

# Cutaneous nontuberculous mycobacterial infection in Thailand

## A 7-year retrospective review

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### Abstract

A remarkable increase in the prevalence of cutaneous nontuberculous mycobacterial (NTM) infection has occurred worldwide. However, updated data regarding cutaneous NTM infection in Thailand is limited.

This study aim to describe the clinical manifestations, pathogenic organism, and prognostic factors of cutaneous NTM infections among patients living in Thailand.

The electronic medical records of all patients with confirmatory diagnosis of cutaneous NTM infection from either positive cultures or polymerase chain reaction were retrospectively reviewed at a university-based hospital.

From 2011 to 2017, a total of 88 patients with a confirmed diagnosis of cutaneous NTM infection were included. *Mycobacterium abscessus* was the most common pathogens followed by *M haemophilum* and *M marinum* (61.4%, 10.2%, and 8.1%, respectively). Nodule and plaque were 2 most common lesions (26.4% and 25.5%, respectively) and lower leg is the most common site of involvement (50.9%). The majority of patients presented with single lesion (67%). Seven patients (7.9%) had history of surgical procedure and/or cosmetic injection before the development of lesion and all pathogenic organisms in this group were rapidly growing mycobacteria. Sweet's syndrome and erythema nodosum were the 2 most common reactive dermatoses, presented in 3.4% and 2.3%, respectively. The majority of patients infected with cutaneous *M haemophilum* infections were immunocompromised and lacked history of preceding trauma (77.8%). Patients with cutaneous NTM that receiving less than 3 medications was associated with higher disease relapse (odds ratio 65.86;  $P = .02$ ).

*M abscessus* is the most common pathogen of cutaneous NTM infection in Thailand. The prevalence of *M haemophilum* is increasing and should be particularly cautious in immunocompromised patients. Rapidly growing mycobacteria should be suspected in all cases of procedure-related cutaneous NTM. We recommend at least 3 antibiotics should be considered for cutaneous NTM infection to reduce the rate of relapse.

**Abbreviations:** HIV = human immunodeficiency virus, NTM = nontuberculous mycobacteria, PCR = polymerase chain reaction.

**Keywords:** granuloma, injectable, *Mycobacterium abscessus*, *Mycobacterium haemophilum*, surgery

### 1. Introduction

The nontuberculous mycobacteria (NTM) are free-living, non-motile, acid-fast bacilli that can be present in numerous environmental sources including water, soil, food products, and domestic and wild animals.<sup>[1]</sup> The NTM pathogens were first

classified by Runyon in 1954 based upon the rate of growth in vitro and pigment production following exposure to light.<sup>[2]</sup> Due to advances in identification utilizing genomic analysis, more than 170 species of mycobacteria have been identified.<sup>[3]</sup> NTM pathogens compose a diverse group of environmental organisms that can produce clinical disease in any body tissue, including the skin and soft tissue. NTM can cause a broad range of infections that vary depending on the particular NTM species and the host immunity. There are 6 major clinical syndromes caused by NTM infection;

- (1) pulmonary infection,
- (2) disseminated infection,
- (3) local nontender lymphadenitis,
- (4) chronic granulomatous infections of bursae, joints, tendon sheaths, and bones,
- (5) catheter-related infections,
- (6) skin and soft-tissue infections.<sup>[4]</sup>

The incidence of cutaneous nontuberculous mycobacterial infections has increased dramatically during the past several years due to numerous factors including the increase application of immunosuppressive therapies and more frequent use of surgical and cosmetic procedures. In addition, vast improvement in the detection of NTM via cultures and polymerase chain reaction

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(PCR)-based techniques allows more accurate diagnosis.<sup>[5]</sup> Almost all NTM species have been incriminated in cutaneous disease. The most common species in the United States and Europe are *Mycobacterium marinum* and the rapidly growing mycobacteria.

A drastic shift of mycobacterium species was observed in many countries from previous reports.<sup>[5,6]</sup> The latest reviews on cutaneous NTM infection in Thailand dated back almost 2 decades ago from 1994 to 2001.<sup>[7]</sup> In this study, we aimed to describe the clinical manifestations, pathogenic organisms, and prognostic factors for cutaneous NTM infection in Thailand between 2012 and 2018.

