Rapidly Growing Mycobacteria

Clinical and Microbiologic Studies of 115 Cases

Xiang Y. Han, MD, PhD,[1] Indra Dé, MD, PhD,[1] and Kalen L. Jacobson, MD[2]

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Abstract

We analyzed clinical and microbiologic features of 115 cases involving rapidly growing mycobacteria (RGM) isolated at the University of Texas M.D. Anderson Cancer Center, Houston (2000-2005) and identified by 16S ribosomal RNA gene sequencing analysis. At least 15 RGM species were included: Mycobacterium abscessus *(43 strains [37.4%]),* Mycobacterium fortuitum *complex (33 strains [28.7%]), and* Mycobacterium mucogenicum *(28 strains [24.3%]) most common, accounting for 90.4%. Most* M abscessus *(32/43) were isolated from respiratory sources, whereas most* M mucogenicum *(24/28) were from blood cultures. Antimicrobial susceptibility tests showed that* M abscessus *was the most resistant species;* M mucogenicum *was most susceptible. From blood and catheter sources, 46 strains (40.0%) were isolated; 44 represented bacteremia or catheter-related infections. These infections typically manifested high fever (mean temperature, 38.9°C), with a high number of RGM colonies cultured. All infections resolved with catheter removal and antibiotic therapy. Six strains (*M abscessus *and* M fortuitum *only) were from skin, soft tissue, and wound infections. There were 59 strains from respiratory sources, and 28 of these represented definitive to probable infections. Prior lung injuries and coisolation of other pathogenic organisms were common. Overall, 78 RGM strains (67.8%) caused true to probable infections without direct deaths.*

Mycobacterium is probably the best-studied bacterial genus and currently contains more than 100 species.[1,2] Several reasons account for this: *Mycobacterium tuberculosis* is one of the oldest and most common causes of infection and death worldwide; *Mycobacterium avium* frequently causes bloodstream infection in patients with AIDS[3]; the spectrum of pathogenicity varies widely across the species, from strict pathogens to essentially nonpathogens[4]; the niches and reservoir are diverse, from human to animal to environmental[5-7]; all species are characteristically stained as acid-fast bacilli (AFB); and all disease-causing species elicit granulomatous tissue reactions.

Rapidly growing mycobacteria (RGM) are the Runyon group IV organisms that usually form colonies within 7 days of incubation as opposed to slow-growing mycobacteria, ie, Runyon groups I, II, and III and the *M tuberculosis* complex group, that require longer incubation. RGM have emerged as significant human pathogens, causing various infections in healthy and immunocompromised hosts. Although the general recognition of RGM can be made with confidence, further species identification has been difficult, particularly by biochemical methods, as with many nontuberculous slow growers.

As a result of the widespread use of 16S ribosomal RNA (rRNA) gene sequencing, more than 50 new *Mycobacterium* species have been described since 1990.[1,2,8] Many clinical and reference laboratories worldwide, including ours, have adopted the 16S sequencing method to routinely identify various mycobacteria[9-15] to improve turnaround time and accuracy. In this study, we analyzed the microbiologic and clinical features of 115 RGM strains.

Materials and Methods

Study Setting and Patients

The RGM strains were consecutive (sporadic) isolates from January 2000 to December 2005 at the University of Texas M.D. Anderson Cancer Center, Houston, a 500-bed comprehensive cancer center. Most patients with RGM isolates had a primary diagnosis of cancer. Anticancer chemotherapy often required use of indwelling central venous catheters (CVCs).

Cultures for Bacteria and RGM

Blood cultures were performed using the BACTEC 9240 Plus aerobic/F bottles (BD Diagnostic Systems, Sparks, MD) and Isolator tubes (Wampole Laboratories, Princeton, NJ). BACTEC bottles were incubated for 7 days at 37°C with aeration. Isolator tubes were incubated for 4 days at 37°C with 5% carbon dioxide, and these cultures allowed quantitation of bacterial colonies.[16] Approximately 30,000 blood cultures were performed annually in the institution.

Cultures for mycobacteria followed standard techniques and were incubated for 8 weeks.[4] Sterile specimens were inoculated into media directly, whereas nonsterile specimens from the respiratory tract and others sources were decontaminated first by treatment with a mucolytic agent (*N*-acetylcysteine) and alkaline (sodium hydroxide). Culture media included the Lowenstein-Jensen tube and the BacT/Alert MB liquid medium (BioMerieux, Durham, NC). The culture of nonsterile specimens was supplemented with amphotericin B and nalidixic acid in the liquid medium to inhibit molds and non-AFB.

Species Identification

All RGM were identified through sequencing analysis of the 16S rRNA gene as described previously.[10] The method amplified and sequenced the first 650 base pairs of the gene. The sequences were queried to the GenBank,[17] and the best sequence matches (99.5%-100%) to a type strain yielded species identification. For the *Mycobacterium fortuitum* complex, the sequences could not distinguish the following very closely related species, some of which were newly described[2]: *Mycobacterium peregrinum* vs *Mycobacterium septicum*, *Mycobacterium farcinogenes* vs *Mycobacterium senegalense*, and among the *Mycobacterium porcinum* group (*M porcinum*, *Mycobacterium bonickei*, *Mycobacterium houstonense*, and *Mycobacterium neworleansense*). Within our sequenced region, *Mycobacterium chelonae* and *Mycobacterium abscessus* also had identical sequences; to differentiate them, an additional downstream 500 base pairs were amplified and sequenced,[10] which separated the 2 species by 3 nucleotides.

