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Nontuberculous mycobacteria pulmonary infection in medical intensive care unit: the incidence, patient characteristics, and clinical significance

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Abstract *Background:* The clinical significance of nontuberculous mycobacteria (NTM) pulmonary infection in medical intensive care unit (ICU) is still unclear. *Materials and methods:* We conducted a retrospective study in the medical ICUs of a medical center in Taiwan from January 1999 to June 2007. Patients with NTM isolated from respiratory specimens within 1 month before or during the ICU course were identified. Those who fulfilled the diagnostic criteria of NTM pulmonary infection were identified and compared with patients with NTM colonization and control subjects who were culture-negative for mycobacteria. *Results:* Among the 5,378 patients admitted to medical ICUs, 2,866 (53.3%) had received mycobacterial culture for respiratory specimens. NTM were isolated from 169 (5.8%) patients. Of them, 47 (27.8%) were considered NTM pulmonary infection. *M. avium* complex and *M. abscessus* were the most common pathogens. Within 100 days after ICU admission, significantly more patients with NTM infection died than those with NTM colonization and control subjects (47 vs. 8 vs. 14%, $P < 0.001$). Twenty-one (49%) patients with NTM pulmonary infection received anti-NTM treatment, with four experiencing adverse effects. Although statistically insignificant, anti-NTM treatment was associated with prolonged survival for those who died in the ICU and shorter ICU stay for those who survived the ICU course. *Conclusion:* Our findings suggest that NTM pulmonary infection seems to associate with higher mortality in medical ICUs. Anti-NTM treatment is probably associated with a better outcome. Therefore, keeping a high suspicion when NTM is isolated and using careful consideration when starting anti-NTM treatment should be emphasized.

Keywords Nontuberculous mycobacteria · Pulmonary infection · Intensive care unit

Introduction

Unlike *Mycobacterium tuberculosis* (Mtb), nontuberculous mycobacteria (NTM) exists in the environment and can be isolated from clinical specimens due to true infection, colonization, or even contamination [1]. It is an important clinical concern since the rate of NTM pulmonary infection has increased over the last 10 years

[2–4]. The reasons for this increase are not clear, but probably result from an enlarged population of acquired immunocompromised individuals, chronic lung disease, and prolonged mechanical ventilation [2, 5–9]. In our hospital, among the patients with acid-fast smear-positive respiratory specimens in 2006, 35% were due to NTM [10]. In fact, NTM pulmonary infection remains a diagnostic challenge even under the contemporary guidelines of the American Thoracic Society [1]. Because the presence of NTM in respiratory specimens is not pathognomonic for NTM infection, treatment is not deemed necessary by every clinician [11]. Even in disseminated NTM disease, a previous study revealed that adequate treatment was not started until 130 days after the initial visit [12]. However, the mortality rate can exceed 50% within 5 years [11, 13, 14].

In patients with complicated and critical conditions, such as those admitted to intensive care unit (ICU), the clinical significance of NTM in respiratory specimens and the prognostic impact of NTM pulmonary infection are even more difficult to understand than in stable patients [11, 15]. Therefore, we conducted a retrospective study including all medical ICU patients with NTM being isolated from respiratory specimens within a period of 8.5 years to evaluate the clinical significance of the presence of NTM and compare the demographic characteristics, clinical manifestations, and outcome in patients with NTM pulmonary infection with those with NTM colonization and control subjects whose respiratory samples were culture-negative for mycobacteria.

Materials and methods

Subject of study

This study was conducted in National Taiwan University Hospital, a tertiary-care referral center with 2,150 beds in northern Taiwan, and was approved by the Institutional Review Boards of the hospital. We reviewed the mycobacterial laboratory registry database and identified all patients who had undergone mycobacterial culture for respiratory specimens between January 1999 and June 2007. Among them, only those with the mycobacterial culture performed within 1 month before or during admission to medical ICUs were included for further analysis. In our hospital, mycobacterial culture for respiratory specimens is usually ordered in the following three conditions: (1) typical radiographic findings of post-primary pulmonary tuberculosis, i.e. patchy, poorly defined consolidation particularly in the apical and posterior segments of the upper lobes and with cavitation [16]; (2) contact history of active tuberculosis [17]; or (3) a poor clinical response to anti-bacterial antibiotics, defined as no improvement of symptoms, radiographic findings, or laboratory data within 3 days after antibiotics [18]. Mycobacterial culture was performed as previously described [19]. Mycobacterial species were identified by using biochemical testing [20].

