ON-LINE SUPPLEMENT

AN OFFICIAL ATS/IDSA STATEMENT: DIAGNOSIS, TREATMENT AND PREVENTION OF NONTUBERCULOUS MYCOBACTERIAL DISEASES

NTM Writing Committee

TAXONOMY

New NTM* 1990-2006

Mycobacterium avium subsp. *paratuberculosis*	1990
Mycobacterium avium subsp**.** *silvaticum*	1990
Mycobacterium cookii	1990
Mycobacterium alvei	1992
Mycobacterium confluentis	1992
Mycobacterium madagascariense	1992
Mycobacterium peregrinum	1992
Mycobacterium brumae	1993
Mycobacterium celatum	1993
Mycobacterium genavense	1993
Mycobacterium hiberniae	1993
Mycobacterium intermedium	1993
Mycobacterium chlorophenolicum	1994
Mycobacterium branderi	1995
Mycobacterium interjectum	1995
Mycobacterium mucogenicum	1995
Mycobacterium conspicuum	1996
Mycobacterium hodleri	1996

Mycobacterium lentiflavum	1996
Mycobacterium hassiacum	1997
Mycobacterium mageritense	1997
Mycobacterium novocastrense	1997
Mycobacterium triplex	1997
Mycobacterium bohemicum	1998
Mycobacterium heidelbergense	1998
Mycobacterium goodii	1999
Mycobacterium murale	1999
Mycobacterium tusciae	1999
Mycobacterium wolinskyi	1999
Mycobacterium botniense	2000
Mycobacterium elephantis	2000
Mycobacterium kubicae	2000
Mycobacterium septicum	2000
Mycobacterium doricum	2001
Mycobacterium frederiksbergense	2001
Mycobacterium heckeshornense	2001
Mycobacterium immunogenum	2001
Mycobacterium holsaticum	2002
Mycobacterium lacus	2002
Mycobacterium palustre	2002
Mycobacterium vanbaalenii	2002
Mycobacterium montefiorense	2003
Mycobacterium shottsii	2003

Mycobacterium boenickei	2004
Mycobacterium brisbanense	2004
Mycobacterium canariasense	2004
Mycobacterium chimaera	2004
Mycobacterium cosmeticum	2004
Mycobacterium houstonense	2004
Mycobacterium nebraskense	2004
Mycobacterium neworleansense	2004
Mycobacterium parascrofulaceum	2004
Mycobacterium parmense	2004
Mycobacterium psychrotolerans	2004
Mycobacterium pyrenivorans	2004
Mycobacterium saskatchewanense	2004
Mycobacterium florentinum	2005
Mycobacterium pseudoshottsii	2005
Mycobacterium arupense	2006
Mycobacterium aubagnense	2006
Mycobacterium bolletii	2006
Mycobacterium colombiense	2006
Mycobacterium conceptionense	2006
Mycobacterium fluoranthenivorans	2006
Mycobacterium massiliense	2006
Mycobacterium monacense	2006
Mycobacterium phocaicum	2006

*A comprehensive list of all validated NTM species can be found online at

www.bacterio.cict.fr/m/mycobacterium.html

LABORATORY PROCEDURES

Blood culture systems for mycobacteria. Currently, the Isolator system (Wampole Laboratories, Cranbury, NJ) and the BACTEC Myco/F (Becton Dickinson Microbiology Systems, Sparks MD) and non-radiometric liquid media such as BACTEC Myco/F lytic medium, ESP Myco (Trek Diagnostic System, Westlake, OH), MB/BacT ALERT 3D (BioMérieux, Marcy L'Etoile, France) are available for mycobacterial culture of blood.

