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Nontuberculous Mycobacterial Disease

A Comprehensive Approach to Diagnosis and Management

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Respiratory Medicine

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The volume is dedicated to my colleague, mentor, and friend, Richard J. Wallace, Jr., whose contributions to the study of NTM diseases are unsurpassed. His profound and enduring influence on everyone currently working in the field is also unsurpassed. It is my incalculable good fortune to have worked with him over the last 40 years.

Fig. 1 Richard J. Wallace, Jr., Emanuel Wolinsky, Barbara Brown-Elliott circa 1990

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Nontuberculous Mycobacterial Disease: An Introduction and Historical Perspective

David E. Griffith

I want to begin this volume on nontuberculous mycobacterial (NTM) disease with a plea and an admonition. First, many aspects of NTM disease are difficult to understand, counterintuitive, and even paradoxical. I am repeatedly reminded about how poorly the nuances and idiosyncrasies of NTM disease are generally understood through years of interactions with clinicians who seek my advice about NTM disease management. Many aspects of NTM disease defy easy explanations and require sometimes detailed background information to build an adequate context for interpretation and comprehension. The reader is strongly encouraged to use this volume as more than a quick reference or handbook on NTM disease management. Rather, each chapter should be read in its entirety to promote an in-depth understanding of NTM disease with all of the attendant complexities, contradictions, and knowledge gaps. There are no shortcuts.

Second, many aspects of NTM disease defy the kind of evidence-based analysis and conclusions that would support rigorous or robust evidence-based recommendations. The necessary accumulation of information to achieve that goal is simply not yet available. In the absence of a better evidence base, many recommendations for NTM management have their origin in "expert opinion," and many recommendations in this volume reflect that reality. Clinicians faced with difficult NTM management decisions still require guidance, even the imperfect guidance of expert opinion. Controversial areas where strong opinions are offered will be evident to the reader who will be savvy enough to judge the merits of those opinions and to seek alternative opinions.

Interest in the "nontuberculous mycobacteria" or NTM is a relatively recent phenomenon that has now reached unprecedented levels. Although NTM were identified more than a century ago, their role as human pathogens was generally perceived

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as minor, even inconsequential during most of that time. For the purposes of this volume, the NTM are comprised of species in the genus *Mycobacterium* excluding species in the *M. tuberculosis* complex and *M. leprae.*

The term "nontuberculous mycobacteria" (NTM) is now in common use but is not universally endorsed as the collective term for these organisms. Alternative names such as "atypical mycobacteria," "mycobacteria other than tuberculosis" (MOTT), or "environmental mycobacteria" have been championed with variable penetrance into the NTM vernacular. "Atypical mycobacteria" is probably the most commonly used alternative label and presumably referred to isolation of a mycobacterial species other than "typical" *M. tuberculosis*. It seems inappropriate now because strictly from the perspective of isolation frequency, the "atypical" mycobacteria far outnumber "typical" *M. tuberculosis* isolates in major mycobacteriology laboratories in the United States. While "environmental mycobacteria" is appealing from taxonomic and pathophysiologic standpoints, the label NTM is now so firmly entrenched it cannot be easily displaced and is our preferred, if imperfect, term for this group of organisms.

For most of its history in the United States, NTM disease knowledge and understanding was impeded by the difficulty separating NTM pathogens and associated clinical disease syndromes from disease caused by *M. tuberculosis*. Clinical NTM isolates, especially those from respiratory specimens, were often regarded as contaminants and dismissed as clinically insignificant. It was also generally assumed that NTM pathogens and disease would respond favorably to antituberculosis antimicrobials leading to inevitable and understandable frustration when they did not. The lack of therapeutic response was probably also an unintentional disincentive to aggressively recognize and diagnose NTM disease, especially NTM lung disease. Clearly, the identification of NTM pathogens and recognition of their clinical significance have markedly improved. However, an easy separation between NTM disease and tuberculosis continues to be an ongoing and evolving process especially in the developing world, where due to a lack of available resources to isolate, identify, or treat NTM pathogens, mycobacterial disease is often initially assumed to be caused by *M. tuberculosis.*

The emergence of NTM pathogens and disease as subjects of serious interest in the United States can be dated roughly to the publication in 1980 of a state-of-the-art review in the American Review of Respiratory Disease by Dr. Emanuel Wolinsky titled, *Nontuberculous Mycobacteria and Associated Diseases* [1]. This highly influential manuscript, published almost 40 years ago, was the first comprehensive and more importantly widely read NTM disease review and represents a clear watershed moment in the recognition and appreciation of NTM disease. Progress in the NTM disease realm has been nothing short of remarkable since then. This brief introduction highlights some important milestones in that progress with chapter references to guide the reader to more detailed information and discussion about specific NTM disease aspects.

At the time of the Wolinsky manuscript, there were approximately 40 recognized NTM species that were identified utilizing insensitive phenotypic and biochemical characteristics including colony morphology and patterns of nutrient metabolism

[1, 2]. A widely adopted early NTM classification system based on this approach was eponymously labeled the Runyon classification system after Dr. Ernest H. Runyon [3]. The speed and accuracy of mycobacterial species identification dramatically improved first with high-performance liquid chromatography (HPLC), closely followed by the introduction of molecular laboratory methods, including DNA probes and gene sequencing techniques [4–7]. High-performance liquid chromatography and DNA probes are rapid and widely available but are restricted to identification of some commonly isolated NTM species including *Mycobacterium avium* complex (MAC), *M. kansasii*, and *M. gordonae*.

