should be inoculated onto one or more solid medias and into a liquid medium. Use of solid media as the primary or sole culture is no longer recommended by us or by the CDC (104), given the greater recovery rate and more rapid recovery of all mycobacteria, including *M. tuberculosis*, in rapid broth systems (104–107). Mycobacterial blood cultures may use a single medium, with the BACTEC 13A broth (105) or the lysis centrifugation method with plating on 7H10 or 7H11 (Isolator; Wampole Laboratories, Cranbury, New Jersey) being the recommended methods. Two general types of solid media are available: egg-potato-base media (commonly, Lowenstein-Jensen agar) and a clear agar-base media (commonly, Middlebrook 7H10 or 7H11 agar). Quantitation of growth on agar plates (generally 0 to 4+) is important to estimates of clinical significance and responses to therapy, and it is recommended for all samples other than blood cultures. Blood cultures using the Isolator System can also be quantitated, which may be useful for similar reasons. Because of its greater recovery rate for *M. avium* complex and ease of quantitation, Middlebrook 7H10 or 7H11 agars are the preferred solid media. Lowenstein-Jensen is an excellent medium for recovery of *M. tuberculosis*, but is generally inferior to Middlebrook agar as an all-purpose medium for both *M. tuberculosis* and NTM (105, 106).

The broth medium can involve one of several automated commercial systems, including radiolabeled BACTEC 12B broth used in the BACTEC TB 460 radiometric system (Becton Dickinson Instruments Systems, Sparks, Maryland), and the nonradiolabeled ESP Culture System II (Difco Laboratories, Detroit, Michigan) (107). For lower volume laboratories, the recently introduced mycobacterial growth indicator tubes with a fluorescent detection system (MGIT; Becton Dickinson Microbiology Systems, Cockeysville, Maryland) or biphasic agar/broth (Septi-Chek AFB System; Becton Dickinson Microbiology Systems) may prove more practical.

Most slowly growing NTM produce detectable growth in 2 to 4 wk on the solid media and in 1 to 2 wk with the BACTEC system. Cultures are generally incubated at 35–37° C for 6 wk. All of the currently recognized NTM pathogens will grow on these media in this time except *M. haemophilum*, *M. genavense*, and *M. conspicuum*. If *M. haemophilum* is suspected, a commercial paper surface containing hemin (X factor) used to identify *Haemophilus influenzae* should be added to the surface of the 7H10 or 7H11 plate (108), or hemin or ferric ammonium citrate should be incorporated into the medium. *Mycobacterium genavense* often grows only from the blood in BACTEC 13A medium or comparable broth media, and requires incubation for at least 8 wk (109). Some authors have identified better growth in the slightly acidic (pH 6) radiometric Middlebrook 7H12 broth (pyrazinamide test medium). *Mycobacterium conspicuum* will grow in BACTEC media at 35–37° C but will only grow on solid media at lower temperatures, 22–31° C (63). The presence of an AFB smear-positive sample with no growth on solid media should immediately bring to mind *M. haemophilum*, *M. conspicuum*, or *M. genavense*. Because of the relatively poor growth of *M. genavense* (only approximately 50% of autopsy-proven cases are culture-positive [39]), molecular techniques such as polymerase chain reaction are the optimal method of identification (39).

The major modification of culture techniques for recovering NTM species is the need to incubate all skin or soft tissue samples at two temperatures: 35° C and 28–32° C. This is because a number of the common pathogens of these tissues, including *M. haemophilum*, *M. ulcerans*, *M. marinum*, and *M. chelonae*, may grow only at the lower temperatures, especially on primary isolation. Five to ten percent CO_2 enhances the growth of some NTM species, such as *M. haemophilum*, and should be used for primary isolation because of its definite growth enhancement for *M. tuberculosis*.

Identification of Nontuberculous Mycobacteria

Traditional identification of NTM, as well as *M. tuberculosis*, has relied upon statistical probabilities of presenting a charac-

teristic reaction pattern in a battery of biochemical tests. The niacin test was the most useful for separating NTM and *M. tuberculosis* because the former is usually negative, whereas isolates of *M. tuberculosis* are positive. Runyon devised the first good scheme for grouping NTM based on growth rates and colony pigmentation (69). Species identification has become more sophisticated and the number of potential pathogens has increased since this scheme was introduced.

A more appropriate grouping currently for these organisms is based on the type of clinical disease they produce: lymphadenitis, cutaneous disease, disseminated disease, and pulmonary disease. Grouping of the NTM by this scheme is shown in Table 2.

Because of the extremely slow nature of traditional biochemical tests, most clinical and public health laboratories now use one or more rapid diagnostic methods for species identification (110, 111). These rapid methods are recommended for identification of the NTM when possible; they include HPLC, the BACTEC NAP test, and commercial DNA probes. The HPLC examines the mycolic acid fingerprint patterns that differ among most species or complexes of mycobacteria (112). Recent increased sensitivity of this technique using fluorescence detection has allowed identification directly from the sputum sample in approximately 50% of AFB smear-positive samples of *M. tuberculosis* and 33% of *M. avium* complex (113). A small number of species (complexes) are not separable by HPLC, including most of the pathogenic rapidly growing mycobacterial species. Two additional techniques for rapid identification of NTM are currently in use. These are the species-specific DNA probes and the BACTEC NAP test. Commercial nonradiolabeled DNA probes complementary to ribosomal RNA are available for identifying isolates of *M. tuberculosis*, *M. gordonae*, *M. kansasii*, *M. avium*, and *M. intracellulare*. They are highly sensitive and specific, providing species identification using a culture directly from BACTEC broth within 2–4 h. The presence or absence of serpentine cording on AFB smear of the BACTEC 12B bottle (114) and the time required for the bottle to turn positive (115) will help the laboratory decide which probe (*M. tuberculosis* or *M. avium* complex) should be used initially.

The BACTEC TB 460 system can be used to differentiate between *M. tuberculosis* and the NTM using a selective growth inhibitor called NAP (*p*-nitro-α-acetylamino-β-hydroxypropiophenone) (116). This compound, at a concentration of 5 μg/ml, inhibits the growth of *M. tuberculosis* complex but not NTM (with the exception of *M. genavense*). The average time for the NAP test is 5 d. However, a species identification schema other than the use of DNA probes for NTM has not been worked out for use with the BACTEC, and such identification must depend on one of the previously discussed methods.

Because of its generally poor growth, identification of *M. genavense* can be difficult (43, 109). A presumptive identification can be made on the basis of organism morphology (small, coccobacillary forms on AFB smear), failure to grow on subculture to solid media, a negative nucleic acid probe for *M. avium* complex, and a positive NAP test (39). *Mycobacte-*

TABLE 2

CLASSIFICATION OF THE NONTUBERCULOUS MYCOBACTERIA RECOVERED FROM HUMANS

Clinical Disease	Common Etiologic Species	Features of the Common Species		Unusual Etiologic Species
		Geography	Morphologic Features*	
Pulmonary disease	1. *M. avium* complex	Worldwide	Usually not pigmented; slow growth (> 7 d)	1. *M. simiae* 2. *M. szulgai*
	2. *M. kansasii*	USA, coal mining regions, Europe	Pigmented; often large and beaded on acid-fast stain	3. *M. fortuitum* 4. *M. celatum*
	3. *M. abscessus*	Worldwide but mostly USA	Rapid growth (< 7 d); not pigmented	5. *M. asiaticum* 6. *M. shimodii*
	4. *M. xenopi*	Europe, Canada	Slow growth; pigmented	7. *M. haemophilum*
	5. *M. malmoense*	UK, northern Europe	Slow growth, not pigmented	8. *M. smegmatis*
Lymphadenitis	1. *M. avium* complex	Worldwide	Usually not pigmented	1. *M. fortuitum*
	2. *M. scrofulaceum*	Worldwide	Pigmented	2. *M. chelonae*
	3. *M. malmoense*	UK, northern Europe (especially Scandinavia)	Slow growth	3. *M. abscessus* 4. *M. kansasii* 5. *M. haemophilum*
Cutaneous disease	1. *M. marinum*	Worldwide	Photochromogen; requires low temperatures (28–30° C) for isolation	1. *M. avium* complex 2. *M. kansasii* 3. *M. nonchromogenicum*
	2. *M. fortuitum* 3. *M. chelonae* 4. *M. abscessus*	Worldwide, mostly USA	Rapid growth; not pigmented	4. *M. smegmatis* 5. *M. haemophilum*
	5. *M. ulcerans*	Australia, tropics, Africa, SE Asia	Grows slowly, pigmented	
Disseminated disease	1. *M. avium* complex	Worldwide	Isolates from patients with AIDS usually pigmented (80%)	1. *M. abscessus* 2. *M. xenopi* 3. *M. malmoense*
	2. *M. kansasii*	USA	Photochromogen	4. *M. genavense*
	3. *M. chelonae*	USA	Not pigmented	5. *M. simiae*
	4. *M. haemophilum*	USA, Australia	Not pigmented; requires hemin, often low temperatures, and CO_2 to grow	6. *M. conspicuum* 7. *M. marinum* 8. *M. fortuitum*

* Photochromogen: isolate is buff-colored in the dark but turns yellow with brief exposure to light.

rium genavense is one of the few mycobacteria, other than the *M. tuberculosis* complex, which is inhibited by NAP.