Selection criteria of patients

In this study, NTM pulmonary infection was considered definite if all the following were met [1]: (1) at least two respiratory specimens or one bronchial washing/brushing sample being culture-positive for the same NTM species; (2) presence of respiratory symptoms; (3) chest radiography or computed tomography demonstrating new patch(es) of consolidation, nodular infiltrates, cavitary lesions, or multifocal bronchiectasis; and (4) no bacterial pathogens being isolated from respiratory specimens at the same time. NTM pulmonary infection was considered probable if a patient fulfilled the second and third criteria of definite NTM and had three respiratory specimens that yielded the same NTM species, yet bacterial pathogens were isolated at the same time. The definite and probable groups were considered as NTM pulmonary infection. Because the presence of NTM in respiratory samples can result from environmental contamination, only patients who fulfilled the first criterion of microbiology but were not considered to have NTM pulmonary infection were considered as NTM colonization (colonization group) [1]. Those who had a radiographic response to anti-bacterial antibiotics were classified into NTM colonization even if they had two respiratory samples that were culture-positive for the same NTM. For each patient with NTM pulmonary infection, an age-, gender-, and APACHE II score-matched control subject for whom mycobacterial culture was performed during ICU admission for $\geq$3 respiratory samples with the results being all negative was selected as control group.

Clinical data

The medical records were reviewed. The chest images were noted as in our previous study [21]. Radiographically, presence of reticulonodular lesions compatible with pulmonary fibrosis and multifocal bronchiectasis were categorized as structural lung change. The adequacy of anti-NTM treatment was judged according to the ATS guidelines [1]. Patients were followed for 100 days after ICU admission or until death or discharge from the hospital.

Statistics

The inter-group differences were compared by using One-Way ANOVA for numerical variables and chi-square test for categorical variables. Adjustments for multiple

comparisons were made by applying the Bonferonni method. Survival curves within 100 days since ICU admission for each class of variables were generated using the Kaplan-Meier method and were compared using the log-rank test. Variables having a significant difference ($P < 0.05$) were further tested by multivariate Cox proportional hazard regression analysis.

Results

From January 1999 to June 2007, a total of 4,779 respiratory specimens were culture-positive for NTM (Table 1). During this period, a total of 5,378 patients were admitted to our medical ICUs. Of them, 2,866 (53.3%) received mycobacterial culture of respiratory specimens. NTM was isolated from 337 samples from 169 patients collected within 1 month before or during admission to the medical ICUs. Of them, 47 (27.8%) had NTM pulmonary infection (24 (14.2%) definite and 23 (13.6%) probable), and 25 (14.8%) had NTM colonization. *Mycobacterium avium* complex was the most common NTM species. The medical records were not available for four patients with NTM pulmonary infection and one in the colonization group. Therefore, a total of 43 patients with NTM pulmonary infection, 24 with NTM pulmonary colonization, and another 43 age-, sex-, and APACHE-II score-matched control subjects were further investigated.

Clinical data

Statistically, no significant difference was noted in the age, gender, and cause of ICU admission among the three groups (Table 2). Previous tracheostomy was significantly associated with the colonization group ($P < 0.001$). Structural lung change was predominantly found in patients with NTM pulmonary infection ($P < 0.001$). Underlying co-morbid condition was more frequent in the control group ($P = 0.015$). The most common was malignancy in the NTM infection group, but diabetes mellitus in the other two groups. HIV serostatus was checked in 15 (35%), 10 (42%), and 10 (42%) patients in the NTM infection, NTM colonization, and control groups, respectively. The prevalence of HIV/AIDS was not significantly different. Respiratory failure was the most common indication for ICU admission in all groups.

Chronic obstructive pulmonary disease (COPD) was previously diagnosed in 10 (23.3%) patients with NTM infection, 5 (20.8%) with NTM colonization, and 7 (16.3%) in the control group. The prevalence was not significantly different among the three groups ($P = 0.722$). Among patients with NTM infection, pulmonary function test was performed in eight and revealed severe obstructive in 2, mild obstructive in 1, severe restrictive in 2, moderate restrictive in 1, mixed obstructive and restrictive defect in 1, and normal in the remaining one. Two patients with NTM colonization underwent pulmonary function test. The results were moderate obstructive in 1 and severe restrictive in another. Univariate analysis revealed that COPD did not associate with 100-days mortality in ICU ($P = 0.989$).

