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## Bloodstream infections with rapidly growing nontuberculous mycobacteria

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### ABSTRACT

**Background:** Bloodstream infections (BSI) with rapidly growing mycobacteria (RGM) resulted in recent nosocomial outbreaks predominantly in immunocompromised patients. A little is known about the clinical implications of RGM BSI with different species.

**Methods:** We conducted a multicenter retrospective cohort study of patients with RGM BSI from November 2011 to December 2020. Demographic data, clinical presentation, laboratory and radiographic findings and microbiological characteristics were used to tabulate descriptive statistics. We performed a comparative analysis of patients with BSI due to *Mycobacterium abscessus* complex (MABC) vs. other RGM.

**Results:** We identified 32 patients with positive blood cultures for RGM, 4/32 (12.5%) were considered to have unclear significance. The most common source for RGM BSI was intravascular catheters (14/28, 50%). Compared to other sources, patients with catheter-related bloodstream infection (CRBSI) received a shorter course of antimicrobial therapy (median [IQR]: one month [0.37–2.25] vs. six months [2–12]), ( $P = 0.01$ ). The most common species isolated were MABC (12/28, 42.9%), followed by *Mycobacterium fortuitum* group (6/28, 21.4%) and *Mycobacterium chelonae* (6/28, 21.4%). Compared to other RGM, MABC BSI was more likely to be secondary to skin and soft tissue infection, associated with longer hospital stay ( $P = 0.04$ ) and higher death rates despite a higher number of antimicrobial agents used for empirical and directed therapy per patient.

**Conclusion:** MABC BSI is associated with an overall more resistant profile, longer hospital stay, and higher death rate despite a more aggressive therapy approach.

### 1. Introduction

Non-tuberculosis mycobacteria (NTM) comprise a phenotypically diverse array of acid fast-organisms [1]. Rapidly growing mycobacteria (RGM) typically show a mature growth within seven days of incubation on solid agar. With recent advances in laboratory techniques, the Runyon criteria based on colony morphology and growth rate have been replaced by molecular methods for early identification and classification of NTM [1,2].

RGM are environmental bacteria with main reservoirs of soil, bio-aerosols, drinking, and natural water [3,4]. The majority are not considered human pathogens; however, recent outbreaks from contaminated hospital water systems prompted the researchers to focus on the pathogenesis of these organisms [5–7]. The mycolic acid-containing outer membrane provides an extra hydrophobicity, resulting in higher adherence capacity to plumbing surfaces and water

distribution systems [3]. Furthermore, after initial attachment of RGM to the biomaterials, implants, and plumbing surfaces, they can form biofilms through different mechanisms which are more resistant to disinfectants, sterilizing agents, and antibiotics than planktonic forms [8–10]. For instance, *M. abscessus* and *M. chelonae* biofilms are associated with extensive cording associated with higher pathogenicity [8,9]. Lastly, similar to *Legionella*, RGM can interact with amoeba trophozoites and cyst stages in water systems that may increase human infection capacity [11].

Common infections caused by RGM are skin and soft tissue, catheter-related bloodstream, pulmonary, intra-abdominal, and prosthetic joint infections [12–14]. They have a predilection for causing disease in special patient populations, including immunosuppressed patients and those with anatomic barrier disruption. Due to increase in the number of individuals with immunosuppression, the management of RGM infections is of a great importance [15,16]. For this reason, we aim to

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contribute to the literature by sharing our experience with RGM bloodstream infection (BSI) at a multi-site tertiary hospital system.

## 2. Methods

### 2.1. Data collection

We retrospectively reviewed electronic medical records of all adult patients ( $\geq 18$  years old) with a positive blood culture with RGM from November 2011 to December 2020 at three Mayo sites in Arizona, Rochester, and Florida. The central microbiology laboratory provided a comprehensive patient list. Demographic, clinical, microbiologic, treatment and outcome data were collected and managed using Research Data Capture (REDCap) hosted by Mayo Clinic [17]. Descriptive statistics and susceptibility patterns were tabulated. Quick sequential organ failure assessment (qSOFA) score at the time of blood culture collection was calculated using an automated medical calculator. The Mayo Clinic Institutional Review Board reviewed and approved the study.

