

Mycobacterium mucogenicum and Mycobacterium neoaurum Bloodstream Infection in Immunocompromised Hosts

Armelle Pérez-Cortés Villalobos

University of Toronto

Coleman Rotstein (✉ coleman.rotstein@uhn.ca)

University Health Network <https://orcid.org/0000-0003-1413-0968>

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Abstract

Background

Mycobacterium mucogenicum and *Mycobacterium neoaurum* are an infrequent cause of bloodstream infection in humans. When they are isolated from blood, it is not unusual for them to be considered to be contaminants initially.

Methods

A retrospective chart review of patients diagnosed with *M. mucogenicum* and *M. neoaurum* bacteremia was conducted from January 1998 to December 2018 at the University Health Network, Toronto, Canada.

Results

We identified 28 patients who had bloodstream infection caused by these organisms. These patients were immunocompromised hosts, patients with chronically indwelling vascular access devices or injection drug users. In 28.5% of the patients the isolation of these mycobacteria was considered colonization, 82% of the cases received antimicrobial therapy and in 95% of the patients the central line was removed.

Conclusions

The removal of the vascular access device and treatment with either single or combination antimicrobial therapy produced successful outcomes for these infections.

Background

With the expansion of the immunocompromised patient population, infections due to nontuberculous mycobacteria (NTM) are increasing in frequency¹, and their impact is significant as they may produce considerable patient morbidity. As a result, more familiarity with these organisms and the infections that they may produce is required. There are currently more than 150 species of NTM that are divided into rapidly, intermediate and slowly growing species².

Rapidly growing mycobacteria produce mature colonies on solid media within 7 days. There are about 20 species of rapidly growing NTM that are capable of infecting human beings³. Of interest among the rapidly growing NTM, are two less commonly isolated mycobacteria, *Mycobacterium mucogenicum* and *Mycobacterium neoaurum*. They are ubiquitous in the environment, including household water, potting soil, animals, birds and vegetables. These organisms have been increasingly noted to be the cause of significant infections in immunocompromised hosts.

The current literature highlights that the most common infection caused by *M. mucogenicum* and *M. neoaurum* is catheter-related bloodstream infection (CRBSI)⁴⁻⁷. The frequent use of indwelling intravascular catheters in immunocompromised individuals has been accompanied by NTM CRBSI, especially in patients with underlying malignancies⁹.

These organisms have the ability to form a protective biofilm, which plays a role in CRBSI. Biofilms in turn confer decreased penetration to antimicrobials, enhance the potential of resistance and are integral to device-related infections⁹. These organisms are also able to tolerate disinfectants, chlorination and extreme temperatures.

M. mucogenicum and *M. neoaurum* infections are seen more often in long-term central intravenous catheters causing catheter-related sepsis, but they may also occur with peritoneal or shunt catheters. Central nervous system infections involving *Mycobacterium mucogenicum* are rare but serious, particularly for immunocompromised patients resulting in meningitis due to this organism⁵. Skin and soft tissue infections caused by these organisms have also been reported^{4,10}.

In immunocompromised patients, *M. mucogenicum* or *M. neoaurum* isolated from the bloodstream should be considered as true pathogens. The treatment of these NTM CRBSI involves catheter removal combined with antibiotic therapy³. These species are usually susceptible to multiple antimicrobial agents including aminoglycosides, ceftazidime, clarithromycin, minocycline, doxycycline, quinolones, trimethoprim/sulfamethoxazole, and imipenem¹¹. Currently, there is no guidance or consensus on the appropriate antimicrobial therapy (whether single agent or combination therapy) for these infections or the duration of treatment for infections caused by NTM⁸.

Further information is needed to better understand the epidemiology including predisposing host factors, antibiotic susceptibility patterns, and appropriate duration of therapy for these infections particularly bloodstream infections caused by *M. mucogenicum* and *M. neoaurum*.

Methods

A retrospective chart review of patients diagnosed with *M. mucogenicum* and *M. neoaurum* bacteremia was conducted from January 1998 to December 2018 at the Toronto General Hospital and Princess Margaret Cancer Centre of the University Health Network, Toronto, Ontario, Canada. This project was approved by the Research Ethics Board of the University Health Network.

