

# Contents

## **Preface: Things They Are a Changing in the Field of Nontuberculous Mycobacteria** **xiii**

Shannon Kasperbauer and Rachel Thomson

## **Environmental Sources and Transmission of Nontuberculous Mycobacteria** **661**

Jennifer R. Honda

The field of environmental nontuberculous mycobacteria (NTM) is benefiting from a new era of genomics that has catapulted our understanding of preferred niches, transmission, and outbreak investigations. The ability to forecast environmental features that promote or reduce environmental NTM prevalence will greatly improve with coordinated environmental sampling and by elevating the necessity for uniform disease notifications. Studies that synergize environmental biology, isolate notifications, and comparative genomics in prospective, longitudinal studies, particularly during climate changes and weather events, will be useful to solve longstanding NTM public health quandaries.

## **Global Epidemiology of Nontuberculous Mycobacterial Pulmonary Disease: A Review** **675**

D. Rebecca Prevots, Julia E. Marshall, Dirk Wagner, and Kozo Morimoto

Nontuberculous mycobacterial (NTM) isolation and pulmonary disease (NTM-PD) have continued to increase in most regions of the world, driven mainly by *Mycobacterium avium*. Single-center studies also support increasing trends as well as a persistent burden of undiagnosed NTM among persons suspected of having tuberculosis (TB), in countries with moderate-to-high TB prevalence. Cumulative exposure to water and soil presents an increased risk to susceptible hosts, and trace metals in water supply are recently recognized risk factors. Establishing standard case definitions for subnational and national surveillance systems with mandatory notification of NTM-PD are needed to allow comparisons within and across countries and regions.

## **Host Susceptibility to Nontuberculous Mycobacterial Pulmonary Disease** **723**

Ho Namkoong and Steven M. Holland

Nontuberculous mycobacteria (NTM) pulmonary disease is a chronic progressive pulmonary infectious disease caused by low virulence pathogens. The existence of host susceptibility to NTM infection has been recognized from a high incidence among Asians compared to other populations in the United States, a high incidence among slender, middle-aged women, and the presence of familial clusters. Recent whole exome sequencing and genome-wide association studies have identified immune, CFTR, cilia, connective tissue and ion homeostasis genes as host susceptibility genes. Large-scale international collaborative studies and functional analyses are expected to elucidate host susceptibility in the future.

**Investigation and Management of Bronchiectasis in Nontuberculous Mycobacterial Pulmonary Disease**

731

Pamela J. McShane

Patients with nontuberculous mycobacterial (NTM) lung infection require life-long attention to their bronchiectasis, whether or not their NTM infection has been cured. The identification of the cause of bronchiectasis and/or coexisting diseases is important because it may affect therapeutic strategies. Airway clearance is the mainstay of bronchiectasis management. It can include multiple breathing techniques, devices, and mucoactive agents. The exact airway clearance regimen should be customized to each individual patient. Chronic pathogenic airway bacteria, such as *Pseudomonas aeruginosa*, may warrant consideration of eradication therapy and/or chronic use of maintenance inhaled antibiotics.

**Culture, Identification, and Antimicrobial Susceptibility Testing of Pulmonary Nontuberculous Mycobacteria**

743

Reeti Khare and Barbara A. Brown-Elliott

Nontuberculous mycobacteria (NTM) typically cause opportunistic pulmonary infections and reliable laboratory results can assist with diagnosis of disease. Microscopy can detect acid-fast bacilli from specimens though it has poor sensitivity. Solid and liquid culture are used to grow NTM, which are identified by molecular or protein-based assays. Because culture has a long turnaround time, some assays are designed to identify NTM directly from sputum specimens. When indicated, phenotypic susceptibility testing should be performed by broth microdilution as per the guidelines from the Clinical Laboratory Standards Institute. Genotypic susceptibility methods may be used to decrease the turnaround time for some antimicrobials.

**Diagnostic Criteria and the Decision to Treat Nontuberculous Mycobacterial Pulmonary Disease**

757

David E. Griffith and Timothy R. Aksamit

The diagnosis of nontuberculous mycobacterial (NTM) pulmonary disease is based on three criteria: patient's symptoms, radiographic findings, and microbiologic results. The microbiologic criterion is the most complicated because it requires more than one positive sputum acid-fast bacilli culture. Clinicians are challenged to apply the diagnostic criteria in the context of variable patient symptoms, NTM pathogenicity, and host susceptibility. The decision to treat NTM pulmonary disease entails assessment of the risks and benefits of therapy and the patient's wishes and ability to receive treatment.

**Treatment of *Mycobacterium avium* Complex Pulmonary Disease: When Should I Treat and What Therapy Should I Start?**

771

Minh-Vu H. Nguyen and Charles L. Daley

Treatment of *M avium* pulmonary disease requires a three-drug, macrolide-based regimen that is administered for 12 months beyond culture conversion. The regimen can be administered 3 days a week in non-cavitary, nodular bronchiectatic disease but should be given daily when cavitary disease is present. For treatment refractory disease, amikacin liposome inhalation suspension is added to the regimen. Parenteral amikacin or streptomycin should be administered in the setting of extensive radiographic involvement or macrolide resistance. Recurrence of disease is common

and often due to reinfection. Novel and repurposed agents are being evaluated in clinical trials.

