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Treatment and Prevention of Hospital Infections (D Vilar-Compte, Section Editor)

Infections and Outbreaks of Nontuberculous Mycobacteria in Hospital Settings

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Abstract

Purpose of Review Nontuberculous mycobacterial (NTM) infections in the hospital setting are a complex and often challenging entity. The goal of this review is to discuss diagnostic and treatment strategies for established as well as emerging nosocomial NTM infections.
Recent Findings NTM outbreaks have been documented in a variety of hospital settings. Contamination of medical devices or aqueous solutions is often implicated in the spread of infection. More recently, the slow grower *M. chimaera* has been reported in the setting of contaminated heater-cooler devices used for cardiopulmonary bypass and extracorporeal membrane oxygenation. In addition, increases in medical tourism for cosmetic surgery have led to outbreaks of rapidly growing mycobacteria.
Summary Diagnosis and treatment of nosocomial NTM pose many challenges for the clinician. Surgical resection or debridement as well as combination antimycobacterial therapy is a mainstay in therapeutic management. Strict infection control and prevention practices are critical to the identification and cessation of outbreaks.

Introduction

Nosocomial NTM infections have become an increasingly prevalent reality in the healthcare setting. Given their ubiquitous environmental presence, NTM can be challenging from the perspective of infection prevention as well as treatment. Hospital-associated infection has been reported in the literature as early as the 1930s, following the isolation of *M. fortuitum* from an abscess that developed post-intramuscular vitamin injection [1•, 2]. Since that time, numerous additional NTM species have been identified and linked to nosocomial disease. Nosocomial NTM infections include a broad array of entities ranging from surgical site and skin/soft tissue infections, catheter-associated bloodstream infections to heater-cooler device-related infections, and pseudo-outbreaks. Table 1 demonstrates the wide variety of clinical syndromes that have been reported in the hospital setting.

Therapy is often complex, requiring 3–4 antimycobacterial agents based on susceptibility patterns with a lengthy duration of treatment in many settings to achieve disease control and favorable outcomes. The antimicrobial regimen typically includes aminoglycosides, macrolides (except in the setting of inducible resistance due to the *erm* gene), carbapenems, occasionally fluoroquinolones, and additional agents as indicated. In the setting of surgical site infections, aggressive surgical debridement, resection, and removal of involved foreign material are often necessary. NTM bacteremia in the setting of intravenous catheter placement warrants the removal of the affected catheter to prevent relapse of disease. Infection control is tantamount in identifying potential outbreaks; however, this can often prove difficult given the ubiquitous nature of many NTM species, as well as their resistance to many standard infection prevention strategies.

Table 1. NTM classification by clinical syndrome in nosocomial settings

Clinical syndrome classification				
	Respiratory infection/colonization	**Intravascular infection**	**Surgical infection**	**Pseudoinfection**
Rapid growers				
M. chelonae	x	x	x	x
M. fortuitum	x	x	x	x
M. abscessus				
Subsp. abscessus	x	x	x	
Subsp. massiliense	x	x	x	
Subsp. bolletii	x	x	x	x
Slow growers				
M. avium complex	x	x		x
*M. chimaera***			x	
M. xenopi	x			x
M. kansasii		x		
M. gordonae		x	x	

x Indicates reported outbreaks in the literature
***M. chimaera* is a species within *M. avium* complex

Nosocomial NTM Respiratory Infection/Colonization

Background

Nosocomial NTM outbreaks have been reported due to hospital water supply contamination and subsequent respiratory tract involvement. In many cases, isolation of NTM occurs within the context of pseudo-outbreaks, which is discussed in detail in a subsequent section. Respiratory NTM infection is of particular concern within the cystic fibrosis (CF) patient population. Large studies have estimated that the prevalence of pulmonary NTM among CF patients is between 6 and 13% [3]. While acquisition of *M. abscessus* is typically attributed to contaminated water or soil, recent studies have demonstrated human-to-human transmission in patients with cystic fibrosis [4–6]. Two outbreaks of *M. abscessus* with genetically identical isolates were reported by Bryant et al. in the UK among a CF population, raising concern for cross-infection [7]. Kapnadak et al. described an *M. abscessus* subsp. *massiliense* outbreak at an academic adult CF center following an index case in which five additional cases occurred within the subsequent 8 months and were confirmed by polymerase chain reaction-restriction enzyme analysis [8].