We identified patients with infection due to *M. mucogenicum* and *M. neoaurum* cultures through a search of the Microbiology Laboratory database of the Mount Sinai Hospital. The microbiological isolates were confirmed with Geno Type Mycobacterium Assay for identification of Mycobacterial Species or by matrix assisted laser desorption ionization (MALDI-TOF) if available. Only two isolates of *M. mucogenicum* had in vitro susceptibility testing, that was done by a microdilution minimum inhibitory concentration (MIC) method. Susceptibility testing for the mycobacterial isolates was performed at the Public Health Ontario

Laboratories. We excluded patients who were younger than 18 years old or whose source of the culture was other than the bloodstream.

Data collection included patient demographics, comorbidities, major underlying predisposing condition, origin of the positive blood culture for *M. mucogenicum* and *M. neoaurum*, microorganism susceptibility patterns if available, presence and site of intravascular catheters, clinical manifestations, treatment regimen and duration, as well as outcome.

We used the Centers for Disease Control definition of central line-associated bloodstream infection.¹² This was defined as a patient who had at least one of the following signs or symptoms: fever ($> 38^{\circ}\text{C}$), chills or hypotension, had a microorganism identified in blood not related to an infection at another site and whose microorganism was identified by culture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions. We employed the differential time to positivity i.e. the growth of organism from blood samples drawn from a catheter hub at least 2 hours before microbial growth is detected in a blood sample obtained from a peripheral vein, in order to define CRBSI¹³. Catheter-related infection was also determined by the presence of ≥ 15 colony forming units on the vascular access device tip according to the semiquantitative method of Maki¹⁴.

Descriptive statistics were employed as appropriate to compare patients with successful outcomes to those with unfavourable outcomes.

Results

Between January 1998 to December 2018, we identified 81 isolates of *M. mucogenicum*, 24 of which were blood culture isolates, 3 from dialysis fluid, and 54 respiratory isolates from bronchoalveolar lavage fluid or sputum. *M. mucogenicum* was not considered to be a significant pathogen if the origin was the respiratory tract. We also identified 4 blood culture isolates of *M. neoaurum*. Therefore, we assessed a total of 28 episodes of bacteremia.

Of the 24 patients who developed *M. mucogenicum* bacteraemia, 15/24 (62.5%) were male, with a mean age was 53.3 years (21–87 years). Of the 4 patients who developed *M. neoaurum* bacteremia, 3/4 (75%) were male and the mean age was 52.5 years (24–78 years).

The patient characteristics are shown in Table 1.

Table 1
Patient demographics

	<i>Mycobacterium mucogenicum</i> Bacteremia n = 24	<i>Mycobacterium neoaurum</i> Bacteremia n = 4
Male	15 (62.5%)	3 (75%)
Age	Mean 53.3 (21–78 years)	Mean 52.2 (24–78 years)
Underlying disease	13 Hematological malignancy 6 (46%) Allogenic HSCT 4 (30%) Acute leukemia 1 (8%) Autologous HSCT 1 (8%) Multiple myeloma 1 (8%) Lymphoma 5 IV Drug users 3 Autoimmune diseases 1 Kidney transplant recipient 1 Solid tumor 1 Chronic kidney disease on hemodialysis	3 Hematological malignancy 2 (66.6%) Allogenic HSCT 1 Solid tumor
Steroid use	18 (75%)	4 (100%)
HSCT = hematopoietic stem cell transplant; IV = intravenous		

The most frequent comorbidity noted in the patients was hematological malignancies (Table 1). Twenty-five per cent of the patients had a history of allogeneic stem cell transplant in the *M. mucogenicum* bacteremia group and 50% in the *M. neoaurum* group. Most of the patients were receiving corticosteroids: 75% in the *M. mucogenicum* group and 100% in the *M. neoaurum* group. In 71.4% (20/28) of the bacteremias reviewed, a central venous access device was in place.

While 68% of the patients were lymphocytopenic, only 4 (14%) were neutropenic at the time of the bacteremia (Table 2). Concomitant bloodstream infection with another pathogen was very common in the *M. neoaurum* group (75%) two patients had concomitant infection with methicillin-susceptible *Staphylococcus aureus* (MSSA) and one with *Micrococcus luteus*. Of note, the time to positivity of the blood culture for both *M. mucogenicum* and *M. neoaurum* was consistently greater than 24 hours.