Nontuberculous mycobacterial species identification expanded in an almost explosive manner with the widespread application of 16S rRNA gene sequencing, a gene thought to be highly preserved within NTM species [7]. Utilizing this and other molecular-based techniques, the number of recognized NTM species continues to expand and has grown to approximately 200 [8]. It is now apparent that the 16S rRNA gene analysis, by itself, does not always satisfactorily discriminate between all NTM species and/or subspecies [7, 9–11]. The process of NTM organism identification has become sufficiently complex that discriminating between some NTM species and subspecies requires either multigene sequencing or whole-genome sequencing [7, 9–11]. Even then, controversy persists about the degree of difference between NTM isolates that is necessary for species versus subspecies determination and differentiation [10, 11]. Overall, however, molecular methods have revolutionized the microbiologic evaluation of NTM including rapid and accurate methods for clinical NTM isolate identification, molecular epidemiology investigations and discovery of innate NTM resistance mechanisms [12–14]. This important and rapidly changing field is discussed in detail in chapters "The Modern Mycobacteriology Laboratory and Its Role in NTM Disease Diagnosis and Management" and "In Vitro Drug Susceptibility Testing for NTM and Mechanisms of NTM Drug Resistance" with focused discussion in several other chapters.

Genotyping environmental and clinical NTM isolates has provided invaluable insights into the identification of NTM environmental niches and possible routes of NTM pathogen acquisition [12, 15–17]. This approach is a necessary element for developing disease prevention strategies which are discussed in chapters "Environmental Niches for NTM and Their Impact on NTM Disease" and "Healthcare Associated NTM Outbreaks and Pseudo-outbreaks". Genotyping clinical *Mycobacterium avium* complex (MAC) isolates from MAC lung disease patients also allows discrimination between true disease relapse isolates and (presumed) reinfection isolates which is discussed in chapter "*Mycobacterium avium* Complex Disease" [18, 19].

Ironically, the new molecular laboratory methods have so radically changed our view and understanding of NTM pathogens and disease that the advances have outpaced the capability of most mycobacterial laboratories to adopt and perform these invaluable services. Currently, most clinicians do not have access to laboratories utilizing these invaluable methods which have proven indispensable for optimal NTM patient management.

At the time of Dr. Wolinsky's manuscript, there was little data and limited understanding about the epidemiology of NTM disease. Initial efforts to estimate NTM disease prevalence in the United States suggested that it was 1–2 cases/100,000 population based on NTM isolation prevalence calculated at the Centers for Disease Control and Prevention (CDC) [20, 21]. Because NTM disease was not reportable, the NTM isolates received by the CDC were not part of a comprehensive national survey of NTM isolates or disease. Currently a minority of states within the United States have mandatory NTM reporting with variable requirements for the information that is collected.

Aside from the absence of a national or universal reporting requirement, the second major impediment to accurate determination of NTM disease prevalence is that in contrast to tuberculosis, a single NTM isolate is not necessarily an indication of active NTM disease, especially lung disease [22–26]. Unlike tuberculosis, NTM isolation prevalence from respiratory specimens does not equate to actual NTM lung disease prevalence. This frustrating observation is primarily due to the possibility that clinical specimens can be contaminated by NTM from environmental sources. Patients with suspected NTM lung disease, therefore, must meet a set of diagnostic criteria that are difficult to apply retrospectively in epidemiologic investigations without obtaining detailed information from the patient's medical record. The challenges of NTM disease diagnosis are discussed in detail in chapters "Epidemiology of NTM Disease: United States" and "Epidemiology of NTM Disease: Global".

Some investigators have undertaken the tedious analysis that is necessary for accurate NTM case definition [27–30]. Other investigators have utilized alternative epidemiologic tools such as querying extensive insurance-based patient databases utilizing diagnostic codes [31, 32]. While estimates of NTM disease prevalence vary, the available data consistently show that NTM prevalence in the United States is increasing. Mandatory NTM disease reporting would provide more accurate estimates of prevalence but would also facilitate new insights into incidence, which has been an elusive goal so far. Chapter "Epidemiology of NTM Disease: United States" discusses in detail the current understanding of NTM disease epidemiology in the United States.

Investigators outside the United States are providing a clearer picture of global NTM disease epidemiology [33–35]. Nontuberculous mycobacterial infections in the developed world have broadly comparable epidemiology to that in the United States although some important differences, particularly in Western Europe exist. Why those differences exist is unclear, but their investigation offers opportunities for better understanding of multiple NTM disease aspects beyond epidemiology.

Unfortunately, NTM disease epidemiology remains poorly described in large areas of the developing world. Even in these areas, however, NTM epidemiologic information is becoming more accessible in part because of the expanding availability of rapid and accurate tuberculosis diagnostic tools such as the Cepheid GeneXpert TB/RIF technology [36, 37]. This platform gives a first approximation of NTM disease prevalence by identifying patients whose respiratory specimens are acid-fast bacilli (AFB) smear positive but nucleic acid amplification negative for

tuberculosis. As with NTM disease prevalence in developed countries, it is highly likely that the extent of NTM disease in the developing world will be much higher than is currently appreciated with an inevitable attendant demand on limited resources for treating the expanding number of NTM disease patients. Global NTM disease epidemiology is discussed in detail in chapter "Epidemiology of NTM Disease: Global".

When the Wolinsky manuscript was published, NTM lung disease pathophysiology was assumed to be analogous to tuberculosis with the notable exception that NTM lung disease pathogens had not been demonstrated to be transmissible between humans. It was also known that NTM were environmental organisms that inhabited specific niches including natural water sources inviting speculation that NTM lung disease might be the consequence of organism inhalation after naturally occurring aerosolization of the organism [15, 38–41].

Recently there have been multiple reports describing isolation of NTM respiratory pathogens from environmental sources including household or municipal water, and with the aid of organism genotyping, it has also been shown that some clinical NTM respiratory isolates are genotypically identical to household water NTM isolates [15, 42, 43]. These observations are strong evidence that municipal water is the source of NTM respiratory pathogens, especially *Mycobacterium avium* complex (MAC), for some patients with NTM lung disease. Municipal water is also a known environmental niche for NTM respiratory pathogens such as *M. kansasii* and *M. xenopi* as well as nosocomially acquired pathogens such as *M. abscessus* and *M. chimaera* [12, 15, 43]. The demonstration of NTM acquisition from specific environmental sources is a necessary prerequisite for developing NTM disease prevention strategies. The environmental acquisition of NTM is discussed in chapters "Environmental Niches for NTM and Their Impact on NTM Disease" and "Healthcare Associated NTM Outbreaks and Pseudo-outbreaks" including recommendations for the investigation of nosocomial NTM outbreaks and pseudo-outbreaks.