Susceptibility Tests

The in vitro antimicrobial susceptibility of these RGM was tested using the broth dilution method at a reference laboratory (Focus Technologies, Cypress, CA). The results were collected prospectively and interpreted according to the criteria established by the Clinical Laboratory Standards Institutes (formerly National Committee for Clinical Laboratory Standards), which apply to the vast majority of RGM.[18]

Clinical Assessment and Definitions

The criteria established by American Thoracic Society,[19] along with our previous experience,[20] were used to categorize the clinical significance of RGM infections as definitive, probable, possible, or contamination. When a copathogen was isolated, a judgment was made of the relative significance of each organism according to its typical pathogenicity and clinical characteristics.

Catheter-related infections were judged according to published guidelines.[21] Exit-site or pocket infections met clinical and microbiologic criteria, including inflammation-associated signs and symptoms with or without concomitant bacteremia and fever and isolation of mycobacteria from exudates or fluid at the catheter site.

Data Analysis

When appropriate, statistical analyses were performed by using the χ^2 test or Fisher exact method.

Results

Prevalence, Species, and Isolation Sources

The 115 RGM strains (from 115 patients) accounted for 22.6% (115/508) of all mycobacterial strains isolated during the 6 years. The RGM prevalence rate was 1.24% of patients who had cultures (115/9,240).

These strains encompassed at least 15 species, and the distribution is shown in **Table 1**. *M abscessus*, *M fortuitum* complex, and *Mycobacterium mucogenicum* were the most common species, accounting for 43 (37.4%), 33 (28.7%), and 28 (24.3%) strains, respectively, or together 90.4%. Others included *Mycobacterium neoaurum* and closely related "*Mycobacterium lacticola,*" *Mycobacterium cosmeticum*, *Mycobacterium goodii*, *Mycobacterium canariasense*, *Mycobacterium brumae*, *Mycobacterium mageritense*, and unnamed organisms that matched best with *M mucogenicum* (526/534 nucleotides [98.5%]) and *M neoaurum* (607/623 [97.4%]).

The *M fortuitum* complex included *M fortuitum, M peregrinum* or *M septicum* (not distinguished in this study), *M porcinum* group (*M porcinum, M bonickei, M houstonense,* and *M neworleansense*) (not distinguished), *M brisbanense,* and *M farcinogenes* or *M senegalense* (not distinguished).

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Table 1
Species Identification and Isolation Sources of 115 Rapidly Growing Mycobacteria

Species	No. of Cases	Blood	Airway	Blood and Airway	Other
Mycobacterium abscessus	43	6	30	2	Blood and skin, 1; skin, 2; ascites, 1; CSF shunt, 1
Mycobacterium mucogenicum	28	24	4	0	
Mycobacterium fortuitum complex					
Mycobacterium fortuitum	14	5	5	1	Wound, 2; CVC tip and wound, 1
Mycobacterium peregrinum or *Mycobacterium septicum*[*]	8	1	7	0	
Mycobacterium porcinum group[†]	5	1	4	0	
Mycobacterium brisbanense	3	1	1	0	Skin, 1
Mycobacterium farcinogenes or *Mycobacterium senegalense*[*]	3	1	1	0	Gallbladder, 1
Mycobacterium neoaurum group[‡]	4	4	0	0	
Mycobacterium cosmeticum	2	1	1	0	
Mycobacterium goodii	1	0	1	0	
Mycobacterium canariasense	1	0	1	0	
Mycobacterium brumae	1	1	0	0	
Mycobacterium mageritense	1	0	1	0	
Mycobacterium mucogenicum–like	1	0	1	0	
Total	115	45	57	3	10

CSF, cerebrospinal fluid; CVC, central venous catheter; rRNA, ribosomal NA.
[*] Identical sequenced region of the 16S rRNA gene, not distinguished in this study.
[†] Includes *M porcinum*, *Mycobacterium bonickei*, *Mycobacterium houstonense*, and *Mycobacterium neworleansense* that differ by 0 to 2 nucleotides in 16S rRNA genes. They were not distinguished in the study.
[‡] Includes 2 strains of *M neoaurum*, 1 strain of "*Mycobacterium lacticola*," and 1 strain of a *M neoaurum*–like organism.

As shown in Table 1, the sources of these RGM included 57 (49.6%) strains from the respiratory samples, 45 (39.1%) strains from blood, 6 strains from skin tissue or wound, 3 strains from the blood and respiratory tract simultaneously, 1 strain from wound and catheter tip simultaneously, and 1 each from ascites, cerebrospinal fluid (CSF), and gallbladder. All 45 blood isolates were cultured using routine aerobic blood cultures.

