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Nontuberculous mycobacterial infections: a potential complication of cosmetic procedures☆

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ABSTRACT

Interest in surgical and non-surgical cosmetic procedures has increased significantly over the last few decades. Billions of dollars are spent on these procedures annually. Although the associated risk is generally low, multiple cases of skin and soft tissue infections have been reported. Nontuberculous mycobacteria (NTM), in particular *M. chelonae, M. fortuitum*, and *M. abscessus*, have been increasingly identified as causative of numerous cosmetic procedure–related infections worldwide. This has therefore become a public health concern. Delays in diagnosis and appropriate management may occur given subtleties in diagnostic methods. The purpose of this review is to highlight the NTM-related skin and soft tissue infections associated with more common cosmetic procedures, describe methods of identification, and outline best treatment practices.

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Background

The nontuberculous mycobacteria (NTM) represent an emerging and increasingly recognized etiology of skin and soft tissue infections associated with injections and minor surgical procedures in the United States. Because these organisms require laboratory techniques other than the standard gram stain with aerobic and anaerobic culture and sensitivity for identification, and tend not to respond to courses of typical antibacterial agents effective against streptococci and staphylococci, delay in diagnosis and appropriate antimicrobial management may occur. The purpose of this review is to highlight the typical mycobacteria that are causative of infections associated with more common cosmetic procedures, and to describe methods of identification and best treatment practices.

Epidemiology

The NTM group of organisms consists of more than 125 species, defined as mycobacteria species other than *M. tuberculosis* and *M. leprae*. These organisms are found worldwide and are ubiquitous in the environment. Tap water is the primary reservoir for human transmission, but NTM are also found in soil, animals, vegetable matter, and birds (Mandell et al., 2009). NTM-related infections are acquired through environmental exposures. There have been no documented cases of human-to-human or animal-to-human transmission. An abnormal immune system, involving, for example, a decline in CD4+ T cell count or macrophage dysfunction, is prone to NTM infection. Similar to other intracellular pathogens, NTM are phagocytized and killed by normal functioning macrophages in response to IFN- production, up-regulated by interleukin-12 (IL-12). As such, deficiencies or abnormalities in this positive feedback loop, acquired or genetic, increase the risk of NTM infections (Griffith et al., 2007). Tumor necrosis factor α (TNF) plays a critical role in control of infection by intracellular organisms, as evidenced by well-documented risk of reactivation tuberculosis in patients receiving TNF inhibitor therapy (Keane, 2004). IFN- and IL-12 control mycobacteria through the up-regulation TNF α, made predominantly by monocytes/macrophages. An increased risk of NTM infections is therefore theoretically plausible during TNF inhibitor therapy, and most experts recommend treating and controlling known NTM infections in this setting.

The most common clinical manifestations of NTM infection in the United States include pulmonary disease, lymphatic disease, skin and soft tissue infections, and disseminated disease. *Mycobacterium avium complex* (MAC), *M. fortuitum*, and *M. kansasii* are the most common isolates in the US, with reports of all three most common in the Southeastern United States (Griffith et al., 2007). The incidence of NTM infections related to cosmetic procedures is on the rise and increasingly becoming a public health concern. NTM have been recently implicated in skin and soft tissue infections following pedicure, mesotherapy, laser resurfacing, breast augmentation, tattoos, implants and fillers, body piercings, liposuction, Mohs micrographic surgery, punch biopsies, and injections.

Microbiology

Mycobacteria are aerobic, non-motile, acid-fast bacilli, in that they have the ability to retain dyes after washing of alcohol decolorization. The rate of growth and presence of pigmentation are used to

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preliminarily identify NTM. NTM are classified into (1) rapid growing mycobacteria (RGM) with subsets of pigmented and nonpigmented organisms, which form mature colonies on culture in less than 7 days; (2) slow-growing mycobacteria with subsets of nonchromogens (do not produce pigment), scotochromogens (produce pigment in the absence of light) and photochromogens (produce yellow pigment with light exposure), which form mature colonies on culture in more than 7 days (Table 1). We will focus primarily on the organisms that most commonly cause skin and soft tissue infections in the United States: *M. abscessus*, *M. fortuitum* and *M. chelonae*.