Clinical Presentation

Among CF patients affected by nosocomial NTM outbreaks, pulmonary manifestations of infection may include declines in FEV1, worsening respiratory status, and constitutional symptoms not otherwise explained by routine CF exacerbations related to common pyogenic bacteria (e.g., *Pseudomonas aeruginosa*). New parenchymal findings including pulmonary infiltrates on thoracic imaging may also be noted [9]. *M. abscessus* infection can often result in delays and increase barriers related to lung transplantation in CF patients which may have an impact on their ultimate long-term outcomes.

Treatment

M. abscessus is the most drug-resistant NTM and is notoriously difficult to treat, as the organism carries a high level of intrinsic drug resistance. *M. abscessus* pulmonary infection is not considered curable unless surgical resection can be performed. Medical therapy is complex and typically includes parenteral agents such as amikacin, imipenem or cefoxitin, and macrolides [4]. Tigecycline, linezolid, and rarely fluoroquinolones may also be administered depending on available susceptibility patterns. Additional difficulties in medical management of *M. abscessus* infection include the widespread occurrence of inducible macrolide resistance mediated by the *erm*(41) gene [4, 5]. This is particularly of concern among *M. abscessus* subspecies *abscessus* and *M. abscessus* subspecies *bolletii* in which the rates of resistance are high. Conversely, while *M. abscessus* subspecies *massiliense* also express the *erm*(41) gene, it is nonfunctional due to deletions within the gene sequence, making this subspecies more susceptible to macrolides overall [10]. Duration of therapy is determined by sputum culture conversion (yet, this goal is often not achieved with *M abscessus*), with ideally 12 months of negative cultures per American Thoracic Society (ATS) guidelines.

In clinical practice, however, it is uncommon for most patients to tolerate a year of parenteral therapy given inevitable toxicities and intolerances [11••]. There are differences in treatment outcomes according to subspecies, with a recent study noting that patients infected with *M. massiliense* as opposed to *M. abscessus* demonstrated better treatment responses, as did the use of azithromycin versus clarithromycin [12].

Prevention

Biofilm production is believed to be a contributing factor promoting the growth of nontuberculous mycobacteria in water piping and collection systems [1, 13].

Many species of NTM are also relatively resistant to chlorination, making sterilization sometimes difficult. *M. avium* and *M. abscessus* are among a few species that demonstrate this characteristic. In addition, many of the slow-growing NTM species are relatively resistant to glutaraldehyde and formaldehyde [1•]. These intrinsic factors pose important infection control challenges in the containment of these infections. In the case of the previously mentioned outbreaks, strict patient isolation, close monitoring of affected CF patients, and environmental measures were ultimately utilized successfully [14].

Intravascular Catheter and Injection-Associated NTM Infections

Background

While intravascular catheter-associated NTM infections remain rare, there have been increasing reports implicating rapidly growing mycobacteria. Several studies indicate an increased risk for catheter site infection and subsequent bacteremia in immunocompromised hosts [15, 16]. In these situations, *M. fortuitum*, *M. mucogenicum*, and *M. chelonae* were often implicated. Lengthy duration of catheter placement and prior long-term antimicrobial therapy are other risk factors for bloodstream infection [17].

A wide variety of NTM species have also been identified in infections associated with hemodialysis catheters. This is particularly true among the rapid growers, where contaminated potable water or aqueous solutions are felt to be causative agents [18]. Outbreaks have also been documented due to *M. fortuitum*, *M. chelonae*, *and M. mucogenicum* in patients on continuous peritoneal dialysis, often times resulting in peritonitis [15, 18]. *M. abscessus* and *M. chelonae* have also been implicated in disseminated infection when hemodialysis filters were contaminated during routine cleaning [18, 19, 20].

Clinical Presentation

Rapidly growing mycobacterial bloodstream infections are typically less virulent compared to the more common gram-positive or gram-negative bloodstream infection [17]. Despite this, when rapid growers are isolated from blood culture media, they should generally be regarded as pathogenic. Systemic symptoms such as fever, rigors as well as localized symptoms including erythema and pain at the site of the intravascular device are common [17]. Bloodstream infections related to indwelling devices such as cardiac implantable electronic devices and prosthetic cardiac valves may also occur, and typically present in a subacute manner. Unfortunately, mortality rates in the setting of cardiac and valvular disease have been estimated to be as high as 25% [21, 22].

The most commonly isolated organisms in bloodstream infection include *M. fortuitum* complex, *M. mucogenicum*, *M. abscessus*, *M. chelonae*, and *M. neoaurum* [21]. Diagnosis can be challenging given their relative rarity. Routine blood cultures will often yield rapidly growing mycobacteria. Unfortunately, traditional laboratory tests are unable to differentiate among species of rapidly growing mycobacteria, resulting in the need for reference laboratories as well as molecular methods to provide a specific identification [21], which often results in delays in treatment.