M abscessus was isolated significantly more from the respiratory tract (32/43 [74%] with 2 double sources) than all other strains (28/72 [39%] with 1 double source counted) (χ^2 = 13.6; $P < .001$). Conversely, most *M mucogenicum* strains were from blood (24/28 [86%]), far more common than all other strains (25/87 [29%] with 4 double sources counted) (χ^2= 28.1; $P < .001$), even when the dominant respiratory *M abscessus* strains were excluded (16/44 [36%]) (χ^2= 16.9; $P < .001$). *M fortuitum* complex strains were from diverse sources. These differences suggest different biologic behavior on the part of these organisms, such as possible tissue "tropism," ie, *M abscessus* for respiratory tract and *M mucogenicum* for blood and catheter.

Susceptibility to Antibiotics

The antimicrobial susceptibility was determined in 105 of 115 strains; the results are shown in **Table 2**. Amikacin was the antibiotic with least resistance, with only 2 *M abscessus* strains intermediately susceptible or resistant; all others were susceptible. The susceptibility of other antibiotics varied considerably among species.

For the 40 *M abscessus* strains, all but 1 (98%) were also susceptible to clarithromycin, and 30 (75%) were susceptible or intermediately susceptible to cefoxitin. However, few strains (<20%) were susceptible to ciprofloxacin, trimethoprim-sulfamethoxazole (TMP-SMZ), and minocycline.

For the 31 *M fortuitum* complex strains, all were susceptible to ciprofloxacin, 25 (81%) were susceptible to imipenem, and 22 (71%) were susceptible to TMP-SMZ. The susceptibility to cefoxitin and clarithromycin varied among the component species: only 1 (7%) of the 14 *M fortuitum* strains was susceptible to cefoxitin in comparison with 11 (65%) of the 17 other *M fortuitum* complex strains (P = .001; Fisher exact test); similarly, 4 (29%) of the 14 *M fortuitum* strains were susceptible to clarithromycin, compared with 13 (76%) of the 17 other strains (P = .009). The susceptibility rates to doxycycline and minocycline were less than half of the strains tested.

All 25 *M mucogenicum* strains were susceptible to cefoxitin, clarithromycin, imipenem, and TMP-SMZ. In addition, 22 strains (88%) were susceptible to ciprofloxacin, and approximately half of the tested strains were susceptible to doxycycline and minocycline. The susceptibility patterns of the remaining 7 RGM species (strains) were similar to those of *M mucogenicum*. Overall, *M mucogenicum* was the most susceptible RGM species.

General Clinical Features

The 115 patients included 66 men and 49 women with a median age of 56.5 years (range, 12-82 years). The underlying diseases included hematologic cancers (54/115 [47.0%]), solid

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Table 2
Antimicrobial Susceptibility of 105 Rapidly Growing Mycobacteria

		Strains Tested																								
		All															Some									
		Amikacin			Cefoxitin			Ciprofloxacin			Clarithromycin			Imipenem			TMP-SMZ*			Doxycycline				Minocycline			
Mycobacterium Species	No.	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	R	NT	S	I	R	NT	S	I	R	NT
abscessus	40	38	1	1	6	24	10	3	6	31	39	0	1	7†	24†	9†	5	26	9	2	1	2	35	2	3	30	5
mucogenicum	25	25	0	0	25	0	0	22	3	0	25	0	0	25	0	0	25	0	0	6	2	1	16	7	2	7	9
fortuitum	14	14	0	0	1	12	1	14	0	0	4	1	9	11	2	1	8	6	0	2	0	2	10	4	2	5	3
peregrinum or *septicum*	6	6	0	0	5	1	0	6	0	0	6	0	0	5	1	0	5	1	0	0	0	0	6	0	4	2	0
porcinum group	5	5	0	0	4	1	0	5	0	0	3	1	1	4	1	0	3	2	0	0	0	3	2	0	1	1	3
brisbanense	3	3	0	0	1	1	1	3	0	0	3	0	0	2	0	1	3	0	0	2	0	0	1	0	1	0	2
farcinogenes or *senegalense*	3	3	0	0	1	1	1	3	0	0	1	1	1	3	0	0	3	0	0	0	0	1	2	0	0	0	3
neoaurum group	3	3	0	0	3	0	0	3	0	0	2	1	0	3	0	0	3	0	0	0	0	0	3	2	1	0	0
cosmeticum	1	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	1
goodii	1	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0	0	1	0
canariasense	1	1	0	0	0	1	0	1	0	0	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	1	0
brumae	1	1	0	0	0	0	1	1	0	0	1	0	0	0	0	1	1	0	0	0	0	0	1	1	0	0	0
mageritense	1	1	0	0	1	0	0	1	0	0	0	0	1	1	0	0	1	0	0	0	0	0	1	0	1	0	0
mucogenicum–like	1	1	0	0	0	1	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	1	1	0	0	0
Total	105	103	1	1	49	42	14	65	9	31	87	4	14	65	28	12	61	35	9	13	3	9	80	17	15	47	26