In terms of specimen collection for laboratory evaluation, potential sources of contamination, such as tap water, should be avoided, because environmental mycobacteria may be present. Aseptic collection of as much fluid as possible by needle aspiration or surgical procedures is recommended. Swabs are not recommended for sample collection because they often result in limited culture material, decreasing chances for recovery of NTM. The recommended method for staining clinical specimens is the fluorochrome technique. The Gram stain will not reliably detect mycobacteria. In many cases, the NTM, especially the RGM, may be more sensitive to the AFB decolorization procedure and may not stain at all with fluorochrome stains, so negative smears do not necessarily mean that NTM, especially RGM, are not present in a clinical sample (Griffith et al., 2007). Histopathology of tissue specimens obtained from skin biopsy may yield additional helpful information, as certain morphological characteristics, such as granulomatous changes, lymphohistiocytic infiltrate, as well as special stains for AFB may indicate mycobacterial infection. However, culture would still be necessary to identify a specific organism and determine specific antimicrobial susceptibility (see below) (Drage et al., 2010).

The optimal temperature for most cultures for NTM is between 28 and 37°C with rare exception (*M. haemophilum, M. ulcerans*). Cultures for RGM and *M. marinum* should be incubated at 28 to 30°C. All skin, joint fluid, and bone specimens should be cultured at 28 to 30°C and at 35 to 37°C (Tortoli, 2003). Most NTM grow within 2 to 3 weeks on subculture.

Clinical Manifestations

There has been a significant surge in popularity of cosmetic procedures in recent years. According to the American Society for Aesthetic Plastic Surgery (http://www.surgery.org/), in 2011 alone, approximately 9 million non-surgical and surgical cosmetic procedures, most commonly botulinum toxin and liposuction (2.6 million and 325,332 procedures, respectively) were performed. The reported increased incidence of cutaneous NTM infections over the last few decades is likely to be associated with higher demand for and more frequent performance of cosmetic procedures (Wentworth et al., 2013). RGM, in particular *M. chelonae, M. fortuitum and M. abscessus* have been commonly reported as causative of skin and soft tissue infections (SSTIs) related to non-surgical cosmetic procedures including tattoos, permanent eyebrow makeup, dermal fillers, laser resurfacing and mesotherapy. Infections related to surgical cosmetic procedures such as liposuction, breast augmentation, Mohs surgery, and facelifts have also been reported, as well as pedicure and foot bath related infections.

Permanent tattoos are created by intradermal injection of imperishable ink, which is dispersed throughout the epidermis and upper dermis. The manipulation of the skin barrier and the presence of pigment activate the immune system to phagocytize the pigment, producing the image. Tattoos have become increasingly popular in recent years worldwide. The number of adults with one or more tattoos in the US has increased from 14% in 2008 to 21% in 2012 (LeBlanc et al., 2012). Multiple reports across Western Europe, Australia, and the US of NTM have surfaced as causes of tattoo-associated skin and soft tissue infections (Atkins and Gottlieb, 2014), which has prompted numerous investigations by the Food and Drug Administration (FDA). One of the first such reports, published online in 2009, documents an outbreak of *M. chelonae* in 6 patients who had received tattoos at a single establishment; diagnosis of NTM was delayed in all 6 cases, and no clear source was identified (inks, soaps, water were culture negative) (Drage et al., 2010). In January 2012, 19 individuals were reported in Rochester, New York, who presented with persistent red papules on the gray areas of tattoos within 3 weeks of acquiring the tattoo (Kennedy et al., 2012). There were 14 confirmed cases of *M. chelonae* tattoo associated infections in Monroe County New York and 1 confirmed case of *M. abscessus* tattoo associated infection reported in Colorado (Centers for Disease Control and Prevention, 2012). The FDA investigated many of these reported cases and discovered that the inks contained mycobacteria, contaminated during manufacturing of black or grey inks or when the inks were diluted with tap water. The fact that tattoo artists and establishments in many communities are not subject to mandatory health inspections and that the ink and tattoo equipment do not require FDA approval, may contribute to the increase in the incidence of tattoo related SSTIs. The CDC now recommends that all tattoo inks to be manufactured or diluted with sterile water only.