Radiographically, there were significant differences among the NTM infection, NTM colonization, and control groups in the prevalence of pulmonary consolidation (31 (72%) vs. 11 (46%) vs. 32 (74%), $P = 0.04$), and reticulonodular shadowing (23 (51%) vs. 2 (8%) vs. 4 (9%), $P < 0.001$). Of the colonization group, 5 (21%) patients had negative radiographic findings. In the NTM infection group, 15 (35%) patients with reticulonodular shadowing had cavitary lesions, whereas none in the other two groups did.

At the beginning of the ICU course, the APACHE II scores (Table 2), hemogram, and biochemistry, was not significantly different among the NTM infection, NTM colonization, and control groups. However, the control group had the highest serum creatinine (1.2 ± 0.7 vs. 1.5 ± 1.4 vs. 2.3 ± 2.1 mg/dl, $P = 0.009$) and ratio of arterial oxygen pressure divided by fraction of supplemental

Table 1 Number of isolates and patients with different NTM species in different clinical conditions during the 8.5 years

Mycobacterial species	Numbers of NTM isolates and patients in intensive care unit					All isolates in our hospital ($N = 4,779$)
	NTM infection		NTM colonization		Contamination	
	Isolates ($N = 175$)	Patients ($N = 47$)	Isolates ($N = 65$)	Patients ($N = 25$)	Patients ($N = 97$)	
M. avium complex	67 (38.3%)	20 (42.6%)	27 (41.5%)	11 (44%)	33 (34%)	1,527 (31.9%)
M. abscessus	29 (16.6%)	8 (17%)	24 (36.9%)	8 (32%)	13 (13.4%)	898 (18.8%)
M. chelonae	34 (19.4%)	7 (14.9%)	4 (6.2%)	2 (8%)	2 (2.19%)	546 (11.4%)
M. fortuitum	10 (5.7%)	3 (6.4%)	7 (10.8%)	2 (8%)	13 (13.4%)	646 (13.5%)
M. kansasii	27 (15.4%)	7 (14.9%)	2 (3.1%)	1 (4%)	13 (13.4%)	310 (6.5%)
Others	8 (4.6%)	2 (4.3%)	1 (1.5%)	1 (4%)	23 (23.7%)	852 (17.8%)

Table 2 Clinical characteristics

	NTM infection ($N = 43$)	NTM colonization ($N = 24$)	Matched control ($N = 43$)
Age: year, mean (range)	69.7 (19–95)	67.7 (28–91)	69.8 (19–96)
Age > 65	28 (65%)	16 (67%)	28 (65%)
Male gender	25 (58%)	20 (83%)	25 (58%)
Structural lung change*,[a]	25 (58%)	5 (21%)	5 (12%)
Having received tracheostomy*	7 (16%)	10 (42%)	4 (9%)
Underlying co-morbid condition*	19 (44%)	8 (33%)	29 (67%)
Malignancy	14 (33%)	2 (8%)	8 (19%)
AIDS	2 (5%)	2 (8%)	2 (5%)
Diabetes mellitus	2 (5%)	3 (13%)	11 (33%)
End-stage renal disease	1 (2%)	1 (4%)	4 (12%)
Cirrhosis of liver	2 (5%)	0	0
Autoimmune disease	0	0	4(9%)
Cause of ICU admission			
Respiratory failure	35 (81%)	18 (75%)	29 (67%)
Pneumonia	32 (74%)	15 (63%)	28 (65%)
COPD with AE	1 (2 %)	3 (13%)	1 (2%)
Pneumothorax	2 (5%)	0	0
Sepsis, other than pneumonia	5 (12%)	2 (8%)	10 (23%)
Seizure	1 (2%)	1 (4%)	0
Attempted suicide	1 (2%)	0	0
DKA/NKHS	0	1 (4%)	2 (5%)
Cardiovascular disease	1 (2%)	2 (8%)	2 (5%)
APACHE II—initial (mean ± SD)	22.8 ± 6.9	21.6 ± 7.8	22.8 ± 7.8
APACHE II—24 h (mean ± SD)	20.2 ± 6.6	19.1 ± 8.0	21.2 ± 7.5

