Original Article

Infections Caused by Rapidly Growing *Mycobacteria* spp in Children and Adolescents With Cancer

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Background. Rapidly growing mycobacteria (RGM) infections in pediatric oncology patients have not been completely characterized.
Methods. We reviewed medical records of oncology patients at St. Jude Children's Research Hospital (St. Jude) from 1990 to 2010 with RGM infections and summarized the results of previously published cases.
Results. Twenty-five St. Jude patients had 27 episodes of infection. Approximately half of the cases occurred in patients with hematological malignancies and in males; infections were more common in white patients. Most patients were not neutropenic or lymphopenic. The most common causative species were *Mycobacterium chelonae*, *Mycobacterium abscessus*, and *Mycobacterium fortuitum*. Most isolates were susceptible to amikacin and clarithromycin; all were susceptible to at least 1 of these. Treatment regimens varied considerably, particularly with respect to the duration of antimicrobial chemotherapy. Two St. Jude patients died; both had pulmonary infections. The literature search identified an additional 58 cases of infection. Localized catheter-associated infections were more common than bloodstream infections in the current series than in previous reports, and outbreaks were not recognized. Otherwise, the demographic and clinical characteristics of patients were similar.
Conclusions. Localized catheter-associated infections were most common in this largest reported single center experience reported to date. Pulmonary infection is uncommon in children but, as in adults, has a high mortality rate. Relatively short-term antimicrobial treatment and surgical debridement of infected tissue, if present, may be as effective for catheter-associated infections as prolonged antimicrobial use and may reduce adverse drug effects in these patients, who are vulnerable to drug-drug interactions and toxicity.

Key words. cancer; infection; mycobacteria; pediatric

Runyon classified rapidly growing mycobacteria (RGM) as those species that form mature colonies on solid agar within 7 days [1, 2]. Exposure to these organisms, which are widely distributed in water and soil, may lead to superficial and invasive infections [1]. There are no robust data on the epidemiology of RGM infection in humans, but many cases have been reported in patients with cancer [2–6]. The optimal type and duration of therapy for these infections has not been definitively established.

Anecdotally, we suspected differences existed in the epidemiology of RGM infections between different geographic regions [3, 7–35]. Some evidence also suggests that differences in underlying malignancies and medical comorbidities between adults and children may influence the nature of RGM infections in these populations, but the type and extent of these differences has not been confirmed [3].

To better understand the complete spectrum of RGM disease in children with cancer, we reviewed the medical records of patients with infections caused by RGM over a 21-year period at our institution and summarized the available epidemiological and clinical information from published reports of RGM infections in pediatric oncology patients.

METHODS

Setting and Study Population

St. Jude Children's Research Hospital (St. Jude) is the nation's only National Cancer Institute-designated pediatric Comprehensive Cancer Center. The medical records of patients < 21 years of age who were treated for RGM infection from January 1990 to December 2010 were reviewed. Demographic and clinical characteristics were abstracted

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from health information records. Fever was defined as an oral temperature >38° C. Neutropenia was defined as an absolute neutrophil count (ANC) <1000/mm^3, and lymphopenia was defined as an absolute lymphocyte count (ALC) <1000 cells/mm^3. The St. Jude Institutional Review Board approved the study with waiver of consent.

Central line-associated infections were defined according to Infectious Diseases Society of America (IDSA) clinical practice guidelines [36]. Pulmonary infections were categorized according to American Thoracic Society (ATS)/IDSA criteria [1]. Disseminated infection was considered to be present, as in other publications, if there were multiple cutaneous abscesses, visceral involvement, or isolation of organisms from blood and clinical evidence of deep infection [37]. Skin and soft tissue infection were defined as the isolation of RGM from wound discharge or biopsy of inflamed soft tissue.