Permanent eyebrow makeup involves multiple injections of pigment into the dermis. Twelve cases of *M. haemophilum*-associated skin lesions of the eyebrows and ipsilateral cervical lymphadenopathy associated with permanent eyebrow makeup procedure were reported in Switzerland in 2009 (Giulieri et al., 2011). In addition, *M. haemophilum* was confirmed as the causative organism in 2 patients who presented with nodular lesions of the eyebrows where permanent makeup had been applied (Wollina, 2011).

Injection of dermal fillers such as silicone, collagen, and hyaluronic acid into the face has become increasingly popular to decrease the appearance of wrinkles. The first 3 cases of *M. chelonae* skin and soft tissue infections associated with dermal injections were confirmed in Oregon in 2008. The clinic's water supply was identified as the source of the isolates (Rodriguez et al., 2013).

Laser resurfacing is an modality used to refine and rejuvenate the skin. One case report describes the development of multiple erythematous papules and pustules diffusely over the face, neck, and chest 2 weeks after undergoing laser resurfacing. *M. abscessus* was implicated (Culton et al., 2013). In another reported case, the patient developed painful pustular lesions on her neck 9 days after the procedure, and *M. chelonae* was identified (Culton et al., 2013).

Mesotherapy is a technique that involves injection of plant extracts, homeopathic agents, pharmaceuticals, vitamins, and other bioactive

Table 1
Microbiological classification of NTM. Adapted from Mandell, Douglas and Bennett's: Principles and Practice of Infectious Diseases, pages 2844–50 (Mandell et al., 2009).

Rapid Growing Mycobacteria		Slow Growing Mycobacteria		
Pigmented	Non-pigmented	Photochromogens	Scotochromogens	Nonchromogens
M. abscessus	*M. mageritense*	*M. kansasii*	*M. gordonae*	*M. avium complex*
M. chelonae	*M. wolkinsky*	*M. marinum*	*M. scrofulaceum*	*M. haemophilum*
M. fortuitum				*M. malmoense*
M. mucogenicum				*M. simiae*
M. smegmatis				*M. szulgai*
				M. ulcerans
				M. xenopi

(NTM, Nontuberculous mycobacteria).

Table 2
Toxicities of primary agents used to treat NTM infections (Griffith et al., 2007).

Drug	Toxicities
Clarithromycin	Nausea, vomiting, diarrhea*, hepatitis, many drug interactions
Ciprofloxacin/moxifloxacin	Nausea, vomiting, diarrhea*, headache, insomnia, tendonitis
Amikacin/tobramycin	Nephrotoxicity, ototoxicity, dizziness, vertigo, ataxia [monitor serum levels]
Rifampin/rifabutin	Orange discoloration of secretions, nausea, vomiting, hypersensitivity reaction, hepatitis, cytopenias, multiple drug interactions
Cefoxitin	Hypersensitivity, cytopenias, diarrhea*
Imipenem	Nausea, vomiting, diarrhea*, hypersensitivity, seizure, confusion, hepatitis, cytopenias
Tetracyclines	Nausea, vomiting, diarrhea*, photosensitivity, rash, dizziness, vertigo, pseudotumor cerebri
Sulfonamides	Nausea, vomiting, diarrhea*, cytopenias, hypersensitivity
Linezolid	Cytopenias, peripheral neuropathy, nausea, vomiting, diarrhea
Tigecycline	Nausea, vomiting, photosensitivity, pseudotumor cerebri, pancreatitis

(NTM, Nontuberculous mycobacteria).
* including *Clostridium difficile* colitis.