CLSI, Clinical and Laboratory Standards Institute; I, intermediately susceptible; NT, not tested; R, resistant; S, susceptible; TMP-SMZ, trimethoprim-sulfamethoxazole.
* Interpretative category "Intermediate" is not indicated in the CLSI for TMP-SMZ.
† The CLSI recommends that imipenem results should not be reported for *M abscessus* because of problems with reproducibility and interpretation. The data are listed for completeness.

tumors (57/115 [49.6%]), and noncancer diagnoses (4/115 [3.5%]). Of the patients, 46 (40.0%) underwent chemotherapy 1 month or less before isolation of the organism. Profound neutropenia (absolute neutrophil count, ≤500/μL [0.5×10^9/L) was present in 25 patients (21.7%) within a week before or after culture. More than half of the patients (63/115 [54.8%]) had active cancer at the time of recovery of RGM. In 45 patients (39.1%), there were other underlying conditions, some overlapping with cancer, such as graft-vs-host disease, chronic obstructive pulmonary disease (COPD), diabetes, heart disease, and HIV infection. Concurrent steroid use was found in 22 patients (19.1%). Of the 115 patients, 45 (39.1%) were taking antibiotics before isolation of RGM.

All except 8 patients had symptoms that included fever, cough, chills, shortness of breath, tender wound or central venous catheter (CVC) site, or skin lesions. Nonspecific or overlapping symptoms also existed. Absence of symptoms was most likely due to prior or concurrent antibiotic or steroid use. Six patients did not receive any antibiotic treatment because of resolution of symptoms before culture results were obtained. The duration of therapy varied widely among the patients, from 2 weeks to 2 years, but mostly was 2 to 4 weeks. Whenever possible, patients were treated with specific antibiotics based on susceptibility results; clarithromycin was usually included.

The 115 patients were categorized into the following groups according to the sites of infection: 1, bloodstream and catheter-related infections; 2, skin tissue and wound infections; and 3, respiratory tract infections. In addition, 3 patients had RGM isolated from unusual sites, ie, ascites with associated peritonitis and concurrent isolation of *M abscessus* and *Staphylococcus aureus*, *M abscessus* from a CSF shunt, and *M farcinogenes* (or *M senegalense*) from the gallbladder. The latter 2 cases had insufficient data to suggest infection. Overall, 78 RGM strains (67.8%) caused true to probable infections.

Group 1: Bloodstream and Catheter-Related Infections

In 45 patients (39.1%), RGM were isolated from blood that was drawn through the catheter or a peripheral vein or both, and 1 patient had RGM from the catheter tip and exit wound **Table 3**. Of these 46 cases, *M mucogenicum* accounted for most (24/46 [52%]), followed by *M abscessus* (6 cases), *M fortuitum* (6 cases), *M neoaurum* group (4 cases), and 1 case each of the *M porcinum* group, *M farcinogenes* (or *M senegalense*), *M peregrinum*, *M brumae*, *M cosmeticum*, and *M brisbanense*. With doubtful clinical significance in only 2 cases, ie, 1 with *M mucogenicum* isolated from peripheral blood and 1 with *M cosmeticum* from autopsy blood, all other 44 cases were significant infections. The bacteriologic and clinical data for the 44 cases are shown in Table 3 and **Table 4**.

Nineteen cases met the definition of catheter-related bloodstream infection with positive paired CVC and peripheral blood cultures. With 1 of the paired cultures negative or not

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Table 3
Rapidly Growing Mycobacteria Species Causing Catheter-Related Infections (n = 44)*

Species	No. of Strains	Positive Blood Drawn From		
		Catheter	Periphery	Both
Mycobacterium mucogenicum	23	10	4	9
Mycobacterium abscessus	6	3	2	1
Mycobacterium fortuitum	6	3†	0	3
Mycobacterium neoaurum group	4	0	1	3
Mycobacterium farcinogenes or *Mycobacterium senegalense*	1	1	0	0
Mycobacterium peregrinum or *Mycobacterium septicum*	1	1	0	0
Mycobacterium porcinum group	1	0	0	1
Mycobacterium brisbanense	1	0	0	1
Mycobacterium brumae	1	0	0	1
Total	44	18	7	19

* Two probable contaminants (see text), *Mycobacterium cosmeticum* and *Mycobacterium mucogenicum*, are not listed.
† Including 1 case from the catheter tip only with exit site infection.

drawn, 18 cases were positive for CVC blood and 7 for peripheral blood. One case (with *M fortuitum*) was positive only for removed catheter tip after a febrile episode with exit-site infection (blood not drawn) (Table 3). Clinically, 40 of 44 cases had a fever (mean temperature, 38.9°C; range, 37.5°C-40°C) with associated chills in 7 cases, inflamed CVC or Port-A-Cath (Smiths Medical, St Paul, MN) exit site in 5 cases, and skin granuloma on biopsy (but negative culture) in 1 case by *M abscessus* (double-source infections detailed separately in subsequent text). The 4 nonfebrile cases were all caused by *M mucogenicum*; the symptoms were nonspecific, overlapping with underlying or comorbid diseases, and the patients were receiving prophylactic antibiotics, steroids, or both. Thus, the pathogenicity of *M mucogenicum*, despite abundance, is likely lower than other common RGM.