Antimicrobial Susceptibility Testing

Although there are specific recommendations from the CDC, ATS, and the National Committee for Clinical Laboratory Standards (NCCLS) regarding which isolates of *M. tuberculosis* should have antimicrobial susceptibility tests, which test methods to use, and which antimicrobial agents to test, the same is not true for the NTM. There are however, sufficient data now available to make temporary recommendations regarding when, how, and to which agents the NTM should be tested. Recommendations will differ for different groups or species of the NTM (Table 3). Although routine testing of all NTM is discouraged, there are circumstances where susceptibility testing is warranted, including having baseline data available if the patient does not respond to therapy, or when relapses occur.

Slow-growing Mycobacteria

Antimicrobial susceptibility testing of the slow-growing mycobacteria can be performed using either the agar proportion or the radiometric (BACTEC) methods used for testing *M. tuberculosis* (117–125). However, the two methods give varying results between some NTM and antimicrobial agents, with the radiometric broth method tending to give lower minimal inhibitory concentrations (MICs) than the agar method (118, 119). Too little experience is available with the antibiotic gradient strip method (E-test; AB Biodisk, Piscataway, NJ) to make any general recommendations on its use.

The agar proportion method uses Middlebrook 7H10 or 7H11 agar and the modified method of proportions, defining resistance as growth on the drug-containing medium of 1% or more of the number of colonies that grow on the drug-free control medium. Details of the agar proportion method are included in the 1990 ATS statement "Diagnostic Standards and Classification of Tuberculosis" (3), and a more detailed description is now available as a tentative standard (for *M. tuberculosis*) by the NCCLS (126).

The radiometric BACTEC method is a more rapid method combining antimicrobial agents, the mycobacterium, and a C^{14}-labeled substrate in a broth medium. Resistance is determined by the rate and amount of labeled CO_2 produced, which is directly proportional to the rate and amount of growth that occurs in the broth medium. The BACTEC method has been widely used by some laboratories for testing all drugs for the NTM, but at present no universally agreed-upon method has been developed.

Mycobacterium avium *complex*. When and how isolates of the *M. avium* complex should be tested remains controversial (127). Recent data suggest that the radiometric broth method is more reliable than the agar method for testing the *M. avium*

TABLE 3

ANTIMYCOBACTERIAL AGENTS TO CONSIDER FOR SUSCEPTIBILITY TESTING OF NONTUBERCULOUS MYCOBACTERIA

Mycobacterium Species or Group	Proven Utility Clinically Relevant	Uncertain Relevance	Susceptibility Testing Results of No Benefit
Slowly growing NTM			
M. avium complex	Clarithromycin*	Amikacin Ciprofloxacin Ethambutol Ethionamide Rifabutin Rifampin Streptomycin	Isoniazid Pyrazinamide
M. kansasii	Rifampin	Amikacin Ciprofloxacin Clarithromycin* Ethambutol Isoniazid Rifabutin Streptomycin Sulfonamide	Pyrazinamide
M. marinum	Doxycycline or Minocycline Ethambutol Rifampin Sulfonamide	Amikacin Ciprofloxacin Clarithromycin* Rifabutin	Isoniazid Pyrazinamide
Other slowly growing NTM			
M. haemophilum *M. malmoense* *M. simiae* *M. szulgai* *M. xenopi*	Clarithromycin*‡ Ethambutol‡ Rifampin‡	Amikacin Ciprofloxacin Isoniazid Rifabutin Streptomycin	Pyrazinamide
Rapidly growing NTM			
M. abscessus	Amikacin	Cefmetazole	Clofazimine
M. chelonae	Cefoxitin	Imipenem	Ethambutol†
M. fortuitum	Ciprofloxacin	Ofloxacin	Isoniazid
M. mucogenicum	Clarithromycin*	Tobramycin (*M. chelonae* only)	Pyrazinamide
M. smegmatis	Doxycycline or Minocycline Sulfonamides		Rifampin Streptomycin

* Class drug for macrolides (clarithromycin, azithromycin, roxithromycin).
† Ethambutol is clinically useful for *M. smegmatis*.
‡ Proven utility/clinically relevant for some but not all species.

complex. There is, however, considerable controversy regarding the size of the inoculum, the drug concentrations to use, and interpretation of the BACTEC results. Strains of the complex are almost always resistant to the relatively low drug concentrations of isoniazid, rifampin, streptomycin, and ethambutol used for defining susceptibility of *M. tuberculosis*. Using higher concentrations of the antituberculous agents with specific NTM breakpoints for susceptibility and resistance, determination of MICs, or determination of the activity of combined drugs are some of the newer approaches that may be helpful in predicting clinical response (118, 120, 121, 128). Such a benefit has not yet been shown by clinical trials, so susceptibility testing of *M. avium* complex isolates to the antituberculosis drugs is not recommended.

Other drugs have also been tested, including amikacin, rifabutin (118, 122, 123), ciprofloxacin (124, 125), clofazimine (129), azithromycin (127), and clarithromycin (127). Changes in MICs of the antituberculosis drugs following unsuccessful therapy of *M. avium* complex disease have been difficult to demonstrate. Such changes have been readily demonstrable with microbiologic relapses following monotherapy with clarithromycin, however (130). Pretreatment isolates with this drug have MICs $\leq$ 4.0 μg/ml when done in media with a pH of 7.4. Post-therapy or relapse isolates following macrolide therapy have MICs to clarithromycin of $>$ 32 μg/ml (105, 130–132) and a point mutation involving one of two base pairs in the 23S ribosomal macrolide binding site (131, 132).

Susceptibility testing should not be performed on pretreatment or initial isolates against clarithromycin, but it should be performed with clarithromycin for all isolates from patients on prior macrolide therapy, including those on macrolide prophylaxis for disseminated disease. The recommended clarithromycin resistance breakpoint is $>$ 32 μg/ml for broth or agar with pH corrected to 7.4 (105). Until more data are available, patients on azithromycin should have their isolates characterized as susceptible or resistant based on clarithromycin susceptibility values.

Alterations or changes in MICs following treatment or prophylaxis failure have also been difficult to demonstrate with rifabutin. For this reason, testing of susceptibility to rifabutin even after therapy is not recommended. Because of lack of standardization, results of testing other nontuberculous drugs such as amikacin, clofazimine, and ciprofloxacin should be used with caution.

Mycobacterium kansasii. Although wild strains of *M. kansasii* are initially susceptible to rifampin, acquired resistance does develop during therapy (133, 134). Since the correct history of therapy may not be known, all initial isolates of *M. kansasii* should be tested against rifampin, using the agar proportion method and the interpretive criteria for *M. tuberculosis* (resistance breakpoint of 1 μg/ml) (134). Also, testing should be performed when the patient's sputum fails to convert from smear- and/or culture-positive or when a relapse occurs during therapy. Treatment for rifampin-susceptible isolates is empiric and is not influenced by susceptibility to drugs other than rifampin (i.e., ethambutol and isoniazid); hence their routine testing is not recommended. A rifampin-resistant isolate could be tested against ciprofloxacin or ofloxacin, clarithromycin, ethambutol, streptomycin and a sulfonamide (e.g., sulfamethoxazole) (133, 134).

Other slow-growing nontuberculous mycobacteria. Susceptibility testing of infrequently isolated species of NTM may be helpful, since knowledge of susceptibility patterns is limited. Pulmonary infections caused by *M. malmoense*, *M. xenopi*, and *M. szulgai* have been successfully treated with combinations of ethambutol, isoniazid, rifampin, and most recently clarithromycin (70, 135–137), whereas ciprofloxacin, clarithromycin, and rifampin are suggested for treating *M. haemophilum* infection (60, 61). Thus, susceptibility tests for these slow-growing NTM might include these five drugs. The agar proportion and broth methods have usually been used for testing. For *M. marinum*, several methods have been used (138), with the desired test drugs being rifampin, ethambutol, doxycycline or minocycline, clarithromycin, and a sulfonamide.

Rapidly Growing Nontuberculous Mycobacteria

Because of differences in susceptibilities among species of rapidly growing mycobacteria and even within species, susceptibility testing should be performed on all clinically significant isolates as well as isolates that have been recovered after treatment failure or relapse. Antimicrobial susceptibility testing of the rapidly growing mycobacteria differs from the other NTM. Most drugs are different, although the methods are similar to those used to test other bacteria (138–142). Most infections are caused by three species; *M. abscessus*, *M. chelonae*, and *M. fortuitum* (91). A primary panel of drugs for these species could include amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, imipenem, and a sulfonamide. The most convenient method for susceptibility testing is to use microtiter MIC trays containing cation-supplemented Mueller-Hinton broth. Agar dilution, agar disk elution, and disk diffusion methods have also been used. Details of these methods can be found in several laboratory handbooks, including the American Society for Microbiology's *Manual of Clinical Microbiology* (142).

TREATMENT OF *Mycobacterium kansasii* DISEASE

Disease caused by *M. kansasii* is the second most common NTM pulmonary disease in the United States. It occurs in geographic clusters and affects primarily adult white men, but it can affect patients of any sex, race, or age. Pulmonary disease is the most frequent clinical presentation. The organism frequently exhibits a beaded or cross-barred appearance on acid-fast stain, and produces rough buff-colored colonies that develop a yellowish pigmentation because of the deposition of beta-carotene crystals after exposure to light. Disease-producing strains are usually highly catalase-positive. Recent DNA-based studies suggest that up to five taxonomic groups or subspecies are present among both environmental and human isolates (143).