### 2.2. Case definition

True BSI was defined as growth of RGM from one or more blood cultures, with clinical evidence of infection (fever  $> 38.3$  °C, chills, sepsis, or septic shock). We considered catheter-related bloodstream infection (CRBSI) if there is RGM growth from blood cultures obtained from a peripheral line and central line with a differential time to positivity ( $> 2$  h); growth of RGM from a central venous catheter that is accompanied by systemic toxicity, local signs of infection, or if no alternative source is found and patient's sepsis resolved after catheter removal. We applied ATS/IDSA guidelines for diagnostic criteria of NTM pulmonary infection [18]. Mycobacterial growth from a single culture bottle or set was considered as "unclear significance" if incompatible with the clinical syndrome, and resolved without specific therapy, judged by the treating providers, and didn't lead to any recurrence \relapse.

Active malignancy was described as a hematological malignancy that is not in complete remission or regionally advanced or metastatic cancer or administration of chemotherapy or radiotherapy within the last six months of the presentation with RGM BSI. We defined the immunocompromised state as the presence of steroid use (a glucocorticoid dose equivalent to  $> 7.5$  mg total daily prednisone for a minimum of four weeks), other immunosuppressive medication use, solid organ or bone marrow transplant, any autoimmune condition, active malignancy, end-stage renal disease, or diabetes mellitus with end-organ damage. Attributable mortality was determined through review of medical records, and postmortem examination reports, if available. We accepted death attributable if the RGM infection directly resulted in or led to events leading to the death of the patient within 1–2 months.

### 2.3. Identification

Mycobacterial cultures grown in solid media or broth suspension were identified using matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), 16S rRNA gene sequencing or biochemical analysis as appropriate.

Susceptibility testing was performed using broth microdilution technique. Clinical and Laboratory Standards Institute (CLSI) breakpoints were used to interpret categorical susceptibilities [19,20]. Final susceptibility reading of clarithromycin took place after 14 days from the set-up date unless the resistance was noted before this date due to concerns of the *erm* gene, which results in inducible resistance to macrolides in many RGM. Patients with unclear significance were excluded from analysis of clinical characteristics and outcomes however included in antimicrobial susceptibility analysis.

## 2.4. Statistical analysis

Descriptive and comparative statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. The *P*-value for statistical significance was set to  $< 0.05$ . Normality of scale and ordinal variables were assessed with Shapiro-Wilk test. *P*-Value was generated using Fischer's exact test, independent *t*-test, Mann-Whitney *U* test depending on data type and normality.

## 3. Results

### 3.1. Patient characteristics

A total of 32 patients had a positive blood culture with RGM species. Four patients (12.5%) had positive blood cultures with unclear significance leaving 28 patients for analysis. The mean patient age was 52.6 (25–89) years. Sixteen (57.1%) were females. A total of six patients had solid organ transplantation, of which three had kidney transplants, two had lung transplants, and one had heart transplants. Five patients were stem cell transplant recipients. Five patients had an active hematologic malignancy, four of which were also stem cell transplant recipients. Nineteen (67.9%) cases were on an immunosuppressant medication at the time of BSI. Additionally, eight patients had diabetes mellitus, four of which had end-organ damage (nephropathy, neuropathy, or retinopathy). There were two patients on hemodialysis and five patients with a history of IBD (Table 1). There were no statistically significant differences between cases with MABC infection vs. other RGM in terms of solid organ or stem cell transplantation history, active malignancy, use of steroids, antimetabolites, calcineurin inhibitors, or other immunosuppressive medications.

