Mycobacterium abscessus Complex Infections: A Retrospective Cohort Study

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Background. Infections caused by Mycobacterium abscessus group strains are usually resistant to multiple antimicrobials and challenging to treat worldwide. We describe the risk factors, treatment, and clinical outcomes of patients in 2 large academic medical centers in the United States.

Methods. A retrospective cohort study of hospitalized adults with a positive culture for M. abscessus in Miami, Florida (January 1, 2011, to December 31, 2014). Demographics, comorbidities, the source of infection, antimicrobial susceptibilities, and clinical outcomes were analyzed. Early treatment failure was defined as death and/or infection relapse characterized either by persistent positive culture for M. abscessus within 12 weeks of treatment initiation and/or lack of radiographic improvement.

Results. One hundred eight patients were analyzed. The mean age was 50.81 ± 21.03 years, 57 (52.8%) were females, and 41 (38%) Hispanics. Eleven (10.2%) had end-stage renal disease, 34 (31.5%) were on immunosuppressive therapy, and 40% had chronic lung disease. Fifty-nine organisms (54.6%) were isolated in respiratory sources, 21 (19.4%) in blood, 10 (9.2%) skin and soft tissue, and 9 (8.3%) intra-abdominal. Antimicrobial susceptibility reports were available for 64 (59.3%) of the patients. Most of the isolates were susceptible to clarithromycin, amikacin, and tigecycline (93.8%, 93.8%, and 89.1%, respectively). None of the isolates were susceptible to trimethoprim/sulfamethoxazole, and only 1 (1.6%) was susceptible to ciprofloxacin. Thirty-six (33.3%) patients early failed treatment; of those, 17 (15.7%) died while hospitalized. On multivariate analysis, risk factors significantly associated with early treatment failure were disseminated infection (odds ratio [OR], 11.79; 95% confidence interval [CI], 1.53–81.69; P = .04), acute kidney injury (OR, 6.55; 95% CI, 2.4–31.25; P = .018), organ transplantation (OR, 2.37; 95% CI, 2.7–23.1; P = .005), immunosuppressive therapy (OR, 2.81; 95% CI, 1.6–21.4; P = .002), intravenous amikacin treatment (OR, 4.1; 95% CI, 0.9–21; P = .04), clarithromycin resistance (OR, 79.5; 95% CI, 6.2–771.2; P < .001), and presence of prosthetic device (OR, 5.43; 95% CI, 1.57–18.81; P = .008).

Conclusions. Our cohort of 108 M. abscessus complex isolates in Miami, Florida, showed an in-hospital mortality of 15.7%. Most infections were respiratory. Clarithromycin and amikacin were the most likely agents to be susceptible in vitro. Resistance to fluoroquinolone and trimethoprim/sulfamethoxazole was highly common. Macrolide resistance, immunosuppression, and renal disease were significantly associated with early treatment failure.

Keywords. Mycobacterium abscessus; infections; clinical outcome; treatment failure; epidemiology; erm gene.

Rapidly growing mycobacteria are ubiquitous environmental organisms increasingly recognized as important human pathogens [1–4]. The Mycobacterium abscessus complex is a species of rapidly growing mycobacteria first described by Moore and Frerichs in 1953 [5]. It was only in 1992, after its separation from the Mycobacterium chelonae group, that the M. abscessus group strains acquired recognition as important human pathogens associated with significantly higher fatality rates than any other rapidly growing mycobacteria [5]. M. abscessus strains are responsible for a wide spectrum of infections in immunocompetent and immunocompromised hosts [2].

M. abscessus are usually found in water, soil, and dust and have been associated with infections after cosmetic and plastic surgery, invasive medical procedures employing contaminated equipment or material, and accidental injury where the wound is contaminated by soil [6]. Transplantation and cancer are also associated with M. abscessus group infections [6]. Isolates are usually resistant to multiple antimicrobials and are challenging to treat worldwide [7,8]. Precise epidemiologic data are lacking, but as with other nontuberculous mycobacteria (NTM), prevalence seems to be increasing [1]. The advent of an aging population and an increase in the number of immunosuppressed...
individuals suggest that the prevalence of NTM disease will increase [9]. A study by Adjemian et al. identified South Florida as a high-risk area for pulmonary nontuberculous mycobacterial disease [10]. Despite the increasing incidence of NTM infections including M. abscessus, data characterizing the clinical outcomes and risk factors for treatment failure are limited. We describe the risk factors, treatment, and clinical outcomes of patients in 2 large academic medical centers.

METHODS

This was a retrospective cohort study of hospitalized adults with a positive culture for M. abscessus group strains at Jackson Memorial Hospital (a 1558-licensed bed tertiary care teaching hospital) and the University of Miami Hospital (a 550-licensed bed academic and community hospital), both located in Miami, Florida, between January 1, 2011, and December 31, 2014. For the purpose of our study, not all M. abscessus isolates were sub-speciated; therefore, all cultures are reported as M. abscessus group. A list of all adults who had a positive M. abscessus culture sent during the study period and who were admitted to 1 of the 2 tertiary care hospitals was obtained from the corresponding hospital microbiology laboratory records. Only patients with new M. abscessus complex infections diagnoses were included. Data were collected for patients’ demographics, comorbidities, the source of infection, antimicrobial susceptibilities, antimicrobial therapy, immunosuppressive regimen, and clinical outcomes by retrospectively reviewing electronic medical records. When there were multiple positive cultures corresponding to a single or multiple episodes of infections from a single patient, only the first isolate of M. abscessus was included.