When the Wolinsky manuscript was published, NTM lung disease was regarded as clinically and radiographically similar to tuberculosis, and clearly NTM lung disease does sometimes present radiographically with upper lobe fibrocavitary changes similar to reactivation tuberculosis [1, 23, 44]. Currently, however, in the United States NTM lung disease, especially MAC lung disease, is now more commonly associated with nodular and bronchiectatic radiographic changes [23–25, 45]. Recognition of this shift has influenced the way that many NTM experts view NTM lung disease pathophysiology. Specifically, there is growing consensus that many (perhaps most) NTM lung disease patients not only require exposure to NTM but also must have a vulnerability or susceptibility to NTM infection such as structural lung abnormalities associated with bronchiectasis or obstructive lung disease [46, 47]. For many NTM lung disease patients, the infection is the consequence of the underlying anatomic lung abnormality or predisposition rather than a primary event. Recent work suggests that some patients with "idiopathic" bronchiectasis have polygenic mutations, the sum of which predispose to bronchiectasis and NTM infection [46, 47]. The role of NTM in cystic fibrosis, a disease associated with

severe and progressive bronchiectasis, is discussed in chapter "NTM Disease Associated with Cystic Fibrosis". The management of bronchiectasis, which is an essential element in the comprehensive treatment of the NTM lung disease patient, is discussed in chapter "Management of Lung Diseases Associated with NTM Infection".

The identification of both genetic and acquired factors predisposing to NTM infection is rapidly expanding and is discussed in chapters "Vulnerability to NTM Lung Disease or Systemic Infection Due to Genetic /Heritable Disorders" and "Acquired immune Dysfunction and NTM Disease". Nontuberculous mycobacterial lung infection has, in general, not been found to be associated with systemic immune deficiency, although extrapulmonary and disseminated NTM disease is usually a consequence of systemic immune dysfunction or suppression [25, 48]. The role of NTM infection in children who represent another special and vulnerable host is discussed in chapter "NTM Disease in Pediatric Populations".

When the Wolinsky manuscript was published, NTM treatment was based on the principles of tuberculosis therapy. There was a limited armamentarium of antituberculosis drugs whose use was guided by in vitro susceptibility test breakpoints established for *M. tuberculosis* but not validated for NTM [1, 23]. One study suggested that MAC lung disease treatment success depended on the number of antituberculosis drugs used (up to five or six), including second-line TB drugs such as ethionamide and cycloserine [49]. The limitations of this approach were recognized at the time although few studies were done that critically evaluated the use of traditional antituberculosis medications in NTM disease [50].

In the mid-1980s, a seismic shift occurred in NTM disease with the advent of the acquired immunodeficiency syndrome (AIDS) epidemic and the emergence of MAC as a lethal pathogen [51–53]. These catastrophic events created a sense of urgency in the effort to find effective MAC therapy. Multiple antibiotics and combinations of antibiotics were tried with the new macrolide drugs, clarithromycin and azithromycin, emerging as the foundation of effective disseminated MAC therapy and prophylaxis [54–56]. It is noteworthy that this once feared AIDS-related infection is now infrequently encountered due to the success of antiretroviral therapy for AIDS.

Over the subsequent three decades, multiple studies demonstrated the utility of macrolide-based regimens for treating MAC lung infections [19, 57–62]. Regrettably, MAC lung disease therapy has stagnated with almost no significant innovations since the introduction of macrolide-based regimens. The recent introduction of an inhaled liposomal amikacin suspension (ALIS) for treatment of pulmonary MAC disease may prove to be an important exception to this generally bleak picture [63, 64]. While treatment outcomes have been generally favorable, MAC treatment success is still not comparable to the almost universally favorable TB treatment outcomes. Additionally, many other NTM respiratory pathogens such as *M. xenopi*, *M. malmoense*, *M. abscessus*, and *M. simiae* remain even more difficult to treat than MAC [25, 65]. The many challenges for treating MAC and other NTM pathogens as well as suggested treatment strategies are discussed in detail in chapters "In Vitro Drug Susceptibility Testing for NTM and Mechanisms of NTM Drug Resistance", "General Management Principles for NTM Lung Disease",

"*Mycobacterium avium* complex Disease", "NTM disease caused by *M. kansasii, M. xenopi, M. malmoense* and Other Slowly Growing NTM", and "*Mycobacterium abscessus* Disease and Disease Caused by Other Rapidly Growing NTM".

Since the publication of the Wolinsky manuscript, the presence of a particularly troublesome and frustrating aspect of NTM therapy has been repeatedly confirmed. For reasons that are not yet well understood, in vitro antibiotic susceptibility results for multiple NTM pathogens may not be predictive of treatment success or failure with a specific antibiotic [66, 67]. For MAC, for instance, the only antibiotic agents where in vitro susceptibility predicts in vivo response are macrolides and amikacin [25, 66]. Understanding the nuances and limitations of in vitro susceptibility testing for NTM is of such importance that the topic is covered in two chapters in this volume (chapters "The Modern Mycobacteriology Laboratory and Its Role in NTM Disease Diagnosis and Management" and "In Vitro Drug Susceptibility Testing for NTM and Mechanisms of NTM Drug Resistance"). The reader will note that the two chapters approach NTM in vitro susceptibility testing from different perspectives and with different areas of emphasis, but practical management considerations largely coincide between the two chapters. Both perspectives are valuable and instructive, and the reader is strongly encouraged to read both chapters in detail.