### 3.2. Clinical presentation

The most common source of BSI was intravascular catheters, with a total of 14 patients (50%). Respectively, other common sources of BSI included skin and soft tissue infection (SSTI) ( $n = 7$ ), respiratory ( $n = 3$ ), and others ( $n = 4$ ). Other sources included neurostimulator, automated implantable cardioverter-defibrillator (AICD), left ventricular assist device, and intrabdominal infections. Of seven patients with SSTI, one had a single versus six patients had multiple skin lesions; four patients had preceding percutaneous inoculation (etc. trauma or surgery); four patients had involvement of musculoskeletal system (including one patient with tenosynovitis, one with osteomyelitis and two with septic arthritis). These four patients underwent surgical debridement in addition to antimicrobial therapy. One patient had an infection of neurostimulator device implanted for neurogenic claudication. Notably, *M. fortuitum*

**Table 1**  
Baseline Characteristics of Patient Population.

	n = 28
Age, mean $\pm$ SD, y	52.6 $\pm$ 16.2
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	24.1 $\pm$ 5.2
Female, n (%)	16 (57.1)
White, n (%)	22 (78.6)
Diabetes, n (%)	
None or diet-controlled	20 (71.4)
Uncomplicated	4 (14.3)
End-organ damage	4 (14.3)
Hemodialysis, n (%)	2 (7.1)
Hematologic malignancy, n (%)	5 (17.9)
Solid organ transplant, n (%)	6 (21.4)
Stem-cell transplant, n (%)	5 (17.9)
Inflammatory bowel disease, n (%)	5 (17.9)
Steroids, n (%)	12 (42.9)
TNF-alpha inhibitor, n (%)	3 (10.7)
Antimetabolite, n (%)	8 (28.6)
Calcineurin inhibitors, n (%)	8 (28.6)

N = number; y = year; BMI = body mass index; kg = kilogram; m = meter

group grew in blood cultures seven weeks after the implantation of the device, as well as in cultures obtained from the thoracolumbar space, battery pocket, and lead extensions. Initial symptoms were fever, nausea and vomiting, and surgical wound dehiscence in the thoracolumbar region. Another patient had *M. fortuitum* group infection of his AICD three years after the implantation. Both the generator pocket and device leads had laboratory-confirmed infection with *M. fortuitum* group. Lastly, there was one case whose disease course was complicated by CRBSI during the same admission, although the initial presentation of BSI was due to SSTI. Hence, the patient was included in SSTI group for analysis.

The source of RGM BSI differed between patients with MABC and non-MABC BSI (Table 2). The most common source of BSI was SSTI in MABC group, while intravascular catheters was the most common source for other RGM species ( $P = 0.007$ ). Also, all of four cases deemed as unclear significance were in the non-MABC group. Overall, there were no statistical differences in qSOFA score, white blood cell count, hemoglobin, and serum creatinine between patients with MABC BSI and other RGM. We had three patients with *Mycobacterium mucogenicum/phocaicum* isolated from blood cultures due to CRBSI. Interestingly, all three cases had Crohn's disease, and two out of three were on total parenteral nutrition through central access due to CD complications. All five patients with active hematological malignancy had CRBSI with either *M. chelonae* or *M. fortuitum* group.

**Table 2**  
Clinical Characteristics of Rapidly Growing Mycobacteria Bloodstream Infection.

	<i>M. abscessus</i> <i>complex</i> (n = 12)	Other rapidly growing mycobacteria (n = 16)	P-value
qSOFA score, median (IQR)	0 (0–2)	0 (0–1)	0.21 <sup>–</sup>
Clinical presentation, n (%)			<b>0.007<sup>^</sup></b>
CRBSI	2 (16.7)	12 (75)	
SSTI	5 (41.7)	2 (12.5)	
Other	5 (41.7)	2 (12.5)	
WBC, median (IQR), 10 <sup>9</sup> /L	7.25 (4–14.1)	4.8 (3.1–9.6)	0.27 <sup>–</sup>
Hg, median (IQR), g/dL	9.25 (8.3–11)	9.9 (9.1–11.1)	0.49 <sup>–</sup>
sCr, median (IQR), mg/dL	0.9 (0.6–1.5)	1 (0.8–1.1)	0.64 <sup>–</sup>
Empirical therapy, n (%)	11 (91.7)	13 (81.3)	0.61 <sup>^</sup>
No of empirical agents, median (IQR)	3 (3–3)	2 (2–3)	<b>0.04<sup>–</sup></b>
No of directed agents, median (IQR)	3 (3–3)	2 (1.25–2.75)	<b>0.006<sup>–</sup></b>
Duration of therapy, n (%)			0.32 <sup>^</sup>
< 4 weeks	1 (8.3)	5 (31.3)	
≥ 4 weeks	7 (58.3)	9 (56.3)	
None	3 (25)	2 (12.5)	
Missing	1 (8.3)	0	
Hospital stay, median (IQR), days	9 (4–37)	3 (2–9)	<b>0.045<sup>–</sup></b>
Death <sup>1</sup> , n (%)	7 (58.3)	5 (31.3)	<b>0.03<sup>^</sup></b>
Death possibly attributable to RGM disease <sup>1</sup> , n (%)	4 (33.3)	0	–
Time to death, median (IQR), days	107 (37–246)	143 (116–701)	0.17 <sup>–</sup>