Microbiological specimens were obtained at treating clinicians' discretion. ARUP Laboratories (Salt Lake City, UT) performed blood cultures when sent for mycobacterial culture. Memphis Pathological Laboratory ([MPL] Memphis, TN) performed mycobacterial cultures of specimens from other sites (such as lung) before 2006, and Focus Diagnostics ([FD] Cypress, CA) performed these tests thereafter. Isolates were speciated at reference laboratories or at the Tennessee Department of Health Microbiology Laboratory (Nashville, TN). Susceptibility testing was performed using the broth microdilution method at FD, Mayo Medical Laboratories ([MML] Rochester, MN), or National Jewish Health (Denver, CO). Samples that were sent for routine bacterial culture were processed and stained at the St. Jude Clinical Microbiology Laboratory, and isolates positive by acid-fast staining were sent for both identification and susceptibility testing to MPL (1994–2003), to FD (2003–2009), and to MML thereafter.

Literature Review

We searched the PubMed database for English language articles relating to mycobacterial infections. Additional articles were obtained by reviewing references of retrieved publications. We systematically collected demographic information, the results of diagnostic tests for mycobacterial infection, complete blood count and differentials and diagnostic imaging, the type and duration of therapy, and outcomes of those infections that occurred in children. Studies that included any demographic or clinical features were included.

Statistical Analysis

Statistical analysis was performed using the Stata 9 software package (StataCorp, College Station, TX). Descriptive statistics are presented as numbers and percentages (categorical variables) or median and range (continuous variables). The χ^2, Fisher exact, or Mann-Whitney U tests were used to compare groups. P values $< .05$ (2-tailed test) were considered statistically significant. Rates of infection were estimated as (no. of infections ÷ total no. of patient care days) x 100 000.

RESULTS

Of a total of 8202 cancer patients treated at St. Jude during the study period, 25 developed 27 RGM infections (0.4 cases/100 000 patient days) (Tables 1 and 2). The number of infections ranged from 0 to 4 per year. Two patients had

Table 1. Demographic and Clinical Characteristics of 27 Episodes of RGM Infection in 25 Patients

Characteristic	
Median age, years (range)	3.6 (0.9–17.1)
Male sex, number (%)	15 (56)
Race, number (%)	
White	25 (93)
African-American	2 (7)
Other	0 (0)
Cancer diagnosis, number (%)	
Hematological malignancy	14 (52)
Solid tumor	10 (37)
Brain tumor	3 (11)
Median time since cancer diagnosis, months (range)	9 (0–83)
No. receiving cancer chemotherapy in preceding month (%)	15 (56)
No. receiving other immunosuppressive therapy (%)	2 (7)
No. receiving corticosteroids in preceding month (%)	12 (43)
Median duration of catheter use prior to infection, months (range)	7 (1–23)
Median ANC, cells/mm^3 (range)	1900 (1–12 300)
No. patients with neutropenia (%)	9 (33)
Median ALC, cells/mm^3 (range)	1218 (111–4018)
No. patients with lymphopenia (%)	10 (37)
Type of infection, number (%)	
All catheter-related infections (%)	23 (85)
Disseminated	3 (13)
Disseminated + tunnel	1 (4)
Non-disseminated bacteremia	2 (7)
Non-disseminated bacteremia + tunnel	1 (4)
Exit site infection	8 (30)
Tunnel	6 (26)
TID pocket	2 (7)
Pulmonary	2 (7)
Skin/soft tissue	2 (7)
Causative species, number (%)	
M chelonae	7 (30)
M abscessus	6 (26)
M fortuitum	6 (26)
M fortuitum/chelonae complex	3 (11)
M mucogenicum	2 (8)
M fluoranthenivorans	1 (4)
M immunogenum	1 (4)
M smegmatis	1 (4)

Abbreviations: ANC, absolute neutrophil count; ALC, absolute lymphocyte count; *M*, *Mycobacterium*; TID, totally implantable device.