Molecular laboratory techniques have provided tools for investigating paradoxical NTM antibiotic resistance and have made us aware of multiple factors possessed by NTM that are associated with innate or natural drug resistance [66, 67]. These innate resistance factors may not be reflected in the MIC of the organism for specific drugs. This is the most vexing and counterintuitive characteristic of NTM lung disease for clinicians and the area where experience with tuberculosis is least helpful. Probably the best known example of this phenomenon is the inducible macrolide resistance gene, or *erm* gene, present in *M. abscessus* subsp. *abscessus* and subsp. *bolletii* as well as other mycobacterial species, such as *M. fortuitum* and even *M. tuberculosis* [13]. The activity of this gene can only be detected in vitro by preincubation of the organism in the presence of macrolide. While *erm* gene activity is only one mechanism of innate NTM drug resistance, its recognition has been transformative for how we approach patients with *M. abscessus* respiratory disease (chapters "In Vitro Drug Susceptibility Testing for NTM and Mechanisms of NTM Drug Resistance" and "*Mycobacterium abscessus* Disease and Disease Caused by Other Rapidly Growing NTM").

Ultimately, the future of NTM lung disease therapy will be guided by recognition of innate antibiotic resistance mechanisms and the discovery of ways to overcome them. The complexities of in vitro susceptibility testing for treating NTM disease are discussed in chapters "Laboratory Diagnosis and Antimicrobial Susceptibility Testing of Nontuberculous Mycobacteria" and "In Vitro Drug Susceptibility Testing for NTM and Mechanisms of NTM Drug Resistance" as well as multiple other chapters. For successful management of NTM infections, clinicians must become familiar with the idiosyncratic behavior of NTM pathogens. There is no substitute for having this knowledge.

Unfortunately, the discussion of NTM antibiotic drug resistance does not end with innate drug resistance. Many NTM pathogens including MAC and *M. abscessus* subsp. *abscessus* are also vulnerable to acquired mutational drug resistance, a

mechanism for acquired drug resistance well known to clinicians who treat tuberculosis. For instance, macrolides must be protected by effective companion drugs in MAC treatment regimens to avoid the emergence of macrolide resistance through selection of organisms with a 23S rRNA mutation. This occurrence is associated with poor treatment response and poor overall outcome [68]. Acquired mutational drug resistance occurs with other NTM pathogens, notably the *rpoβ* gene and acquired *M. kansasii* rifamycin resistance. This type of antibiotic resistance is both predictable and avoidable if the clinician is aware of the risk for specific NTM pathogens and the necessary steps to avoid it. Again, there are no shortcuts and no substitutes for this knowledge. The management of NTM pathogens in the context of both innate and acquired drug resistance mechanisms is discussed in chapters ""In Vitro Drug Susceptibility Testing for NTM and Mechanisms of NTM Drug Resistance", "General Management Principles for NTM Lung Disease", "*Mycobacterium avium* Complex Disease", "NTM disease caused by *M. kansasii, M. xenopi, M. malmoense* and Other Slowly Growing NTM", and "*Mycobacterium abscessus* Disease and Disease Caused by Other Rapidly Growing NTM".

In large part because of antimicrobial resistance, surgical intervention is important for management of both pulmonary and extrapulmonary-pulmonary NTM disease and is discussed in chapter "Surgical Management of NTM Diseases" as well as chapters discussing treatment of specific NTM pathogens. Surgical resection of diseased lung has consistently been shown to be effective for selected NTM lung disease patients [13]. Surgery is a sufficiently important potential adjunct to medical therapy for NTM lung disease that it should be considered whenever possible. Surgical debridement of diseased tissue is absolutely essential for successful therapy of NTM skin, soft tissue, and bone infections.

Since 1990, there have been three NTM statements sponsored or co-sponsored by the American Thoracic Society [23–25]. These documents summarized contemporary knowledge about NTM with recommendations for treating specific NTM pathogens. As much as anything else, they focused attention on the numerous and persistent NTM disease knowledge gaps and the sparse evidence base for making NTM disease management recommendations. The NTM statements did, however, provide treatment recommendations based on the limited evidence base and expert opinion. The MAC lung disease recommendations proved to be effective if imperfect and less reliably effective than TB therapy. In that context, it is instructive that two studies have shown that there is poor adherence to the published treatment guidelines worldwide which may account for some of the frustration experienced by clinicians related to ineffective therapy [69, 70].

Unquestionably, many weaknesses and gaps in our knowledge of NTM disease remain. We need better understanding of environmental niches and mechanisms of organism acquisition. For NTM lung disease especially, we need markers of disease activity so that we can predict which patients will have progressive disease and require therapy. That type of marker would allow eliminating the confusing and the sometimes insensitive and nonspecific NTM disease diagnostic criteria. Equally important we need the ability to identify those patients with NTM lung disease who are likely to relapse after successful therapy. Overall, we need more efficient ways

to define and predict the course of NTM lung disease. We need better ways to determine NTM disease prevalence and ultimately incidence. Making NTM disease uniformly reportable in the United States and globally would go a long way toward accomplishing those goals, although, without tools that improve diagnostic accuracy, even universal case reporting would probably still entail considerable inaccuracies. The most pressing need is for new and more effective antimicrobial agents, a process that will be driven by improved understanding of NTM drug resistance mechanisms. We will need new approaches to NTM disease prevention, a process only possible with early identification of patients at risk for developing NTM lung disease and better understanding of NTM environmental niches and mechanisms of organism acquisition from these niches.

The reader is once again strongly encouraged to read each chapter for a comprehensive overview of the complexities, subtleties, and paradoxes of NTM disease and its treatment. The understanding of NTM disease is clearly nascent, but we are experiencing an exciting acceleration in the pace of discovery and knowledge. It is also remarkable that progress so far has been accomplished largely without extramural funding from national (the United States) and international funding agencies, although that bleak scenario may be gradually improving. Convincing extramural funding sources that NTM disease, especially lung disease, is a growing international health burden and that committing research dollars to this field will yield important and widely applicable results are major priorities and challenges. A vital element in this task is procuring funding for prospective treatment trials which are necessary not only for critical evaluation of current treatment strategies but also to establish optimal study designs for testing new drugs as they become available [63, 64].