Table 2
Clinical characteristics

	<i>Mycobacterium mucogenicum</i> Blood culture n = 24	<i>Mycobacterium neoaurum</i> Blood culture n = 4
Fever	20 (83%)	2 (50%)
Hemodynamical instability	0	0
Hemoglobin (g/dL)	103.8 (66–146)	96.5 (75–113)
White count (x10 E9/L)	6.08 (0.1–11.5)	8.3 (2.7–17.7)
Neutropenia (patients) ($< 0.5 \times 10^9/L$)	4 (16%)	0
Patients with lymphopenia ($\leq 1 \times 10^9/L$)	15 (62.5%)	4 (100%)
Platelet count (x10e9/L)	141 (6-474)	144 (99–175)
Coinfection with another microorganism	0	3 (75%)
Central line present	16 (66.6%)	4 (100%)
Mean time to culture positivity (Hours)	35.58 (3–120)	24.5 (8–36)
Number of positive blood cultures	16 (67%)	2 (50%)
One	3 (12%)	2 (50%)
Two	2 (9%)	
Three	3 (12%)	
Four		

With regards to management, central venous access device removal ensued in 95% (23/24) of the *M. mucogenicum* infection and 75% with *M. neoaurum*. However, none of the tip cultures were positive. Antimicrobial therapy was administered in 23 of the 28 (82%) episodes of bacteremia. The antibiotic susceptibilities of the 2 *M. mucogenicum* isolates are demonstrated in Table 3. Therapy with a single antimicrobial agent was undertaken in only 35% (8/23); while combination therapy was initiated in 65% (15/23 episodes). In addition, moxifloxacin was part of the combination regimen in all 15 courses of

combination therapy. Most commonly, moxifloxacin was paired with amikacin and/or a carbapenem in 6 episodes (40%) each respectively (Table 4).

Table 3
Microbiological Susceptibility of 2 Isolates of *M. mucogenicum*

<i>Mycobacterium mucogenicum</i>	Amikacin	Cefoxitin	Ciprofloxacin	Clarithromycin	Doxycycline	Imipenem	Linezolid	Moxifloxacin	Tobramycin	Septera
Isolate 1	S	S	S	S	S	S	S	S	S	S
Isolate 2	S	I	S	S	S	S	R	I	S	S
S = Sensitive I = Intermediate										

Table 4
Outcomes

	<i>Mycobacterium mucogenicum</i> n = 24	<i>Mycobacterium neoaurum</i> n = 4
Considered colonization	8 (28.5%)	1 (25%)
Received antimicrobial treatment	20 (83%)	3 (75%)
Single agent	8/20 (40%)	0
Combination therapy	12/20 (60%)	3 (100%)
Single agent	8 (40%)	3 (100%)
Ciprofloxacin or Moxifloxacin	2 (25%)	1 (33.3%)
Ceftazidime or Ceftriaxone	3 (38%)	1 (33.3%)
Meropenem	1 (12%)	1 (33.3%)
Piperacilin/Tazobactam	2 (25%)	
Combinations used	12 (60%)	
Moxifloxacin/Pipercillin tazobactam	3 (25%)	
	0	
Moxifloxacin/ Doxycycline	1(8%)	
Moxifloxacin/Azithromycin	3 (25%)	
Moxifloxacin/Imipenem	2 (17%)	
Moxifloxacin/Amikacin or tobramycin	1 (8%)	
Moxifloxacin/TMP-SMX	2 (17%)	
Moxifloxacin/Carbapenem/Amikacin		
Moxifloxacin/Doxycycline/Amikacin		
Duration therapy (days)	20.6 (7–42)	22.5 (12–34)
Line removal	16/16 (100%)	3/4 (75%)
Positive catheter tip	0	0
30 day survival	100%	100%
1-year survival	21 (87.5%)	3 (75%)

The outcomes for these cases of bacteremia were varied (Table 4). In 9 (32%) patients, the organisms were initially considered colonization/contaminant. In the *M. mucogenicum* group, the organism isolated was initially considered to be a contaminant in 4 patients, but all of them had repeated blood cultures that were also positive and were treated. In addition, 3 patients with positive blood cultures were discharged and there were no available records to assess whether the infection was ever treated. In one patient, the first blood culture was considered a contaminant and because the repeat blood cultures were negative no treatment was provided. In the *M. neoaurum* group, only one patient did not receive treatment, as he had coinfection with methicillin-susceptible *Staphylococcus aureus* (MSSA) and only received therapy with cefazolin.