Broth (liquid) media culture systems for mycobacteria. The BACTEC 460TB System is a semi-automated radiometric system for the detection of mycobacteria. The instrument monitors the metabolism of [^{14}C] palmitic acid as a carbon source which is converted to $^{14}CO_2$ by mycobacteria. The rate and amount of $^{14}CO_2$ are directly proportional to the growth rate of the organisms in the media. The average time to detection for NTM is less than 7 days. Other continuously monitored, fully automated, non-radiometric systems have also recently been introduced for the growth and detection of NTM. These systems include the BACTEC 9000MB and the BACTEC MGIT 960 (Becton Dickinson) along with the ESP (Extra Sensing Power) Culture System II (Trek Diagnostic Systems) and the MB/BacT ALERT 3D (BioMérieux). The BACTEC 9000MB System uses the same fluorescence quenching based oxygen sensor as does the previously described MGIT System while the ESP Culture System is based on detection of pressure change in the head-space above the broth media resulting from gas production or consumption due to the growth of microorganisms. The MB/BacT ALERT 3D System utilizes a colorimetric CO_2 sensor to detect growth in broth. Disadvantages of these brothsystems include inability to observe mycobacterial colony morphology, difficulty in ascertaining mixed cultures, extensive use of syringes and needles, and the necessity of radioisotope disposal. In clinical studies, detection and recovery rates for all of these broth-culture systems are comparable to each other and superior to those of conventional solid media.

Susceptibility Testing for Taxonomy (Identification) of RGM

Preliminary taxonomic differentiation of the RGM may be facilitated with selected drugs and some antimicrobial susceptibility results using broth microdilution MICs and agar disk diffusion. Briefly, *M. chelonae* and *M. abscessus* isolates can be differentiated from *M. fortuitum* on the basis of polymyxin b susceptibility. *M. chelonae* isolates can be differentiated from *M. abscessus* isolates on the basis of cefoxitin susceptibility.

Genotypic Methods for Identification of NTM

INNO-LiPA INNO-LiPA Mycobacteria (Innogenetics, Ghent, Belgium) is a line probe assay-based on reverse-hybridization technology. The system is currently available only in Europe. However, the kit includes probes for all of the common NTM species based on species and intraspecies specific polymorphisms of the mycobacterial 16S-23S internal transcribed spacer region (ITS) obtained with amplification by PCR. The ITS of approximately 280 bp which separates the 16S and 23S rDNA is responsible for species-specific or intraspecies polymorphisms in some species of NTM and is known to be more polymorphic than the 16S rRNA region (1). The kit may be used with species grown on solid or in liquid culture media (2). Currently, probes are available for 16 species of nontuberculous mycobacteria including *M. xenopi, M. gordonae, M. avium, M. intracellulare, M. scrofulaceum, M. chelonae* (3 probes), and *M. kansasii* (3 probes). The *M. kansasii* probes are designed to identify at least 5 groups within this species, a unique feature of this method. There is also a MAIS probe that reacts with *M. avium, M. intracellulare, M. scrofulaceum, M. malmoense, M. haemophilum,* and the "MAI-X" isolates (defined as "intermediate" MAC by positive hybridization with MAC AccuProbe and a negative reaction with separate *M. avium* and *M. intracellulare* probes) (3). Recent improvements have been made with this assay that increase the number of identifiable NTM species to include *M. celatum, M. simiae, M. ulcerans, M. malmoense, M. haemophilum,* and *M. smegmatis.* However, the probe designed to be specific for the *M. fortuitum* complex and *M. smegmatis* may also cross-react with *M. thermoresistible, M. agri, M. alvei, M. mageritense,* and *M. senegalense* and thus should be used cautiously when testing species within the *M. fortuitum*

complex (3). Rare strains of *M. fortuitum* and *M. gordonae* do not hybridize with their specific line probes. Furthermore, strains of the newly described species, *M. parascrofulaceum,* which hybridized with the MAIS probe and the species specific *M. scrofulaceum* probe have recently been described (4). In another study, the recently described (but not officially validated) species, *M. sherrisii,* hybridized with the line probe specific for *M. simiae* and also produced a weak band corresponding with the line probe specific for *M. gordonae* (5).

