Invasive *Mycobacterium abscessus* Complex Infection After Cardiac Surgery: Epidemiology, Management, and Clinical Outcomes

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Background. We recently mitigated a clonal outbreak of hospital-acquired *Mycobacterium abscessus* complex (MABC), which included a large cluster of adult patients who developed invasive infection after exposure to heater-cooler units during cardiac surgery. Recent studies have detailed *Mycobacterium chimaera* infections acquired during cardiac surgery; however, little is known about the epidemiology and clinical courses of cardiac surgery patients with invasive MABC infection.

Methods. We retrospectively collected clinical data on all patients who underwent cardiac surgery at our hospital and subsequently had positive cultures for MABC from 2013 through 2016. Patients with ventricular assist devices or heart transplants were excluded. We analyzed patient characteristics, antimicrobial therapy, surgical interventions, and clinical outcomes.

Results. Ten cardiac surgery patients developed invasive, extrapulmonary infection from *M. abscessus* subspecies *abscessus* in an outbreak setting. Median time from presumed inoculation in the operating room to first positive culture was 53 days (interquartile range [IQR], 38–139 days). Disseminated infection was common, and the most frequent culture-positive sites were mediastinum (n = 7) and blood (n = 7). Patients received a median of 24 weeks (IQR, 5–33 weeks) of combination antimicrobial therapy that included multiple intravenous agents. Six patients required antibiotic changes due to adverse events attributed to amikacin, linezolid, or tigecycline. Eight patients underwent surgical management, and 6 patients required multiple sternal debridements. Eight patients died within 2 years of diagnosis, including 4 deaths directly attributable to MABC infection.

Conclusions. Despite aggressive medical and surgical management, invasive MABC infection after cardiac surgery caused substantial morbidity and mortality. New treatment strategies are needed, and compliance with infection prevention guidelines remains critical.

Keywords. *Mycobacterium abscessus*; nontuberculous mycobacteria; hospital outbreak.

Nontuberculous mycobacteria (NTM) are emerging pathogens increasingly implicated in healthcare-associated infections and outbreaks [1, 2]. NTM commonly colonize municipal water, and patients can acquire NTM from healthcare facilities after contact with tap water, ice, aerosols, or medical equipment contaminated with NTM [3].

Contamination of heater-cooler units (HCUs) used in cardiac bypass surgery recently instigated a large, global outbreak of > 100 confirmed invasive and often disseminated postoperative infections from *Mycobacterium chimaera* [4]. Whole genome sequencing of *M. chimaera* isolates obtained worldwide from cardiac surgery patients and HCUs strongly implicated point-source HCU contamination by a colonized water source at a manufacturing site in Germany [5]. However, other waterborne NTM can also colonize HCUs and generate aerosols in the operating room, leading to invasive infections from other NTM species via the same mechanism [2, 6]. For example, investigators at 2 hospitals showed that cases of *Mycobacterium wolinskyi* surgical site infection following cardiac surgery were associated with NTM contamination of an HCU and the HCU water supply, respectively [7, 8].

Three other recently reported cardiac surgery outbreaks of invasive mycobacterial infections were caused by the rapidly growing mycobacterium, *Mycobacterium abscessus* complex (MABC). Each outbreak occurred at hospitals in the southeastern United States and implicated contaminated hospital water systems or HCUs [9–12]. One of these outbreaks occurred at our hospital where investigators mitigated a large, clonal outbreak of MABC linked to colonization of a new hospital

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addition's water system [12]. This outbreak included > 20 patients who underwent cardiac surgery from 2013 through 2015 and developed invasive postoperative MABC infection.

Investigation of outbreaks caused by *M. chimaera* or MABC in cardiac surgery patients have illustrated the importance and complexity of measures required to prevent these infections [12–19]. Furthermore, the global outbreak of invasive *M. chimaera* infection has also begun to generate valuable data on the epidemiology, clinical management, and outcomes of these often devastating infections [4, 20–23]. However, published clinical data on extrapulmonary, invasive MABC infection remain limited [24–28], especially among cardiac surgery patients [3, 29–33]. Patients who develop extrapulmonary MABC infection typically require months of combination intravenous antimicrobial therapy and surgical debridement, but the optimal clinical management and expected outcomes of cardiac surgery patients with these infections are not known.

This study describes the patient characteristics, medical and surgical management, and clinical outcomes among cardiac surgery patients at our hospital who developed invasive MABC infection.

METHODS

Duke University Hospital (DUH) is a 957-bed tertiary care hospital in central North Carolina. In July 2013, a new hospital addition opened, which included 160 intensive care unit and intermediate beds, as well as 16 operating suites [12].

We identified all patients with growth of MABC from any clinical specimen obtained at our hospital from 2013 through 2016. Our case definition required that a patient had undergone cardiac surgery at DUH prior to diagnosis. We excluded 2 groups of cardiac surgery patients from this analysis: (1) patients who had acquisition of MABC unlikely to be directly related to cardiac surgery at DUH, including patients who had positive cultures from only the respiratory tract; and (2) patients who at time of diagnosis had ventricular assist devices (VADs) in place or had undergone heart transplantation [34, 35]. We defined date of diagnosis to be the date of collection of the first positive culture. We considered the inoculation event to be the cardiac bypass surgery that most immediately preceded diagnosis.

For case patients, we reviewed clinical characteristics, including cardiac history, comorbidities, indication for surgery, and presenting signs and symptoms of infection. We also analyzed clinical data for 2 years following diagnosis, including detailed data on antimicrobial therapy and associated adverse events (AEs). Finally, we evaluated surgical management, burden of hospitalizations, and clinical outcomes, including mortality data.