CRBSI = catheter-related bloodstream infection; SSTI = skin and soft tissue infection; WBC = white blood cell; Hg = hemoglobin; qSOFA = quick sequential organ failure assessment; sCr = serum creatinine; IQR = interquartile range; SD = standard deviation. (1) = Outcome of two patients from MABC group is missing.

(<sup>\*</sup>) independent *t* test, (<sup>^</sup>) = Fischer's exact test; (<sup>–</sup>) = Mann-Whitney *U* test were used for statistical analysis.

### 3.3. Microbiology

A total of 35 different isolates were obtained from 32 patients. The most common isolates were MABC (n = 14, 40%), *M. fortuitum* group (n = 8, 22.9%), *M. chelonae* (n = 6, 17.1%), others (n = 4, 11.4%), and *M. mucogenicum/phocaicum* (n = 3, 8.6%). Others included *M. canariensis*, *M. vaccae*, *M. diernhoferi* and a *Mycobacterium* sp. MABC isolates demonstrated a more resistant susceptibility profile when compared with non-MABC isolates (Supp. Fig. 1). All MABC isolates were resistant to moxifloxacin, tobramycin, trimethoprim-sulfamethoxazole (SXT), ciprofloxacin, and doxycycline, intermediate to imipenem, sensitive to amikacin (Table 3). Nine out of 14 isolates were tested for minocycline susceptibility, which were all resistant. One isolate (7.1%) was sensitive, and 13 isolates (92.9%) were intermediate to cefoxitin (Table 3). All six *M. chelonae* isolates were uniformly resistant to ciprofloxacin, moxifloxacin, SXT, cefoxitin and susceptible to clarithromycin and tobramycin. *M. fortuitum* group showed an overall more favorable resistance profile compared with MABC (Supp. Fig. 1). All *M. fortuitum* group isolates were sensitive to ciprofloxacin, moxifloxacin, and amikacin. Seven out of eight isolates were susceptible to SXT, imipenem and resistant to clarithromycin (Table 3). Tigecycline susceptibility was tested in 35 isolates, and it had an overall acceptable minimum inhibitory concentration (Table 4).

### 3.4. Treatment and outcome

All the patients with CRBSI had line removal. Thirteen of these patients received adjunctive targeted antimicrobial therapy, whereas two were managed with line removal alone. One patient declined directed therapy, one patient decided to pursue hospice care and comfort measures, and one patient died while being treated with empiric antimicrobial therapy. Patients treated empirically for MABC infection received a significantly higher number of antibiotics than those with other RGM BSI (Table 2) ( $P = 0.04$ ). Also, a higher number of directed-antimicrobials were used for MABC patients versus other RGM ( $P$ -value = 0.006).

The cases with CRBSI had a significantly shorter duration of therapy when compared with non-CRBSI cases (median, [IQR]: 1 month [0.37–2.25] vs. 6 months [2–12]), ( $P = 0.01$ ). There was no statistically significant difference between CRBSI and non-CRBSI groups in terms of decision to start empirical therapy, number of agents used in directed therapy, hospital stay, death rate, and time to death.