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Pyrosequencing The conventional sequencing method for identification of the NTM are limited by the length of the nucleic acid sequence and the time required to interpret long sequences. Pyrosequencing technology is a novel method of nucleic acid sequencing that rapidly determines short sequences (typically 20-30 bases of DNA) in a semi-automated mode. The method also differs from conventional sequencing methods in that no gels or dyes are required. The biotinylated PCR product is processed to a single strand DNA template. The sequencing primer is then hybridized to the DNA template. Nucleotide incorporation of the complementary nucleotides results in light generation evidenced by peaks forming a program. These peaks are then evaluated using instrument software for isolate identification. In previous studies this method has compared favorably with conventional and other molecular methodologies (1).

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Clinical Presentations and Diagnostic Criteria

Pulmonary Disease: Chest radiographs and high resolution chest computed tomography (HRCT) scans

E1) Chest radiograph: 66 year-old man, smoker, with MAC lung disease associated with large right upper lobe cavity and bilateral reticulonodular densities. Patient also has indwelling catheter for aminoglycoside administration.
E2) Chest radiograph: 41 year-old female, smoker, with MAC lung disease associated with left apical confluent density with cavitation.
E3a) Chest radiograph: 73 year-old non-smoking female with MAC lung disease associated with diffuse bilateral nodular and reticulonodular densities.
E3b) HRCT from the same patient demonstrating bilateral nodular densities and bronchiectasis.
E4a) Chest radiograph: 79 year-old non-smoking female with MAC lung disease associated with primarily mid-lung nodular and reticulonodular densities and cavitation.
E4b) HRCT from the same patient demonstrating nodules and bronchiectasis.
E4c) HRCT from the same patient demonstrating nodules, bronchiectasis and cavitation.

E5a) Chest radiograph: 55 year-old non-smoking female with MAC lung disease associated with cavitary right middle lobe (RML) density.

E5b) Lateral chest radiograph from the same patient with primarily RML density.

E5c) HRCT from the same patient showing destruction of the RML with bronchiectasis, and nodules in the lower lobes.

E6) Chest radiograph: 42 year old man, smoker, with *M. kansasii* disease associated with bilateral upper lobe reticulonodular densities.

E7) Chest radiograph: 77 year-old man, smoker, with M. kansasii disease associated with bilateral mid and upper lung field reticulonodular densities with cavitation.

E8a) Chest radiograph: 70 year-old female, non-smoker, with *M. abscessus* disease associated with bilateral reticulonodular densities and cavitation.

E8b) HRCT from the same patient showing nodules and bronchiectasis in right middle lobe, lingula and lower lobes.

E8c) HRCT from the same patient showing nodules, bronchiectasis and cavitation.

E9) HRCT from 22 year old male, non-smoker, with cystic fibrosis and *M. abscessus* lung disease. Patient with diffuse nodular and reticulonodular densities including "tree-in-bud" appearance of densities in lung periphery.

E10a) Chest radiograph: 30 year old male, non-smoker, with hypersensitivity-like lung disease associated with diffuse reticular densities following hot-tub exposure.

E10b) HRCT same patient showing diffuse "ground glass" appearance of lung parenchyma.

Skin, Soft Tissue, Bone Infection

E11) *M. abscessus* sternal wound infection following median sternotomy.

E12) *M. marinum* infection of 5^{th} digit after scraping hand on the hull of a boat.

E13) *M. marinum* nodular lesions on hand following trauma cleaning a fish tank.

E14) M. chelonae lesion on the hand (with closely associated area of previous debridement) following penetrating injury to the hand.

E15) Cutaneous *M. chelonae* lesions associated with disseminated *M. chelonae* disease in a patient with rheumatoid arthritis on chronic oral steroid therapy.