Table 2. Demographic Characteristics and Laboratory Test Results of 25 Patients With 27 Episodes of Infection Caused by RGM

Episode	Sex/ Age (yrs)	Underlying Conditions	Site of Infection	Type of Catheter	Duration of Catheter Use* (months)	ANC /mm^3	ALC /mm^3	Organism	Antimicrobial Therapy (months)	Adjunctive Therapy	Outcome
1	F/9	RMS	Disseminated (blood, lung)	H2	8	700	170	*M abscessus*	CLAR/AMK x 1; followed by CLAR x 5	CVL removed	Cured
2	F/15	OS	Disseminated (blood, lung)	H1	12	2000	731	*M mucogenicum*	CLAR/IMP x 0.5; followed by CLAR x 5.5	CVL removed	Cured
3	M/2	RB	Probable disseminated (blood, lung)	H1	7	8200	4018	*M chelonae*	CLAR/AMK x 1; followed by CLAR x 4	CVL removed	Cured
4	F/3	EP	Probable disseminated (blood, lung, tunnel)	H2	2	0	432	*M chelonae*	CLAR/CIP x 12	CVL removed	Cured
5	F/3	AML, HSCT	CLABSI	H2	8	12 300	1950	*M mucogenicum*	CLAR x 2	CVL removed	Cured
6	F/3	RB	CLABSI	TID	3	0	0	*M fluoranthenivorans*	CLAR/MER x 1; followed by CLAR/LIN x 2	CVL removed	Cured
7	M/1	AST	CLABSI, tunnel	H2	3	900	550	*M fortuitum*	CLAR/MER x 2	CVL removed	Cured
8	M/3	ALL	TID pocket	TID	6	1500	252	*M fortuitum*	CIP/LIN x 4	CVL removed	Cured
9	M/6	ALL	TID pocket	TID	6	4800	1752	*M abscessus*	CLAR/LIN x 4	CVL removed, debridement	Cured
10	F/5	ALL	Tunnel	H1	8	858	1404	*M abscessus chelonae/fortuitum*	CLAR x 2	CVL removed, debridement	Cured
11	M/2	ALL	Tunnel	H1	7	506	1320	*M chelonae/ fortuitum*	CLAR/AMK x 0.5	CVL removed, debridement	Cured
12	M/5	AML, HSCT	Tunnel	H2	23	6666	1414	*M fortuitum chelonae*	CLAR x 1	CVL removed	Death -progressive AML 6 months after diagnosis
13	M/3	ALL	Tunnel	H1	6	1855	2337	*M chelonae*	CLAR/AMK x 0.5, followed by CIP x 4	CVL removed	Cured
14	M/2	ALL	Tunnel	H1	7	432	1116	*M chelonae/ fortuitum*	CLAR x 6	CVL removed, debridement	Cured
15	F/2	LCH	Tunnel	H1	15	3400	1368	*M chelonae/ fortuitum*	CLAR x 0.5	CVL removed, debridement	Cured
16	M/4	ALL	Exit site	H1	16	4080	900	*M chelonae*	CLAR x 6	CVL removed, debridement	Cured
17	M/2	RB	Exit site	H1	18	5500	NA†	*M immunogenum*	CLAR x 6	CVL removed, debridement	Cured
18	F/5	NB	Exit site	H1	23	1800	448	*M smegmatis*	CLAR x 6	CVL removed, debridement	Death - progressive NB 5 months after diagnosis
19	F/4	ALL	Exit site	H1	3	1610	1715	*M chelonae*	CLAR x 1.5	CVL removed, debridement	Cured
20	M/2	MB	Exit site	H2	6	1900	NA	*M abscessus*	CLAR x 6	CVL removed, debridement	Cured
21	M/4	ALL	Exit site	H1	19	400	902	*M abscessus*	AMK/TMP/SMX x 0.5, followed by TMP/SMX x 2.5	CVL removed, debridement	Cured

22	M/5	ALL	Exit site	H1	7	1900	1596	*M fortuitum*	CLAR/AMK x 1, followed by CLAR x 3	CVL removed	Cured
23	F/17	DES	Exit site	H1	1	4884	737	*M fortuitum*	None	None	Distant soft tissue abscess‡
24	F/18	DES	Surgical wound infection	none		5478	1056	*M fortuitum*	CLAR/CIP + MIIN x 3; followed by CIP + MIN x 3	Debridement	Persistent sinus tract
25	M/1	ALL	Cutaneous	H1	0.5	92	2208	*M chelonae*	CLAR x 2	Debridement	Cured
26	M/16	2° AML, HSCT, BOOP	Pulmonary	H2	19	3200	111	*M chelonae*	LIN/MER/AMK x 0.75	None	Death - respiratory failure 2 months after diagnosis
27	F/13	WT	Pulmonary	none		7500	1632	*M abscessus*	Multiple courses (including CLAR, LIN, AMK, MER) over 42 months	None	Relapse Death - progressive RGM infection 42 months after diagnosis