Untreated strains of *M. kansasii* are inhibited by rifampin, isoniazid, ethambutol, ethionamide, streptomycin, and clarithromycin at concentrations readily achievable in the serum with usual therapeutic doses (134, 144, 145). Because the concentrations of antituberculous drugs used in susceptibility testing were chosen for their usefulness with *M. tuberculosis*, and because *M. kansasii* is less susceptible to these drugs, some isolates of the latter species may be reported resistant to isoniazid at 0.2 or 1 μg/ml and to streptomycin at 2 μg/ml. These isolates are susceptible to slightly higher drug concentrations (134, 144), and laboratory reports of resistance to the low concentrations of these two drugs have no clinical or therapeutic significance as long as a rifampin regimen is being used (146). Thus, when clinically indicated, isoniazid and/or streptomycin should be used against *M. kansasii* regardless of their *in vitro* susceptibility results. *Mycobacterium kansasii* is also susceptible *in vitro* to clarithromycin (134), sulfamethoxazole (133), amikacin (133), the newer quinolones (125), and rifabutin (134), although there is limited information on the clinical usefulness of these drugs (133, 134). Isolates are usually resistant to achiev-

able serum levels of *p*-aminosalicylic acid, capreomycin, and pyrazinamide. Acquired resistance to rifampin, ethambutol, and isoniazid has been demonstrated in isolates from treatment failure cases (133, 134, 145), and resistance to the first two agents is reliably demonstrated by current *M. tuberculosis* susceptibility test methods (134).

Treatment

The natural history of pulmonary disease caused by *M. kansasii* in patients receiving no drug treatment has been assessed (147). In general, the history has shown persistence of sputum positivity and progression of clinical and radiographic disease. On this basis, patients with pulmonary disease should receive drug therapy.

There have been no randomized comparative trials of treatment for disease caused by *M. kansasii*, comparing one drug regimen with another or with no drug treatment at all. There have been, however, several retrospective and prospective studies of various treatment regimens (145–151) that have given us a good basis for drug therapy recommendations. Earlier reports of treatment with antimycobacterial drugs in the prerifampin period were disappointing when compared with the much higher success rates achieved in treating tuberculosis with these same drugs. The sputum conversion rates at 6 mo ranged from 52 to 81%, and relapse rates of approximately 10% were seen in patients achieving an initial response (145, 148). Surgical resection was often recommended to achieve better initial control and prevent relapse. The advantage of adding surgery was never established, however (148).

With the advent of rifampin, the picture changed considerably for the better. Four-month sputum conversion rates with rifampin-containing regimens were 100% in 180 patients from three studies (145, 146, 149). There were two treatment failure cases, however (an incidence of 1.1%). These patients converted their sputa but then became culture-positive again while still receiving therapy. Both had been treated with isoniazid, rifampin, and ethambutol, and both failures were associated with the development of rifampin resistance (145). Long-term relapse rates with rifampin-containing regimens also appear to be very low, with only one relapse recorded among 134 patients (0.8%) who received long-term follow-up in three studies (145, 146, 150). Surgery is now considered to have no role in managing routine cases of pulmonary disease.

The current recommendation for treatment of pulmonary disease caused by *M. kansasii* in adults is the regimen of isoniazid (300 mg), rifampin (600 mg), and ethambutol (25 mg/kg for the first 2 mo, then 15 mg/kg) given daily for 18 mo with at least 12 mo of negative sputum cultures. In patients who are unable to tolerate one of these three drugs, clarithromycin would seem a reasonable alternative, but its effectiveness has not been established by clinical trials (*see below*). Pyrazinamide is *unacceptable* as an alternate or third drug for *M. kansasii* because all isolates are resistant.

The use of intermittent drug regimens or short-course treatment for *M. kansasii* has not been studied enough to recommend it. One study of 40 patients did demonstrate that adding intermittent streptomycin at 1 g twice weekly for the first 3 mo to the previously recommended three-drug regimen given for 12 mo resulted in apparent cure of all but one patient (149). A trial of daily low-dose ethambutol (15 mg/kg) and daily rifampin given for 9 mo sponsored by the British Medical Research Council was completed in 155 adult patients (151). Sputum conversion was achieved in 99.4% of patients, but with a relapse rate of 10% with a 5 year follow-up. This suggests that isoniazid does not contribute greatly to the treatment of *M. kansasii*; however, 9 mo is not a long enough treatment period for the studied two-drug regimen.

In adult patients whose organisms have become resistant to rifampin as a result of previous therapy, a regimen consisting of high-dose daily isoniazid (900 mg), pyridoxine (50 mg daily), high-dose ethambutol (25 mg/kg per day), and sulfamethoxazole (1.0 gm three times per day) until the patient is culture-negative for 12 to 15 mo has been under investigation (133, 134). The oral therapy has been combined with daily or five times per week streptomycin or amikacin for the initial 2 to 3 mo, followed by intermittent streptomycin or amikacin for a total of 6 mo. Results with this regimen described sputum conversion in 18 of 20 patients (90%) after a mean of 11 wk, with only one relapse (8%) among patients who were culture-negative for at least 12 mo on therapy (134). The excellent *in vitro* activity of clarithromycin against *M. kansasii* (134) suggests this agent will also be highly useful in retreatment regimens, perhaps allowing for omission of the aminoglycoside. The newer quinolones may also be potentially useful in this setting but have not been studied.

For treatment of extrapulmonary disease in adults, the regimen of antimycobacterial drugs should be the same as for pulmonary disease. Pulmonary disseminated disease has been described in patients with AIDS (59), and it is the second most common NTM that produces disease in this setting (51). Of the cases detailed in the literature, most have been fatal (59). In the treatment of lymph node disease in children, excision of all accessible nodes at the time of the initial biopsy should be done, since the etiologic agent is probably an NTM other than *M. kansasii*, for which excision is the indicated treatment.

The use of protease inhibitors for the treatment of HIV disease complicates the management of *M. kansasii* disease because rifampin dramatically enhances the metabolism of these drugs and cannot be used with them concurrently. Options for treating HIV-infected patients who receive a protease inhibitor are to substitute clarithromycin for rifampin in the standard regimen, or to substitute rifabutin 150 mg/d for rifampin if the patient is receiving indinavir. None of these regimens have been studied clinically; however, they appear likely to be successful.

TREATMENT OF PULMONARY *Mycobacterium avium* COMPLEX DISEASE (*M. avium, M. intracellulare*)

Medical treatment of *M. avium* complex pulmonary disease in HIV-negative patients has historically been frustrating and disappointing. In the few studies in which initial sputum conversion rates have been high (> 80%), long-term follow-up to establish continued sputum conversion is rarely documented (152–156). Relapses after medical therapy with premacrolide treatment regimens are common, and the best outcomes have frequently been in those patients subjected to resectional surgery (157, 158). Recent significant advances in the drugs available for treatment of *M. avium* complex have been made, however, and there is now greater expectation that pulmonary *M. avium* complex disease can be effectively treated (defined as high rates of sputum conversion with long-term culture negativity) with medications alone.

The major limitations for effective therapy have been the absence of antimicrobial agents with low toxicity and good *in vivo* activity against the organism. Most first-line antituberculosis drugs have 10–100 times less *in vitro* activity against *M. avium* complex isolates than against *M. tuberculosis*. This diminished activity may be due to the lipophilic cell wall of *M. avium* complex, which prevents drug penetration (159).

The major therapeutic advances in the treatment of pulmonary *M. avium* complex disease have come as a result of prog-

ress in treating disseminated *M. avium* complex in the setting of HIV disease. Recent studies have shown excellent *in vivo* and clinical activity against *M. avium* complex by the newer macrolides, clarithromycin and azithromycin, presumably due to the high phagocyte and tissue levels achieved by these agents. (The structure of azithromycin is technically an azalide; however, because of the close similarity of azalides to macrolides, the term macrolide will be used to refer to both in subsequent discussion.) Human trials of patients with disseminated *M. avium* complex disease and AIDS have shown both newer macrolides to have clinical and microbiologic activity as monotherapy (160–163) and clarithromycin to have clinical and microbiologic activity in drug combinations (162). Studies have also demonstrated significant sterilizing activity of both azithromycin and clarithromycin with short-term initial treatment as single agents in pulmonary *M. avium* complex disease (164, 165). Although it is not appropriate to treat patients with disease (outside of clinical trials) with single agents, these are the first studies demonstrating significant *in vivo* activity of any single agent for pulmonary *M. avium* complex disease.

Rifabutin, a derivative of rifamycin S, has been shown to be more active *in vitro* than rifampin against isolates of *M. avium* complex (117). Peak serum rifabutin concentrations are much lower than those of rifampin and exceed the MICs for only approximately 70% of *M. avium* complex strains (123). The relevance of this finding is uncertain, given higher levels of the drug in tissue than in serum. Rifabutin has demonstrated effectiveness as a prophylactic agent against disseminated *M. avium* complex disease in AIDS (54), and there is some evidence of improved clinical response of pulmonary *M. avium* complex disease in HIV-negative patients when rifabutin is added to multidrug regimens (166). The newer macrolides and rifabutin form the basis of improved treatment regimens for pulmonary *M. avium* complex disease.