Quantitative blood cultures showed that the colony counts were usually high with a median range of 51 to 100 colonies (up to >1,000) per 10 mL of blood cultured. The antibiotic treatment varied, most with at least one of the following: clarithromycin, amikacin, and ciprofloxacin. Of 42 patients with a catheter, 35 (83%) had catheter removal that was required to clear the infection or was no longer needed for antineoplastic therapy; the others had unknown catheter status. All infections resolved (Table 4); however, 1 patient died 3 weeks after isolation of *M abscessus* from the catheter blood, which was the initiating event for admission and eventual death. The infections were not related to the presence or absence of neutropenia (data not shown).

Table 4
Clinical Features of 44 Catheter-Related Rapidly Growing Mycobacteria Infections

Feature	Result
M/F ratio	29:15
Mean (range) age (y)	48.4 (12-72)
No. of underlying tumors	
Lymphoma and myeloma	14
Leukemia	12
Breast cancer	4
Melanoma	4
Sarcoma	2
Other solid tumors	8
No. of febrile cases	40
Mean temperature (range)	38.9°C (37.5°C-40°C)
Median (range) of colonies on culture of 10 mL of blood	51-100 (<10->1,000)
Antibiotic treatment	Various (eg, clarithromycin, amikacin, ciprofloxacin)
No. of cases with central venous catheter removal	35
Outcome	All resolved

Group 2: Skin and Soft Tissue Infections

Seven patients (6.1%) had RGM involvement in skin tissue or wounds. Of the 7 cases, 6 represented significant infections with AFB demonstrated from skin biopsy or wound (3 cases with granulomatous inflammation) and 1 or more positive cultures from the same and/or other source (respiratory tract or blood). Data for these patients, 4 with *M abscessus* and 2 with *M fortuitum*, are shown in **Table 5**. The first patient was neutropenic and had pneumonia and skin rash despite prophylactic ciprofloxacin, to which the *M abscessus* strain was intermediately susceptible. The second patient also had disseminated infection. The other 4 patients all had localized infections, and 3 of them required surgical intervention. In the only case of probable contamination, *M brisbanense* was not demonstrated on the special stain of the skin biopsy specimen, and the inflammatory response was nonspecific.

Group 3: Bronchopulmonary Infections

In 59 patients (51.3%, including 2 double sources), RGM were isolated at least once from respiratory sources, such as sputum, bronchial wash, bronchoalveolar lavage, or sinuses. *M abscessus* was by far the most common species (31/59 [53%]), followed by others.

Most patients (52/59 [88%]) had cough, shortness of breath, or fever. Radiologic evidence of infection was common

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Table 5
Features of Skin, Soft Tissue, and Wound Rapidly Growing Mycobacteria Infections

Case No./ Sex/Age (y)	Underlying Cancer (ANC/μL)	Pathogen/Source	Manifestations and Findings	Antibiotic Therapy	Outcome
1/F/67	Lymphoma (150)	*Mycobacterium abscessus*/ bronchial wash	Skin rash, fever, pneumonia*	Azithromycin, aztreonam, clarithromycin, levofloxacin, linezolid, amikacin	Resolved
2/M/52	Prostate cancer (3,620-7,820)	*M abscessus*/skin tissue and blood	Nodular tender rash with granuloma	Moxifloxacin, clarithromycin, azithromycin, ciprofloxacin	Resolved
3/F/37	None (3,860)	*M abscessus*/skin abscess	Thigh mass with pus and granuloma	Cefoxitin, clarithromycin, amikacin	Resolved
4/M/86	Mycosis fungoides (4,700)	*M abscessus*/skin	Arm skin plaque with granuloma	Oral clarithromycin, topical erythromycin	Resolved
5/F/63	Lung cancer (6,970)	*Mycobacterium fortuitum*/ wound discharge	Pus from inflamed thoracotomy site	Cephalexin	Resolved
6/F/38	Breast cancer (5,490)	*M fortuitum*/wound abscess	Inflamed incision site	Azithromycin, moxifloxacin	Resolved

ANC, absolute neutrophil count (given in conventional units; to convert to Système International units [$\times 10^9$/L], multiply by 0.001).
* This case of disseminated *M abscessus* infection was not counted toward respiratory cases in Table 6.

(54/59 [92%]) but nonspecific, including nodules, infiltrates, and pleural effusions. In 39 patients (66%) there were preexisting lung conditions, including the following (some overlapping): cavitary lesions associated with lung cancer, previous tuberculosis, or *Mycobacterium kansasii* or chronic *M abscessus* infection, 5 cases; prior mycobacterial infections, with tuberculosis (5 cases) and *Mycobacterium avium-intracellulare* complex (MAIC; 5 cases) most common, 12 cases total; and COPD, congestive heart failure, radiation fibrosis, bronchiectasis, or primary or metastatic or suspected lung cancer, 23 cases.