Data are no. (%), unless otherwise indicated
AIDS acquired immunodeficiency syndrome; *APACHE* acute physiology and chronic healthy evaluation; *COPD with AE* chronic obstructive pulmonary disease with acute exacerbation; *DKA* diabetic ketotic acidosis; *NKHS* non-ketotic hyperosmolar syndrome

* Significant difference ($P < 0.05$) between the three groups
[a] Structural lung change was considered if reticulonodular lesions compatible with pulmonary fibrosis and multifocal bronchiectasis were present on chest images

oxygen concentration (PaO_2/FiO_2) (252.2 ± 107 vs. 247.4 ± 119 vs. 337 ± 168 mmHg, $P = 0.001$), and the lowest arterial pressure of carbon dioxide ($PaCO_2$) (53.8 ± 23.4 vs. 57.3 ± 26.9 vs. 40.2 ± 11.8 mmHg, $P = 0.002$).

Treatment and outcome

Table 3 and Fig. 1 show that the ICU-mortality and 100-days mortality were highest in the NTM infection group. Though statistically insignificant, the weaning rate was highest in the control group. Univariate survival analysis revealed that NTM pulmonary infection was associated with a poor outcome ($P = 0.008$; hazard ratio (HR): 7.2; 95% CI: 1.7–30.8). To exclude the potential confounding effect on NTM infection for survival, a multivariate Cox regression analysis, containing other variables that were significantly different among the three groups during univariate analysis were performed. These variables included NTM infection, structural lung change, tracheostomy, and

Table 3 Outcome of patients

	NTM infection		NTM colonization All ($N = 24$)	Control All ($N = 43$)
	Untreated ($N = 22$)	Treated ($N = 21$)		
Weaning rate	8 ($n = 19$, 42%)	6 ($n = 16$, 38%)	9 ($n = 18$, 50%)	27 ($n = 37$, 73%)
MV day: days ± SD	6.25 ± 3.1	10.2 ± 10.2	16.0 ± 9.6	11.33 ± 12.3
ICU-mortality*	5 (26%)	6 (29%)	2 (8%)	2 (5%)
ICU-stay: days ± SD	21.4 ± 15.7	22.4 ± 16.4	20.7 ± 19.3	18.0 ± 15.2
Survived: days ± SD	22.7 ± 16.4	18 ± 11.4	17 ± 14.8	18.0 ± 15.3
Dead: days ± SD	17.0 ± 13.7	33.3 ± 22.5	61 ± 21.2	18.1 ± 15.1
100-days mortality*	10 (45.6%)	10 (47.6%)	2 (8.3%)	6 (14%)

Data are no. (%), unless otherwise indicated
ICU intensive care unit; *MV* mechanical ventilation; *NTM* nontuberculous mycobacteria
* Significant difference ($P < 0.05$) between NTM infection, NTM colonization and control groups

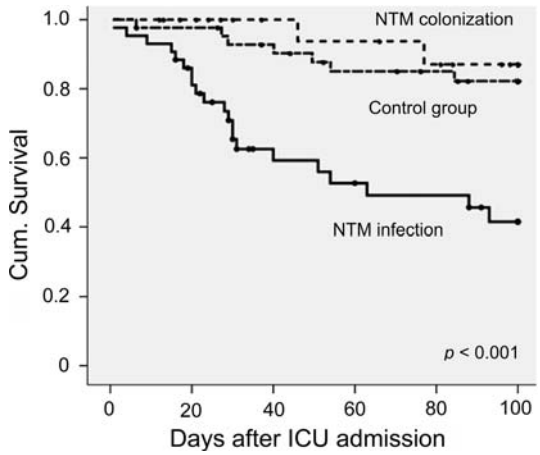

Fig. 1 Survival curve for patients with NTM pulmonary infection, colonization, or control group plotted using the Kaplan-Meier method. *Black dots* represent patients who were still alive at the end of the study

underlying co-morbid conditions. The results revealed NTM pulmonary infection still had significant prognostic impact ($P = 0.004$; HR: 8.7; 95% CI: 2.0–38.5), and none of the other three variables was an independent prognostic factor (structural lung change: HR = 1.6, 95% CI: 0.7–3.7; tracheostomy: HR = 0.9, 95% CI: 0.3–2.3; underlying co-morbid condition: HR = 0.7, 95% CI: 0.3–1.5).