Infectious disease physicians extracted all clinical data from the electronic medical record and adjudicated attribution of antibiotic-related AEs and deaths. AEs with objective definitions included renal toxicity ($\geq 50\%$ reduction in creatinine clearance or antibiotic changed), anemia (required blood transfusion or antibiotic changed), leukopenia (required granulocyte-colony stimulating factor or antibiotic changed), thrombocytopenia (required platelet transfusion or antibiotic changed), and development of *Clostridioides difficile* colitis. AEs defined subjectively included hearing loss; tinnitus; nausea, vomiting, and diarrhea; and peripheral neuropathy. Study physicians recorded these qualitative AEs if they deemed them to be clinically significant. Therapy-limiting AEs were defined as AEs that required changes in antibiotic regimen.

Standard mycobacterial culture methods were utilized and previously described [12]. Isolates from each case patient underwent susceptibility testing using Clinical and Laboratory Standards Institute guidelines, molecular subspecies identification, and molecular fingerprinting at the Mycobacteria/Nocardia Research Laboratory at the University of Texas Health Science Center in Tyler, Texas, as previously described [12].

Calculations were performed in SAS software, version 9.4 (SAS Institute, Cary, North Carolina). The institutional review boards at Duke University and the University of Texas Health Science Center approved this investigation and research.

RESULTS

Patient Characteristics and Presentation of Infection

Over the 4-year study, 38 patients with a history of cardiac surgery at DUH had subsequent positive cultures for MABC. We excluded 28 of these patients due to presence of VADs or heart transplants at time of diagnosis (n = 20) [34, 35], positive respiratory cultures in the absence of extrapulmonary infection (n = 6), and invasive MABC infections unlikely related to cardiac surgery performed at DUH (n = 2).

The 10 patients who met the case definition for this study were adults without notable immunosuppression and relatively few noncardiac comorbidities (Tables 1 and 2). However, most patients had severe cardiac illnesses preceding their cardiac surgery and underwent complicated and prolonged surgical procedures. Surgeries for all patients required cardiopulmonary bypass and use of HCUs (Supplementary Table). Seven patients underwent cardiac valve surgery, and 9 patients had cardiothoracic prosthetic material in place after surgery. All patients had infections linked to cardiac surgeries performed after the opening of the new hospital addition's operating suites in July 2013 and before the May 2015 institution of a new HCU disinfection and maintenance protocol [12].

Four patients were diagnosed with MABC infection during index cardiac surgery hospitalizations. These patients had prolonged postoperative hospitalizations and multiple associated complications that preceded the diagnosis of MABC disease, and their initial site of infection was the bloodstream

Table 1. Characteristics of 10 Patients Who Developed Extrapulmonary *Mycobacterium abscessus* Subspecies *abscessus* Infection After Cardiac Surgery

Characteristic	No.	(%)
Age at diagnosis, y, median (IQR)	66	(51–76)
Male sex	7	70
Race/ethnicity		
White	9	90
Black	1	10
Hispanic	0	0
Preoperative noncardiac comorbidities		
CKD III, IV, or V	4	40
Obesity (BMI > 30 kg/m^2)	3	30
Diabetes mellitus	1	10
Intravenous drug use	1	10
Indications for cardiac surgery		
Valvular disease	5	50
Coronary artery disease	4	40
Cardiac or vascular infection	3	30
Types of cardiac surgeries		
Valve replacement or repair	7	70
Vascular graft placement	5	50
Coronary artery bypass grafting	4	40
Presenting symptoms of infection		
Fever	6	60
Sternal wound drainage	6	60
Weight loss	3	30
Laboratory abnormalities at time of diagnosis		
Anemia (hemoglobin < 10 g/dL)	7	70
Leukocytosis (WBC count ≥ 10 × 10^9/L)	3	30
Elevated LFTs (any liver enzyme or total bilirubin ≥ 2 times ULN)	2	20
Thrombocytopenia (platelet count < 100 × 10^9/L)	1	10
First site of culture-proven infection		
Bloodstream	5	50
Mediastinum	4	40
Sternal wound	1	10

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; IQR, interquartile range; LFT, liver function test; ULN, upper limit of normal; WBC, white blood cell.

(Supplementary Table). The remaining 6 patients were discharged from cardiac surgery hospitalizations without suspected mycobacterial infection but were readmitted with subacute signs and symptoms of MABC infection, including 5 patients readmitted with sternal wound drainage (Figure 1). In addition to sternal wound drainage (n = 6), the other most common presenting symptom of MABC infection was fever (n = 6) (Table 1). Laboratory abnormalities were variable and nonspecific; anemia was common in this cohort of postoperative patients.

Median time from cardiac surgery to first positive culture was 53 days (interquartile range [IQR], 38–139 days [range, 2–324 days]; Figure 2). The first positive culture was obtained from either blood (n = 5; median time from surgery to positive culture, 38 days) or sternal wound/mediastinum (n = 5; median time from surgery to positive culture, 107 days) (Table 1).

Six patients ultimately developed disseminated disease with culture-proven infection at 2 or more noncontiguous sites (Table 2). Four patients developed culture-proven infections of cardiothoracic prosthetic material, and additional patients likely had unproven involvement of cardiothoracic hardware (Supplementary Table). No patients had proven or suspected mycobacterial ocular disease, bone marrow infiltration, or hepatitis.

Microbiology Data

In addition to positive mycobacterial-specific cultures, 5 of 7 patients with mycobacteremia had at least 1 positive blood culture performed on routine media. However, diagnosis of infection outside of the bloodstream occurred in 8 patients and uniformly required mycobacterial-specific tissue or fluid cultures.

Susceptibility testing demonstrated that isolates obtained from all 10 patients were multidrug resistant with nearly identical susceptibility profiles, including *erm* gene–mediated resistance to clarithromycin (Table 3). Molecular fingerprinting, including multilocus sequence typing and pulsed-field gel electrophoresis (PFGE), confirmed a clonal outbreak of *M. abscessus* subspecies (subsp) *abscessus*: isolates had the same unique *erm* and *rpoβ* gene combination and were clonal via PFGE [12].