Abbreviations: ALC, absolute lymphocyte count; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AMK, amikacin; ANC, absolute neutrophil count; AST, astrocytoma; BOOP, bronchiolitis obliterans-organizing pneumonia; CIP, ciprofloxacin; CLABSI, central line-associated bloodstream infection; CLAR, clarithromycin; CVL, central venous line; DES, desmoid tumor; EP, ependymoma; F, female; H1, single lumen Hickman catheter; H2, double lumen Hickman catheter; HSCT, hematopoietic stem cell transplant; IMP, imipenem; LCH, Langerhans cell histiocytosis; LIN, linezolid; M, male; *M*, *Mycobacterium*; MB, medulloblastoma; MER, meropenem; MIN, minocycline; NB, neuroblastoma; OS, osteosarcoma; RB, retinoblastoma; RGM, rapidly growing mycobacteria; RMS, rhabdomyosarcoma; TID, totally implantable device; TMP/SMX, trimethoprim-sulfamethoxazole; WT, Wilm's tumor.

*Duration of catheter use at time of infection.

†Not available.

‡Episode 24.

2 infections each. One previously reported patient had a Hickman catheter exit site infection caused by *Mycobacterium fortuitum,* followed 6 months later by an abdominal surgical site infection caused by the same organism (episodes 23 and 24) [38]. A second child had an *M fortuitum* exit site infection (episode 22) then, 7 months later, a totally implanted device (TID) pocket infection caused by *Mycobacterium abscessus* (episode 9).

Overall, patients were relatively young (median 3.6 years). Infections were equally common in males and females, and approximately half of the patients had hematological malignancies. Infections were disproportionately more common in white patients than other races (93% of patients with RGM infection vs 75% of all patients; $P = .028$). Most patients had received cancer chemotherapy (56%) or other immunosuppressive therapy (11%) within 1 month of onset of their infection. Infections were more common in winter (46%) than in other seasons, but this difference was not statistically significant.

In most cases, the etiology of infections was not immediately suspected and patients received empirical antimicrobial therapy that was not effective against RGM. Overall, 94% of the isolates were susceptible to amikacin, 90% were susceptible to clarithromycin, and all were susceptible to at least 1 of these.

Catheter-Related Infections: Localized Central Venous Line Infections

There were a total of 23 intravascular catheter-related infections in 22 patients in this series (Table 1). The most common forms of infection were localized central venous line (CVL)-associated infections (n = 16; 59%), including 8 exit site, 6 tunnel, and 2 TID pocket infections. The median age of 16 patients with localized infections was 3.7 years of age (range, 1.6–17.1 years). The median time from cancer diagnosis was 10 months (range, 1–32 months); CVL had been placed a median of 7 months previously (range, 1–23 months). Discharge from the catheter site was reported in 12 (71%) of exit or tunnel tract infections; in 10 cases (59%), this discharge was a distinctive green color. Acid-fast stains of pus were obtained in 10 episodes and were positive in 5 cases. The median duration of symptoms prior to diagnosis of catheter-associated infections was 8 days (range, 1–33 days).

One patient with an exit site infection was not treated (episode 23). All other patients had CVL removed and 12 underwent additional surgical debridement. They received antimicrobial therapy (8 combination, 8 clarithromycin only) for a median of 12 weeks (range, 2–26 weeks). Combination therapy, when used, was prescribed for a median of 2 weeks (1–16 weeks). Tunnel tract infections were treated for a median of 4 weeks, exit site infections were treated for 26 weeks, and TID pocket infections were treated for 16 weeks.