Coisolated pathogens were present in 24 cases (41%), including cytomegalovirus, parainfluenza virus, respiratory syncytial virus, *Acinetobacter* species, *Escherichia coli*, *Haemophilus* species, *Nocardia* species, *Pseudomonas* species, *S aureus*, *Stenotrophomonas maltophilia*, *Streptococcus pneumoniae*, *Aspergillus* species, and *Pneumocystis jiroveci*.

The clinical significance was assessed for each case **Table 6**. Four cases were definite infections: 1 patient with stem cell transplantation met American Thoracic Society criteria for *M abscessus* pneumonia with the organism being isolated from bronchoalveolar lavage fluid and blood, and the pneumonia was considered the source of bacteremia; 2 patients, 1 with *M abscessus* infection and 1 with *M fortuitum* infection, had the RGM isolated from respiratory tract and blood, but the pulmonary infection was deemed probable, not definite; 1 patient with *M abscessus* had nodular lung infection with bronchiectasis and tissue granulomas. Of the cases, 24 represented probable infections, and 31 were possible to doubtful infections. For all 28 cases of definite and probable infections, *M abscessus* accounted for 18 (64%), followed by *M fortuitum* (4 cases), *M mucogenicum* (3 cases), and other species (3 cases). The probable infection by *M mageritense*, a species described in 1997 with relatively limited clinical experience,[22] occurred in a 61-year-old man who had COPD and

Table 6
Clinical Significance of Infection in 59 Patients With Rapidly Growing Mycobacteria From Respiratory Sources

Species	No. of Strains	Category of Infection		
		Definite	Probable	Possible to Doubtful
Mycobacterium abscessus	31	3	15	13
Mycobacterium peregrinum or *Mycobacterium septicum*	7	0	1	6
Mycobacterium fortuitum	6	1	3	2
Mycobacterium mucogenicum	4	0	3	1
Mycobacterium porcinum group	4	0	0	4
Mycobacterium farcinogenes or *Mycobacterium senegalense*	1	0	1	0
Mycobacterium brisbanense	1	0	0	1
Mycobacterium goodii	1	0	0	1
Mycobacterium canariasense	1	0	0	1
Mycobacterium cosmeticum	1	0	0	1
Mycobacterium mucogenicum–like	1	0	0	1
Mycobacterium mageritense	1	0	1	0
Total	59	4	24	31

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lung nodules without cancer, and the organism was isolated from a sputum specimen. The patient was lost to follow-up.

Discussion

Recognized infections caused by RGM include pulmonary disease, cutaneous and wound infections, catheter-related bacteremia, lymphadenitis, and, infrequently, meningitis, endocarditis, and keratitis, as well as other rare infections.[23,24] Among patients with cancer, 3 earlier studies from our institution examined RGM pulmonary infections and catheter-related infections.[25-27] The present study of 115 cases represents the largest series for patients with cancer and the largest series for blood and catheter-related RGM infections. These RGM infections did not show any predilection for sex or type of malignancy. Recent chemotherapy, neutropenia, and concurrent steroid use were not significant predisposing factors for disease, consistent with previous findings.[25,27,28] No mortality resulted directly from infection with RGM, consistent with overall low virulence of these organisms. In a separate analysis, Han[29] found a seasonal occurrence of these RGM, ie, low in the winter and spring and high in the summer and fall, which followed the changes of temperature and rainfall by 2 to 6 weeks in Houston.

Microbiologic Features

The RGM strains involved at least 15 species, 10 of which were established or recognized since 1990,[1,2,30] including *M brisbanense*, *M brumae*, *M canariasense*, *M cosmeticum*, *M farcinogenes* or *M senegalense*, *M goodii*, *M mageritense*, *M peregrinum* or *M septicum*, *M porcinum* group, and unnamed *M mucogenicum*–like organisms. In addition, species status for *M abscessus* and *M mucogenicum* was also established after 1990 despite earlier recognition. The most commonly isolated species, in order of frequency, were *M abscessus*, *M mucogenicum*, *M fortuitum*, *M peregrinum* or *M septicum*, *M porcinum* group, and *M neoaurum* group.

All tested RGM strains except two were susceptible to amikacin. Similarly, Yakrus et al[31] at the Centers for Disease Control and Prevention (CDC) also found that only 1 of 75 strains of *M abscessus* and *M chelonae* was resistant to amikacin, and Swenson et al[32] found amikacin to be most active against *M fortuitum* biovariants. Clarithromycin was the second most active drug, effective against 39 of 40 *M abscessus* strains, all 25 *M mucogenicum* strains, and most other RGM except *M fortuitum* (4/14). The CDC study also found 68% susceptibility to this antibiotic among the *M abscessus* and *M chelonae* strains.[31] Clarithromycin has been shown to be effective against *M chelonae* cutaneous infections.[33] Recently, Nash et al[34] found intrinsic resistance to macrolide antibiotics among several RGM species, such as *M mageritense*, *M boenickei*, *M goodii*, *M houstonense*, *M neworleansense*, *M porcinum*, and *Mycobacterium wolinskyi*. Our results (Table 2) are similar to these findings. Several previous *M mageritense* strains were also resistant to clarithromycin.[35]