Clinical Management and Outcomes

All patients received combination antimicrobial therapy, initially with long courses of induction therapy consisting of at least 3 agents (Table 2). However, patients completed a median of only 8 weeks (IQR, 5–11 weeks) of initial antibiotic regimens because therapy frequently resulted in antibiotic-related AEs requiring changes in therapy. The median total duration of therapy was 24 weeks (IQR, 5–33 weeks), including brief courses of therapy for 2 patients who died from MABC disease within 5 weeks of diagnosis. The most common antibiotic regimen consisted of amikacin, imipenem, and tigecycline (n = 7), but most patients received numerous additional antibiotics during their complicated treatment courses (Table 3).

Multiple strategies were implemented to limit anticipated AEs associated with high-risk antibiotics. For example, patients receiving amikacin typically underwent baseline and surveillance audiology assessments [36], took concomitant *N*-acetylcysteine to decrease risk of ototoxicity [37], underwent close laboratory monitoring of renal function and drug levels, and transitioned to aminoglycoside-sparing regimens after completing many weeks of initial induction therapy. Linezolid was usually dosed at 600 mg once daily rather than the twice-daily dosing regimen commonly used for bacterial infections [38]. Two patients received tedizolid and tolerated 200-mg once-daily dosing, including 1 patient who tolerated long-term suppression with tedizolid for > 80 weeks [39]. Finally, 2 patients developed gastrointestinal

Table 2. Characteristics, Clinical Management, and Survival of 10 Patients Who Developed *Mycobacterium abscessus* Subspecies *abscessus* Infection After Cardiac Surgery

Patient No.	Age, y[a]	Sex	Preoperative Noncardiac Comorbidities	Indication for Surgery	Type of Surgery	Sites of Culture-proven Infection	Majority Antibiotic Regimen (Total Duration, wk)[b]	Procedural Interventions	Time Alive After Diagnosis, wk (Death Attribution)
1	60–70	F	CKD IV, obesity	RV infarct, RV failure, and tricuspid regurgitation after CABG	Tricuspid valve replacement	Bloodstream, pleural fluid	Clarithromycin, cefoxitin, imipenem (2)	Chest tube placement; VATS with decortication	4 (attributable)
2	80–90	M	None	Mitral valve dysfunction, atrial fibrillation	MV repair, ablation of atrial fibrillation, LAA clip	Bloodstream	Amikacin, imipenem, tigecycline (3)	None	4 (attributable)
3	60–70	F	None	Abdominal aortic aneurysm, CAD	CABG, aortic grafting, AVR	Bloodstream, mediastinum	Imipenem, tedizolid, tigecycline (27)	Sternal debridement (×3)	27 (attributable)
4	40–50	M	CKD IV	Aortic graft infection, CAD	CABG, redo aortic grafting, AVR, and temporary RVAD	Bloodstream, mediastinum, pacemaker pocket	Amikacin, imipenem, tigecycline (45)	Sternal debridement (×2), omental flap	46 (attributable)
5	60–70	M	Hemodialysis	Aortic valve endocarditis with aortic root abscess	Replacement of aortic root, coronary reconstruction	Bloodstream	Amikacin, imipenem, tigecycline (5)	None	12 (not directly attributable)
6	80–90	M	CKD IV, obesity	Aortic stenosis and pseudoaneurysm, CAD, tricuspid regurgitation	AVR, tricuspid valve repair, CABG, aortic pseudoaneurysm repair	Bloodstream, mediastinum	Amikacin, imipenem, tigecycline (11)	Sternal debridement (×2), myocutaneous flap	44 (not directly attributable)
7	60–70	M	None	Right ventricular rupture after CABG	RV graft placement	Bloodstream, mediastinum, RV outflow tract	Amikacin, imipenem, tigecycline (32)	Sternal debridement, removal of RV outflow tract graft and vegetation, omental flap	63 (not directly attributable)
8	30–40	M	IV drug use	Tricuspid valve endocarditis	Tricuspid valve replacement	Abdominal wall, mediastinum	Amikacin, imipenem, tigecycline (33)	Sternal debridement (×2), abdominal wall debridement, removal of epicardial pacing lead	82 (not directly attributable)
9	50–60	M	Diabetes, obesity	LVAD no longer required	LVAD explant with retention of LV apical plug	Mediastinum, pericardium	Amikacin, azithromycin, imipenem, tedizolid (85)	Sternal drain placement; Sternal debridement (×3), LV aneurysm repair with removal of LV apical plug, omental flap	>104 (NA)
10	70–80	F	None	CAD	CABG	Mediastinum	Amikacin, imipenem, tigecycline (20)	Sternal debridement (×2), myocutaneous flap	>104 (NA)

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; IV, intravenous; LAA, left atrial appendage; LV, left ventricle; LVAD, left ventricular assist device; MV, mitral valve; NA, not applicable; RV, right ventricle; RVAD, right ventricular assist device; VATS, video-assisted thorascopic surgery.

[a]Ages are given in ranges to protect identities of individual patients.

[b]Majority antibiotic regimen is the combination of antibiotics that was used for the longest duration during the treatment course. Total duration includes all treatment time periods, regardless of antibiotic combination. Azithromycin, clarithromycin, and tedizolid were administered orally unless a patient could not take oral medications. Other listed antibiotics were administered intravenously.