Nontuberculous Mycobacterial Species: Clinical Aspects and Treatment Guidelines

Mycobacterium avium Complex (MAC)

Controversies and Unresolved Questions in the Management of MAC Lung Disease

There is not demonstrated superiority of one macrolide (clarithromycin or azithromycin) in the management of MAC lung disease. There have been no head to head trials comparing clarithromycin and azithromycin containing regimens for MAC lung disease. Limited information based on the open noncomparative trials suggests that clarithromycin may be more effective than azithromycin, but the differences are generally less than 10%. It is assumed that the two agents can be used interchangeably in MAC treatment regimens. For instance, patients intolerant of clarithromycin can be tried on azithromycin (and vice versa). It has been observed that patients who have hypersensitivity responses (usually rash) to clarithromycin can be successfully treated with azithromycin (and vice versa).

The issue of the optimal dose for either of the macrolides also remains unresolved. Doses of clarithromycin greater than 1000 mg/day are associated with increased mortality in AIDS patients, however, a similar association has not been demonstrated in non-AIDS patients. The incidence of intolerance or toxicity clearly increases with higher doses of both drugs, e.g., clarithromycin greater than 1000 mg daily or azithromycin greater than 250-300 mg daily, but dose-response data are not available to answer whether higher doses are associated with greater treatment efficacy or whether response rate relates more to serum level than to dose (1-3).

There is not a demonstrated advantatge of routinely including an injectable agent (amikacin or streptomycin) early in MAC treatment regimens.. Most published studies of MAC lung disease patients treated with a macrolide-containing regimen have employed an injectable agent early (in the first 2-4 months) in the course of therapy (4-10). There have been no studies directly comparing the efficacy of macrolide-containing regimens with or without inclusion of an injectable drug. Early studies with traditional antituberculous medications (isoniazid, rifampin and ethambutol) suggested that the addition of streptomycin early in the treatment course improved microbiologic response

rates (11). Additionally, there are no studies comparing the relative efficacy of various parenteral drugs with activity against MAC such as streptomycin, amikacin or kanamycin.

There is not demonstrated superiority of one rifamycin (rifabutin or rifampin) in the treatment of MAC lung disease, but because of frequent adverse events with rifabutin, most experts recommend rifampin. The choice of a rifamycin, rifampin or rifabutin, has also not been directly compared. There are theoretical reasons to believe that rifabutin, a derivative of rifamycin S, is superior to rifampin including better in vitro activity than rifampin for MAC (12,13). Rifabutin also has better in vivo activity than rifampin for prophylaxis and treatment of disseminated MAC disease in studies of HIV sero-positive patients. (13-15). Lastly, rifabutin has less hepatic cytochrome P450 stimulation than rifampin (16) resulting in less effect on clarithromycin levels than rifampin. The clinical consequences of this reduction in plasma concentration of clarithromycin are uncertain and measured clarithromycin levels in peripheral blood may not adequately reflect its antimycobacterial efficacy. No study has yet demonstrated that the combination of rifampin and clarithromycin leads to increased treatment failure rates or that rifampin-containing regimens promote the emergence of macrolide-resistant MAC isolates. Unlike clarithromycin, serum levels of azithromycin appear to be unaffected by the addition of companion drugs including rifampin or rifabutin.

However, rifabutin is also frequently associated with side effects and toxicity. In multidrug regimens that contain rifabutin, rifabutin is the drug least well tolerated and most often associated with adverse events including those that require alteration or discontinuation of medication (4-6, 8-10,17-19). In particular, the combination of rifabutin with clarithromycin, which increases rifabutin levels, can cause significant leukopenia, uveitis and polyarthralgia, warranting considerable caution and close observation when administering this drug combination. While azithromycin does not affect rifabutin levels and is theoretically a better companion drug than clarithromycin, rifabutin toxicity is still a major problem with azithromycin containing regimens (17). Lastly, rifabutin is currently more expensive than rifampin.

There have not been studies evaluating 2-drug vs 3-drug regimens for the treatment of MAC lung disease, but in general, 2-drug regimens are not recommended.