Ciprofloxacin and imipenem were also active against most RGM strains except *M abscessus,* to which the organism showed susceptibility of 7.5% and 17.5% respectively. Brown-Elliott et al[36] also demonstrated poor activity of ciprofloxacin and gatifloxacin against *M abscessus*. Others reported similar results.[31,32] Thus, the higher antibiotic resistant profiles of *M abscessus* are consistent findings. Imipenem has been shown to be the most active β-lactam against the *M fortuitum* complex[37]; our results support this finding. In addition, our data further showed that, within the complex, *M fortuitum* was infrequently susceptible to cefoxitin and clarithromycin, whereas other component species were more susceptible (Table 2). Thus, distinction among these species may have some clinical usefulness; more experience in coming years will tell.

M abscessus and Associated Infections

M abscessus was the most common RGM in this study, accounting for 37.4% (43/115) of all strains. It caused a total of 29 definite to probable infections, involving the airway, bloodstream, cutaneous tissue, and ascites, with dissemination in a few cases. An additional 13 respiratory strains and 1 strain from a CSF shunt were of low clinical significance.

The airway was the major source of *M abscessus*, accounting for 74% (32/43; Table 1). This finding agrees with the data from Griffith et al,[38] who noted that *M abscessus* caused 82% of the 154 cases of pulmonary RGM infections and that nodular bronchiectasis, similar to that caused by MAIC, was a typical finding. Thus, like most other mycobacterial pathogens (such as *M tuberculosis*, *M kansasii*, and MAIC), *M abscessus* mainly infects the lungs and respiratory tract. In addition, our data also suggest that, in disseminated infections, the organism likely originated from the lungs. Dissemination and other types of infections caused by *M abscessus* have been reported previously.[23]

A somewhat surprising finding of this study was the lack of *M chelonae*, an RGM previously considered common. There are a few explanations. First, *M chelonae* used to consist of subspecies *chelonae* and subspecies *abscessus* before the latter was elevated to species status in 1992,[39] and the distinction had been difficult and rarely made. Thus, only *M chelonae* has been reported and known. Second, recent studies found *M abscessus* to be indeed more common than *M chelonae*. The study by Griffith et al[38] (from Tyler, TX) noted a single (0.7%) *M chelonae* isolate as compared with 82% for *M abscessus*. In nonpulmonary RGM cases, *M abscessus* strains also outnumbered *M chelonae* strains by 2.5 to 1.[24] Similarly, the CDC study of 75 strains of *M abscessus* and *M chelonae* found more *M abscessus* (61%) than *M chelonae* (39%).[31] Third, geographic

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variation may exist: the CDC strains represented wider referral, whereas the Tyler strains and ours were from Texas. Environmental mycobacteria are known to be more common in the southern coastal states with diverse niches.[6,7]

M mucogenicum and Associated Infections

Perhaps the most interesting finding of this study is the observation of *M mucogenicum* as the dominant RGM species responsible for bloodstream and catheter-related infections, accounting for 52% (23/44) (Table 3). In fact, most *M mucogenicum* strains (24/28 [86%]) were isolated from blood and catheter sources (Table 1). Previously known as *M chelonae*–like organism,[40] the name *M mucogenicum* was proposed in 1995 to reflect its phylogenetic distance from *M chelonae* but closeness to *M fortuitum* and to denote its mucoid colonies.[41] This organism is the most frequently isolated mycobacterial species from environmental water sources.[5] Thus, the abundance and the mucoid cell surface, the latter generally known to favor catheter colonization, likely contributed to the frequent isolation from blood and catheter. Fortunately, *M mucogenicum* showed the highest susceptibility to antibiotics (Table 2), and all infections resolved on catheter removal and/or antibiotic treatment. The rare isolation of *M mucogenicum* from the respiratory specimens could also be contributed to by the pretreatment with mucolytics and sodium hydroxide and addition of antibiotics in the culture medium that might inactivate this organism more than other RGM because of its mucoid cell surface and low resistance to antibiotics. We have noticed over the years that such adequate pretreatment reduces contamination by *Mycobacterium gordonae*.

Wallace et al[40] also found that, of 87 *M mucogenicum* strains analyzed, 8 caused catheter sepsis, whereas the respiratory isolates were rarely clinically significant. Our study also had no definite respiratory infections caused by the organism. *M mucogenicum* has also been reported to cause an outbreak of water-associated CVC-related bacteremias[42] and 2 cases of fatal meningitis in immunocompetent patients.[43]

M fortuitum Complex and Associated Infections

It is well known that *M fortuitum* (complex) causes a wide range of infections involving various wounds, catheters, lungs, and others.[23] The *M fortuitum* complex has 3 biovars: *M fortuitum*, *M peregrinum*, and biovariant 3.[23] In addition, the complex probably also includes *M septicum*, *M farcinogenes*, and *M senegalense* because the 16S rRNA gene of *M septicum* differs from that of *M peregrinum* by a mere 4 nucleotides,[1,44] and the 16S rRNA genes of *M farcinogenes* and *M senegalense* (identical) are 8 (~0.5%) nucleotides divergent from that of *M fortuitum*.[1]