Since the publication of the Wolinsky manuscript, the study of NTM disease has been completely transformed. A fledgling field in 1980 has acquired legitimacy and momentum with a sound footing in clinical and basic science. There are many reasons to be optimistic about continued and accelerating progress with NTM disease. First among them is the proliferation of investigators around the world including the very talented investigators who contributed to this volume. I am immensely grateful to them for their excellent contributions. I am also impressed, humbled, and inspired by the superb quality of their innovative work. It is clear to me that over the next 40 years, there will be further exponential expansion of NTM disease knowledge and understanding. The inevitable result will be achievement of the ultimate goal, improved outcomes for our patients.

Bibliography

1. Wolinsky E. Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis. 1979;119(1):107–59.
2. Runyon EH. Identification of mycobacterial pathogens utilizing colony characteristics. Am J Clin Pathol. 1970;54(4):578–86.
3. Runyon EH. Atypical mycobacteria: their classification. Am Rev Respir Dis. 1965;91:288–9.
4. Jost KC Jr, Dunbar DF, Barth SS, Headley VL, Elliott LB. Identification of Mycobacterium tuberculosis and M. avium complex directly from smear-positive sputum specimens and

BACTEC 12B cultures by high-performance liquid chromatography with fluorescence detection and computer-driven pattern recognition models. J Clin Microbiol. 1995;33(5):1270–7.
5. Louro AP, Waites KB, Georgescu E, Benjamin WH Jr. Direct identification of Mycobacterium avium complex and Mycobacterium gordonae from MB/BacT bottles using AccuProbe. J Clin Microbiol. 2001;39(2):570–3. 8: Pauls RJ, Turenne CY, Wolfe JN, Kabani A. A high proportion of novel mycobacteria species identified by 16S rDNA analysis among slowly growing AccuProbe-negative strains in a clinical setting. Am J Clin Pathol. 2003;120(4):560–6
6. Cloud JL, Carroll KC, Cohen S, Anderson CM, Woods GL. Interpretive criteria for use of AccuProbe for identification of Mycobacterium avium complex directly from 7H9 broth cultures. J Clin Microbiol. 2005;43(7):3474–8.
7. Griffith DE, Brown-Elliott BA, Benwill JL, Wallace RJ Jr. Mycobacterium abscessus. "Pleased to meet you, hope you guess my name...". Ann Am Thorac Soc. 2015;12(3):436–9.
8. LPSN. bacterio.net web. List of prokaryotic names with standing in nomenclature. http://www.bacterio.net/-classification.html
9. Tettelin H, Davidson RM, Agrawal S, Aitken ML, Shallom S, Hasan NA, Strong M, de Moura VC, De Groote MA, Duarte RS, Hine E, Parankush S, Su Q, Daugherty SC, Fraser CM, Brown-Elliott BA, Wallace RJ Jr, Holland SM, Sampaio EP, Olivier KN, Jackson M, Zelazny AM. High-level relatedness among Mycobacterium abscessus subsp. massiliense strains from widely separated outbreaks. Emerg Infect Dis. 2014;20(3):364–71.
10. Tortoli E, Kohl TA, Brown-Elliott BA, Trovato A, Leão SC, Garcia MJ, Vasireddy S, Turenne CY, Griffith DE, Philley JV, Baldan R, Campana S, Cariani L, Colombo C, Taccetti G, Teri A, Niemann S, Wallace RJ Jr, Cirillo DM. Emended description of Mycobacterium abscessus, Mycobacterium abscessus subsp. abscessus and Mycobacteriumabscessus subsp. bolletii and designation of Mycobacterium abscessus subsp. massiliense comb. nov. Int J Syst Evol Microbiol. 2016;66(11):4471–9.
11. Adekambi T, Sassi M, van Ingen J, Drancourt M. Reinstating Mycobacterium massiliense and Mycobacterium bolletii as species of the Mycobacterium abscessus complex. Int J Syst Evol Microbiol. 2017;67(8):2726–30.
12. van Ingen J, Kohl TA, Kranzer K, Hasse B, Keller PM, Katarzyna Szafrańska A, Hillemann D, Chand M, Schreiber PW, Sommerstein R, Berger C, Genoni M, Rüegg C, Troillet N, Widmer AF, Becker SL, Herrmann M, Eckmanns T, Haller S, Höller C, Debast SB, Wolfhagen MJ, Hopman J, Kluytmans J, Langelaar M, Notermans DW, Ten Oever J, van den Barselaar P, Vonk ABA, Vos MC, Ahmed N, Brown T, Crook D, Lamagni T, Phin N, Smith EG, Zambon M, Serr A, Götting T, Ebner W, Thürmer A, Utpatel C, Spröer C, Bunk B, Nübel U, Bloemberg GV, Böttger EC, Niemann S, Wagner D, Sax H. Global outbreak of severe Mycobacterium chimaera disease after cardiac surgery: a molecular epidemiological study. Lancet Infect Dis. 2017;17(10):1033–41.
13. Nash KA, Brown-Elliott BA, Wallace RJ Jr. A novel gene, erm(41), confers inducible macrolide resistance to clinical isolates of Mycobacterium abscessus but is absent from Mycobacterium chelonae. Antimicrob Agents Chemother. 2009;53(4):1367–76.
14. van Ingen J, Boeree MJ, van Soolingen D, Mouton JW. Resistance mechanisms and drug susceptibility testing of nontuberculous mycobacteria. Drug Resist Updat. 2012;15(3):149–61.
15. Wallace RJ Jr, Iakhiaeva E, Williams MD, Brown-Elliott BA, Vasireddy S, Vasireddy R, Lande L, Peterson DD, Sawicki J, Kwait R, Tichenor WS, Turenne C, Falkinham JO 3rd. Absence of Mycobacterium intracellulare and presence of Mycobacterium chimaera in household water and biofilm samples of patients in the United States with Mycobacterium avium complex respiratory disease. J Clin Microbiol. 2013;51(6):1747–52.
16. Bryant JM, Grogono DM, Rodriguez-Rincon D, Everall I, Brown KP, Moreno P, Verma D, Hill E, Drijkoningen J, Gilligan P, Esther CR, Noone PG, Giddings O, Bell SC, Thomson R, Wainwright CE, Coulter C, Pandey S, Wood ME, Stockwell RE, Ramsay KA, Sherrard LJ, Kidd TJ, Jabbour N, Johnson GR, Knibbs LD, Morawska L, Sly PD, Jones A, Bilton D, Laurenson I, Ruddy M, Bourke S, Bowler IC, Chapman SJ, Clayton A, Cullen M, Daniels T, Dempsey O, Denton M, Desai M, Drew RJ, Edenborough F, Evans J, Folb J, Humphrey H,