Catheter-Related Infections: Bacteremic Infections

There were 7 catheter-associated bloodstream infections (CLABSI), including 4 with disseminated disease (RGM isolated from biopsies of pulmonary nodules and/or blood). Two patients had concurrent tunnel tract involvement. The median age of 7 patients with CLABSI was 3.3 years (range, 1.4–15.3 years); 2 (29%) were male. Infections occurred a median of 8 months after cancer diagnosis (range, 8–37 months); catheters were placed a median of 7 months previously (range, 3–12 months). Fever was reported in 3 of 4 patients with disseminated infections and 2 of 3 patients with uncomplicated bacteremia. All patients had CVL removed and received combination or sequential combination/single-agent antimicrobial therapy for a median of 20 weeks (range, 8–52 weeks). Combination therapy was prescribed for a median of 6 weeks (range, 2–52 weeks). One patient with a concurrent exit site infection underwent surgical debridement. All patients were cured.

Patients with bacteremia were more likely to have solid tumors than those with localized infections (86% vs 0%; $P = .019$) and to be febrile (6% vs 71%; $P = .003$). The proportion of children who had received immunosuppressive therapy within 1 month of infection and who were neutropenic or lymphopenic was similar in the 2 groups. Compared to patients with localized infections, those with CLABSI had lower ANC (median, 900/mm^3 vs 1855/mm^3) and ALC (median, 731/mm^3 vs 1320/mm^3), but these differences were not statistically significant. All patients with localized and bacteremic catheter-associated infections were cured and none relapsed.

Other Infections

A 1-year-old with acute lymphoblastic leukemia developed a slowly enlarging subcutaneous nodule on his thigh (episode 25); *Mycobacterium chelonae* was isolated from a tissue biopsy. After failing to improve with clarithromycin monotherapy, he underwent wide tissue excision; *M chelonae* was again isolated from resected tissue. He recovered after an additional 6 weeks of clarithromycin.

Two patients had primary pulmonary infections (episodes 26 and 27). A 16-year-old patient with secondary acute myelogenous leukemia developed increasing respiratory distress 214 days after hematopoietic stem cell transplant. His transplant was complicated by chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia (BOOP) with cystic bronchiectasis. *Mycobacterium chelonae* was isolated from serial sputum samples. Despite

initiation of antimycobacterial therapy, the patient's sputum cultures remained positive and he died of progressive bronchiolitis obliterans-organizing pneumonia (BOOP) 2½ months after the diagnosis of his infection. A 13-year-old patient with chronic pulmonary cavities resulting from radiofrequency ablation of metastatic Wilm's tumor presented with a several week history of fever and worsening pulmonary infiltrates. *Mycobacterium abscessus* was repeatedly isolated from bronchoalveolar lavage fluid. Exacerbations of the patient's lung disease were treated with combination antimycobacterial therapy, but she died of progressive respiratory insufficiency 42 months later. Recognition of infection in both of these patients was delayed (time from onset of symptoms 3.4 and 6.7 weeks, respectively). Their deaths were the only ones attributable to RGM infection in this series.

Literature Review

An additional 58 cases of RGM infections in pediatric oncology patients were reported in 27 articles published between 1983 and 2012 [7, 9–14, 16–18, 21–27, 30–35, 39–42]. Most were small case series (describing 1–11 patients). Including patients in this report, there were a total of 85 infections, including 18 disseminated infections, 42 uncomplicated CLABSI, 17 exit site, 6 tunnel, and 2 TID pocket infections (Table 3). Thirteen (31%) CLABSIs were associated with nosocomial outbreaks [15, 17, 25]. The demographic and clinical characteristics of previously reported cases were similar to those in this series, except that localized catheter-associated infections were uncommon and *Mycobacterium mucogenicum* infections were more frequent.

All patients with disseminated infections had CVL removed and received antimicrobial therapy (2 single agent, 10 combination, and 6 sequential) for a median duration of 6 weeks (range, 1–52 weeks). Fifteen patients (83%) were cured. Treatment failures occurred in an *M abscessus* infection treated with combination therapy for an unspecified duration of time, an *M chelonae* infection treated with imipenem for 1 week, and an *M fortuitum* infection treated with combination therapy for 26 weeks.