In our cohort, 12 patients died with a median survival of 6.5 months (IQR, 3.5–9.4). Overall, there were four patients whose death could be attributable to mycobacterial infection. These cases had BSI with MABC, which was resistant to multiple antimicrobials. Origin of BSI was SSTI in two cases, pulmonary in one case, and one case attributed to intravascular catheters.

## 4. Discussion

Rapidly growing mycobacteria include at least 70 different species that are ubiquitous in nature [1]. They are opportunistic pathogens with predilection for causing disease in special patient populations, including immunosuppressed patients and those with anatomic barrier disruption [1,3].

We found significant differences in clinical presentation, management, and outcomes between MABC and other RGM species BSI. First, the majority of MABC BSI originated from SSTI, whereas other RGM had intravascular catheters as the predominant source of BSI. Not surprisingly, MABC BSI was overall more resistant and more challenging to treat. Overall, a higher number of antimicrobials were used to manage MABC infected patients compared to patients with other RGM infections. The number of antibiotics used for the empiric management of MABC infection was significantly higher than of RGM. Also, a higher number of directed antimicrobials were used for MABC patients. When

**Table 3**  
Rapidly Growing Mycobacteria Antimicrobial Susceptibility Profiles.

Antimicrobial agents	<i>M. abscessus</i> complex (14) No. (%)			<i>M. chelonae</i> (6) No. (%)			<i>M. fortuitum</i> group (8)* No. (%)		
	S	I	R	S	I	R	S	I	R
Amikacin	14 (100)	–	–	5 (83.3)	1 (16.7)	–	8 (100)	–	–
Cefoxitin	1 (7.1)	13 (92.9)	–	–	–	6 (100)	–	8 (100)	–
Ciprofloxacin	–	–	14 (100)	–	–	6 (100)	8 (100)	–	–
Clarithromycin	4 (28.6)	1 (7.1)	9 (64.3)	6 (100)	–	–	–	1 (12.5)	7 (87.5)
Doxycycline	–	–	14 (100)	1 (16.7)	–	5 (83.3)	1 (12.5)	–	7 (87.5)
Imipenem	–	14 (100)	–	–	4 (66.7)	2 (33.3)	7 (87.5)	1 (12.5)	–
Linezolid	1 (7.1)	2 (14.3)	11 (78.6)	3 (50)	3 (50)	–	4 (50)	4 (50)	–
Moxifloxacin	–	–	14 (100)	–	–	6 (100)	8 (100)	–	–
TMP/SMX	–	–	14 (100)	–	–	6 (100)	7 (87.5)	–	1 (12.5)
Tobramycin	–	–	14 (100)	6 (100)	–	–	–	–	7 (100)

S = sensitive; I = intermediate; R = resistant; TMP-SMX = trimethoprim-sulfamethoxazole. The breakpoints from CLSI were applied to interpret categorical susceptibilities. (\*) tobramycin susceptibility result was missing for one patient.

**Table 4**  
Tigecycline Susceptibility of Rapidly growing Mycobacteria.

Minimum inhibitory concentration	<0.25 µg/mL	2.5–0.5 µg/mL	>0.5 µg/mL
No. of isolates	16	19	0
% (Percentage)	45.7	54.3	0

compared to other RGM species, patients infected with MABC had a higher death rate. Although the current study size is small, our findings support the previous reports postulating the significant differences in the pathogenesis of MABC from other NTMs. However, virulence factors of MABC are not fully understood and a larger scale studies are needed [21,22].

RGM BSI has been described in mostly immunosuppressed patients, frequently secondary to malignancies and their entailed therapies [23–26]. Mizusawa et al. showed in a small cohort of 17 immunocompetent patients that 94% of patients were persons who inject drugs (PWID), highlighting the role of skin barrier breakdown in this patient population. Additionally, 100% of those patients had peripherally inserted central catheter line and were receiving intravenous (IV) antibiotics for another primary infection prior to being diagnosed with RGM BSI [23]. Other comorbidities listed in those previous studies match those seen in our cohort including gastrointestinal pathology, diabetes mellitus, ESRD, and autoimmune disease [27–32].