Clinical Presentations

The natural history of *M. avium* complex lung disease is unpredictable in HIV-negative patients. Some patients maintain a stable clinical and radiographic picture for years, whereas others have a relatively rapid progression of their disease. The variability in the natural history of *M. avium* complex lung disease appears to relate in part to the presence of two types of clinical disease and presentation. The traditional presentation of *M. avium* complex lung disease has been as apical fibrocavitary lung disease, sometimes with huge cavities, in males in their late 40s and early 50s who have a history of heavy cigarette smoking and, frequently, alcohol abuse. This form of disease is generally progressive within 1 to 2 yr if left untreated. More recently, it has become apparent that *M. avium* complex lung disease also presents as bilateral nodular and interstitial/nodular disease or as isolated right middle lobe or lingular disease, predominantly in elderly nonsmoking females (71–74, 167). These syndromes were often referred to as *M. avium* complex "colonization," with bronchiectasis considered to be the only real disease. This form of disease (nodular bronchiectasis) tended to have a much slower progression, such that long term follow-up (5–10 yr) was often needed to show clinical or radiographic changes. For the nodular bronchiectatic forms of *M. avium* complex lung disease, sputum submission for AFB analysis was often delayed months to years as the patient had radiographic and symptomatic progression.

In the past, many patients with nodular bronchiectatic *M. avium* complex disease received a variety of nonspecific measures ("pulmonary toliet") rather than specific antimycobacterial therapy for their pulmonary disease. These nonspecific therapies included bronchodilators, postural drainage, smoking cessation, and broad spectrum antibiotics (77). Clearly, these measures may be appropriate and can be associated with symptomatic improvement in bronchiectasis unrelated to any effect on *M. avium* complex. Before the development of newer, more active agents against *M. avium* complex, it had been proposed that patients in this group with a stable clinical picture (usually over 3–6 mo) and minimal symptoms, and those whose sputum "cleared" with nonspecific therapy, should not be treated. However, based on recent studies using chest HRCT scans, these patients have specific radiographic features of parenchymal disease in addition to their multifocal bronchiectasis (71–74). The term "colonization" is, therefore, incorrect. The appropriate distinction is not between colonization and invasive disease but between those patients with the disease of nodular bronchiectasis who require immediate therapy directed at *M. avium* complex and those in whom such a decision can be delayed. If a decision is made to observe such a patient (e.g., one with minimal symptoms and radiographic findings such that the treatment seems worse than the disease, or one with other major medial problems), it is incumbent upon the treating physician to continue collecting respiratory specimens for AFB analysis as well as follow-up chest radiographs and/or CTs over a relatively long period of time (perhaps the patient's entire lifetime), as the *M. avium* complex disease will likely progress at some time and the patient's symptoms and chest radiographs will likely worsen. We recommend careful evaluation of each respiratory *M. avium* complex isolate in the context of the patient's overall status. In general, almost any patient with two or three positive respiratory cultures for *M. avium* complex has *M. avium* complex lung disease. Although not all patients with an *M. avium* complex respiratory isolate will require immediate therapy, the clinician must resist the temptation to make facile clinical decisions, particularly if that decision is to not treat a patient with a *M. avium* complex respiratory isolate. As treatment regimens improve both in effectiveness and the ability of the patient to tolerate the medications, there should be less reluctance to treat *M. avium* complex lung disease at an earlier stage. For patients with substantial symptoms and/or advanced or progressive radiographic abnormalities, an observation period is not needed to establish the need for therapy.

Drug Treatment

Drug therapy for *M. avium* complex disease involves multiple drugs; therefore, the risk of drug toxicities is relatively high. Additionally, the optimal therapeutic regimen has yet to be established. For these reasons, the treatment of *M. avium* complex disease may best be served by physicians experienced in pulmonary or mycobacterial diseases.

With empiric combination regimens that include clarithromycin and usually ethambutol and a rifamycin (rifampin or rifabutin), sputum conversion rates for pulmonary *M. avium* complex disease in adult patients able to tolerate the medications are about 90% (164, 168, 169). Rifabutin is the preferred rifamycin because it is more active *in vivo* than rifampin against *M. avium* complex, but it may also produce more problematic adverse events (uveitis, leukopenia). All untreated strains of *M. avium* complex are macrolide susceptible (clarithromycin MICs of 0.25 of 4.0 μg/ml), while microbiologic relapses associated with symptom recurrence reveal isolates with MICs of > 32 μg/ml (170). Patients with either pulmonary or disseminated *M. avium* complex do not respond to macrolide-containing regimens in which the macrolide is the sole or principle agent if the patient's isolate is macrolide resistant *in vitro* (161,

164, 168, 169). Isolates of *M. avium* complex resistant to clarithromycin are cross-resistant to azithromycin (170).

The newer macrolides are the cornerstone of contemporary therapy for pulmonary *M. avium* complex disease, as they are for disseminated *M. avium* complex disease. Initial therapy for adult HIV-negative patients with *M. avium* complex disease needing treatment should consist of a minimum three-drug regimen of clarithromycin (500 mg twice a day) or azithromycin (250 mg/d or 500 mg three times a week), rifabutin (300 mg/d) or rifampin (600 mg/d), and ethambutol (25 mg/kg per day for 2 mo followed by 15 mg/kg per day). For patients of small body mass and/or an age over 70, clarithromycin at 250 mg twice a day or azithromycin 250 mg three times a week may be better tolerated. Studies are currently ongoing to determine the feasibility and efficacy of both azithromycin- and clarithromycin-containing regimens with all drugs given intermittently (three times weekly) for pulmonary *M. avium* complex disease.

The potential and method for treating pediatric patients (e.g., those with underlying cystic fibrosis) with the above regimen has not been studied, nor have drug doses for the newer agents such as clarithromycin and rifabutin.

Intermittent streptomycin for the first 2 to 3 mo of therapy may be considered, in addition to the above regimen, for extensive disease. The exact dose of streptomycin in this multidrug regimen will depend on the patient's age and weight. For extensive disease, we recommend at least 2 mo of intermittent (twice or three times weekly) streptomycin, although longer therapy with streptomycin may be desirable in patients with very extensive disease or for those who do not tolerate other agents. There are no data, however, comparing clarithromycin-containing regimens with and without an aminoglycoside. The patient and physician should be alert to signs and symptoms of streptomycin toxicity, and these may prevent completion of the full course of therapy. Because ototoxicity due to streptomycin is often irreversible, patients receiving streptomycin should be instructed in the signs and symptoms of toxicity (unsteady gait, tinnitus, diminished hearing) at the start of therapy and again on subsequent visits, with discontinuation or decrease in dosage or frequency if suggestive signs of toxicity occur. Suggested doses of streptomycin based on patient age and weight are shown in Table 4.

The optimal length of drug therapy for *M. avium* complex lung disease has not been established. Recommendations in the premacrolide era were that patients be treated for 18 to 24 mo without considering how long the sputum culture results were negative. This recommendation was based on empiric data, in part, drawing from the early experience in treating tuberculosis. With macrolides, a shorter length of therapy seems acceptable. Only two long-term studies of *M. avium* complex lung disease have been reported to date, both investigating clarithromycin (168, 169). One study using 12 mo of culture negativity as the treatment endpoint observed no pulmonary disease relapses with a mean follow-up of 18 mo (168), while the second study, which used 7 to 9 mo of culture negativity, resulted in no early pulmonary disease relapses with a mean follow-up of 7 mo (169). Early relapses with less than 10 mo of culture negativity were seen in the first study. These initial studies suggest that culture negativity of 10 to 12 mo while on a clarithromycin-containing regimen is adequate for most patients.

TABLE 4

SUGGESTED DOSES OF STREPTOMYCIN RELATIVE TO AGE AND WEIGHT IN PATIENTS WITH NORMAL SERUM CREATININE*

Weight and Age	Initial Therapy†	Maintenance Therapy‡
⩾ 50 kg and ⩽ 50 yr	1 g 5×/wk	1 g 3×/wk
< 50 kg and ⩽ 50 yr	500 mg 5×/wk	750 mg 2×/wk
> 50 kg and 50–70 yr	500 mg 5×/wk	750 mg 2×/wk
> 70 yr	750 mg 2×/wk	750 mg 2×/wk

* These doses have not been established as optimal by clinical trials. The reduced doses with age reflect the reduced renal funtion and increased risk of toxicity with streptomycin seen in patients older than 50 yr.

† For the first 6 to 12 wk of therapy as tolerated.

‡ For subsequent therapy as tolerated.

Acid-fast bacilli smears and cultures of sputum should be obtained monthly during therapy for pulmonary *M. avium* complex disease to assess response, then periodically after completion of therapy to evaluate possible relapse. The desired endpoint is negative sputum cultures; patients who respond to therapy should develop negative AFB smears and cultures. One or more cultures containing small numbers of *M. avium* complex organisms (single colonies on solid media or positive liquid media cultures only) may occur after sputum conversion and should not necessarily be interpreted as indicative of treatment failure or relapse. Rather, these culture results should be interpreted in light of the patient's overall clinical status.