Isalska B, Jensen-Fangel S, Jönsson B, Jones AM, Katzenstein TL, Lillebaek T, MacGregor G, Mayell S, Millar M, Modha D, Nash EF, O'Brien C, O'Brien D, Ohri C, Pao CS, Peckham D, Perrin F, Perry A, Pressler T, Prtak L, Qvist T, Robb A, Rodgers H, Schaffer K, Shafi N, van Ingen J, Walshaw M, Watson D, West N, Whitehouse J, Haworth CS, Harris SR, Ordway D, Parkhill J, Floto RA. Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacterium. Science. 2016;354(6313):751–7.

17. van Ingen J, Boeree MJ, Dekhuijzen PN, van Soolingen D. Environmental sources of rapid growing nontuberculous mycobacteria causing disease in humans. Clin Microbiol Infect. 2009;15(10):888–93.
18. Wallace RJ Jr, Zhang Y, Brown BA, Dawson D, Murphy DT, Wilson R, Griffith DE. Polyclonal Mycobacterium avium complex infections in patients with nodular bronchiectasis. Am J Respir Crit Care Med. 1998;158(4):1235–44.
19. Wallace RJ Jr, Brown-Elliott BA, McNulty S, Philley JV, Killingley J, Wilson RW, York DS, Shepherd S, Griffith DE. Macrolide/Azalide therapy for nodular/bronchiectatic mycobacterium avium complex lung disease. Chest. 2014;146(2):276–82.
20. O'Brien RJ, Geiter LJ, Snider DE Jr. The epidemiology of nontuberculous mycobacterial diseases in the United States. Results from a national survey. Am Rev Respir Dis. 1987;135(5):1007–14.
21. O'Brien RJ. The epidemiology of nontuberculous mycobacterial disease. Clin Chest Med. 1989;10(3):407–18.
22. Griffith DE, Brown-Elliott BA, Wallace RJ Jr. Diagnosing nontuberculous mycobacterial lung disease. A process in evolution. Infect Dis Clin North Am. 2002;16(1):235–49.
23. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am Rev Respir Dis. 1990;142(4):940–53. Erratum in: Am Rev Respir Dis 1991 Jan;143(1):204.
24. 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. Medical section of the American Lung Association. Am J Respir Crit Care Med. 1997;156(2 Pt 2):S1–25.
25. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K, ATS Mycobacterial Diseases Subcommittee, American Thoracic Society, Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367–416. Review. Erratum in: Am J Respir Crit Care Med 2007 Apr 1;175(7):744–5. Dosage error in article text.
26. Jankovic M, Sabol I, Zmak L, Jankovic VK, Jakopovic M, Obrovac M, Ticac B, Bulat LK, Grle SP, Marekovic I, Samarzija M, van Ingen J. Microbiological criteria in non-tuberculous mycobacteria pulmonary disease: a tool for diagnosis and epidemiology. Int J Tuberc Lung Dis. 2016;20(7):934–40.
27. Cassidy PM, Hedberg K, Saulson A, McNelly E, Winthrop KL. Nontuberculous mycobacterial disease prevalence and risk factors: a changing epidemiology. Clin Infect Dis. 2009;49(12):e124–9.
28. Winthrop KL, McNelley E, Kendall B, Marshall-Olson A, Morris C, Cassidy M, Saulson A, Hedberg K. Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. Am J Respir Crit Care Med. 2010;182(7):977–82.
29. Winthrop KL, Varley CD, Ory J, Cassidy PM, Hedberg K. Pulmonary disease associated with nontuberculous mycobacteria, Oregon, USA. Emerg Infect Dis. 2011;17(9):1760–1.
30. Henkle E, Hedberg K, Schafer S, Novosad S, Winthrop KL. Population-based incidence of pulmonary nontuberculous mycobacterial disease in Oregon 2007 to 2012. Ann Am Thorac Soc. 2015;12(5):642–7.
31. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med. 2012;185(8):881–6.