Most patients with uncomplicated CLABSI (39 of 42; 93%) had CVL removed. Antimycobacterial therapy was prescribed for 31 (74%) patients (7 single agent, 15 combination, and 3 sequential) for a median of 4 weeks (range, 1 day–24 weeks). All patients improved but 4 relapsed, including 2 untreated patients, 1 whose CVL was removed but did not receive antimicrobial therapy and 1 whose CVL was removed and who received 4 weeks of combination antimicrobial therapy. In a univariable analysis, cure was associated with CVL removal (odds ratio [OR], 37.00; 95% confidence interval [CI], 2.27–602.68; $P = .011$) and antimicrobial therapy (OR, 11.25; 95% CI, 1.03–123.24; $P = .048$). When controlled for antimicrobial therapy, catheter removal remained significantly associated with cure (OR, 25.68; 95% CI, 1.17–562.69).

No additional tunnel or TID pocket infections were identified. Most patients with exit site infections (15 of 17; 88%) had CVL removed and 8 of 17 (47%) had additional surgical debridement. Sixteen patients received antimicrobial therapy (7 single agent, 7 combination, and 2 sequential) for a median of 6 weeks (range, 2–24 weeks). All patients improved and 8, who underwent CVL removal, local debridement, and received antimicrobial therapy, were cured. Two of 7 patients who had CVL removal and received antimicrobial therapy, but not local debridement, relapsed, as did an untreated patient and another who had CVL removal but not local debridement or antimicrobial therapy. Cure was significantly associated with CVL removal (OR, 6.50; 95% CI, 1.47–28.80; $P = .014$) and antimicrobial therapy (OR, 4.33; 95% CI, 1.23–15.2; $P = .022$). The median duration of antimicrobial therapy in patients who did not relapse was 12 weeks (range, 2–26 weeks).

DISCUSSION

This series represents the largest single center experience with RGM infections in pediatric oncology patients reported to date. The overall incidence of RGM infections at St. Jude is somewhat lower than that reported in the only other population-based study (2.9 cases per 100 000 patient-days) [3], and localized infectious complications of CVL were diagnosed more commonly in our population and bacteremia and pulmonary infections less commonly than in previous reports [2–5, 8, 11, 20–22, 24, 28, 29, 31, 35, 39]. Contamination of CVL or dressings may predispose to local infections; breaks in hygiene may be more likely to occur in the relatively young patients in the current series. There may also be qualitative differences in patients' environmental exposure to RGM across different geographical regions. Numbers and types of *Mycobacteria* spp colonizing showerhead biofilms, for example, vary greatly across the United States [43]. The relatively late onset of RGM infections relative to cancer diagnosis may reflect increasing exposure to environmental sources of RGM, both in healthcare settings or, as patients become healthier, through activities that bring them in contact with soil and water.

A recent review of RGM infections in cancer patients found almost half of adults with these infections who

Table 3. Demographic and Clinical Characteristics of Patients During 85 Episodes of Catheter-Related RGM Infection, According to Type of Infection*