## 2. Methods

### 2.1. Data collection

The electronic medical records of patients with cutaneous NTM infections who visited a university-based hospital in Bangkok, Thailand (Ramathibodi Hospital, Mahidol University, Bangkok, Thailand) between January 2012 and December 2018 were retrospectively reviewed. The study was approved by institutional review board for human research (protocol number 11-61-29)

The diagnosis of cutaneous NTM was confirmed by histopathology and microbiologic study. Histopathologic evaluation consisted of the routine process of tissue staining consisting of hematoxylin-eosin and Ziehl–Neelsen in cases suspected of cutaneous NTM infections. Most tissue samples were processed according to the standard methods for mycobacterial culture including blood agar, Löwenstein–Jensen agar, and BD MGIT Mycobacteria Growth Indicator Tube (Becton, Dickinson U.K. Limited, Berkshire, UK). All culture specimens were incubated at 37°C and 30°C to detect *M haemophilum* and *M marinum* infections. Culture isolates were detected to the species level using partial sequencing of the 16S rRNA gene. PCR for mycobacterial results were identified by AnyplexMTB/NTM Real-time Detection (Seegen Inc., Seoul, Korea). Clinical, epidemiological, and microbiological data were collected.

Patients who had compatible cutaneous lesion and histopathologic findings consistent with cutaneous NTM infection and positive microbiologic evidences (positive cultures and/or PCR results) were included in this study.

### 2.2. Statistical analysis

A Chi-squared test was used to compare differences in categorical data while continuous variables were compared by an independent *t* test. A *P*-value of <.05 was considered statistically significant. All analyses were performed using the computer software (STATA/SE version 14.1, STATA Corp LLC, College station, TX).

## 3. Results

During the 7-year study period, 149 patients with the presumed diagnosis of cutaneous NTM infections based on clinical and histopathology were identified. A total of 88 patients (female 66, male 22) who had positive PCR and/or culture for NTM infection were included in this study. The median age of patients was 51 years (range 2–90). The median time from the onset of symptom to the diagnosis of NTM was 4 weeks (1–156 weeks). Twenty-four of 88 patients (27.3%) were immunocompromised while 64 were immunocompetent host. Insulin-independent diabetes

mellitus, post-organ transplantation treated with immunosuppressive drugs, and malignancy were found in 9 (10.2%), 8 (9.1%), and 7 (8.0%) patients respectively. There were 3 patients with adult-onset immunodeficiency. None of our patients had human immunodeficiency virus (HIV) infection. Of 8 patients with post-organ transplantation, 5 had *M haemophilum* infection. Data on the clinical characteristic is demonstrated in Table 1.

Of 88 patients who had positive tissue cultures and/or PCR for NTM, 84 had identifiable pathogenic species while in the remaining 4 the organism was unidentifiable. Among 84 patients with detectable NTM species, the most common pathogen was *M abscessus* (54 cases; 61.4%), followed by *M haemophilum*, *M marinum*, and *M fortuitum* which were positive in 9 (10.2%), 7 (8.1%), and 6 (6.8%) cases, respectively. Tissue imprint for

**Table 1**  
Characteristics of cutaneous nontuberculous mycobacterial infections.

Variables	Result
Median age at diagnosis, yr (ranges)	51 (2–90)
Gender (n=88)	
Female	66 (75%)
Male	22 (25%)
Immunocompromised hosts (n=24)*	
Diabetes mellitus	9 (10.2%)
Post-organ transplantations	8 (9.1%)
Malignancy	7 (8%)
Adult-onset immune deficiency syndrome	3 (3.4%)
Autoimmune diseases	2 (2.3%)
Previous history of skin trauma (n=24)	
Procedure-related	
Surgery	5 (5.7%)
Cosmetic procedure	2 (2.3%)
Mosquito bite	7 (7.9%)
Aquatic-related injury	6 (6.8%)
Wood splinter	4 (4.5%)
Number of lesions (n=88)	
Single	59 (67%)
2 lesions	13 (14.8%)
3 lesions	7 (7.9%)
4 lesions	2 (2.3%)
≥5 lesions	7 (7.9%)
Morphology (n=110)†	
Nodule	29 (26.4%)
Plaque	28 (25.5%)
Papule	18 (16.4%)
Abscess	14 (12.7%)
Patch	7 (6.3%)
Pustule	6 (5.5%)
Ulcer	5 (4.5%)
Cellulitis-liked lesions	2 (1.8%)
Sporotrichoid lesions	1 (0.9%)
Site (n=108)‡	
Legs	55 (50.9%)
Forearms	17 (15.8%)
Trunk	11 (10.2%)
Face	9 (8.3%)
Hands	8 (7.4%)
Feet	6 (5.6%)
Genitalia	2 (1.8%)

\* Some patients had more than 1 underlying diseases.

† Some patients had more than 1 lesions.

‡ Some patients had more than 1 sites of involvement.