substances into the dermis and subcutaneous tissue for the purposes of weight loss and cellulite reduction. NTM infections associated with mesotherapy have been linked to contaminated material being injected by non-physicians (Sanudo et al., 2007). Eleven cases of *M. chelonae*-related erythematous, tender, subcutaneous draining nodules at the injection site were reported in 2006–2007 (Regnier et al., 2009). Five cases of *M. chelonae* were reported in Colombia during 2004–2005, in which patients presented with localized skin lesions to the area of mesotherapy (Sanudo et al., 2007). In 2001, 3 cases were reported because they developed painful nodules after receiving mesotherapy caused by *M. fortuitum* in Spain (Nagore et al., 2001). *M. abscessus* has also been implicated in skin infections after mesotherapy in 17 otherwise healthy subjects in 2009 in Spain (Galmes-Truyols et al., 2011) and 3 patients in Thailand in 2011 (Wongkitisophon et al., 2011). In 2005, Virginia Department of Health and the CDC investigated and outbreak of skin lesions unresponsive to antimicrobial therapy patients who receive mesotherapy by a non-licensed practitioner in the District of Columbia. *M. chelonae* and *M. haemophilum* were both identified as the causative isolates (Centers for Disease Control and Prevention, 2005).

Liposuction has become a very common surgical cosmetic procedure. Thirty four cases of cutaneous abscesses within 6 months after undergoing liposuction by a single practitioner caused by *M. chelonae* were reported in 2002 (Meyers et al., 2002). Two cases of *M. fortuitum* associated SSTIs presenting with recurrent abscesses following abdominal plastic surgery and liposuction were reported in France in 2008 (Regnier et al., 2008). Additionally, more recent cases of recurrent abdominal abscesses following abdominoplasty and liposuction have been reported (Bax et al., 2014; Kim and Mascola, 2010).

A case of *M. abscessus* infection presented as multiple erythematous papules post-Mohs procedure (Fisher and Gloster, 2005). In 2003, the New Jersey Department of Health and Senior Services investigated 8 cases of *M.chelonae* SSTI following facelift procedures (Centers for Disease Control and Prevention, 2004). *M. fortuitum* SSTI following a bilateral facelift presenting with a maxillary nodule was also reported (Angeli et al., 2004). The use of contaminated gentian violet, a marking solution, has been associated to many surgical site infections following facelifts and blepharoplasty (Murillo et al., 2000).

Breast augmentations are performed frequently for either cosmetic or reconstructive purposes (Vinh et al., 2006). Infections following breast augmentation are rare, with a risk of 1–3% (Feldman et al., 2009; Heistein et al., 2000). Infections are most commonly due to normal skin flora and infrequently due to mycobacteria (Heistein et al., 2000). Cases of *M. fortuitum* related wound infection post breast implant placement were described (Lizaso et al., 2011; Vinh et al., 2006). Two cases of *M. fortuitum* and 1 case of *M. chelonae* breast infections after bilateral reduction mammoplasty were documented (Boettcher et al., 2010).

Multiple pedicure-associated NTM infection, referred to as furunculosis, most commonly due to RGM, have been registered within the United States. An outbreak in North Carolina during 2005–2008, involving 40 cases of pedicure-associated furunculosis due to *M. fortuitum*, *M. abscessus*, *M. bolletii*, and *M. chelonae*, presenting with pustules, plaques, nodules, pustules persisting on the lower extremities (Stout et al., 2011). The outbreak was linked to mycobacteria present in the biofilm in the foot baths and water intake pipes. A common finding identified among infected individuals was recent shaving of legs prior to the pedicure. In California during 2000, a large outbreak was identified, consisting of 110 cases of pedicure-associated furunculosis caused by *M. fortuitum*, associated with suboptimal cleaning practices of pedicure foot baths at a single nail salon (Stout et al., 2011).

Therapy

As discussed previously, species identification and antimicrobial susceptibility testing is critical in the management of patients with skin and soft tissue infections caused by NTM. Degrees of susceptibility to oral agents vary by NTM species, and prolonged combination therapy is frequently indicated, particularly in cases of severe, deeper seated infections. For serious skin and soft tissue disease caused by rapid growers, including *M. abscessus, chelonae*, and *fortuitum*, a minimum of 4 months of combination therapy is likely necessary, with consideration of longer durations when bone is involved (Griffith et al., 2007). Surgical debridement and removal of infected foreign material should always be pursued in conjunction with antimicrobial therapy when feasible, to maximize the chances of cure. Specific therapeutic options are addressed by NTM species.