Treatment

The duration of NTM bloodstream infection treatment is not well established in the literature; however, at least 4 weeks of 3- to 4-drug combination therapy is warranted [21]. *M. fortuitum* is typically susceptible to aminoglycosides, imipenem, and co-trimoxazole; however, caution should be used with macrolides as several studies have demonstrated that M. *fortuitum* contains the inducible *erm* gene which can confer macrolide resistance [11••, 21, 23]. *M. abscessus* spp. often also possess the *erm* gene and are intrinsically one of the most resistant species among rapidly growing mycobacteria. *M. chelonae* isolates are typically susceptible to tobramycin, clarithromycin, linezolid, imipenem, amikacin, doxycycline, ciprofloxacin, and clofazimine. Of note, *M. chelonae* is intrinsically resistant to cefoxitin, and thus, imipenem is the preferred beta-lactam [11••]. In addition to appropriate antimicrobial therapy, removal of the affected catheter is an important part of effective management. One series found that among 12 patients with rapidly growing mycobacteria catheter-associated bacteremia, the rate of relapsing bacteremia in immunocompromised patients was 75% of those with delayed catheter removal compared to 0% of those with immediate catheter removal [15]. This highlights the importance of both appropriate antimycobacterial therapy as well as prompt removal of intravascular devices when possible.

Prevention

As discussed previously, rapidly growing mycobacteria have the propensity to grow on biofilms associated with intravascular catheter placement, resulting in subsequent colonization versus infection [21]. Adherence to strict infection control procedures is essential in the prevention of catheter-associated bloodstream infections. The American Thoracic Society recommends avoiding contamination of intravenous catheters with tap water given the ubiquitous nature of NTM species [11••]. *M. fortuitum* and *M. abscessus* are particularly difficult to eradicate, as these species are fairly resistant to commonly used disinfectants including organomercurials, chlorine, formaldehyde, and alkaline glutaraldehyde [11••].

Surgical Infections

Rapidly growing nontuberculous mycobacteria are ubiquitous environmental organisms typically found in nonsterile water sources. Outbreaks in surgical settings have typically been due to exposure to nonsterile water or breach in sterile technique [24]. NTM-associated prosthetic joint infections are an

uncommon but serious complication following joint arthroplasty [25]. *M. fortuitum*, *M. smegmatis*, *M. bovis*, and *MAI* are among the most common NTM reported in this setting. One recent outbreak of *M. chelonae* manifesting as keratitis was reported following LASIK surgery. The same strain was later isolated from distilled water in the surgical facility [26]. Another outbreak of *M. abscessus* subsp. *bolletii* was related to contaminated laparoscopic surgical equipment [27]. More recently, there has been a surge of reported NTM outbreaks in the setting of lipotourism as well as cardiac surgery discussed in detail below.

a. Lipotourism

Skin and soft tissue infections (SSTI) due to nontuberculous mycobacteria have been increasingly recognized as an important entity that is frequently underdiagnosed [28]. Within the past several years, outbreaks related to cosmetic surgery and implants in immunocompetent patients have been reported, particularly in the setting of medical tourism [29]. Many of these procedures involve removal of body fat or breast augmentation/reduction in developing nations, and these practices have been aptly named lipotourism [30]. The scope of these outbreaks is currently unknown, as identification of infection relies on case reporting. Several rapidly growing mycobacterial species have been implicated, with the majority caused by *M. abscessus*, *M. chelonae*, and *M. fortuitum*.

Clinical Presentation

The clinical presentation of SSTI due to rapidly growing mycobacteria can be variable and diagnostic delays are common, as this entity is often not suspected until the occurrence of clinical failure or recurrence despite standard SSTI treatment. In general, both *M. chelonae* and *M. abscessus* present with multiple skin lesions, while *M. chelonae* can cause severe cutaneous disease [30]. *M. fortuitum* on the other hand classically presents as a lone subcutaneous nodule at the site of surgery [30]. Lesions may spontaneously drain and be variably painless or painful. Systemic features are occasionally present, and may include fever, weight loss, fatigue, nausea, and vomiting [29]. Diagnosis is established via biopsy of cutaneous lesions with corresponding culture and histopathology data [30].

Treatment

The mainstay of therapy involves surgical debridement and/or drainage (including removal of all foreign material, if present) along with antimycobacterial therapy. Unfortunately, these rapidly growing mycobacteria are often drug resistant and targeted antimycobacterial therapy can be fraught with challenges due to toxicity. A significant proportion of patients may require repeated debridements. While there is no consensus on drug regimen, duration of therapy following surgical intervention is prolonged and often on the order of 6–12 months [24].