There have been no studies evaluating 2 drugs versus 3 drug regimens for MAC lung disease. In HIV sero-positive patients with disseminated MAC, the combination of ethambutol and clarithromycin was as effective for conversion of blood cultures to negative as ethambutol, clarithromycin and rifabutin, although the emergence of macrolide resistant isolates was significantly greater with the 2-drug regimen (14). There is concern that, with a large burden of organisms associated with MAC lung disease, especially cavitary MAC lung disease, that 2-drug therapy regimens, either daily or intermittent, would predispose to the emergence of macrolide resistant MAC isolates. As an alternative to macrolide/ethambutol, two-drug regimens including macrolide/rifamycin (especially rifampin) and macrolide/quinolone should not be used.

The roles for other medications such as fluoroquinolones and clofazimine in the treatment of MAC lung disease is not established. A recent study from Canada involving patients primarily with nodular bronchiectatic disease suggested that clofazimine with clarithromycin and ethambutol was effective and prevented the emergence of MAC resistant isolates (20). However, no control group of clarithromycin and ethambutol (without clofazimine) was included for comparison. Clofazimine has not been effective for treatment or prophylaxis of disseminated MAC disease and is contraindicated for AIDS patients because of increased mortality in some clofazimine-containing regimens (21,22). Some experts believe that clofazimine is valuable in multi-drug regimens for treating MAC. Currently, clofazimine is available in the United States for treatment of MAC disease only with an IND application to the FDA for each patient. The role of other agents, especially the 8-methoxy fluoroquinolone, moxifloxacin, is also unclear. It is unknown if these agents have activity against MAC as monotherapy or in multidrug treatment combinations. Fluoroquinolones as a drug class have known and variable in vivo activity against MAC. Common use in the treatment of respiratory infections, including the inadvertent or intentional use as monotherapy in MAC-infected patients, may have contributed to a substantial incidence of resistance in MAC isolates. The lack of proven utility of these agents, particularly as monotherapy, should warrant substantial caution by clinicians when considering their use in patients who have known or suspected MAC infections.

Given the apparent lack of correlation between *in vitro* susceptibility testing and clinical response in MAC lung disease for agents other than the macrolides, the value of adding additional drugs to which the organism appears susceptible *in vitro* to standard therapy is unknown.

Previous unsuccessful or failed therapy for MAC lung disease, with or without a macrolide, decreases the chances for subsequent treatment success, even with macrolide susceptible MAC isolates. Patients who have failed prior MAC therapy, with or without a macrolide, have lower sputum conversion rates with macrolide containing treatment regimens, even with macrolide susceptible MAC isolates, than do patients with no prior therapy (4,7-10,17). The explanation for this observation is not clear but may reflect unidentified host factors that inhibit treatment response regardless of the regimen utilized or unidentified differences in nonmacrolide drug susceptibilities.

Some beneficial effect of macrolide containing treatment regimens for patients with bronchiectasis could be due to immune modulating effects of the macrolide. There is evidence that macrolides may have an immune modulating effect for patients with bronchiectasis associated with panbronchiolitis and CF (23). It is possible that some of the symptomatic and radiographic improvement seen with macrolide treatment regimens in patients with nodular bronchiectatic disease might be due to this effect. Available evidence does not yet support the use of macrolides, particularly as monotherapy, as anti-inflammatory therapy in adult patients with bronchiectasis unrelated to CF.

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***M. kansasii* Lung Disease**

See radiograhs above.

***M. abscessus* Disease**

See radiographs above.

See skin lesion above.

***M. chelonae* Disease**

See skin lesion above.

***M. marinum* Disease**

See skin lesion above.

Other NTM Pathogens

M. asiaticum

The Organism *M. asiaticum* is a rarely isolated NTM species that was previously identified as *M. simiae*. Accurate identification of this organism requires molecular methods.