None of the patients had disseminated disease or another infection site caused by the mycobacterial infection. The 30-day survival was 100% in both groups and one-year survival was 87.5% in the *M. mucogenicum* and 75% in the *M. neoaurum* 75% groups, respectively.

Discussion

This case series highlights that *M. mucogenicum* and *M. neoaurum* may produce significant infection in immunocompromised hosts. Commonly, these pathogens produce morbidity by causing CRBSI in this population.

Previous reports of bacteremia caused by these rapidly growing mycobacteria have focused in immunocompromised hosts. However, in this case series we found that all the immunocompetent patients, had an intravascular indwelling catheter at the time of diagnosis, this association has also been reported in the past¹⁶. We also found that 5 patients were chronic injection drug users. Therefore, the use of intravenous drugs should be recognized as a risk factor for the development of infections caused by these organisms.

Of note lymphocytopenia, was present in 68% of our patients, rather than neutropenia and may have predisposed our patients to these infections. Furthermore, these organisms have a predilection for causing CRBSI as was seen in our series (68% of the patients). Of significance, *M. mucogenicum* can form a biofilm on venous access devices thus rendering it resistant to killing by antimicrobials.^{3,6} As a result, it is strongly advised that vascular access devices be removed. In this case series the central line was removed in 95% of the patients, very similar to what has been reported in other studies (96%)³.

With regard to the management of these bloodstream infections, in our series 5 of 28 episodes (18%) were not treated with antimicrobial therapy. Indeed, the isolation of these organisms in blood cultures may be somewhat delayed further casting doubt on their significance and delaying appropriate antimicrobial therapy. A testament to this issue was that it was surprising that 5 patients didn't receive any antimicrobial therapy with purported activity against *M. mucogenicum* in our case series but they recovered by means of venous access device removal. Thus, underscoring the need for removal of the venous access as a key component for successful treatment of these bacteremias. Combination

antimicrobial therapy involving moxifloxacin with amikacin or a carbapenem may be preferred. Sixty-five per cent of the patients in our series received a combination of antimicrobial agents involving moxifloxacin with another agent. Nevertheless, one active antimicrobial agent may be adequate. This would require verification in a randomized clinical trial.

These organisms have often been considered to be contaminants. Indeed, their clinical significance was not appreciated until persistent bacteremia was noted with resolution of the infection only after venous access removal with or without antimicrobial therapy as noted in 9 cases in our series. It should be noted that co-infections with *Staphylococcus aureus* may occur with *M. neoaurum* as noted in 2 of our patients.

As this was a retrospective review, our analysis was limited by the availability of the data. Thus, we did encounter missing information. Moreover, management of these bacteremias was also hampered by the lack antimicrobial susceptibility in all isolates. However, the data do underscore the morbidity caused by *M. mucogenicum* and *M. neoaurum* in immunocompromised hosts.

Conclusions

In summary, this report focuses on the morbidity of bacteremia caused by *M. mucogenicum* and *M. neoaurum* in immunocompromised patients that is often related to venous access devices and use of IV drugs. It highlights the need for venous access device removal and therapy with antibiotics that should include moxifloxacin.

Abbreviations

- Nontuberculous mycobacteria (NTM)
- Catheter-related bloodstream infection (CRBSI)
- Matrix assisted laser desorption ionization (MALDI-TOF)
- Minimum inhibitory concentration (MIC)
- Methicillin-susceptible *Staphylococcus aureus* (MSSA)

Declarations

ETHICS APPROVAL

This project was approved by the Research Ethics Board of the University Health Network, Toronto, Canada.

CONSENT FOR PUBLICATION

Not applicable. This manuscript does not contain any individual person's data in any form.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed in the current study are available from the corresponding author on request.

COMPETING INTERESTS

Dr. Coleman Rotstein is a member of the editorial board of Biomed Central Infectious Diseases (Associate editor).

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AUTHORS CONTRIBUTIONS

Conception and design: All authors

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