Prevention

The etiology of these outbreaks is uncertain, although likely environmental contamination of water systems and antiseptic solutions has played a role in their occurrence. Biofilm production in combination with infection control lapses has made eradication difficult [31]. In addition, many species of NTM are relatively resistant to chlorination, making sterilization challenging as well [1•]. *M. abscessus* is one such species that demonstrates this characteristic. The Centers for Disease Control in the USA has been active in identifying cases from the Dominican Republic (DR) and working with the DR Ministry of Health, and one such investigation led to the closure of a surgical clinic [24]. Despite the challenges associated with eradication, robust attempts aimed at water chlorination and sterilization of surgical devices at medical facilities are still strongly recommended as an important infection control and prevention measure.

b. Heater-Cooler Devices

While NTM infections in the context of cardiac surgery were previously rare, in the last several years, cases of severe infection *chimaera* have been reported. Though other NTM species have also been identified in this setting, *M. chimaera* has emerged as a dominant pathogen for uncertain reasons [32]. *M. chimaera* is a recently described slow-growing mycobacterium that is a variant of the *Mycobacterium avium* complex [33]. In 2014, a cluster of six cases of severe infection was reported in cardiac surgery patients at the University Hospital Zurich [33]. Similar cases were subsequently reported in the USA, the Netherlands, and Germany shortly thereafter. Investigations undertaken postulated that contaminated water tanks and aerosols of heater-cooler devices (HCD) used in the setting of cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO) were the cause of infection. The HCD system is comprised of compressors that adjust water temperature, tubing through which the water is pumped to the device and circulated externally, and heat exchangers associated with oxygenation and cardioplegia equipment [13, 32, 34]. The water that circulates within this system is at risk for containing pathogenic micro-organisms. In one outbreak investigation, Sax et al. recovered *M. chimaera* isolates from five independent HCD, as well as an air sample associated with one of the HCD isolates suggesting aerosolization of *M. chimaera* from the unit [35]. In addition, the highest level of aerosol was located at the rear of the HCD [35]. The majority of *M. chimaera* isolates implicated in infection have been recovered from the Sorin 3T, LivaNova PLC model of HCD, although contamination is considered to be a widespread issue [36, 37]. Additional clusters of *M. wolinskyi* and *M. abscessus* following cardiac surgery are thought to be related to HCD as well [38•]. Whole-genome sequencing in other studies have confirmed identical isolates in multiple 3T HCD among patients around the world [39].

Clinical Presentation

Reported cases of *M. chimaera* have demonstrated a wide variety of clinical syndromes within the context of recent cardiothoracic surgery. Disease presentation includes fever, weight loss, and other nonspecific findings such as shortness of breath, and/or localized wound infections, mediastinitis, and sternal osteomyelitis [40]. Hematologic abnormalities such as anemia, thrombocytopenia, and lymphocytopenia are often reported [40]. In one case series, 18 cases diagnosed over the course of 7 years demonstrated several cases of endocarditis with or without aortic root abscess and disseminated infection [33]. Several case reports of disseminated *M. chimaera* infection have been reported by Kohler et al., all of which occurred following cardiothoracic surgery and thought to be due to airborne contamination of HCD [40]. Zweifel et al. recently described anterior and intermediate uveitis, and multifocal choroidal ocular lesions in the case of five patients diagnosed with disseminated *M. chimaera* infection [41]. Unfortunately, in many cases of disseminated disease, patients are misdiagnosed initially with connective tissue disease and initiated on immunosuppressive agents [42]. An important feature in several of these cases is that despite endovascular infection and disseminated disease, not all cases had macroscopic evidence of vegetations (in patients with post-cardiac surgery endocarditis) as part of their clinical presentation.

The relatively slow growth of *M. chimaera* poses a challenge in regard to diagnostic strategies. In addition, given that *M. chimaera* is a species within *Mycobacterium avium complex*, many laboratory assays are unable to specifically identify this species, leading to delays in accurate diagnosis [32]. Mycobacterial culture both on tissue and blood and in some cases urine samples, as well as molecular studies such as 16S rRNA gene sequencing are recommended in suspected cases. Deep OR tissue cultures may increase the yield in identifying this infection as opposed to superficial swabs, and therefore, generous collection of tissue samples is encouraged in the appropriate clinical setting.