	Disseminated (n = 18)	CLABSI (n = 42)	Exit Site (n = 17)	Tunnel Tract (n = 6)	TID pocket (n = 2)
Median age, yrs (range)	4.5 (2–18)	4.5 (0–18)	4 (1–17)	1.5 (1–4)	1.5 (1–2)
Male sex (%)	12 of 17 (71)	24 of 42 (57)	10 of 17 (59)	4 of 6 (67)	2 of 2 (100)
Hematological malignancy (%)	10 of 17 (59)	23 of 41 (56)	13 of 16 (81)	6 of 6 (100)	2 of 2 (100)
HSCT (%)	4 of 17 (24)	9 of 42 (21)	1 of 16 (6)	0 of 6 (0)	0 of 2 (0)
Neutropenia (%)	1 of 11 (9)	19 of 30 (63)	2 of 16 (13)	1 of 6 (17)	0 of 2 (0)
Lymphopenia (%)	8 of 14 (57)	23 of 27 (85)	4 of 7 (57)	0 of 6 (0)	1 of 2 (50)
Causative species					
M chelonae	9 of 18 (50)	6 of 42 (14)	6 of 17 (35)	1 of 6 (17)	0 of 2 (0)
M abscessus	2 of 18 (11)	0 of 42 (0)	2 of 17 (13)	0 of 6 (0)	1 of 2 (50)
M chelonae-abscessus	1 of 18 (6)	1 of 42 (2)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M fortuitum	2 of 18 (11)	10 of 42 (24)	7 of 17 (41)	1 of 6 (17)	1 of 2 (50)
M fortuitum/chelonae complex	0 of 18 (0)	0 of 42 (0)	0 of 17 (0)	4 of 6 (67)	0 of 2 (0)
M fluoranthenivorans	0 of 18 (0)	1 of 42 (2)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M immunogenum	0 of 18 (0)	1 of 42 (2)	1 of 17 (6)	0 of 6 (0)	0 of 2 (0)
M mucogenicum	2 of 18 (11)	16 of 42 (38)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M smegmatis	0 of 18 (0)	0 of 42 (0)	1 of 17 (6)	0 of 6 (0)	0 of 2 (0)
M aurum	1 of 18 (6)	0 of 42 (0)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M neoaurum	0 of 18 (0)	4 of 42 (10)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M aurum/neoaurum	1 of 18 (6)	0 of 42 (0)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M lacticola	0 of 18 (0)	1 of 42 (2)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M septicum	0 of 18 (0)	1 of 42 (2)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
M hackensackense	0 of 18 (0)	1 of 42 (2)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
Treatment					
Catheter removal	18 of 18 (100)	39 of 42 (93)	15 of 17 (88)	6 of 6 (100)	2 of 2 (100)
Local debridement	0 of 18 (0)	0 of 42 (0)	8 of 17 (47)	4 of 6 (67)	2 of 2 (100)
Antimicrobial	17 of 18 (94)	31 of 42 (74)	16 of 17 (94)	6 of 6 (100)	2 of 2 (100)
Combination	10 of 18 (56)	15 of 31 (48)	7 of 16 (44)	1 of 6 (17)	2 of 2 (100)
Sequential	6 of 18 (33)	3 of 31 (10)	2 of 16 (13)	1 of 6 (17)	0 of 2 (0)
Monotherapy	2 of 18 (12)	7 of 31 (23)	7 of 16 (44)	4 of 6 (67)	0 of 2 (0)
Median duration antimicrobial therapy (weeks)	6 (1–52)	4 (0.1–24)	7 (2–24)	16 (2–26)	16 (16)
Overall cure	16 of 18 (94)	41 of 42 (98)	16 of 17 (94)	6 of 6 (100)	2 of 2 (100)
Relapse	2 of 18 (12)	2 of 42 (5)	3 of 17 (18)	0 of 6 (0)	0 of 2 (0)
Mortality	1 of 18 (6)	1 of 42 (2)	0 of 17 (0)	0 of 6 (0)	0 of 2 (0)
References	[11, 16, 23, 27, 31, 33, 34, 42]	[7, 9, 11–14, 17, 18, 22–27, 30–32, 35, 40, 41]	[10, 21, 24, 39]	Current report	Current report

Abbreviations: CLABSI, central line-associated bloodstream infection; HSCT, hematopoietic stem cell transplant; *M*, *Mycobacterium*; RGM, rapidly growing mycobacteria; TID, totally implantable device.
*Includes patients in present series.

were cared for at a large cancer center had pulmonary disease [3]. Our experience confirms that pulmonary infection is less common in children than in adults but may be as severe as in adults, in whom mortality rates of almost 50% have been described [3]. It has been suggested that high rates of underlying pulmonary comorbidities, such as chronic obstructive pulmonary disease, contribute to the increased incidence of pulmonary infection in older patients [3]. Consistent with this hypothesis, both patients with pneumonia in this series had serious underlying structural lung disease (BOOP and pulmonary cavities).