**Table 2****Comparison of clinical morphology according to pathogenic organisms.**

Organisms	Clinical morphology (%)							
	Nodule	Plaque	Abscess	Papule	Patch	Cellulitis	Sporotrichoid	Others
<i>M abscessus</i>	26.9	21.8	15.4	15.4	5.1	1.3	1.3	12.8
<i>M haemophilum</i>	16.7	33.3	25	16.7	8.3	–	–	8.3
<i>M marinum</i>	20.0	30.0	10	10.0	10	10.0	10.0	–
<i>M fortuitum</i>	14.3	14.3	28.6	14.3	–	–	–	28.5

Acid-fast bacilli staining was positive in 15 out of 54 patients (27.8%) and Acid-fast bacilli staining from histopathology was positive in 8 of 42 patients (19%).

Traumatic injury to the skin was identified in 24 out of 88 patients (27.3%). This includes aquatic-related injury, insect bite, wood splinter injury, and procedure-related injury. All procedure-related NTM infection were linked to rapidly growing pathogens. Two patients had a history of cosmetic injection by unlicensed providers (filler injection and mesotherapy for fat reduction). Both of them suffered from *M abscessus* infection (Table 1). A total of 9 patients had *M haemophilum* infections which occurred without history of skin trauma. Seven out of 9 were immunocompromised patients (77.8%).

Fifty-nine patients (67%) with cutaneous NTM infection presented with single lesion whereas multiple skin lesions occurred in 29 cases (33%). Nodules and plaques were 2 most common skin lesions in cutaneous NTM infection (26.4% and 25.5%, respectively). Other presentations included papules (16.4%), abscesses (12.7%), patches (6.4%), pustules (5.4%), ulcers (4.5%), cellulitis-like lesions (1.8%), or sporotrichoid lesions (0.9%) (Table 1). Clinical morphology in association to the pathogenic organisms is demonstrated in Table 2. The most commonly involved sites were legs 50.9%, followed by forearm (15.8%), trunk (10.2%), and face (8.3%) (Figs. 1 and 2).

Associated symptoms (eg, fever, weight loss, lymphadenopathy, etc) were found in 15 patients (17%). Extra-cutaneous involvement of cutaneous NTM infections was found in 6 cases, of which, pulmonary involvement occurred in 3 patients. Other affected organs were hematologic (blood, lymph node), eye, sinus, or bone and joint. Reactive dermatoses were found in 6 out

of 88 patients (6.8%). Sweet syndrome and erythema nodosum were the 2 most common reactive dermatoses presented in 3 (3.4%) and 2 (2.3%) patients, respectively. They could be found before, concurrent, or after NTM infections.

With regards to treatment, 81 patients were treated at our institute while 7 patients were treated elsewhere. All 81 patients received medical treatments and 58 patients commenced  $\geq 3$  medications. Thirty-four patients had surgical excision together with oral medication. The most commonly-prescribed regimen was combination of clarithromycin, ciprofloxacin, and doxycycline. The mean time to cutaneous remission was 40 ( $\pm 2$ ) weeks. Among 81 patients, 79 patients achieved clinical remission and 2 patients lost to follow-up.

Relapse was defined by the development of cutaneous lesions within 6 months after clinical remission with histological and microbiological confirmation. After achieving cutaneous remission, 74 patients remained on continuous follow-up for a duration of at least 6 months. Among these, 7 patients had relapse. A summary of treatment and outcome is shown in Table 3.

Subgroup analysis on immunocompromised patients showed that the most common organism in this group was *M abscessus* which comprised of 41.7% of immunocompromised subjects, followed by *M haemophilum* (29.2%). A higher prevalence of extracutaneous involvement (20.8% vs 1.6%,  $P < .01$ ), reactive dermatoses (20.8% vs 1.6%,  $P < .01$ ), and relapse (20.8% vs 6.3%,  $P = .044$ ) were observed in immunocompromised compared to immunocompetent hosts (Table 4).

Regarding factors associated with prognosis, there was no clinical or laboratory parameters associated with treatment



**Figure 1.** A 63 yr-old healthy man with cutaneous *Mycobacterium abscessus* infection. He had history of insect bite before the development of the lesion.



**Figure 2.** A 59 yr-old man with hypertension, diabetes, S/P kidney transplant with papulopustular lesions, ulcerated nodules, and abscesses on both feet. Tissue culture and PCR revealed *Mycobacterium haemophilum*. PCR = polymerase chain reaction.