### **Treatment Approaches to *Mycobacterium abscessus* Pulmonary Disease**

785

Michael R. Holt and Timothy Baird

*Mycobacterium abscessus* pulmonary disease is highly antibiotic-resistant, and the current armamentarium of antibiotics yields poor treatment outcomes with significant drug toxicity. Macrolide susceptibility is a key prognostic factor. Optimal drug combinations, duration of therapy, and management of refractory disease are unknown. Surgical resection, performed at centers with experience in surgical management of nontuberculous mycobacterial pulmonary disease, may produce favorable outcomes in select patients. Multiple emerging therapeutic candidates hold promise for more efficacious and tolerable treatment options.

### **Treatment of the Less Common Nontuberculous Mycobacterial Pulmonary Disease**

799

Marie Yan, Sarah K. Brode, and Theodore K. Marras

Nontuberculous mycobacterial pulmonary disease caused by the less common nontuberculous mycobacteria have distinct features depending on the species. Diagnostic evaluation follows the established criteria for all nontuberculous mycobacteria, but with certain qualifications given species-specific and regional differences in pathogenicity. Clinicians should first institute nonpharmacologic management and evaluate clinical, radiologic, and microbiologic factors in the decision regarding antimycobacterial therapy. Treatment is challenging, and evidence-based recommendations are limited for most species. Drug susceptibility testing is used to help with regimen selection; however, this approach is imperfect given the uncertain correlation between in vitro activity and clinical response for most drugs.

### **Medications and Monitoring in Treatment of Nontuberculous Mycobacterial Pulmonary Disease**

815

Alice Sawka and Andrew Burke

In the treatment of nontuberculous mycobacteria (NTM) lung disease, clinicians must consider potential toxicities that may occur as a result of prolonged exposure to a multidrug antibiotic regimen. Frequent clinical and microbiological monitoring is required to assess response and guide treatment duration. This article summarizes toxicity profiles of the antibiotics that are most frequently prescribed for the treatment of NTM lung disease. The role of therapeutic drug monitoring during use of amikacin and linezolid is discussed. The available evidence to guide frequency and extent of medication monitoring during NTM treatment is provided.

### **Nontuberculous Mycobacterial Pulmonary Disease in the Immunocompromised Host**

829

Cara D. Varley, Amber C. Streifel, Amanda M. Bair, and Kevin L. Winthrop

The immunocompromised host is at an increased risk for pulmonary and extrapulmonary NTM infections. Where data are available in these specific populations, increased mortality is observed with NTM disease. Prior to starting therapy for NTM disease, providers should ensure diagnostic criteria are met as treatment is long and often associated with significant side effects and toxicities. Treatment should involve 2 to 4 agents and be guided by cultures and antimicrobial susceptibilities.

Drug interactions are important to consider, especially in those with HIV or transplant recipients. Whenever possible, immunosuppression should be reduced or changed.

**Host-Directed Therapy in Nontuberculous Mycobacterial Pulmonary Disease: Preclinical and Clinical Data Review**

839

Ifeanyichukwu U. Anidi and Kenneth N. Olivier

Standard treatment of nontuberculous mycobacterial pulmonary disease (NTM-PD) infection involves a multi-drug antimicrobial regimen for at least 12 months. The length, complexity, and side effect profile of antibiotic therapy for NTM-PD pose significant difficulties for maintaining patient adherence. Furthermore, physician adherence to NTM guidelines suffers for similar reasons to the extent that a study evaluating treatment approaches across multiple specialties found that only 13% of antibiotic regimens met ATS/IDSA guidelines. For this reason, a great need exists for therapy that augments the current armamentarium of antimicrobial chemotherapeutics or provides an alternative approach for decreasing host mycobacterial burden. As our knowledge of the mechanisms driving protective responses to NTM-PD infections by mammalian hosts expand, these processes provide novel therapeutic targets. These agents, which are commonly referred to as host-directed therapies (HDTs) have the potential of providing the much-needed boost to the nontuberculous mycobacterial therapeutic pipeline. In this review, we will focus on translational research and clinical trial data that detail the creation of therapeutic modalities developed to improve host mechanical protection and immunologic responses to PNTM infection.

**Cystic Fibrosis-Related Nontuberculous Mycobacterial Pulmonary Disease**

847

Timothy Baird and Scott Bell

Non-tuberculous mycobacteria (NTM) infection is a major cause of morbidity in people with cystic fibrosis (pwCF) with rates of infection increasing worldwide. Accurate diagnosis and decisions surrounding best management remain challenging. Treatment guidelines have been developed to assist physicians in managing NTM in pwCF, but involve prolonged and complex mycobacterial regimens, often associated with significant toxicity. Fortunately, current management and outcomes of NTM in CF are likely to evolve due to improved understanding of disease acquisition, better diagnostics, emerging antimycobacterial therapies, and the widespread uptake of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies.

**Surgical Resection in Nontuberculous Mycobacterial Pulmonary Disease**

861

Lauren J. Taylor and John D. Mitchell

Rates of nontuberculous mycobacterial pulmonary disease are increasing worldwide, particularly in the United States and other developed countries. While multi-drug antimicrobial therapy is the mainstay of treatment, surgical resection has emerged as an important adjunct. In this article, we will review the indications for surgery, preoperative considerations, surgical techniques, and postoperative outcomes.