Figure 1. Clinical photographs of *Mycobacterium abscessus* subsp *abscessus* infections following cardiac surgery. *A*, Sternal wound at time of diagnosis of *M. abscessus* subsp *abscessus* mediastinal infection. *B*, Sternal wound and abdominal wall abscess in patient with chronic *M. abscessus* subsp *abscessus* mediastinal infection and infected epicardial pacing lead at abdominal wall. In this cohort, disseminated infection commonly presented with mild, nonpurulent drainage from sternal wounds.
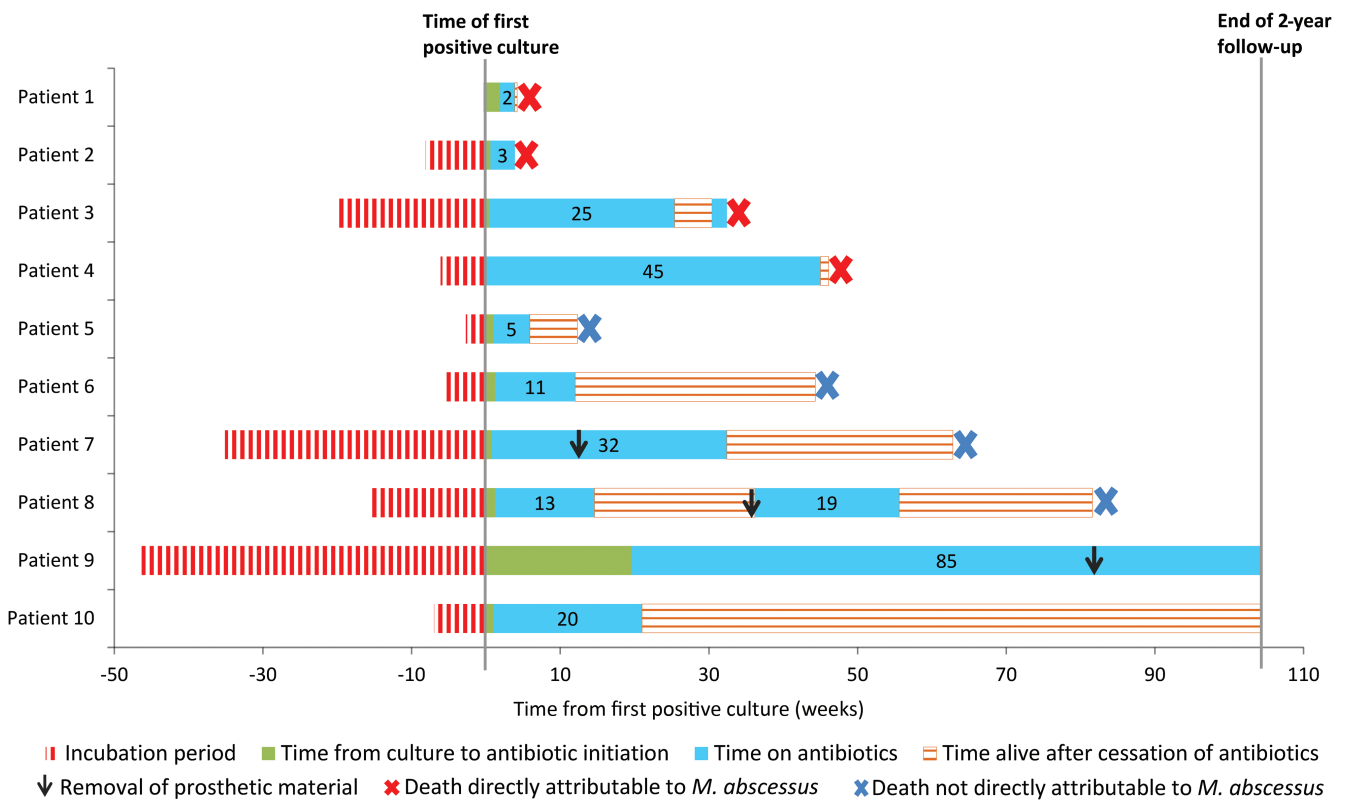

Figure 2. Clinical courses of 10 patients who developed invasive *Mycobacterium abscessus* subsp *abscessus* infection after cardiac surgery. Incubation period is given from time of presumed inoculation in operating room to time that the first positive culture was obtained. Time periods of antibiotic therapy are given in weeks.

Table 3. Antibiotic Susceptibility Testing, Use, and Associated Adverse Events Among 10 Patients Who Developed *Mycobacterium abscessus* Subspecies *abscessus* Infection After Cardiac Surgery

Antibiotic[a]	Susceptibility Data	Used During Treatment Course	Component of Majority Regimen	Duration, wk, Median (range)	Patients With Attributable AEs (No. of Therapy-limiting AEs)[b]
Amikacin	S: 10/10	10/10	8/10	11 (1–36)	Renal injury: 4/10 (3)
					Hearing loss and tinnitus: 2/10 (1)
Azithromycin/ clarithromycin[c]	R: 10/10	5/10	2/10	7 (3–85)	0/5
Cefoxitin	I: 10/10	1/10	1/10	2 (2)	0/1
Imipenem	I: 9/10	10/10	10/10	20 (1–45)	0/10
	R: 1/10				
Linezolid	I: 9/10	5/10	1/10	7 (1–18)	Peripheral neuropathy: 2/5 (2)
	R: 1/10				Gastrointestinal: 1/5 (1)
					Thrombocytopenia: 1/5 (1)
Moxifloxacin	R: 10/10	1/10	0/10	7 (7)	0/1
Tedizolid	Not tested	2/10	1/10	50 (15–84)	0/2
Tigecycline	MIC ≤ 0.25: 9/10	9/10	8/10	11 (3–45)	Gastrointestinal: 4/9 (1)
	MIC = 0.5: 1/10				
Ciprofloxacin	R: 10/10	0/10	0/10	NA	NA
Doxycycline	R: 10/10	0/10	0/10	NA	NA
Minocycline	R: 10/10	0/10	0/10	NA	NA
TMP-SMX	R: 10/10	0/10	0/10	NA	NA

Abbreviations: AE, adverse events; I, intermediate; MIC, minimum inhibitory concentration; NA, not applicable; R, resistant; S, susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Azithromycin, clarithromycin, linezolid, moxifloxacin, and tedizolid were administered orally unless a patient could not take oral medications. Other antibiotics were administered intravenously.