While the above general similarities are observed between the current and previous reports regarding patients' characteristics and exposure, some important contrasting points exist. For example, 17.9% of our patients had active hematological malignancy, and while this still falls within the previously reported range it is lower than some prior studies [29]. Additionally, our series consists of patients with solid organ transplant which is not shared across other cohorts [23–27]. Furthermore, some of those previous reports had individuals with solid organ cancer who developed RGM BSI that may confer a risk factor. There was no patient with active solid organ tumor in current study [28,29]. Similarly, PWID were not seen in our cohort in contrast to several prior studies. Finally, while most of the patients had CRBSI, the rates were overall lower than previous reports. For example, CRBSI was reported in 85%–100% in four earlier studies while the rate was 50% in this study [23,24,28,29]. This could be related to overall differences between baseline characteristics of this cohort, higher proportion of MABC BSI cases, and presence of strict predefined criteria for CRBSI in current study [28,29,33].

Recent MABC outbreaks of postsurgical cardiac infection in the Southeastern United States suggested that colonization of hospital water systems or heater-cooling units were the main transmission routes [5,6]. Recently, Baker et al. reported a case series of 10 patients with invasive MABC infection after cardiac surgery [6]. Interestingly, none of the

patients were immunocompromised, and they all had a subtle clinical presentation. Similar to our study, mortality was very high in these patients despite aggressive therapy, with four deaths attributable to the MABC infection within the first two years after diagnosis [6].

No guidelines are available to guide the management of RGM BSI. In most cases, treatment is individualized and can depend on the treating physician's experience. A common approach shared across different series is line removal in the setting of CRBSI [23,24,27,28,29]. In a small outbreak among five patients with hematologic malignancy, all five were cured with catheter removal alone [24]. In a study of PWID, 74% of cases defervesced with line removal alone with a median follow-up of 45 days [23]. In a review of cancer patients with RGM BSI by Redelman et al., 84% of cases had line removal and antibiotics with a median antibiotic duration of 8 weeks (range: 5–29 weeks). Overall, 1 out of 141 patients died due to RGM infection [28]. In another cohort, a higher cure among patients who received adequate empiric antibiotic therapy versus those on inadequate empiric antibiotics was observed (83% vs. 43%, respectively) [29]. Only 63.2% of patients from this study received adequate empiric antibiotics. The average antibiotic duration was 47.6 days (range: 10–180 days). A high death rate was reported in this series, 28.6%, but only a small percentage was considered secondary to RGM infection by the investigators [29]. In our series, all patients with CRBSI underwent line removal. Twelve of these patients received adjunctive targeted antimicrobial therapy, whereas two were managed with line removal alone. Among 27 patients with known outcomes, one patient declined directed therapy, one patient decided to pursue hospice care and comfort measures, and one patient died while being treated with empirical therapy. In our cohort, twelve patients died, and death was attributed to disseminated mycobacterial infection in four patients. These cases had BSI with MABC, which was multi-drug resistant.

Despite the relatively low number of cases with RGM BSI, we believe that clinical suspicion of the providers play a substantial role in diagnosis of disseminated RGM infections since mycobacterial culture differs from routine bacterial blood cultures in many aspects, including content culture media, need for both solid and liquid culture medium, and duration [34]. In the next several years, molecular methods would further contribute to the identification and reclassification of NTM emphasizing the importance of dedicated laboratory procedures for mycobacterial recovery [35].

Given the retrospective nature of the study spanning ten-year period, the differences in death rate between patients with MABC BSI and other RGM BSI could be possibly confounded by accompanied comorbidities. Acknowledging the limitation, the death rate attributable to RGM infection was reported. Decision regarding ordering bacterial versus mycobacterial blood cultures as well as individual treatment strategies were at providers' discretion without a standardized protocol, which is also a limitation of this study.

## 5. Conclusion

Individuals with MABC BSI have a more resistant susceptibility pattern, longer hospital stay, and higher death rate despite a higher number of empirical and targeted therapy used. It overall portends a poor prognosis when compared with other RGMs. Prompt recognition and effective source control are the mainstays of treatment of RGM BSI.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jctube.2021.100288>.

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