All patients should show clinical improvement within 3 to 6 mo and should convert their sputum to negative within 12 mo on macrolide-containing regimens (168). Thus, patience is required in evaluating response to therapy. However, failure to respond in these time periods should prompt investigation for possible noncompliance or macrolide resistance.

For patients whose disease has failed to respond to a macrolide-containing regimen (usually as a consequence of *in vitro* macrolide resistance, noncompliance, or drug intolerance) and have progressive, symptomatic disease, an alternative drug regimen will be necessary. The treatment for pulmonary *M. avium* complex disease in HIV-negative adult patients as recommended in the first ATS NTM statement published in 1990, consisted of the four-drug regimen of isoniazid (300 mg/d), rifampin (600 mg/d), ethambutol (25 mg/kg per day for the first 2 mo, then 15 mg/kg per day) with streptomycin for the initial 3 to 6 mo of therapy (1). With the use of rifabutin instead of rifampin, this may be a reasonable regimen for patients who are macrolide resistant or intolerant. Which drugs are most useful in treating macrolide-resistant strains is a major issue to be addressed in future studies as resistant strains become more prevalent. Although there are no trials comparing regimens with and without a macrolide for treating pulmonary *M. avium* complex, most experts consider the regimen without a macrolide to be inferior, and one such regimen (rifampin, ethambutol, ciprofloxacin, and clofazimine) has been shown to be inferior to a clarithromycin-containing regimen for disseminated *M. avium* (171).

A number of other drugs have been used in multidrug regimens in the past, but they are limited by toxicity (e.g., cycloserine and ethionamide) or little or no evidence of clinical efficacy (e.g., clofazamine, newer quinolones, capreomycin). Some experts feel that clofazimine 100 mg/d and ciprofloxacin 750 mg twice daily or ofloxacin 400 mg twice daily are useful in the setting of *M. avium* complex lung diseases, although there are no data corroborating their efficacy. Therapy with only two drugs, especially isoniazid and rifampin only, is strongly discouraged and not likely to be effective. Antituberculosis drugs are generally well tolerated, even by the elderly population with *M. avium* complex lung disease.

If patients are unable to tolerate or fail first-line antituberculosis medications, an alternative "salvage" regimen should

be considered with potential agents including ciprofloxacin 750 mg twice daily or ofloxacin 400 mg twice daily, clofazimine 100 mg daily, ethionamide (250 mg twice a day, then increased to three times a day as tolerated), and prolonged use of streptomycin or amikacin (three to five times per week). A multiple drug regimen including these potentially toxic drugs can also be associated with at least short-term conversion of the sputum to AFB-negative. The long-term success rate for salvage regimens is unknown but is likely very low.

The role of immune therapy in patients who fail drug therapy has not been established. Interleukin and gamma interferon have been used in selected patients, and some investigation in this area continues.

Surgical Treatment

Patients whose disease is localized to one lung and who can tolerate resectional surgery might also be considered for surgery, if there has been poor response to drug therapy or if the patient's isolate has become macrolide resistant. For some patients successfully treated by surgical resection, the prognosis has been better than for patients treated medically, although these results predated the use of macrolide-containing regimens (157, 158). Lung resectional surgery for mycobacterial disease is associated with significant morbidity and mortality (172, 173). In one recent series from a thoracic surgeon experienced in mycobacterial surgery, 8 of 38 (21%) of patients undergoing surgery and 8 of 17 (47%) of patients undergoing pneumonectomy developed postoperative bronchopleural fistulae, especially following a right pneumonectomy (172). Whenever possible, this surgery should be performed at centers with thoracic surgeons who have considerable experience with this type of surgery. Overall, the bilateral nature of *M. avium* complex lung disease, the advanced age of the patients, and the frequency of underlying chronic lung disease have limited the number of patients who are good candidates for surgery.

Toxicity Monitoring

Monitoring of patients for toxicity, given the number of drugs and the older age of these patients, is essential. Monitoring should include visual acuity (ethambutol and rifabutin), red-green color discrimination (ethambutol), liver enzymes (clarithromycin, azithromycin, rifabutin, rifampin, isoniazid, ethionamide) (174), auditory and vestibular function (streptomycin, amikacin, clarithromycin, azithromycin), renal function (streptomycin and amikacin), leukocyte and platelet counts (rifabutin) (175, 176), and the central nervous system (cycloserine). Patients who receive both a macrolide and rifabutin must be monitored for the development of toxicity related to the interaction of these drugs (175, 176). Clarithromycin enhances rifabutin toxicity (especially uveitis) while the rifamycins, rifampin more than rifabutin, lower clarithromycin serum drug levels. Details are provided in the section on monitoring for drug toxicity.

TREATMENT OF LOCALIZED EXTRAPULMONARY *Mycobacterium avium* COMPLEX DISEASE

Lymphadenitis

Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis, including those with disease caused by *M. avium* complex and *M. scrofulaceum* (79, 80, 177, 178). The success rate with this procedure is about 95% (79). Incisional biopsy or the use of antituberculosis drugs alone (without a macrolide) has frequently been followed by persistent clinical disease, including sinus tract formation and chronic drainage, and should be avoided (79, 80, 177, 178). For children with recurrent disease, a second surgical procedure is usually performed. An alternative for recurrent disease or for children in whom surgical risk is high (e.g., risk of facial nerve involvement) may be the use of a clarithromycin multidrug regimen such as that used for pulmonary disease (80, 179, 180). Experience with such an approach is limited (179–182), but the proven activity of clarithromycin against *M. avium* complex in other clinical settings and preliminary reports makes this approach appear promising.

A special problem is created by the child who has granulomatous disease with or without AFB on examination of the excised lymph nodes, and whose PPD tuberculin skin test is strongly positive (e.g., more than 15 mm). A course of antituberculosis therapy while awaiting the results of the lymph node culture is reasonable, especially when there are any risk factors for tuberculosis (positive family history, foreign-born child, etc.). If the cultures fail to yield any mycobacteria, antituberculosis therapy should be discontinued unless there are significant risk factors for tuberculosis.

Skin, Tissue, and Skeletal Disease

For adult patients with extrapulmonary, localized *M. avium* complex disease involving skin, soft tissue, tendons and joints, and occasionally bone, a combination of excisional surgery (or surgical debridement) and chemotherapy is usually performed. Whether a three-drug regimen alone in this setting would be adequate is not known. The optimal duration of treatment is also unknown, but drug treatment usually lasts 6 to 12 mo.

TREATMENT OF DISSEMINATED *Mycobacterium avium* DISEASE

Disseminated *M. avium* is associated with an increased mortality in patients with AIDS. In one natural history study, the median survival was 134 d after the first positive blood culture, and only 13% of patients were alive at 1 yr (53). Initially, some clinicians questioned whether *M. avium* was a direct cause of death or only present in persons who were dying of other reasons. Several controlled studies have shown shortened survival in patients with disseminated *M. avium* when compared to cohorts of patients without *M. avium* (183). Based on the increased morbidity and mortality associated with disseminated *M. avium*, prophylaxis should be strongly considered in high-risk patients and therapy should be offered to all patients with established disease.

Early (premacrolide) studies of the treatment of *M. avium* in patients with AIDS demonstrated the ability of multidrug regimens to lower the burden of mycobacteria in the blood and improve symptoms (184, 185). The drugs used in these studies such as ethambutol, clofazamine, rifampin, and ciprofloxacin have been shown to have modest activity *in vitro*, and two of the agents (ethambutol and rifabutin) to have modest activity in single-drug therapy studies of patients with AIDS and *M. avium* (186, 187). A major advance in therapy came with the recognition that clarithromycin and azithromycin were potent agents against *M. avium* complex. Both clarithromycin and azithromycin were shown to markedly reduce the number of bacteria in the blood of patients in small pilot studies (160, 163). In a larger study of 154 adult patients with AIDS and *M. avium* bacteremia, clarithromycin was given as single-drug therapy in doses of 500, 1,000 or 2,000 mg twice daily. All three groups had clearance of bacteremia and reduction in symptoms, although the groups receiving the higher doses had greater toxicity and a higher mortality (161). It was also noted, however, that resistance was a problem, as clinical

relapse and *in vitro* resistance developed in approximately 20% of individuals by 12 wk.

Rifabutin has also been demonstrated to be effective in several small studies of patients with AIDS who had disseminated *M. avium* (184, 188). As monotherapy, it was shown to reduce colony counts in the blood (187). Clearance of bacteremia occurred in 7 of 11 patients receiving rifabutin, clofazamine, and ethambutol, compared to 0 of 13 patients with clofazimine alone in another study (188).

Due to problems with drug resistance, as well as the need to eradicate large numbers of organisms, multidrug therapy is considered essential in the treatment of patients with disseminated *M. avium*. There are currently few well done comparative trials of the many possible multidrug regimens. A Canadian HIV Trials Network study (171) involving 229 patients did demonstrate the combination of clarithromycin, rifabutin, and ethambutol to be superior to rifampin, ethambutol, clofazimine, and ciprofloxacin at both reducing bacteremia (69% versus 29%, $p < 0.001$) and prolonging median survival (8.6 mo versus 5.2 mo, $p = 0.001$).