[b]Attributable AEs are given as a proportion of the number of patients who developed the attributable AE out of the total number of patients who received the antibiotic. Therapy-limiting AEs required changes in antibiotic regimen. Gastrointestinal AEs consisted of clinically significant nausea, vomiting, or diarrhea.

[c]Susceptibility data are given for clarithromycin but do not have interpretable criteria for azithromycin. Other data elements for azithromycin (received by 3 patients) and clarithromycin (received by 2 patients) are combined.

toxicity from tigecycline but were able to continue this agent after the dosing frequency was decreased from the standard 50-mg twice-daily dose to once-daily dosing [40].

Despite strategies designed to decrease risk of AEs, 7 patients developed a total of 15 antibiotic-associated AEs, including 5 patients with gastrointestinal toxicity and 4 patients with acute kidney injury (Figure 3). All 6 patients who received at least 20 weeks of therapy developed antibiotic-related AEs, and 5 of these patients required changes in antibiotic regimen. All but 1 AE was attributed to either amikacin (n = 6), linezolid (n = 4), or tigecycline (n = 4) (Table 3).

Except for 2 patients with mycobacteremia in the absence of known local infection, all patients underwent surgical management for source control (Table 2). Seven patients had confirmed mediastinal infection requiring a total of 15 sternal debridements (median, 2 debridements); 5 patients also underwent flap coverage for sternal defects. Three of 4 patients with confirmed infection of prosthetic material (patients 7, 8, and 9) eventually underwent hardware removal and did not subsequently experience relapse of infection (Figure 2 and Supplementary Table). The remaining patient (patient 4) was not a candidate for removal of an infected aortic graft. This patient died from progressive, disseminated MABC infection despite sternal debridement, flap coverage of the graft, and months of antibiotic therapy. Three additional patients whose deaths were directly attributable to MABC infection (patients 1, 2, and 3) may also have had infection of prosthetic material but were too ill to undergo additional diagnostic studies or removal of their implanted hardware.

During the first 12 months after diagnosis, the 10 patients required a total of 26 hospitalizations (median, 3 [range, 1–6]) and accumulated 423 days of hospitalization (median, 42 days [IQR, 28–55 days]). Eight patients died within 2 years after diagnosis (median, 38 weeks [IQR, 8–55 weeks]) (Figure 2). Four deaths were considered to be directly attributable to MABC infection; these deaths occurred a median of 18 weeks (range, 4–46 weeks) after diagnosis. Five patients completed antimicrobial therapy with presumed clinical cure and did not have evidence of disease relapse off of therapy; however, 4 of these 5 patients also died during study follow-up, a median of 54 weeks (range, 12–82 weeks) after diagnosis and 28 weeks (range, 6–32 weeks) after completion of antibiotics (Supplementary Table). Only 2 patients were alive at the conclusion of the study, and neither patient had remaining cardiothoracic prosthetic material: patient 9 continued to receive chronic suppressive therapy with azithromycin and tedizolid without evidence of active infection, and patient 10 remained well in the outpatient setting for > 18 months after completing antimicrobial therapy.
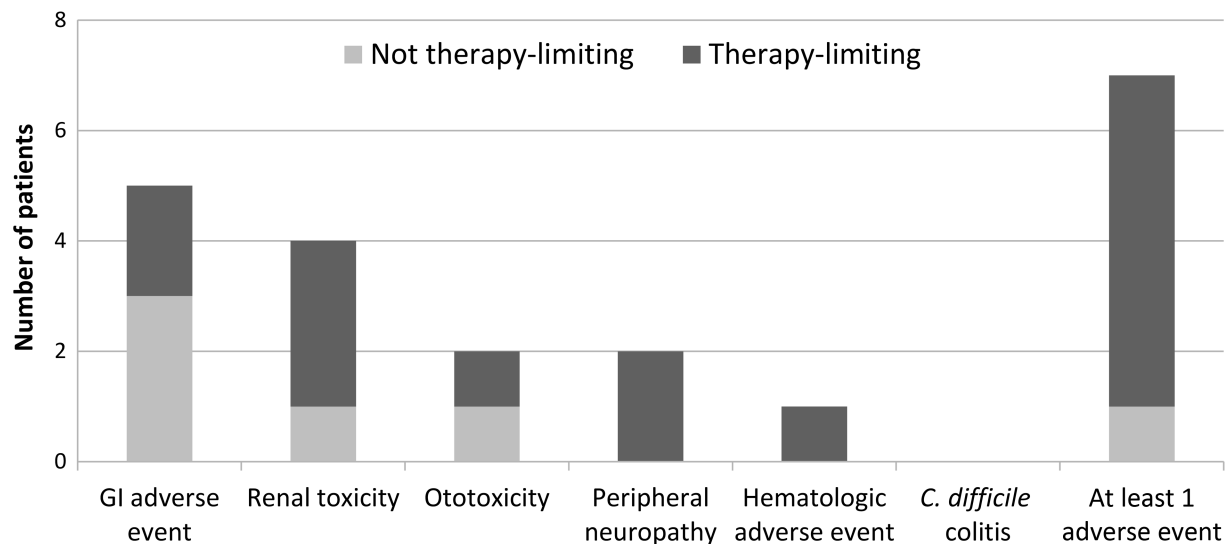
Figure 3. Antibiotic-associated adverse events experienced by 10 cardiac surgery patients treated for invasive *Mycobacterium abscessus* subsp *abscessus* infection. Therapy-limiting adverse events required changes in antibiotic regimen. Gastrointestinal (GI) adverse events consisted of nausea, vomiting, or diarrhea. Both patients with ototoxicity developed hearing loss and tinnitus. The single hematologic adverse event was thrombocytopenia. One patient experienced 2 distinct GI adverse events attributed to different antibiotics; this patient's GI symptoms are represented by a single bar on the figure. Abbreviation: *C. difficile, Clostridioides difficile.*

DISCUSSION

We described the epidemiology, clinical management, and outcomes of 10 cardiac surgery patients who developed invasive MABC infection at a single hospital. All patients were presumed to be infected in the operating room via aerosolization of MABC from HCUs used for cardiopulmonary bypass; incubation periods ranged from 2 days to nearly 1 year. Nearly all patients underwent complex index cardiac surgeries, but preoperative noncardiac comorbidities were uncommon, and no patients were considered to be immunosuppressed.