In the NTM infection group, mycobacterial culture for respiratory samples was performed prior to ICU admission in 31 patients, and was positive for NTM in 13. The 13 patients had a higher 100-day mortality rate than the 30 patients from whom NTM was isolated after ICU admission (61.5 vs. 40%, $P = 0.025$). More patients in the latter had underlying co-morbid condition than in the former (23 vs. 53%, $P = 0.098$). Other clinical characteristics, such as APACHE II score (21.55 vs. 23.4), albumin (3.28 vs. 3.08 g/dl), serum creatinine (1.0 vs. 1.3 mg/dl), and C-reactive protein (13.1 vs. 10.4 mg/dl) were similar in the two subgroups.

Of the 22 patients in the NTM infection or NTM colonization group who died within 100 days after ICU admission, nine patients, including two belonging to the colonization group, had definite causes of death other than NTM infection. Another ten died of respiratory failure due to refractory pneumonia with unknown pathogens. The remaining three patients died of multi-organ failure, one of them having *M. avium-intracellular* complex (MAC) bacteremia. Among the ten patients with NTM infection who were treated and died within 100 days after ICU admission, all had multidrug-resistant enterobacteriae such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, defined as resistance to ≥2 classes of anti-pseudomonal agents, or methicillin-resistant *Staphylococcus aureus*, isolated from their respiratory samples during the following hospital course.

Of the patients with NTM pulmonary infection, treatment for NTM was prescribed in 21 (49%), and was started 21.1 ± 28.3 days on average after ICU admission. Although statistically insignificant, anti-NTM treatment was associated with prolonging survival for those who died in the ICU and with shortening the ICU stay for those who survived the ICU course (Table 3). All eight patients with MAC infection were treated with macrolides-containing regimens, with four not receiving ethambutol. Four of ten patients who were treated for rapid growing mycobacteria infection received macrolide monotherapy. The remaining three received treatment for *M kansasii* or *M. terrae* infection according to the ATS guidelines. Five episodes of adverse effects were reported in four patients, including one each for bone marrow suppression, hepatitis, diarrhea, fever and blurred vision.

Discussion

The 5-year mortality rate has been reported to be around 34–69% in NTM pulmonary infection [11, 14, 22]. However, decision making for treating NTM is a big clinical challenge because NTM are usually considered as colonizers rather than true pathogens in the respiratory tract. In addition, NTM pulmonary infection was usually considered to have chronic indolent disease [1, 23]. Consequently, treatment for NTM is usually delayed. The clinical significance and prognostic impact of NTM in respiratory specimens of patients in medical ICUs is even more obscure, because the issue has been discussed only in few case reports [24–26]. Therefore, decision making for treating NTM in critically-ill patients is extremely difficult. This is probably the reason why anti-NTM treatment was prescribed in only 49% of our NTM infected patients, lower than that reported in non-critical populations (65.5%) [11].

Though the total number of the mortality cases was not sufficiently large for conducting a multivariate Cox proportional hazard regression analysis including four variables [27], our results revealed that NTM pulmonary infection was probably associated with higher mortality in medical ICUs, even after controlling the possible confounding factors. The reasons are not clear, but this is probably because NTM pulmonary infection acts as an underlying co-morbid condition, which in turn deteriorates the pulmonary function and compromises the defense mechanism of the lung, and is associated with difficult eradicating of gram-negative organisms in airway [28]. Another possible explanation is that the prolonged antibiotic treatment including new fluoroquinolone and aminoglycosides for NTM infection could probably induce the emergency of multidrug-resistant *P. aeruginosa* or *A. baumannii* later in the hospital course, which has been

documented to increase the infection-related mortality [29–31]. However, these issues should be further confirmed.

In ICU patients with NTM pulmonary infection, our analysis revealed that the presence of NTM in respiratory samples prior to ICU admission was associated with a worse survival. The finding that 60% (18 in 30) of those with NTM isolated during ICU course did not have NTM prior to ICU admission implies that most of them could be in an earlier course of the NTM infection and probably had better lung function and host defense.