**Table 3****Treatment summary for nontuberculous mycobacterial infections and outcome.**

Medications* (n=81)	
Clarithromycin	70 (86.4%)
Ciprofloxacin	57 (70.4%)
Doxycycline	41 (50.6%)
Rifampicin	10 (12.3%)
Amikacin	8 (9.9%)
Combination therapy (≥3 medications)	58 (71.6%)
Surgical excision	34 patients
Time to cutaneous remission (wk), mean (+/- SD)	40 (+/- 2) wk
Cutaneous relapse	7/74 (9.5%)

\* Other medications included azithromycin 7 (8.6%), trimethoprim/sulfamethoxazole 6 (7.4%), ethambutol 5 (6.2%), levofloxacin 5 (6.2%), imipenem 5 (6.2%), isoniazid 3 (3.7%), amoxicillin clavulanate 2 (2.5%).

response except for disease relapse that occurred to those who received less than 3 medications (Adjusted odds ratio 65.86; 95% confidence interval 2.02–2, 147.18;  $P=.02$ ) (Table 5).

#### 4. Discussion

Several studies have demonstrated that the rate of NTM species isolation is rapidly increasing worldwide<sup>[8–11]</sup> Likewise, cutaneous NTM infection has significantly increased over the past 30 years.<sup>[12,13]</sup> Most studies reported *M marinum* as the most common pathogenic organisms.<sup>[5,14,15]</sup> However, some studies identified rapidly growing mycobacteria as the predominant causative species.<sup>[16,17]</sup> In our study, *M abscessus* is the most common organism causing cutaneous NTM infection. This finding is similar to a study by Mahaisavariya et al which reviewed 40 cases of NTM in Thailand during 1994 to 2001. The predominant organism was rapidly growing mycobacteria responsible for 65% of cases, followed by *M marinum* (30%).<sup>[17]</sup> Our study was conducted at a university-based hospital in Bangkok metropolitan area and located nowhere near rivers, lakes, and so on. which may a contributing factor to why *M marinum* was not the most prevalent organism.

*M haemophilum* was the second most common pathogens identified in our study (10.2%). This finding was not consistent with previous reports.<sup>[8–11]</sup> This could be explained by the fact that many of our patients were immunocompromised host which might predisposing to this infection Moreover, our laboratory unit routinely performs a special culture for *M haemophilum* requiring Lowenstein agar supplemented with ferric compound

**Table 4****Comparison of cutaneous nontuberculous mycobacterial infection features by immune status.**

Characteristics	Immunocompetent, n (%)	Immunocompromised, n (%)	P-value
Age at diagnosis (yr), mean (+/- SD)	47.97 (+/-20.05)	40.19 (+/-20.38)	.44
Gender: female/male	53/11	13/11	.006*
Previous history of trauma	21/37 (56.8%)	3/8 (37.5%)	.322
Extra-cutaneous involvement	1/64 (1.6%)	5/24 (20.8%)	.005*
Reactive dermatoses	1/64 (1.6%)	5/24 (20.8%)	.005*
Relapse	4/64 (6.3%)	5/21 (23.8%)	.044*

SD = standard deviation.

\* statistically significant

**Table 5****Factors associated with relapse.**

Factors associated with relapse	Number of patients with relapse (%)	Adjusted OR (95% CI)	P-value
Number of lesions		20.95 (0.98–447.54)	.05
<2 lesions (n=49)	2 (4.1%)		
≥2 lesions (n=25)	5 (20%)		
Type of Mycobacteria*		15.65 (0.82–300.28)	.07
-Slow growers (n=15)	4 (26.7%)		
-Rapid growers (n=56)	3 (5.4%)		
Number of medications†		65.86 (2.02–2,147.18)	.02
<3 medications (n=20)	5 (25%)		
≥3 medications (n=48)	2 (4.2%)		

CI = confidence interval, OR = odds ratio.

\* Unidentified organisms were excluded from analysis.

† Patients who were treated with only excision were excluded from analysis.

and incubated at 30°C. However, there were increasing number of reports that *M haemophilum* was one of the pathogen that commonly presenting with cutaneous lesions in immunocompromised patients.<sup>[18–22]</sup> The impairment of cell-mediated immunity appears to play a role in the pathogenesis of *M haemophilum* infection. Restoration of cell-mediated immune function during the course of a patient's illness also appears to facilitate the recovery.<sup>[23]</sup> According to a laboratory study in murine models, albino mice with corticosteroids-induced immunosuppression, unlike the immunocompetent mice, developed cutaneous disease after being injected with *M haemophilum*.<sup>[24]</sup> In addition, we also observed a higher relapse rate in *M haemophilum* infection (44.4%) than non-haemophilum mycobacterial infection (6.3%) which might be from the significantly higher number of immunocompromised patients in our study that may determine poorer treatment outcome.