Based on currently available data, it would be advisable to always use a minimum of three drugs—one of which should be clarithromycin (500 mg twice daily) or azithromycin (250 mg or 500 mg daily). Most investigators would use ethambutol as the second agent at a dose of 15 mg/kg per day, although consideration should be given to an initial course of 25 mg/kg for the first 2 mo. Rifabutin has the best potential as the third agent. Use of rifabutin will be problematic, however, in patients also on protease inhibitors, given its induction of the cytochrome P-450 system that metabolizes all currently approved members of this drug class. Clofazimine has also been used, as has a quinolone, but neither seems to contribute much to the regimen, and clofazimine has been associated with a higher mortality in two comparative treatment trials (189). Amikacin (191) and streptomycin are both active, and one or the other should be considered for use in patients with severe symptoms due to *M. avium* complex, especially as part of initial therapy.

It should be noted that drugs used to treat mycobacterial diseases in patients with AIDS are associated with frequent adverse effects, and changes to therapeutic regimens may often be required. Of particular note has been the frequent occurrence of uveitis when doses of clarithromycin higher than 500 mg twice daily have been used in combination with rifabutin doses of 600 mg daily (175). This incidence fell to only 6% (3 of 53 patients) in the Canadian HIV trial when the rifabutin dose was reduced to 300 mg daily, the currently recommended dose (171).

Another problem is the interaction of rifamycins with the recently introduced protease inhibitors (saquinavir, ritonavir, and indinavir) for treatment of AIDS. Rifampin, and to a lesser degree rifabutin, enhances hepatic metabolism of the protease inhibitors, which may result in subtherapeutic levels of these agents and promote the emergence of resistant HIV strains. The protease inhibitors inhibit metabolism, and therefore promote dose-related adverse effects, of the rifamycins (especially rifabutin). Recent recommendations, made in the context of tuberculosis therapy, suggest that rifampin should not be used with the protease inhibitors, but that rifabutin can be used at modified doses with at least one of these agents, indinavir (190). This recommendation would have little impact on the treatment or prophylaxis of disseminated *M. avium* disease since rifabutin is the preferred rifamycin. The impact on the treatment of other NTM such as *M. kansasii*, where rifampin has traditionally been used, is less clear. Alternative strategies include treatment of NTM infections without a rifamycin or withholding the protease inhibitor until the mycobacterial infection has been treated. The improved immune function resulting from aggressive antiretroviral therapy, including a protease inhibitor, might ultimately be the most important factor for clearance of disseminated NTM infection in AIDS patients; therefore, continuing a protease inhibitor is a high priority. Optimal therapy for disseminated NTM disease, especially *M. avium*, requires a multidrug treatment regimen including a rifamycin. Overall, in a patient on protease inhibitors with proven disseminated *M. avium*, it still seems prudent to include rifabutin in the treatment regimen, even if the dose is attenuated. For other NTM, the importance of the rifamycin should be evaluated based on the specific organism being treated.

PROPHYLAXIS OF DISSEMINATED DISEASE IN AIDS

The incidence of disseminated *M. avium* can be reduced by prophylactic antimicrobials. Rifabutin was demonstrated to be effective in two placebo-controlled, double-blind studies. *Mycobacterium avium* bacteremia developed in 8% of adult patients receiving 300 mg of rifabutin daily and in 17% of patients on placebo (54). Because rifabutin is highly active against *M. tuberculosis*, it is probable that daily use of rifabutin would also provide prophylaxis against tuberculosis. Active tuberculosis must be ruled out before initiating rifabutin prophylaxis in order to prevent the development of drug-resistant tuberculosis. Clarithromycin in a dose of 500 mg twice daily was effective in a controlled trial of 667 adult patients in reducing the incidence of *M. avium* complex bacteremia from 16% in the placebo group to 6% in the treatment group (192, 193), while in a related trial it was shown to be more effective than rifabutin (193). Azithromycin at a dose of 1,200 mg once weekly, either alone or in combination with rifabutin, has also been shown to be effective in a published clinical trial involving 693 adult patients (194). The final selection of agents may depend on cost, tolerability, and potential drug interactions of the agents. Rifabutin should generally be avoided in patients on protease inhibitors because it markedly enhances their metabolism and reduces serum levels of the protease inhibitors. Some clinicians and the United States Public Health Service have advocated use of indinavir but not other currently available protease inhibitors (retonavir, saquinquir) with reduced-dose rifabutin if both drugs are deemed essential.

The development of drug resistance during prophylaxis is a concern, and it has already been noted to occur with the use of clarithromycin (192, 193) or azithromycin (194) as monotherapy, but not the rifabutin monotherapy (54) or azithromycin when combined with rifabutin (194). Because of the very high risk of disseminated *M. avium* in persons with advanced HIV infection, prophylaxis should be offered to all patients with < 50 CD4 cells, especially in patients with a history of opportunistic infection (195, 196).

TREATMENT OF RAPIDLY GROWING MYCOBACTERIAL DISEASE

Disease caused by the rapidly growing mycobacteria, especially cutaneous disease, has come to be recognized as relatively common in selected areas of the United States. The southeastern United States from Georgia to Texas appears to be the major endemic area, although disease has been reported from all over the United States. Most clinical disease is sporadic and community acquired, although nosocomial outbreaks or clustered cases have been reported (16–26), and the association of rapidly growing mycobacteria wound infections

with augmentation mammoplasty (23, 93) and cardiac surgery (16, 17, 21, 94) is well recognized.

Most clinical disease (more than 90%) is due to three species of rapidly growing mycobacteria: *M. fortuitum, M. abscessus,* and *M. chelonae* (91). Two taxa originally identified as biovariants within *M. fortuitum* (*M. fortuitum* third biovariant complex, sorbitol-positive and sorbitol-negative) are still undergoing taxonomic evaluation. Both groups may eventually attain species status. *Mycobacterium smegmatis* (197), *M. peregrinum* (91), *M. mucogenicum* (formerly known as the "*M. chelonae*-like organisms" or MCLO) (198), and rarely, chromogenic rapidly growing mycobacteria (199–201) may also occasionally be responsible for human disease.

Mycobacterium fortuitum, M. abscessus, and *M. chelonae* are resistant to the antituberculous agents, but they are susceptible (especially *M. fortuitum*) to a number of traditional antibacterial agents (100, 138–141). Isolates of *M. fortuitum* treatment are susceptible to amikacin (100%), ciprofloxacin and ofloxacin (100%), sulfonamides (100%) cefoxitin (80%), imipenem (100%), clarithromycin (80%), and doxycycline (50%). Isolates of *M. abscessus* are susceptible to clarithromycin (100%), clofazimine, amikacin (90%), and cefoxitin (70%) and imipenem (50%). Isolates of *M. chelonae* are susceptible to amikacin (80%), tobramycin (100%), clarithromycin (100%), imipenem (60%), clofazimine, doxycycline (25%), and ciprofloxacin (20%).

Cutaneous Diseases

Clinical disease caused by the rapidly growing mycobacteria usually follows accidental trauma or surgery in a variety of clinical settings (91). Some minor infections will resolve spontaneously or after surgical debridement. However, several studies of postinjection abscesses in which no therapy was given revealed disease that persisted in most patients for 8 to 12 mo before spontaneously resolving. In two outbreaks of sternal wound infections caused by *M. abscessus* in the era when little was known of chemotherapy or surgery for these organisms, approximately one-third of the patients died of uncontrolled infection (16, 17). Drug therapy or combined surgical and medical therapy clearly produce better results than these historical controls.

No controlled clinical trials of treatment for disease caused by *M. fortuitum, M. abscessus,* or *M. chelonae,* comparing one form of treatment with another or with no drug treatment at all, have been performed. However, susceptibility studies (139–141) have demonstrated excellent *in vitro* activity of drugs such as clarithromycin, imipenem, cefoxitin, cefmetazole, and amikacin. Several case studies (197, 202, 203) and one clinical trial (204) of patients with cutaneous disease treated on the basis of *in vitro* susceptibilities have shown good results.

On the basis of these studies, guidelines have been suggested for drug therapy of nonpulmonary disease caused by rapidly growing mycobacteria (205). Because of variable drug susceptibility among species and even within species and subgroups, susceptibility testing of all clinically significant isolates is essential for good patient management. The first-line antituberculosis drugs (isoniazid, rifampin, pyrazinamide, etc.) have no role in the therapy of rapidly growing mycobacterial disease, with the exception of ethambutol, to which *M. smegmatis* is susceptible (197).

For serious disease caused by *M. fortuitum* and *M. abscessus,* intravenous amikacin is given at a dose of 10 to 15 mg/kg in two divided doses to adult patients with normal renal function (average 400 mg twice a day) to provide peak serum levels in the low 20 μg/ml range. The lower dose (10 mg/kg) should be used in patients over the age of 50; once-daily dosing is unproven clinically but appears reasonable. The amikacin combined with high-dose cefoxitin (12 g/d given intravenously) is recommended for initial therapy (minimum 2 wk) until clinical improvement is evident. For *M. chelonae,* tobramycin is more active *in vitro* than amikacin. Imipenem appears to be a reasonable alternative to cefoxitin for these two species, and it should be used with isolates of *M. smegmatis* and *M. chelonae* that are resistant to cefoxitin (100, 139, 197). Monitoring of renal function, eighth nerve function, and white blood cell counts (for the beta lactams) should be done on patients receiving this regimen. If organisms are susceptible to oral agents, therapy can be switched to one or more of these agents. For *M. abscessus,* the only oral agents available for therapy are clofazimine and clarithromycin (140). For *M. chelonae,* clarithromycin, clofazimine, and (for approximately 20% of strains) ciprofloxacin and doxycycline are the only oral drugs susceptible *in vitro* (100, 140). The only clinical trial for *M. chelonae* skin disease was done with clarithromycin. Of patients (all adults) treated with monotherapy at 500 mg twice a day for 6 mo, all were cured except one patient (8%) who relapsed with an isolate that developed resistance to clarithromycin (204). For serious disease, a minimum of 4 mo of therapy is necessary to provide a high likelihood of cure. For bone infections, 6 mo of therapy is recommended (202).