Among non-critical patients with NTM isolated from their respiratory specimens, the proportion of true infection was 20–25% in the 2000s [15, 32]. In our study, NTM was isolated from respiratory specimens in 5.8% of all patients admitted to our medical ICUs. Among them, 27.8% were considered infection rather than colonization or contamination. The reasons for the enlarging proportion of true infection are still unclear, but probably due to the improvement of the culture technique for NTM and the higher suspicion. In addition, a growing population of chronic lung disease, prolonged mechanical ventilation and immune dysfunction due to the underlying condition, such as AIDS and malignancy has been proposed [2, 6–9]. This finding emphasizes that careful interpretation of the results of mycobacterial culture for respiratory specimens and repeated culture surveillance are extremely important in this population.

The most common species in NTM pulmonary infection were different among different studies; *M. kansasii* in England and Wales, *M. xenopi* in Southeast England, *M. avium* complex (MAC) in the United States, Japan, and South Korea, and MAC and *M. abscessus* in our patients [2, 4, 15, 33–35]. In contrast to previous reports, a higher proportion of rapid growing mycobacteria were found in our series (38 vs. 10% in the United States and less than 5% in Japan) [4, 33, 35]. In our study, the presence of *M. chelonae* isolate in the respiratory tract was more likely to be a true infection than other species (64 vs. 17–34%) although statistically insignificant. Therefore, understanding the local epidemiology is important in the management of patients with NTM isolated from their respiratory specimens.

Radiographically, a much smaller proportion (51%) of our patients with NTM infection had reticulonodular opacity than those (70–90%) in previous reports [15, 36, 37]. In contrast, there was a markedly higher proportion (72%) of our patients with NTM infection having pulmonary consolidation than that (30%) in the study performed by Koh et al. [15]. One possible explanation is that about half of our patients with NTM infection had underlying immunocompromised conditions, probably predisposing to other radiographic manifestations, as it has been reported that only 6% of AIDS patient with NTM pulmonary infection demonstrated typical reticulonodular opacity [38]. In addition, decreased serum albumin level, immobilization, positive pressure ventilation, and severe pulmonary inflammation in critical illness all predispose to the accumulation of pleural effusion, leading to misinterpretation for the pulmonary lesions as consolidation.

Some studies on non-critical patients have revealed that anti-NTM treatment did not improve the outcome [11, 14]. It might be attributed to the small number of patients (31 and 42 in the two studies, respectively) and the presence of confounding factors, such as underlying co-morbid conditions. In addition, the susceptibility tests were usually not routinely performed [39] and the chemotherapy regimens for all NTM species were impossible to be standardized. In contrast, studies on AIDS patients with non-disseminated NTM disease have showed that anti-NTM treatment was beneficial in 2-year follow-up [38, 40]. In our study, treatment for NTM infection also did not improve the outcome. However, among the patients with NTM infection who survived the ICU course, those receiving anti-NTM treatment was associated with a shorter stay in ICU. In addition, among the patients with NTM infection who died in the ICU, anti-NTM treatment was associated with prolong survival (Table 3). Further large-scale prospective studies are necessary to investigate the impact of anti-NTM treatment and to clarify possible confounding factors.

If anti-NTM treatment does improve the outcome of patients in ICU, keeping a high suspicion, establishing the diagnosis early, and starting adequate treatment promptly become very important. Several clinical characteristics were associated with NTM pulmonary infection, including structural lung change without tracheostomy, radiographically reticulonodular shadowing with cavitation, and isolation of *M. chelonae*. For those patients, NTM pulmonary infection should be suspected once having NTM isolated from their respiratory specimens.

Our study has several limitations. First, due to the small number of patients, we could not make any firm conclusions, especially in identifying the reasons for the high mortality rate in NTM infected patients and in analyzing the importance of anti-NTM treatment. Second, in this retrospective study, the number of patients with NTM infection could be underestimated because mycobacterial cultures were performed in 53.3% of ICU patients. In addition, structural lung change that was only mild and beyond the detection threshold of the chest radiography will be missed. Large scale prospective study is needed for further investigation.

Conclusion

Our findings suggest that NTM pulmonary infection probably increases the mortality of the medical ICU

patients. Anti-NTM treatment could possibly improve the outcome. At present, keeping a high suspicion when NTM is isolated and using careful consideration when starting anti-NTM treatment should be emphasized.

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