Treatment

Therapy typically involves a combination of antimycobacterial therapy as well as removal of infected prosthetic material and/or debridement when possible. Despite these efforts, a high crude mortality rate is reported at approximately 50%, particularly in the setting of disseminated infection [39]. In general, the optimal antimicrobial regimen is not fully known, and drug susceptibility testing in NTM therapy remains best validated for macrolides [43]. In the setting of disseminated disease, typically a minimum of three, preferably at least four agents are optimal, including macrolide, rifamycin, ethambutol, and often IV amikacin, with individualization based on site/extent of disease and patients' comorbidities and drug interactions [43].

Prevention

The presence of high cell-surface hydrophobicity is thought to contribute to the relative tolerance of *M. chimaera* to disinfectant efforts within the HCD [32]. In addition, the organism's propensity towards biofilm formation favors disease outbreaks [44]. In one instance, when a previously utilized HCD was dismantled for investigation, the biofilm was observed on surfaces in contact with the internal water reservoir [45]. This finding highlights the difficulty in achieving eradication of NTM in these settings [33]. Studies investigating decontamination found that HCD microbiological sampling counts were reduced only in the setting of internal tubing replacement and refurbishment in addition to the application of standard disinfectants [46].

Pseudoinfection/Outbreaks

Background

Nosocomial pseudo-outbreaks have been reported since the 1960s in the setting of *Escherichia coli* pseudosepticemia [47]. Nosocomial pseudo-epidemics are defined as a cluster of false infections due to instrumental, contact, or laboratory contamination, or "artifactual clustering of true infections" [47, 48]. In 1990, an initial outbreak was reported in Missouri, when an increase in *M. chelonae* isolates was documented [48]. This was later thought to be due to contaminated bronchoscopy equipment, and corroborated when none of the involved patients developed evidence of invasive *M. chelonae* disease and no further positive samples were obtained on repeat bronchoscopy. Since that time, multiple additional pseudo-outbreaks have been identified including *M. gordonae* in bronchoalveolar lavage specimens as well as *M. abscessus* subsp. *bolletii* contaminating endoscopes and disinfection agents [49, 50].

Clinical Presentation

Perhaps the most important feature of pseudoinfection is the disparity between clinical features and laboratory findings [47]. In scenarios where isolated microbiologic data does not support the clinical picture, surveillance of culture results is critical.

Pseudo-outbreaks have been described in a variety of contexts. Pseudoinfection after bronchoscopy should be suspected if unusual NTM species are isolated despite the clinical scenario. Contaminated bronchoscopic equipment is typically due to inadequate disinfection, use of tap water, or defective local anesthetics. Steere et al. reported a *M. gordonae* pseudo-outbreak that was traced to a contaminated bottle of dye added to a topical anesthetic used by the bronchoscopist [1, 51]. Similar outbreaks have been noted in the setting of contaminated bronchoscopic equipment with

M. chelonae, *M. avium* complex, and *M. xenopi* [52–54].

Non-endoscopic pseudo-outbreaks have been reported primarily due to rapidly growing mycobacteria from contaminated solutions or water. For example, one case series from 1997 documented 23 positive *M. abscessus* blood cultures obtained from HIV-infected patients [48, 49]. Further investigation suggested contamination of the culture supplement vial during laboratory procedures. Two pseudo-outbreaks involving *M. fortuitum* involved contaminated ice [55, 56].

Treatment

If clinical investigation does not support invasive disease, therapy is not indicated, as patients are not truly infected [38•]. Unfortunately, upon isolation of positive specimens, patients may undergo unnecessary and costly therapeutic procedures and in some cases, receive antimycobacterials until the issue of true versus pseudoinfection is established with more certainty [38•, 48]. Because of this possibility, it is important that suspected cases be thoroughly investigated, and that the pursuit of additional diagnostics or therapeutics rely on clinical suspicion.

Prevention

Adequate surveillance and infection control procedures are critical in preventing the propagation of nosocomial pseudo-outbreaks. Ongoing quality-control efforts are also important in these settings.

Conclusions

NTM infections acquired in the hospital setting represent an important but challenging spectrum of nosocomial diseases. The last decade has seen a significant surge in outbreaks of these entities ranging from pseudo-outbreaks, skin/soft tissue and post surgical-infections, to disseminated disease. While new diagnostic techniques and greater clinical recognition have led to advances in the management of nosocomial NTM-related diseases, varying antimicrobial susceptibility patterns and resistance to standard infection control procedures continue to present many challenges. Further clinical study remains critical to elucidate optimal diagnostic and treatment strategies, and enhanced infection control practices.

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Compliance with Ethical Standards

Conflict of Interest
Dr. Desai and Dr. Hurtado declare that they have no conflicts of interest.

Human and Animal Rights
This article does not contain any studies with human or animal subjects performed by any of the authors.

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