Clinical Presentation *M. asiaticum* has most frequently been reported as a pulmonary pathogen, however, it has also been reported as a cause of bursitis and tenosynovitis (1-5). Pulmonary disease has been associated with both cavitary and nodular lung disease (1,2).

Treatment The antimicrobial susceptibility pattern is not firmly established due to limited experience with this organism. Some reports suggest that *M. asiaticum* isolates are susceptible to ethambutol, ethionamide, rifampin, isoniazid and streptomycin, while others have reported resistance to isoniazid and rifampin (2,3,5). Treatment success has been reported with antituberculosis medications (1-3,5). The *in vitro* susceptibility of *M. asiaticum* to macrolides and quinolones is also not determined with certainty; however, if an isolate is susceptible to these agents in vitro, they may also be useful in multi-drug treatment regimens.

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M. celatum

The Organism *M. celatum* is indistinguishable from MAC biochemically and previously has shown a weakly positive reaction with the *M. tuberculosis* Accuprobe (GenProbe, San Diego, Ca) (1-5). A modification of the commercial protocol has, however,

apparently remedied this problem. Identification usually requires HPLC or molecular testing.

Clinical Presentation *M. celatum* has most frequently been reported as a cause of disseminated disease in patients with AIDS. Pulmonary disease caused by *M. celatum* has rarely been reported in nonimmunocompromised patients and presents in a manner indistinguishable from other NTM lung diseases including, at least occasionally, with lung cavitation (1-7).

Treatment The antimicrobial susceptibility pattern is not firmly established but recent reports suggest that *M. celatum* isolates are susceptible *in vitro* to amikacin, streptomycin, capreomycin, ethambutol, isoniazid, rifabutin (not rifampin), ofloxacin, ciprofloxacin, clarithromycin, and azithromycin (1,8,9).

The multidrug regimen outlined for pulmonary disease should also be effective for AIDS patients with disseminated disease. *M. celatum* disseminated disease has been reported from a patient receiving rifabutin prophylaxis. It is unknown if macrolide chemoprophylaxis is effective for this organism.

Successful treatment of pulmonary disease has been reported with multidrug therapy including clarithromycin, ethambutol, rifabutin and ciprofloxacin (7).

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M. conspicuum

The Organism *M. conspicuum* grows slowly and may require at least three weeks for the appearance of colonies on solid media. The number of isolates of *M. conspicuum* may have previously been underestimated due to the organism's unusually low temperature growth requirement (22-31° C) on solid media and slow growth. Growth in liquid media occurs only at 37°C. By 16S rRNA gene sequence this species is most closely related to *M. asiaticum* and *M. gordonae*.

Clinical Presentation *M. conspicuum* has been associated with disseminated disease in immunocompromised patients including AIDS patients (1).

Treatment In general, *M. conspicuum* isolates are susceptible to ciprofloxacin, amikacin, rifabutin, clarithromycin or azithromycin with intermediate susceptibility to ethambutol and isoniazid. Isolates are resistant to rifampin and pyrazinamide (1).

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M. shimoidei

The Organism A rarely isolated NTM previously identified as *M. terrae* complex. Firm identification requires molecular methods.

Clinical Presentation Cavitary pulmonary disease is the clinical setting from which most *M. shimoidei* isolates have been reported. (1-3). Most of these patients have had pre-existing or underlying lung disease. There has also been a report of disseminated *M. shimoidei* disease in a patient with AIDS. (4)

Treatment There has been variability in the *in vitro* susceptibilities reported for *M. shimoidei*. Isolates are generally susceptible to ethambutol, rifabutin, streptomycin, kanamycin and ethionamide and generally resistant to isoniazid and rifampin (2,3). Limited data suggest resistance to macrolides and quinolones, however, because of the sparse information available, *M. shimoidei* isolates should be tested against these agents. Clinical response to multi-drug treatment regimens has been poor, perhaps partly attributable to the underlying disease of patients with *M. shimoidei* infections (2-4).

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