32. Prevots DR, Shaw PA, Strickland D, Jackson LA, Raebel MA, Blosky MA, Montes de Oca R, Shea YR, Seitz AE, Holland SM, Olivier KN. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am J Respir Crit Care Med. 2010;182(7):970–6.
33. Hoefsloot W, van Ingen J, Andrejak C, Angeby K, Bauriaud R, Bemer P, Beylis N, Boeree MJ, Cacho J, Chihota V, Chimara E, Churchyard G, Cias R, Daza R, Daley CL, Dekhuijzen PN, Domingo D, Drobniewski F, Esteban J, Fauville-Dufaux M, Folkvardsen DB, Gibbons N, Gómez-Mampaso E, Gonzalez R, Hoffmann H, Hsueh PR, Indra A, Jagielski T, Jamieson F, Jankovic M, Jong E, Keane J, Koh WJ, Lange B, Leao S, Macedo R, Mannsåker T, Marras TK, Maugein J, Milburn HJ, Mlinkó T, Morcillo N, Morimoto K, Papaventsis D, Palenque E, Paez-Peña M, Piersimoni C, Polanová M, Rastogi N, Richter E, Ruiz-Serrano MJ, Silva A, da Silva MP, Simsek H, van Soolingen D, Szabó N, Thomson R, Tórtola Fernandez T, Tortoli E, Totten SE, Tyrrell G, Vasankari T, Villar M, Walkiewicz R, Winthrop KL, Wagner D, Nontuberculous Mycobacteria Network European Trials Group. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. Eur Respir J. 2013;42(6):1604–13.
34. Ito Y, Hirai T, Fujita K, Maekawa K, Niimi A, Ichiyama S, Mishima M. Increasing patients with pulmonary Mycobacterium avium complex disease and associated underlying diseases in Japan. J Infect Chemother. 2015;21(5):352–6.
35. Hu P, Bai L, Liu F, Ou X, Zhang Z, Yi S, Chen Z, Gong D, Liu B, Guo J, Tan Y. Evaluation of the Xpert MTB/RIF assay for diagnosis of tuberculosis and rifampin resistance in county-level laboratories in Hunan province, China. Chin Med J (Engl). 2014;127(21):3744–5025.
36. Wu J, Zhang Y, Li J, Lin S, Wang L, Jiang Y, Pan Q, Shen X. Increase in nontuberculous mycobacteria isolated in Shanghai, China: results from a population-based study. PLoS One. 2014;9(10):e109736.
37. Shao Y, Chen C, Song H, Li G, Liu Q, Li Y, Zhu L, Martinez L, Lu W. The epidemiology and geographic distribution of nontuberculous mycobacteria clinical isolates from sputum samples in the eastern region of China. PLoS Negl Trop Dis. 2015;9(3):e0003623.
38. Wendt SL, George KL, Parker BC, Gruft H, Falkinham JO 3rd. Epidemiology of infection by nontuberculous mycobacteria. III. Isolation of potentially pathogenic mycobacteria from aerosols. Am Rev Respir Dis. 1980;122(2):259–63.
39. Collins CH, Grange JM, Yates MD. Mycobacteria in water. J Appl Bacteriol. 1984;57(2):193–211.
40. Parker BC, Ford MA, Gruft H, Falkinham JO 3rd. Epidemiology of infection by nontuberculous mycobacteria. IV. Preferential aerosolization of Mycobacterium intracellulare from natural waters. Am Rev Respir Dis. 1983;128(4):652–6.
41. Meissner PS, Falkinham JO 3rd. Plasmid DNA profiles as epidemiological markers for clinical and environmental isolates of Mycobacterium avium, Mycobacterium intracellulare, and Mycobacterium scrofulaceum. J Infect Dis. 1986;153(2):325–31.
42. Fujita K, Ito Y, Hirai T, Maekawa K, Imai S, Tatsumi S, Niimi A, Iinuma Y, Ichiyama S, Mishima M. Genetic relatedness of Mycobacterium avium-intracellulare complex isolates from patients with pulmonary MAC disease and their residential soils. Clin Microbiol Infect. 2013;19(6):537–41.
43. Falkinham JO 3rd. Environmental sources of nontuberculous mycobacteria. Clin Chest Med. 2015;36(1):35–41.
44. Iseman MD, Corpe RF, O'Brien RJ, Rosenzwieg DY, Wolinsky E. Disease due to Mycobacterium avium-intracellulare. Chest. 1985;87(2 Suppl):139S–49S.
45. Prince DS, Peterson DD, Steiner RM, Gottlieb JE, Scott R, Israel HL, Figueroa WG, Fish JE. Infection with Mycobacterium avium complex in patients without predisposing conditions. N Engl J Med. 1989;321(13):863–8.
46. Szymanski EP, Leung JM, Fowler CJ, Haney C, Hsu AP, Chen F, Duggal P, Oler AJ, McCormack R, Podack E, Drummond RA, Lionakis MS, Browne SK, Prevots DR, Knowles M, Cutting G, Liu X, Devine SE, Fraser CM, Tettelin H, Olivier KN, Holland SM. Pulmonary