Clinical recognition and diagnosis of MABC infection was challenging in this cohort of patients. Several patients had serious postoperative complications during index cardiac surgery hospitalizations that were thought to be independent of MABC infection and may have delayed recognition of more subtle presentations of MABC disease. In addition, patients who presented as outpatients with sternal wound infections were often treated with empiric antibiotics for several weeks or months before a diagnosis of MABC was made. Subsequent evaluation of patients who initially had relatively benign-appearing incisional surgical site infections often revealed that these patients actually had disseminated infection with mediastinitis and mycobacteremia. Surgical exploration of the sternum revealed nonpurulent wounds that appeared chronically infected, in contrast to the purulent wounds often seen with infections due to typical bacterial pathogens.

Despite long courses of antimicrobial therapy and aggressive surgical debridement, clinical outcomes in most patients were extremely poor. Patients who did not die shortly after diagnosis typically received >6 months of combination antimicrobial therapy, and most patients required changes in antibiotic regimens due to AEs from amikacin, linezolid, or tigecycline. Eight of 10 patients, including all 7 patients with mycobacteremia, died < 2 years after diagnosis.

Not surprisingly, our experience in managing this cohort of patients suggests that removal of cardiothoracic prosthetic material contaminated with MABC, when feasible, improves odds of successful treatment. One patient who was able to undergo removal of cardiac prosthetic material survived 2-year follow-up; the other surviving patient did not have endovascular hardware.

These cases of MABC infection following cardiac surgery share some similarities with reported cases of HCU-related *M. chimaera* infection [4, 20, 21]. Patients described in both cohorts often presented with nonspecific, subacute symptoms. However, many patients in both cohorts were ultimately found to have disseminated infections involving cardiothoracic prosthetic material, required long courses of combined medical and surgical therapy, and had high mortality rates.

Patients with MABC infection also exhibited notable clinical features that differed from the clinical characteristics of patients with *M. chimaera* infection. First, the interval between cardiac bypass surgery and disease onset was typically several weeks to several months for infections from the rapidly growing MABC, compared to a median of > 1 year for infections due to the slow-growing *M. chimaera* [4, 20, 21]. Also, patients with MABC infection more commonly had sternal wound infections, and,

unlike patients with *M. chimaera* infection, did not have evidence of ocular, bone marrow, or liver involvement. Finally, patients with MABC infection usually required induction therapy with 3 intravenous antibiotics because few oral agents were active against the infecting strain of MABC; prolonged use of combination intravenous antibiotic therapy may have increased risk of antibiotic-associated AEs. In contrast, patients with *M. chimaera* infection often received long courses of combination oral therapy, at times with the temporary inclusion of intravenous amikacin for induction therapy.

Our experience highlights important treatment considerations for invasive MABC disease that merit further study. For example, all isolates in this study represented *M. abscessus* subsp *abscessus* with in vitro *erm* gene–mediated macrolide resistance; however, a number of patients were nonetheless treated with macrolides, in particular oral azithromycin, given poor tolerability of other agents and potential for less *erm* induction by azithromycin compared to clarithromycin [41, 42]. In addition, use of tedizolid to treat or suppress NTM disease has rarely been described, but this agent may have a lower risk of AEs than long-term treatment with linezolid [39]. Similarly, tigecycline may have less gastrointestinal toxicity without decreased effectiveness when given as a once-daily 50-mg dose [40]. While patients in this cohort did not receive clofazimine, bedaquiline, eravacycline, or omadacycline, other clinicians have recently reported success with off-label use of these novel agents when treating refractory NTM infections, including MABC [43–46]. Finally, a recent case study reported successful use of bacteriophage therapy targeting disseminated MABC [47]. If supported by additional clinical data, phage therapy could become a viable treatment option for invasive MABC infection.

To our knowledge, this study represents the largest published cohort of cardiac surgery patients with MABC infection in > 30 years, regardless of mechanism of infection [29]. However, other cardiac surgery outbreaks of invasive MABC have recently occurred, and we suspect that many additional hospitals have also had cases that are not yet reported due to long incubation periods, difficulty in confirming diagnosis, and hesitancy to publish outbreaks. We believe that the clinical analysis provided in this study will provide unique reference to clinicians who investigate potential cases of NTM infection after cardiac surgery, treat confirmed postoperative cases, and manage extrapulmonary invasive MABC disease that occurs in other clinical contexts [24–27]. In particular, our experience should encourage clinicians to consider a diagnosis of invasive NTM infection in postoperative cardiac surgery patients, especially if patients have unexplained fever or sternal wound drainage, and to have a low threshold for performing mycobacterial-specific cultures.

We previously described the clinical characteristics and outcomes of MABC infections in patients with VADs or heart transplants at the time of MABC diagnosis [34, 35]. Clinical features and management strategies used for these patients were unique and distinct from those associated with the cardiac surgery patients described in this cohort. For example, patients with VADs underwent specialized surgical management, including assessment of candidacy for either surgical exposure of the infected VAD pump pocket or heart transplantation. Among heart transplant recipients, prolonged incubation periods of > 300 days were common. Furthermore, clinical management after transplant required careful attention to immunosuppression strategies, including potential for cumulative toxicities related to concomitant exposure to MABC therapy and immunosuppression regimens.