Currently, there is no consensus on the definition of treatment failure for M. abscessus complex infections. In this study, early treatment failure was defined as death and/or infection relapse characterized either by persistent positive culture for M. abscessus within 12 weeks of treatment initiation and/or lack of radiographic improvement. Mortality was defined as death related to infection with M. abscessus during a hospital stay or within 12 weeks of admission. Follow-up cultures and radiographs for all patients were evaluated within 12 weeks of M. abscessus treatment. Acute kidney injury was defined based on the Risk, Injury, Failure, Loss, End-Stage Renal Disease criteria [11]. Lung infection was defined according to the American Thoracic Society (ATS) bacteriological criteria as at least 2 positive expectorated sputum culture results or as a positive culture result from at least 1 bronchial wash or lavage or as a lung biopsy with mycobacterial histopathological features and positive culture [1], in addition to the presence of clinical respiratory symptoms, for example, unexplained cough or shortness of breath by other conditions, fever, etc. Skin and soft tissue infections were defined as positive skin or deep tissue cultures with clinical symptoms supportive of skin infection (eg, purulent drainage, inflamed skin, etc.). Abdominal infections included positive intra-abdominal or peritoneal fluid cultures for M. abscessus with clinical documentation of intra-abdominal infection. Disseminated infection was defined as the presence of at least 2 sites of M. abscessus infection. Prosthetic devices were defined as the presence of permanently implanted artificial materials including heart pacemakers or defibrillators, bone prosthesis, and cosmetic implants. Only 1 isolate per patient was included for susceptibility testing, adopting the minimum inhibitory concentration (MIC) cutoffs from the Clinical and Laboratory Standards Institute (CLSI) guidelines [12]. Identification of M. abscessus isolates was performed at the Mycobacteriology Laboratory at the National Jewish Health in Denver, Colorado. The broth microdilution method with cation-supplemented Mueller-Hinton broth was used as recommended by the CLSI [12].

Duplicate patient records, patients aged <18 years, cultures reported as M. abscessus/chelonae, cases with missing clinical notes and/or laboratory data in the electronic medical record, and patients who did not meet the ATS definition criteria for M. abscessus lung infection were all excluded (Figure 1). For statistical analysis, data were collected, pooled, and analyzed using SPSS version 16.0 (SPSS, Chicago, IL). The χ² test was used for comparing categorical variables between groups, except when expected values within cells were <5, in which case the Fisher exact test was used. A P value <.05 was considered to indicate statistical significance. If significance was found, then subsequent multivariate analyses were performed using multiple logistic regression models.

The study was approved by the institutional review boards of the University of Miami and Jackson Health System.

Figure 1. Study design and inclusion and exclusion criteria. Abbreviations: ATS, American Thoracic Society; NTM, nontuberculous mycobacteria.
Two-hundred thirty-seven unique adult patients had a positive culture with \textit{M. abscessus} complex, and 108 were included in the analysis (Figure 1). We excluded 49 duplicate cases, 16 pediatric cases, 15 cultures reported as \textit{M. abscessus}/\textit{M. chelonae}, 5 cases with missing clinical/labatory data, and 44 patients who did not meet the ATS definition criteria for \textit{M. abscessus} lung infection. Those 44 patients were all nonimmunosuppressed patients and did not receive antimycobacterial treatment. Demographic characteristics and distribution of clinical infections are shown in Table 1. The mean age was 50.81 ± 21.03 years. Fifty-seven (52.8%) were females, and 41 (38%) were Hispanics. Eleven (10.2%) of the patients had end-stage renal disease, 34 (40%) were on immunosuppressive therapy, and 40% had chronic lung disease including cystic fibrosis, chronic obstructive pulmonary disease, etc. Fifty-nine organisms (54.6%) were isolated in respiratory cultures, 21 (19.4%) in blood, 10 (9.2%) skin and soft tissue, and 9 (8.3%) intra-abdominal/peritoneal fluid. Antimicrobial susceptibility reports were available for 64 (59.3%) of the patients (Table 2). Clarithromycin, amikacin, and tigecycline were among the most active antimicrobial agents against our isolates (93.8%, 93.8%, and 89.1%, respectively). None of the isolates were susceptible to trimethoprim/sulfamethoxazole, and only 1 isolate was susceptible to ciprofloxacin. Only 44% were susceptible to linezolid and 12% to doxycycline (Table 2). Fewer isolates were tested for clofazimine (n = 31), kanamycin (n = 36), doxycycline (n = 56), and azithromycin (n = 44). The susceptibilities to kanamycin and azithromycin were 100% and 95.5%, respectively (Table 2). Seventy-five patients received antibiotics active against \textit{M. abscessus}, with 28 of those 75 containing at least 1 intravenous agent (Table 3).