Surgery is generally indicated with extensive disease, abscess formation, or where drug therapy is difficult. Removal of foreign bodies such as breast implants, percutaneous catheters, etc., is important, or even essential, to recovery.

Pulmonary Disease

The prevalence of lung disease caused by rapidly growing mycobacteria is unknown; however, it is likely more common than early estimates as these organisms have gained increasing recognition as pathogens. The largest group of patients with this lung disease are elderly (older than 60), Caucasian, female nonsmokers with no predisposing conditions or known lung disease. Underlying disorders that are associated with the disease include lung damage produced by prior mycobacterial infection (usually tuberculosis or *M. avium* complex), gastroesophageal disorders with chronic vomiting, lipoid pneumonia, cystic fibrosis, and bronchiectasis due to a prior respiratory infection (206). The distinguishing feature of patients with a recognized underlying disease is that their rapidly growing mycobacteria lung disease occurs at a younger age, usually less than 50, and almost all patients under 40 have one of these disorders (206).

Although early studies identified most respiratory isolates of rapidly growing mycobacteria as *M. fortuitum,* use of modern identification schemes have shown that *M. abscessus* (formerly *M. chelonae* subspecies *abscessus*) accounts for approximately 80% of rapidly growing mycobacterial respiratory disease isolates, while *M. fortuitum (*formerly *M. fortuitum* biovariant *fortuitum*) accounts for approximately 15% of these isolates (206). An important exception is the small group of patients who have gastroesophageal disorders with chronic vomiting and rapidly growing mycobacterial lung disease, in whom *M. abscessus* and *M. fortuitum* occur with equal frequency. Overall, *M. abscessus* appears to be a more virulent respiratory pathogen than *M. fortuitum*. Obtaining a single respiratory isolate of *M. abscessus* is more likely to indicate significant disease than a single isolate of *M. fortuitum,* although careful clinical evaluation and follow-up is always necessary to determine the significance of an NTM respiratory isolate.

In lung disease due to rapidly growing mycobacteria in patients with no apparent risk factors, the chest radiograph usu-

ally shows multilobar, patchy, reticulonodular or mixed interstitial-alveolar infiltrates with an upper lobe predominance. Cavitation occurs in only approximately 15% of cases (206). The chest radiograph is usually not typical for or suggestive of reactivation pulmonary tuberculosis, which likely accounts for a delay in ordering sputum for AFB analysis and therefore a delay in diagnosis. High resolution computed tomography of the lung frequently shows associated cylindrical bronchiectasis and multiple small (< 5 mm) nodules, a pattern also seen in nonsmokers with *M. avium* complex lung disease (65–68). Interestingly, approximately 15% of patients with *M. abscessus* will also have *M. avium* complex, suggesting the close relationship of the disorders (206). Some patients have positive sputum cultures for *Pseudomonas aeruginosa*, further evidence of bronchiectasis. The radiographic features of this disease in cystic fibrosis are still under investigation.

The usual presenting symptoms are cough and easy fatigability, often attributed for months or years to bronchitis or bronchiectasis. Fever, night sweats, and weight loss occur, but they are much less common and less severe than with *M. tuberculosis*. The constellation of typical presenting symptoms in an elderly nonsmoking patient with no underlying lung disease, a compatible chest radiograph, and multiple positive sputa is sufficient to make a diagnosis. The presence of other diseases or unusual features may necessitate obtaining a lung biopsy (bronchoscopy with transbronchial biopsy) to be certain of the diagnosis.

The natural history of this disease depends primarily on the presence or absence of underlying disorders. For most patients with *M. abscessus* and no underlying disorder, the disease is indolent and slowly progressive. Some patients show little radiographic change over years. More fulminant, rapidly progressive disease can occur, particularly in association with gastroesophageal disorders. Death occurs as a consequence of *M. abscessus* in 20% of cases (206).

Mycobacterium fortuitum isolates, when they do occur, are usually susceptible to multiple oral antimicrobial agents including the newer macrolides and quinolones, doxycycline and minocycline, and sulfonamides (139–141). Drug susceptibilities for this species are essential for effective therapy. Six to twelve months of therapy with two oral agents to which the *M. fortuitum* isolate is susceptible *in vitro* usually results in clinical cure. Unfortunately, the *M. fortuitum* group produces less than 20% of lung disease due to rapidly growing mycobacteria.

Mycobacterium abscessus isolates are usually susceptible *in vitro* only to the parenteral agents amikacin, cefoxitin, and imipenem, and to the newer oral macrolides (clarithromycin and azithromycin). Preliminary studies suggest that monotherapy with the newer macrolides is not sufficient to produce microbiologic cure for *M. abscessus*. Combination therapy of low-dose amikacin plus high-dose cefoxitin for 2–4 wk almost invariably produces clinical and microbiologic improvement, but cost and morbidity prohibit potentially curative courses of treatment (probably 4–6 mo). Surgical resection for limited disease related to prior localized lung disease can also be curative (206). Unfortunately, suppressive therapy, including periodic parenteral antibiotic or oral macrolide therapy, may be all that can be realistically administered to control the symptoms and progression of *M. abscessus* lung disease.

TREATMENT OF *Mycobacterium marinum* DISEASE

A number of treatment modalities have been used for cutaneous disease caused by *M. marinum* (69, 13). These include simple observation for minor lesions, surgical excision, the use of antituberculous agents, and the use of single antibiotic agents. By standard susceptibility testing, these isolates are susceptible to rifampin and ethambutol, intermediately susceptible to streptomycin, and resistant to isoniazid and pyrazinamide. Isolates are also susceptible to clarithromycin, sulfonamides, or trimethoprim-sulfamethoxazole and susceptible or intermediately susceptible to doxycycline and minocycline.

Acceptable treatment regimens in adults include clarithromycin 500 mg twice a day, minocycline or doxycycline at 100 mg twice a day (207–209), trimethoprim-sulfamethoxazole at 160/800 mg twice a day (210), or rifampin (600 mg) plus ethambutol (15 mg/kg) daily (208, 211), with each regimen being given for at least 3 mo. Rifampin alone has also been recommended, but little experience with this regimen has been reported (212). The rate of clinical response is quite variable, and a minimum of 4 to 6 wk of therapy should be given before considering that the patient may not be responding. Surgical debridement may also be important, especially for disease involving the closed spaces of the hand or disease that responds poorly to drug therapy (13, 211). If a lesion is excised surgically, many clinicians provide drug coverage during the perioperative period. It is not clear if longer durations of drug treatment after surgery offer any additional advantage.

TREATMENT OF PULMONARY DISEASE DUE TO OTHER NONTUBERCULOUS MYCOBACTERIA

Although most species of NTM have been reported to cause pulmonary disease, there are only four additional species that merit consideration. Because of the small number of reported cases and the absence of therapeutic trials or treatment of disease caused by these species, only limited recommendations on drug therapy can be made now. In most cases, if there has been satisfactory clinical and bacteriologic response to chemotherapy, a treatment period of 18 to 24 mo is recommended.

Mycobacterium malmoense is a slowly growing, nonpigmented NTM species that causes pulmonary disease. Although rare in the United States, it has been increasingly recognized in England, Wales, and northern Europe. Most isolates are susceptible to ethambutol, and many are susceptible to rifampin and streptomycin. The four-drug regimen recommended for treating *M. avium* complex (before the availability of macrolides and rifabutin) has resulted in clinical and bacteriologic responses in most cases (70, 213). Potential improvements in therapeutic response with the macrolides and rifabutin has not been assessed.

Mycobacterium simiae is a slowly growing, nonpigmented *Mycobacterium* that may be confused with *M. tuberculosis*, as it is the only NTM that is niacin-positive. It is an uncommon cause of pulmonary and disseminated infection, and many patients with respiratory isolates of this species do not have disease. Most isolates are resistant to all first-line antimycobacterial drugs, and response to chemotherapy has been variable (32, 214). For patients with disseminated or progressive pulmonary disease in need of treatment, initial therapy may be started with the four-drug regimen recommended for *M. avium* complex (clarithromycin, ethambutol, rifabutin, and streptomycin), modified as needed using results of susceptibility tests.