The primary limitations of this study were related to the fact that all patients developed infection in an outbreak setting from the same macrolide-resistant clone of *M. abscessus* subsp *abscessus*. This subspecies is the most common MABC subspecies to cause human disease and typically exhibits *erm* gene–mediated macrolide resistance [42, 48]; nonetheless, patients with invasive infection from other MABC subspecies, or even other strains of *M. abscessus* subsp *abscessus*, may have different presentations and responses to therapy (eg, macrolides may be more effective in treating other MABC isolates). Also, clinicians in our health system had an increased index of suspicion for invasive MABC infection in cardiac surgery patients. Reported incubation time from cardiac surgery to diagnosis may have been longer in a non-outbreak setting.

The worldwide cardiac surgery outbreak of *M. chimaera* has begun to produce important clinical data on extrapulmonary *M. chimaera* infections. However, several major cardiac surgery outbreaks of MABC have also recently occurred, and detailed clinical data have not previously been published. Invasive MABC infections cause substantial morbidity and mortality, and they have clinical presentations and treatment strategies that differ from invasive *M. chimaera* infections. Poor clinical outcomes related to invasive MABC infections emphasize the emerging need for new treatment strategies, including further study of novel antibiotics, and importance of adherence to infection prevention guidelines.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

References

1. Kanamori H, Weber DJ, Rutala WA. Healthcare outbreaks associated with a water reservoir and infection prevention strategies. Clin Infect Dis **2016**; 62:1423–35.

2. Crist MB, Perz JF. Modern healthcare versus nontuberculous mycobacteria: who will have the upper hand? Clin Infect Dis **2017**; 64:912–3.

3. Wallace RJ Jr, Brown BA, Griffith DE. Nosocomial outbreaks/pseudo-outbreaks caused by nontuberculous mycobacteria. Annu Rev Microbiol **1998**; 52:453–90.

4. Kasperbauer SH, Daley CL. *Mycobacterium chimaera* infections related to the heater-cooler unit outbreak: a guide to diagnosis and management. Clin Infect Dis **2019**; 68:1244–50.

5. van Ingen J, Kohl TA, Kranzer K, et al. Global outbreak of severe *Mycobacterium chimaera* disease after cardiac surgery: a molecular epidemiological study. Lancet Infect Dis **2017**; 17:1033–41.

6. Allen KB, Yuh DD, Schwartz SB, et al. Nontuberculous mycobacterium infections associated with heater-cooler devices. Ann Thorac Surg **2017**; 104:1237–42.

7. Dupont C, Terru D, Aguilhon S, et al. Source-case investigation of *Mycobacterium wolinskyi* cardiac surgical site infection. J Hosp Infect **2016**; 93:235–9.

8. Nagpal A, Wentink JE, Berbari EF, et al. A cluster of *Mycobacterium wolinskyi* surgical site infections at an academic medical center. Infect Control Hosp Epidemiol **2014**; 35:1169–75.

9. Greenville Health System. GHS releases preliminary results of investigation. Available at: https://www.ghs.org/healthcenter/ghsblog/ghs-releases-preliminary-results-of-investigation/. Accessed 16 September 2019.

10. Children's Hospital New Orleans. Statement regarding mycobacterial infection investigation. Available at: https://www.chnola.org/blog/2017/september/statement-regarding-mycobacterial-infection-inve. Accessed 5 August 2019.

11. Brasted C. At least 12 patients contract rare infection after Children's Hospital heart surgeries: report. Available at: https://www.nola.com/health/article_4c596d4c-04ab-5d60-89f5-79ecf73f195a.html. Accessed 18 March 2020.

12. Baker AW, Lewis SS, Alexander BD, et al. Two-phase hospital-associated outbreak of *Mycobacterium abscessus*: investigation and mitigation. Clin Infect Dis **2017**; 64:902–11.

13. Marra AR, Diekema DJ, Edmond MB. *Mycobacterium chimaera* infections associated with contaminated heater-cooler devices for cardiac surgery: outbreak management. Clin Infect Dis **2017**; 65:669–74.

14. Kanamori H, Weber DJ, Rutala WA. Healthcare-associated *Mycobacterium chimaera* transmission and infection prevention challenges: role of heater-cooler units as a water source in cardiac surgery. Clin Infect Dis **2017**; 64:343–6.

15. Chand M, Lamagni T, Kranzer K, et al. Insidious risk of severe *Mycobacterium chimaera* infection in cardiac surgery patients. Clin Infect Dis **2017**; 64:335–42.

16. Haller S, Holler C, Jacobshagen A, et al. Contamination during production of heater-cooler units by *Mycobacterium chimaera* potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany, April 2015 to February 2016. Euro Surveill **2016**; 21. doi:10.2807/1560-7917.ES.2016.21.17.30215.

17. Schreiber PW, Sax H. *Mycobacterium chimaera* infections associated with heater-cooler units in cardiac surgery. Curr Opin Infect Dis **2017**; 30:388–94.

18. US Food and Drug Administration. Medical devices. Heater-cooler devices. Information for health care providers and staff at health care facilities. Available at: https://www.fda.gov/medicaldevices/productsandmedicalprocedures/cardiovasculardevices/heater-coolerdevices/ucm492583.htm. Accessed 5 August 2019.

19. Centers for Disease Control and Prevention. Contaminated heater-cooler devices. Available at: https://www.cdc.gov/hai/outbreaks/heater-cooler.html. Accessed 5 Auguest 2019.

20. Scriven JE, Scobie A, Verlander NQ, et al. *Mycobacterium chimaera* infection following cardiac surgery in the United Kingdom: clinical features and outcome of the first 30 cases. Clin Microbiol Infect **2018**; 24:1164–70.

21. Kohler P, Kuster SP, Bloemberg G, et al. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery. Eur Heart J **2015**; 36:2745–53.