Delayed recognition of RGM infection was common in this series. If present, green exit site discharge may be an important clue to the etiology of infections. Only 50% of patients had acid-fast stains obtained on exit site discharge, but many that were performed were positive. Our experience suggests that the early recognition of RGM CLABSI is challenging and clinicians must maintain a high index of suspicion for these pathogens. Although most patients were febrile, several had only intermittent low-grade fever and none appeared unwell. Respiratory symptoms were mild or absent, even in patients with extensive pulmonary disease.

The optimal treatment for RGM infections and risk factors for treatment failure are not clear [1]. This review suggests that treatment of these infections is highly variable, both within our own and across different institutions. There are no formal recommendations for therapy of RGM CLABSI, but El Helou et al [44] suggest that uncomplicated bloodstream infections should be treated by catheter removal and a minimum of 4–8 weeks of combination antimicrobial therapy. This strategy appears reasonable for pediatric oncology patients—38 of 39 patients across all studies who were treated in this manner were cured. Likewise, more than 80% of patients with disseminated RGM infections have been cured by catheter removal and at least 20 weeks of combination or sequential antimicrobial therapy. Combination antimycobacterial therapy is recommended, at least initially, because of reports of the rapid emergence of resistance to macrolides and ketolides, resulting from single point *23S rRNA peptidyltransferase* mutations, in patients with *M abscessus*, *M chelonae*, and *M fortuitum* infections who are receiving macrolide monotherapy [45, 46].

Some healthcare practitioners in our institution who were informally surveyed indicated that, in the absence of formal guidance, they treated patients with local catheter-associated infections according to ATS guidelines for skin and soft tissue infections caused by *M abscessus*, *M chelonae*, and *M fortuitum* (adjunctive surgical debridement for "extensive disease, abscess formation, or where drug therapy is difficult," and a minimum of 4 months of combination or sequential antimicrobials) [1]. The strong association of local debridement with cure implies that many or most patients with these infections, as previously suggested, would benefit from this adjunctive therapy [10]. Our data also suggest that, despite patients' compromised immunity, a shorter duration of antimicrobial therapy than recommended may be effective, particularly for patients who have undergone surgical debridement. Significant drug interactions exist between some antimycobacterials (eg, clarithromycin) and chemotherapeutic agents, and others (eg, amikacin) have a greater potential for toxicity when coadministered with cancer chemotherapy. It seems prudent to limit the duration of antimycobacterial therapy when this is feasible for these reasons alone.

This study is subject to the usual limitations of retrospective studies, particularly reporting bias. Because treating physicians rarely described their clinical reasoning, it is also not possible to ascertain whether a particular treatment regimen was advocated because of the severity of mycobacterial infection, the nature of patients' underlying malignancy, and immunological status or clinicians' own uncertainty regarding the adequacy of therapy. Older methods of identifying RGM, such as biochemical tests and mycolic acid pattern analysis, have proven insufficiently sensitive to differentiate between closely related species and subspecies and have largely been supplanted by nucleic acid amplification and matrix-assisted laser desorption ionization time-of-flight mass spectrometry [47, 48]. The identification of causative species in cases published before the introduction of these more sensitive tests may be less reliable than that of more recent reports. The role of *Mycobacterium aurum* in human disease, for example, has been challenged because many or all strains may, in fact, belong to the *Mycobacterium neoaurum-Mycobacterium lacticola* relatedness group [49]. Furthermore, the taxonomic status of RGM continues to evolve and, in some cases, remains controversial [34, 50]. A major strength of this study is inclusion of a large number of patients, all of whom had long-term follow-up (0.5–10 years).

In summary, we describe the largest single center experience with RGM infections in pediatric oncology patients reported to date. Localized catheter-associated infections were the most common form of infection in this series, whereas bacteremic infections have dominated previous pediatric series. Mortality in this series was limited to patients with pneumonia, but all infections were associated with considerable morbidity. Although catheter removal and antimicrobial therapy seem necessary for resolution of RGM infections, the optimal duration of antimicrobial treatment remains uncertain, particularly for localized catheter infections.

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