Immunosuppression is a well-known risk factor for cutaneous NTM infections. Immunocompromised patients from our study consisted of insulin-independent diabetes mellitus, post-organ transplantation treated with immunosuppressive drugs, and malignancy. However, none of our patients had HIV infection. Interestingly, we found 3 cases of adult-onset immune deficiency syndrome who suffered from cutaneous NTM infections. Adult onset immune deficiency, an emerging disease in East Asia particularly in Thailand, results in the production of circulating of antiinterferon-gamma autoantibody.<sup>[18,19]</sup> It is recognized as an acquired immunodeficiency syndrome-like illness in HIV seronegative patients and occurring in otherwise immunocompetent adults.<sup>[20–22]</sup> This finding emphasizes the importance of immune status evaluation in patient who had cutaneous NTM infection.

Skin trauma is another risk factor for cutaneous NTM infections. In the present study, 24 patients (27.3%) had preceding skin injuries and all of them were caused by rapidly growing mycobacteria. The type of skin injury identified in our patients includes wood splinter-related injury, aquatic-related injury, cosmetic procedure, and mosquito bite. In procedure-related infections, the causative organisms were all from rapidly growing mycobacteria, a finding similar to previous case report and series.<sup>[25–27]</sup> Apart from post-operative cutaneous NTM infection, cosmetic procedures, such as filler injection, or mesotherapy may contribute to an increase incidence of NTM infections, which has been confirmed by many authors in recent years.<sup>[26–28]</sup> As our data included procedure-related NTM infections accounting for 7.9% of the study population, the

prevalence of *M abscessus* may have been enhanced compared the higher prevalence of *M marinum* infection documented from previous reports.<sup>[5,14,15]</sup> We emphasize the importance of considering rapidly growing mycobacteria infection and administering empirical antimicrobial agents in cases suspicious of medical procedure-related cutaneous NTM. For mosquito bite and cutaneous NTM infection, there are previous vitro studies documenting that very low dose of *M ulcerans* can penetrate through mosquito bite wound and is sufficient to cause buruli ulcer.<sup>[29,30]</sup> To date, there are still no report on the association between other mycobacterial organisms and cutaneous NTM infection. Further studies are required to prove this possibility.

Regarding cutaneous morphology, nodules and plaques were 2 most common skin lesions in cutaneous NTM infection (26.4% and 25.5%, respectively). Other presentations included abscesses, papules, patches, cellulitis-like lesions, and sporotrichoid lesions. Cellulitis-like lesions and sporotrichoid lesions were commonly caused by *M marinum* and *M abscessus* infections. As for other cutaneous mycobacterium infection, there may be some similarities in terms of cutaneous morphology. For example, nodules and plaques can be found in cutaneous tuberculosis as well as leprosy. In such cases, histopathologic examination and microbiologic study can help differentiate among them.

There are many studies documenting the association between NTM infections and reactive dermatoses such as Sweet syndrome, pustular eruptions, or erythema nodosum.<sup>[31–33]</sup> The correlation and pathogenesis is still unclear, but it is hypothesized that infections may trigger cytokine secretion composed of mainly interleukin 1 mediating the infiltration of neutrophils to the skin lesions.<sup>[34]</sup> In addition, immunosuppression may result in the compensatory hyperactivation of innate immune responses to combat intracellular infections. Furthermore, immune dysregulation of IL-23/Th17, similar to that of generalized pustular psoriasis and acute generalized exanthematous pustulosis may also be responsible for recruitment, activation, and survival of neutrophils in the skin of these patients.<sup>[35]</sup> There seems to be a higher prevalence of reactive dermatoses in disseminated disease (53.8%) than in limited cutaneous form (6.8%).<sup>[22]</sup>

In terms of prognosis, patients that have received less than 3 medications were significantly associated with disease relapse in this study. Corresponding to the previous guideline and recommendations,<sup>[1,36,37]</sup> we recommended the use of 3 antibiotics with at least 1 macrolide for 4 months duration or more to avoid relapse.

There are a few limitations in this study. Due to the retrospective nature, clinical and laboratory data were incomplete. In addition, several culture-negative but highly suspicion cases of cutaneous NTM infections but with compatible clinical and histological findings, were excluded. Therefore, the occurrence of cutaneous NTM infections in the present study may have been underreported.

## 5. Conclusions

*M abscessus* is the most common pathogen for cutaneous NTM infection in Thailand. The prevalence of *M haemophilum* is increasing and should be suspected in all immunocompromised patients. Clinicians should be aware of rapidly growing mycobacteria in all cases of procedure-related cutaneous NTM. We recommended at least 3 medications with at least

1 macrolide for the treatment of cutaneous NTM for at least 4 months duration to reduce the rate of relapse.

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