Mycobacterium szulgai is a slowly growing *Mycobacterium* that has been associated with skin, joint, lymphatic, pulmonary, and disseminated disease (135). When isolated from humans, it should be considered pathogenic. Through 1986, only 24 cases of disease had been reported in the English literature. The organism is usually susceptible to rifampin and higher concentrations of isoniazid, streptomycin, and ethambutol. Enhanced activity of rifampin, ethambutol, and streptomycin

TABLE 5

COMMON SIDE EFFECTS AND TOXICITIES OF DRUGS USED FOR THERAPY OR PROPHYLAXIS OF NONTUBERCULOUS MYCOBACTERIAL DISEASE

Drug	Major Side Effects/Toxicity	Monitoring Procedures
Isoniazid	Hypersensitivity (fever, rash)	Clinical symptoms
	Hepatitis	Clinical symptoms; periodic alanine aminotransferase (ALT) or aspartate aminotransferase (AST) determinations, especially in first 3 mo of therapy
	Increased serum levels of phenytoin (Dilantin™)	Monitor serum levels
	Peripheral neuropathy related to pyridoxine deficiency	Clinical symptoms
Ethambutol	Optic neuritis (loss of red/green color discrimination, loss of visual acuity)	Discontinue drug immediately with subjective visual loss; periodic and symptomatic testing for red/green color discrimination and visual acuity (monthly if receiving 25 mg/kg per day); ophthalmology evalution for symptomatic patients
Rifampin, rifabutin	Orange discoloration of secretions and urine; staining of soft contact lenses	None
	Gastrointestinal disturbance (nausea, vomiting)	Clinical symptoms
	Hypersensitivity (fever, rash)	Clinical symptoms
	Hepatitis	Clinical symptoms; AST or ALT determinations based on symptoms
	Increased hepatic metabolism of numerous agents, including birth control pills, ketoconazole, quinidine, prednisone, oral hypoglycemics (sulfonylureas), digitalis, methadone, warfarin, clarithromycin, and protease inhibitors	Monitor clinical status and appropriate serum levels when possible
	"Flu-like" syndrome, thrombocytopenia, renal failure	Clinical symptoms; platelet count, serum creatinine as indicated
Rifabutin only	Polymyalgia, polyarthralgia, leukopenia, granulocytopenia, anterior uveitis (rifabutin with clarithromycin)	Clinical symptoms, periodic WBC counts
Streptomycin amikacin, tobramycin	Vestibular/auditory toxicity (dizziness, vertigo, ataxia, tinnitus, hearing loss)	Clinical symptoms including changes in hearing, ability to walk, dizziness; periodic hearing tests in high-risk patients or those with auditory/ vestibular symptoms; periodic amikacin serum levels
	Renal toxicity	Periodic serum creatinines; periodic amikacin or tobramycin serum levels
	Hypersensitivity (fever, rash, eosinophilia) (streptomycin)	Clinical symptoms
Ethionamide	Gastrointestinal disturbance (anorexia, nausea, vomiting, abdominal pain, diarrhea)	Clinical symptoms
	Hepatitis	Clinical symptoms; periodic AST or ALT determinations
	Central nervous system (anxiety, depression, altered behavior)	Clinical symptoms
Cycloserine	Peripheral neuropathy	Clinical symptoms
	Central nervous system (depression, altered behavior, confusion, anxiety, psychosis, seizures)	Clinical symptoms, assessment of mental status; serum levels weekly for first month if timely testing available
Azithromycin, clarithromycin	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Decreased hearing	Clinical symptoms
	Hepatitis	Periodic alkaline phosphatase, AST and gamma glutamyl transpeptidase (GGT) for first 3 mo
Clarithromycin only	Inhibited hepatic metabolism of several agents, including rifabutin, some protease inhibitors, Seldane™	Monitor clinical status and appropriate serum levels when possible; avoid use of Seldane

(*continued*)

TABLE 5
CONTINUED

Drug	Major Side Effects/Toxicity	Monitoring Procedures
Ciprofloxacin ofloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Central nervous system (headache, insomnia)	Clinical symptoms
Cefoxitin	Hypersensitivity (fever, rash, eosinophilia)	Clinical symptoms
	Hematologic (anemia, leukopenia)	Periodic blood counts
Tetracyclines (doxycycline, minocycline)	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Cutaneous (photosensitivity, rash, hyperpigmentation)	Clinical symptoms
	Central nervous system (dizziness, vertigo) (minocycline)	Clinical symptoms
Sulfonamides, trimethoprim/ sulfamethoxazole	Gastrointestinal disturbance (nausea, vomiting, diarrhea)	Clinical symptoms
	Hematologic (leukopenia, anemia, thrombocytopenia)	Periodic blood counts
	Hypersensitivity (fever, rash, Stevens-Johnson syndrome)	Clinical symptoms

when used in combination has been shown *in vitro* (215). Most patients treated with these drugs respond to therapy.

Relatively uncommon in the United States, *M. xenopi* has been reported as a common cause of slowly progressive NTM pulmonary disease in western Europe. In southeast England, it is the most common NTM recovered in the laboratory and has been since 1977 (216). Disseminated disease and joint disease caused by this organism have also been reported. *In vitro* susceptibility to antituberculosis agents is variable, although enhanced drug activity has been shown with the combination of rifampin and streptomycin (215). Although some investigators have reported success with surgical therapy similar to that used for selected patients with *M. avium* complex disease, others have had disappointing results (136, 173). Results with drug therapy alone in the premacrolide era have also shown variable results. One recent study of clarithromycin-containing regimens (137) demonstrated an excellent sputum conversion rate compared to these older studies. For most patients, initial therapy should consist of a macrolide, rifampin or rifabutin, and ethambutol with or without initial streptomycin. Patients who fail therapy or who relapse after treatment might be considered for surgery (30, 136, 173).

MONITORING FOR DRUG TOXICITY

Monitoring for drug toxicity of patients who are being treated for NTM disease is important, given the number and type of drugs used and the older age of these patients. It should include monitoring of the visual system including visual acuity (ethambutol), the presence of eye pain and decreased visual acuity or uveitis (rifabutin) (175, 176), and red-green color discrimination (ethambutol); the central nervous system (cycloserine, ciprofloxacin, ofloxacin, ethionamide); the liver (isoniazid, rifampin, ethionamide, clarithromycin, rifabutin) (174, 176); the kidney (streptomycin, amikacin); auditory and vestibular function (streptomycin, amikacin, azithromycin); and hematologic indices (sulfonamides, cefoxitin, rifabutin) (176). Major side effects and monitoring procedures are listed in Table 5.

For the aminoglycosides, this monitoring should include routine questioning about balance, ability to walk (especially in the dark), tinnitus, dizziness, and difficulty hearing. Baseline blood urea nitrogen and creatinine measurements should be obtained, with reduction of the streptomycin dose and/or frequency of administration if these are abnormal. Periodic monitoring of renal function is recommended for high-risk patients receiving drugs daily or five times a week, especially with patients older than 50 yr or who have impairment of renal function. A baseline hearing test should be considered, especially in high-risk patients, and then repeated if signs or symptoms of seventh nerve toxicity appear.

For cycloserine, careful attention should be given to signs of central nervous system toxicity, which may include seizures, lethargy, depression, alterations in personality, and even suicidal ideations. Because toxicity with this drug relates primarily to excessive serum levels (> 40 μg/ml), patients with central nervous system symptoms or abnormal baseline renal function should have serum level determinations. Unfortunately, such tests are not available in most clinics and are rarely available in a timely fashion to help with decisions on dosing. If serum levels are not available, physicians should remember that the drug is excreted by the kidney, and high serum levels tend to occur in the elderly or in the presence of renal failure. A lower dose (e.g., 250 mg twice a day) is often given in such cases, and discontinuation of the drug may be necessary if central nervous system symptoms occur and one cannot monitor serum levels.

Given that isoniazid hepatotoxicity is higher in the older population, some physicians obtain a baseline measurement of aspartate aminotransferase (AST), then repeat this determination at 2, 4, and 8 wk and thereafter during therapy as clinically indicated. Other monitoring considerations are the same as those for patients with tuberculosis (*see* the ATS Statement "Treatment of Tuberculosis and Tuberculosis Infections in Children and Adults" (2, 217).

The incidence of gastrointestinal side effects such as nausea, vomiting, abdominal pain, and cramping is almost prohibitive with ethionamide. These symptoms can be minimized by

starting with a 250 mg single dose, slowly increasing the dose, and administering it with food. In the older patient, limiting the total dose to 500 mg may help reduce toxicity. A good review of side effects and toxicities experienced at the National Jewish Hospital with ethionamide and cycloserine is provided in a study by Lester (218).

Some adverse events with rifabutin are comparable to those seen with rifampin. These include rash, fever, nausea, vomiting, and hepatitis. Several adverse events are unique to rifabutin, including anterior uveitis, skin hyperpigmentation or pseudojaundice, and a polymyalgia/polyarthralgia syndrome (175, 176). The last three adverse events are seen almost exclusively in patients concurrently receiving clarithromycin. These effects can be minimized by giving no more than 300 mg/d of rifabutin when combined with clarithromycin. Leukopenia is also seen with rifampin, but it is much more common with rifabutin. Periodic white blood cell counts should be performed on all patients taking rifabutin, perhaps at monthly intervals. Mild leukopenia is common (8 of 26 or 31% of patients in one series of HIV-negative patients on 600 mg/d developed WBC counts below 4,000 cells/mm^3) (176), and the drug should be discontinued only if cell counts fall below a comfortable range (perhaps 2,500 cells/mm^3 or an absolute granulocyte count of 1,500 or less in HIV-negative patients).

This statement was prepared by an ad hoc committee of the Scientific Assembly on Microbiology, Tuberculosis, and Pulmonary Infections. Members of the committee were:

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