Inherently resistant to standard antituberculous agents, *M. abscessus* has emerged as one of the most difficult NTM to manage with antimicrobial therapy. *M. abscessus* may also acquire resistance to certain agents, for example, via induction of the *erm* gene (erythromycin methylase) conferring resistance to macrolides (Atkins and Gottlieb, 2014; Choi et al., 2012; Griffith et al., 2007). The macrolides are the most reliably active oral agents for the treatment of *M. abscessus* infections, although increasing consideration is given to oxazolidinones, such as linezolid, which may also manifest low MICs. As such, combination therapy with parenteral agents is usually appropriate, specifically with amikacin, the most reliably active parenteral agent, plus one or more others (Griffith et al., 2007). Other agents with varying degrees of activity against the organism are cefoxitin and imipenem. It may be reasonable to deescalate to an oral regimen after initial combination therapy for several weeks, if there is clear evidence of clinical improvement. Given relatively high rates of relapse, however, this strategy must be undertaken with extreme caution (Atkins and Gottlieb, 2014; Regnier et al., 2009; van Dissel and Kuijper, 2009).

Relatively less resistant to antimicrobials than *M. abscessus, M. chelonae* demonstrates frequent susceptibility to clarithromycin, tobramycin, imipenem, and linezolid, and is uniformly resistant to cefoxitin. In general, among the aminoglycosides, tobramycin exhibits more in vitro activity than amikacin (Griffith et al., 2007). *M. fortuitum* is generally regarded as less resistant to antimicrobial agents, and therefore, easier to treat than other rapid growers. Although appropriate therapeutic regimens should still be based upon in vitro susceptibility

testing results, the organism is generally sensitive to a variety of agents, both oral and parenteral, including clarithromycin, cefoxitin, imipenem, amikacin, doxycycline, and trimethoprim/sulfamethoxazole (Lim et al., 2012). In vitro susceptibility to clarithromycin must be interpreted with caution, however, given the ability of the *M. fortuitum* to express the *erm* gene (Griffith et al., 2007). Susceptibility data for other species of NTM, such as *M. hemophilum* are limited and tend to lack standardization, making interpretation of results a challenge. This reinforces the need to obtain minimum inhibitory concentrations for individual clinical isolates to best guide therapeutic choices.

Variability in susceptibilities to antimicrobial agents among different NTM species has generated interest in identifying appropriate salvage regimens for the treatment of these infections. Tigecycline is a glycylcycline antibiotic with broad spectrum antimicrobial activity against both gram positive and gram negative organisms. Structurally related to tetracyclines, it reportedly has good activity against NTM in vitro (Huang et al., 2013; Wallace et al., 2014). Tigecycline was tested for synergistic effect with clarithromycin and amikacin in isolates of rapid growers, showing in vitro synergy with clarithromycin and antagonism with amikacin (Huang et al., 2013). A clinical study of 52 patients with rapid grower NTM infections of the lung and skin/soft tissue/bone resulted in 48% overall clinical improvement with tigecycline-based salvage therapy, with significant numbers discontinuing prematurely due to adverse events (Wallace et al., 2014). Toxicities of antimicrobial agents commonly used to treat NTM infections of the skin and soft tissues are well known and summarized in Table 2.

Conclusions

The last several years have witnessed a surge in medical tourism and interest in cosmetic and aesthetic procedures on a global scale. Taken together with inconsistent infection control procedures in different practice settings, these circumstances dictate a heightened awareness and suspicion for skin and soft tissue infections caused by the NTM. The complexities and idiosyncrasies in diagnosis and treatment require communication between specialists in infectious diseases, dermatology, surgery, and lab medicine, in order to appropriately manage these infections. More stringent regulation and monitoring of procedures and products labeled as “cosmetics” going forward will help reduce baseline rates of these infections and prevent future outbreaks.

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