nontuberculous mycobacterial infection. A multisystem, multigenic disease. Am J Respir Crit Care Med. 2015;192(5):618–28.
47. Chen F, Szymanski EP, Olivier KN, Liu X, Tettelin H, Holland SM, Duggal P. Whole exome sequencing identify the 6q12-q16 linkage region and a candidate gene TTK for pulmonary nontuberculous mycobacterial disease. Am J Respir Crit Care Med. 2017;196:1599.
48. Holland SM, Pierce VM, Shailam R, Glomski K, Farmer JR. Case 28-2017. A 13-month-old girl with pneumonia and a 33-year-old woman with hip pain. N Engl J Med. 2017;377(11):1077–91.
49. Horsburgh CR Jr, Mason UG 3rd, Heifets LB, Southwick K, Labrecque J, Iseman MD. Response to therapy of pulmonary Mycobacterium avium-intracellulare infection correlates with results of in vitro susceptibility testing. Am Rev Respir Dis. 1987;135(2):418–21.
50. Research Committee of the British Thoracic Society. First randomised trial of treatments for pulmonary disease caused by M avium intracellulare, M malmoense, and M xenopi in HIV negative patients: rifampicin, ethambutol and isoniazid versus rifampicin and ethambutol. Thorax. 2001;56(3):167–72.
51. Hawkins CC, Gold JW, Whimbey E, Kiehn TE, Brannon P, Cammarata R, Brown AE, Armstrong D. Mycobacterium avium complex infections in patients with the acquired immunodeficiency syndrome. Ann Intern Med. 1986;105(2):184–8.
52. Mycobacterioses and the acquired immunodeficiency syndrome. Joint position paper of the American Thoracic Society and the Centers for Disease Control. Am Rev Respir Dis. 1987;136(2):492–6.
53. Horsburgh CR Jr, Selik RM. The epidemiology of disseminated nontuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). Am Rev Respir Dis. 1989;139(1):4–7.
54. Chin DP, Reingold AL, Stone EN, Vittinghoff E, Horsburgh CR Jr, Simon EM, Yajko DM, Hadley WK, Ostroff SM, Hopewell PC. The impact of Mycobacterium avium complex bacteremia and its treatment on survival of AIDS patients--a prospective study. J Infect Dis. 1994;170(3):578–84.
55. Shafran SD, Singer J, Zarowny DP, Phillips P, Salit I, Walmsley SL, Fong IW, Gill MJ, Rachlis AR, Lalonde RG, Fanning MM, Tsoukas CM. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group. N Engl J Med. 1996;335(6):377–83.
56. Chaisson RE, Keiser P, Pierce M, Fessel WJ, Ruskin J, Lahart C, Benson CA, Meek K, Siepman N, Craft JC. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic Mycobacterium avium complex disease in patients with HIV infection. AIDS. 1997;11(3):311–7. PubMed PMID: 9147422.
57. Wallace RJ Jr, Brown BA, Griffith DE, Girard WM, Murphy DT. Clarithromycin regimens for pulmonary Mycobacterium avium complex. The first 50 patients. Am J Respir Crit Care Med. 1996;153(6 Pt 1):1766–72.
58. Wallace RJ Jr, Brown BA, Griffith DE, Girard WM, Murphy DT, Onyi GO, Steingrube VA, Mazurek GH. Initial clarithromycin monotherapy for Mycobacterium avium-intracellulare complex lung disease. Am J Respir Crit Care Med. 1994;149(5):1335–41.
59. Griffith DE, Brown BA, Girard WM, Murphy DT, Wallace RJ Jr. Azithromycin activity against Mycobacterium avium complex lung disease in patients who were not infected with human immunodeficiency virus. Clin Infect Dis. 1996;23(5):983–9.
60. Jeong BH, Jeon K, Park HY, Kim SY, Lee KS, Huh HJ, Ki CS, Lee NY, Shin SJ, Daley CL, Koh WJ. Intermittent antibiotic therapy for nodular bronchiectatic Mycobacterium avium complex lung disease. Am J Respir Crit Care Med. 2015;191(1):96–103.
61. Kobashi Y, Abe M, Mouri K, Obase Y, Miyashita N, Oka M. Clinical usefulness of combination chemotherapy for pulmonary Mycobacterium avium complex disease. J Infect. 2010;
62. Kobashi Y, Matsushima T. The microbiological and clinical effects of combined therapy according to guidelines on the treatment of pulmonary Mycobacterium avium complex disease in Japan – including a follow-up study. Respiration. 2007;74(4):394–400.

63. Olivier KN, Griffith DE, Eagle G, JP MG 2nd, Micioni L, Liu K, Daley CL, Winthrop KL, Ruoss S, Addrizzo-Harris DJ, Flume PA, Dorgan D, Salathe M, Brown-Elliott BA, Gupta R, Wallace RJ Jr. Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease. Am J Respir Crit Care Med. 2017;195(6):814–23.
64. Griffith DE, Eagle G, Thomson RM, Aksamit TA, Hasegawa N, Morimoto K et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex. Am J Respir and Crit Care Med, In Press, 2018.
65. van Ingen J, Ferro BE, Hoefsloot W, Boeree MJ, van Soolingen D. Drug treatment of pulmonary nontuberculous mycobacterial disease in HIV-negative patients: the evidence. Expert Rev Anti Infect Ther. 2013;11(10):1065–77.
66. Brown-Elliott BA, Nash KA, Wallace RJ Jr. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. Clin Microbiol Rev. 2012;25(3):545–82.
67. Brown-Elliott BA, Iakhiaeva E, Griffith DE, Woods GL, Stout JE, Wolfe CR, Turenne CY, Wallace RJ Jr. In vitro activity of amikacin against isolates of Mycobacterium avium complex with proposed MIC breakpoints and finding of a 16S rRNA gene mutation in treated isolates. J Clin Microbiol. 2013;51(10):3389–94.
68. Griffith DE, Brown-Elliott BA, Langsjoen B, Zhang Y, Pan X, Girard W, Nelson K, Caccitolo J, Alvarez J, Shepherd S, Wilson R, Graviss EA, Wallace RJ Jr. Clinical and molecular analysis of macrolide resistance in Mycobacterium avium complex lung disease. Am J Respir Crit Care Med. 2006;174(8):928–34.
69. Adjemian J, Prevots DR, Gallagher J, Heap K, Gupta R, Griffith D. Lack of adherence to evidence-based treatment guidelines for nontuberculous mycobacterial lung disease. Ann Am Thorac Soc. 2014;11(1):9–16.
70. van Ingen J, Wagner D, Gallagher J, Morimoto K, Lange C, Haworth CS, Floto RA, Adjemian J, Prevots DR, Griffith DE, NTM-NET. Poor adherence to management guidelines in nontuberculous mycobacterial pulmonary diseases. Eur Respir J. 2017;49(2). pii: 1601855.

Laboratory Diagnosis and Antimicrobial Susceptibility Testing of Nontuberculous Mycobacteria

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Introduction

Prior to the 1990s, clinical mycobacteriology laboratories used phenotypic cultural characteristics and conventional biochemical testing for a large portion of nontuberculous mycobacteria (NTM) species identification [1].

Following the "biochemical era" (and even today), some larger reference laboratories, especially public health laboratories, and some research laboratories relied upon species identification based on chromatographic/chemotaxonomic methods including high-performance liquid chromatography (HPLC) of cell wall mycolic acids, thin-layer chromatography (TLC), and gas-liquid chromatography (GLC).

Beginning in the 1990s, the advent of molecular testing by PCR and gene sequencing for species and subspecies identification of NTM marked a new era for NTM with the subsequent explosion of more than 100 species being described compared to approximately 55 species identified from 1880 to 1990! The definition of a "species" is somewhat of a "moving target" requiring constant modification as newer diagnostic methodologies are introduced. Gene sequencing has now become the accepted reference method for the identification of NTM [2]. As with the previous methodologies, the accuracy and quality

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