22. Tan N, Sampath R, Abu Saleh OM, et al. Disseminated *Mycobacterium chimaera* infection after cardiothoracic surgery. Open Forum Infect Dis **2016**; 3:ofw131.

23. Hamad R, Noly PE, Perrault LP, Pellerin M, Demers P. *Mycobacterium chimaera* infection after cardiac surgery: first Canadian outbreak. Ann Thorac Surg **2017**; 104:e43–5.

24. Novosad SA, Beekmann SE, Polgreen PM, Mackey K, Winthrop KL; *M. abscessus* Study Team. Treatment of *Mycobacterium abscessus* infection. Emerg Infect Dis **2016**; 22:511–4.

25. Lee MR, Sheng WH, Hung CC, Yu CJ, Lee LN, Hsueh PR. *Mycobacterium abscessus* complex infections in humans. Emerg Infect Dis **2015**; 21:1638–46.

26. El Helou G, Viola GM, Hachem R, Han XY, Raad II. Rapidly growing mycobacterial bloodstream infections. Lancet Infect Dis **2013**; 13:166–74.

27. El Helou G, Hachem R, Viola GM, et al. Management of rapidly growing mycobacterial bacteremia in cancer patients. Clin Infect Dis **2013**; 56:843–6.

28. Tejura N, Bontempo G, Chew D. Disseminated *Mycobacterium abscessus* infection secondary to an infected vascular stent: case report and review of the literature. Open Forum Infect Dis **2018**; 5:ofy207.

29. Hoffman PC, Fraser DW, Robicsek F, O'Bar PR, Mauney CU. Two outbreaks of sternal wound infection due to organisms of the *Mycobacterium fortuitum* complex. J Infect Dis **1981**; 143:533–42.

30. Kuritsky JN, Bullen MG, Broome CV, Silcox VA, Good RC, Wallace RJ Jr. Sternal wound infections and endocarditis due to organisms of the *Mycobacterium fortuitum* complex. Ann Intern Med **1983**; 98:938–9.

31. Garcia DC, Nascimento R, Soto V, Mendoza CE. A rare native mitral valve endocarditis successfully treated after surgical correction. BMJ Case Rep **2014**; 2014. doi:10.1136/bcr-2013-202610.

32. Richey LE, Bahadorani J, Mushatt D. Endovascular *Mycobacterium abscessus* infection in a heart transplant recipient: a case report and review of the literature. Transpl Infect Dis **2013**; 15:208–13.

33. Huth RG, Douglass E, Mondy K, Vasireddy S, Wallace RJ Jr. Treatment of *Mycobacterium abscessus* subsp. *massiliense* tricuspid valve endocarditis. Emerg Infect Dis **2015**; 21:535–7.

34. Wolfe CR, Baker AW, Patel CB, et al. *Mycobacterium abscessus* infection in patients with ventricular assist devices. J Heart Lung Transpl **2017**; 36(Suppl 4):S257–8.

35. Maziarz EK, Baker AW, Patel CB, et al. Invasive *Mycobacterium abscessus* infection in heart transplant recipients. J Heart Lung Transpl **2017**; 36(Suppl 4):S25.

36. Vasconcelos KA, Frota SMMC, Ruffino-Netto A, Kritski AL. The importance of audiometric monitoring in patients with multidrug-resistant tuberculosis. Rev Soc Bras Med Trop **2017**; 50:646–51.

37. Kranzer K, Elamin WF, Cox H, Seddon JA, Ford N, Drobniewski F. A systematic review and meta-analysis of the efficacy and safety of *N*-acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB. Thorax **2015**; 70:1070–7.

38. Agyeman AA, Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob **2016**; 15:41.

39. Yuste JR, Bertó J, Del Pozo JL, Leiva J. Prolonged use of tedizolid in a pulmonary non-tuberculous mycobacterial infection after linezolid-induced toxicity. J Antimicrob Chemother **2017**; 72:625–8.

40. Wallace RJ Jr, Dukart G, Brown-Elliott BA, Griffith DE, Scerpella EG, Marshall B. Clinical experience in 52 patients with tigecycline-containing regimens for salvage treatment of *Mycobacterium abscessus* and *Mycobacterium chelonae* infections. J Antimicrob Chemother **2014**; 69:1945–53.

41. Choi GE, Shin SJ, Won CJ, et al. Macrolide treatment for *Mycobacterium abscessus* and *Mycobacterium massiliense* infection and inducible resistance. Am J Respir Crit Care Med **2012**; 186:917–25.

42. Stout JE, Floto RA. Treatment of *Mycobacterium abscessus*: all macrolides are equal, but perhaps some are more equal than others. Am J Respir Crit Care Med **2012**; 186:822–3.

43. Philley JV, Wallace RJ Jr, Benwill JL, et al. Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. Chest **2015**; 148:499–506.

44. McGuffin SA, Pottinger PS, Harnisch JP. Clofazimine in nontuberculous mycobacterial infections: a growing niche. Open Forum Infect Dis **2017**; 4:ofx147.

45. Kaushik A, Ammerman NC, Martins O, Parrish NM, Nuermberger EL. In vitro activity of new tetracycline analogs omadacycline and eravacycline against drug-resistant clinical isolates of *Mycobacterium abscessus*. Antimicrob Agents Chemother **2019**; 63. doi:10.1128/AAC.00470-19.

46. Bax HI, de Vogel CP, Mouton JW, de Steenwinkel JEM. Omadacycline as a promising new agent for the treatment of infections with *Mycobacterium abscessus*. J Antimicrob Chemother **2019**; 74:2930–3.

47. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. Nat Med **2019**; 25:730–3.

48. Choi H, Kim SY, Kim DH, et al. Clinical characteristics and treatment outcomes of patients with acquired macrolide-resistant *Mycobacterium abscessus* lung disease. Antimicrob Agents Chemother **2017**; 61. doi:10.1128/AAC.01146-17.