Recently, a study further divided the third biovariant organisms into 5 species: *M porcinum*, *M boenickei*, *M houstonense*, *M neworleansense*, and *M brisbanense*.[2] The first 4 species diverge by only 0 to 2 nucleotides at the 16S rRNA genes, thus representing a tight group, or the *M porcinum* group in this study. In contrast, the16S rRNA gene of *M brisbanense* differs from the *M porcinum* group by 37 (~2.5% of the gene) nucleotides and from *M fortuitum* by 39 nucleotides, suggesting substantial distance. Thus, *M brisbanense* should be separated from the *M fortuitum* complex, despite its biochemical similarities.

At least 5 species found in our study fell into the *M fortuitum* complex: *M fortuitum*, *M peregrinum* or *M septicum*, *M porcinum* group, *M farcinogenes* or *M senegalense*, and *M brisbanense*, together accounting for 33 (28.7%) of 115 strains. These organisms caused bloodstream, wound, and airway infections. Of the 14 *M fortuitum* strains, infections were diverse; only 2 respiratory strains were of low clinical significance. In contrast, only 2 of 8 *M peregrinum* (or *M septicum*) strains caused infections, ie, 1 blood and catheter-related (Table 3) and 1 airway (Table 6), whereas other strains (all 6 from airway) were insignificant despite the not-so-rare occurrence (7.0%, 8/115). Current experience with *M peregrinum* is limited, and rare infections similar to those caused by *M fortuitum* have been reported and reviewed by Brown-Elliott and Wallace.[23] *M porcinum* was initially described as a porcine pathogen[45] and recently recognized from human clinical isolates.[2] Wallace et al[46] newly analyzed the clinical significance of *M porcinum* and found that the organism caused wound infection, catheter-related bacteremia, and possible pneumonitis. In the present study, 5 *M porcinum* group strains were identified, including 1 from catheter-related bacteremia and 4 from airway with low clinical significance. The catheter-related bacteremia caused by *M brisbanense* (Table 3) likely represented first reported infection by this organism. However, the 2 *M brisbanense* strains, isolated from the airway and skin, were of doubtful significance. Thus, the clinical spectrum of this new RGM is yet to be seen.

Other RGM and Associated Infections

Four strains of *M neoaurum* group organisms were identified in this study, all causing catheter-related bacteremia. These strains included 2 *M neoaurum*, 1 *M lacticola,* and 1 *M neoaurum*–like organism. The *M neoaurum* cases added to the growing list of bacteremic cases caused by this RGM[47]; so far, 10 cases, with ours included, have been reported. A suspected case of *M neoaurum* meningoencephalitis has been reported[48]; however, in our opinion, contamination was more likely.[49] Our *M lacticola* case is the second reported infection by this organism; the first case was reported recently.[50]

M brumae was initially described in 1993 based mainly on environmental isolates.[51] Our case of *M brumae* catheter-related bacteremia was the first reported infection by this organism, the details of which have been described elsewhere.[52]

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Strains of newly proposed species, *M canariasense*,[53] *M goodii*,[54] *M cosmeticum*,[30] and an *M mucogenicum*–like RGM, were also identified in this study, but without clear clinical significance. However, the first 3 species may cause significant infections and outbreaks.[30,53,55]

Nearly all catheter-related infections were characterized by a high fever and high number of colonies from the blood cultured. Many cases (13/30 [43%]) were disseminated, ie, RGM isolated from peripheral and CVC blood samples. With catheter removal, recovery was the rule. No dissemination to other organs was seen.

Summary

Many RGM species, well-known and recently described species, caused significant infections in patients with cancer, including catheter-related bacteremia, disseminated infection, bronchopulmonary infections, dermatitis, cellulitis, and others. Accurate species identification could reveal biologic behaviors of RGM and guide empiric antibiotic therapy. *M abscessus*, *M mucogenicum*, and *M fortuitum* complex accounted for the vast majority of clinically significant RGM isolates. *M abscessus* was the most resistant RGM species, whereas *M mucogenicum* was susceptible to most antibiotics tested in vitro. *M mucogenicum* accounted for most catheter-related bacteremia, whereas *M abscessus* had a predilection for respiratory tract with a tendency to disseminate. Respiratory tract isolates of RGM required microbiologic, histologic, clinical, and radiologic correlation to determine clinical significance because of common coisolation of other microorganisms. Catheter removal was usually required for the management of catheter-related RGM bacteremia.

From the Sections of [1]Clinical Microbiology and [2]Infectious Diseases, The University of Texas M.D. Anderson Cancer Center, Houston.

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Address reprint requests to Dr Han: Section of Clinical Microbiology, The University of Texas M.D. Anderson Cancer Center, Unit 84, 1515 Holcombe Blvd, Houston, TX 77030.

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