Thirty-six (33.3%) patients early failed treatment based on our study criteria; of those, 17 (15.7%) died while hospitalized. On bivariate analysis (Table 4), clarithromycin resistance \((P < .001)\), intravenous amikacin treatment \((P = .04)\), acute kidney injury \((P = .001)\), dialysis \((P = .001)\), solid organ transplant \((P = .005)\), disseminated infection \((P = .04)\), immunosuppressive therapy \((P = .04)\), central line \((P = .015)\), and presence of prosthetic devices \((P = .04)\) were the risk factors significantly associated with treatment failure. On the other hand, receiving treatment with macrolide was found to be significantly associated with lower early treatment failure, with a \(P\) value of .04.

On subsequent multivariate analyses (Table 4), the following variables were significant risk factors for early treatment failure: clarithromycin resistance (odds ratio [OR], 79.5; 95% confidence interval [CI], 6.2–917.1; \(P < .001\)), intravenous amikacin treatment (OR, 4.1; 95% CI, 0.9–21; \(P = .04)\), disseminated infection (OR, 11.79; 95% CI, 1.53–81.69; \(P = .04\)), acute kidney injury (OR, 6.55; 95% CI, 2.4–31.25; \(P = .018\)), presence of prosthetic device (OR, 5.43; 95% CI, 1.57–18.81; \(P = .008\)), immunosuppressive therapy (OR, 2.81; 95% CI, 1.6–21.4; \(P = .002\)), and organ transplantation (OR, 2.37; 95% CI, 2.7–23.1; \(P = .005\)). Treatment with macrolide was found to be protective against early treatment failure (OR, 0.13; 95% CI, 0.002–1.8; \(P = .04\)).

A subgroup bivariate analysis was conducted for the patients who had respiratory infections showing a significant correlation between early treatment failure and the following risk factors: macrolide treatment receipt \((P = .01)\), multiple sites of infection \((P = .04)\), prosthetic device \((P < .001)\), COPD (\(P = .03\)), and acute kidney injury \((P = .04)\) (Table 5). After adjustment for confounders in the multivariate analysis, the presence of prosthetic device (OR, 8.1; 95% CI, 2.3–33; \(P < .001\)), macrolide treatment (OR, 0.14; 95% CI, 0.01–0.5; \(P = .2\)), acute kidney

**Table 1. Demographic and Clinical Characteristics of Patients With Mycobacterium abscessus Complex Infection (n = 108)**

| Characteristic                                      | n = 108 (%) |
|-----------------------------------------------------|-------------|
| Age, mean ± SD, y                                   | 50.81 ± 21.03 |
| Gender                                              |             |
| Male                                                | 52 (47.2)   |
| Female                                              | 57 (52.8)   |
| Ethnicity                                           |             |
| Hispanic                                            | 41 (38.0)   |
| Caucasian                                           | 34 (31.5)   |
| African American                                    | 27 (25.0)   |
| Other                                               | 6 (5.5)     |
| Site of \textit{M. abscessus} complex infection      |             |
| Respiratory                                         | 59 (54.6)   |
| Blood                                               | 21 (19.4)   |
| Skin and soft tissue                                | 10 (9.2)    |
| Abdominal                                           | 9 (8.3)     |
| Bone                                                | 6 (5.6)     |
| Disseminated                                        | 3 (2.8)     |
| Related comorbidities                                |             |
| Cystic fibrosis                                     | 9 (8.3)     |
| HIV                                                 | 17 (15.6)   |
| COPD                                                | 18 (16.5)   |
| Interstitial lung disease                           | 5 (4.6)     |
| Chronic bronchiectasis                              | 12 (10.9)   |
| Diabetes mellitus                                   | 17 (15.6)   |
| Organ transplant                                    | 20 (18.5)   |
| Kidney                                              | 5 (4.6)     |
| Liver                                               | 4 (3.7)     |
| Lung                                                | 5 (4.6)     |
| Heart                                               | 1 (0.9)     |
| Multivisceral                                       | 3 (2.8)     |
| Allogeneic bone marrow                              | 2 (1.9)     |
| Active malignancy                                   | 17 (15.6)   |
| Inflammatory autoimmune disease                    | 6 (5.6)     |
| Liver cirrhosis                                     | 6 (5.6)     |
| Gastroesophageal reflux disease                     | 9 (8.3)     |
| Immunosuppressive therapy in the last 3 mo          | 34 (31.5)   |
| Prednisone                                          | 5 (4.6)     |
| Prednisone + tacrolimus                             | 3 (2.8)     |
| Prednisone + mycophenolic acid + tacrolimus         | 19 (16.1)   |
| Azathioprine                                        | 2 (1.9)     |
| Prednisone + tacrolimus + antithymoglobulin         | 4 (3.7)     |
| Anti–tumor necrosis factor agent                    | 1 (0.9)     |

Abbreviation: COPD, chronic obstructive pulmonary disease.
Table 2. Antimicrobial Susceptibility (In Vitro) *Mycobacterium abscessus* Group (n = 64)

| Antimicrobial Agent                          | Susceptible MIC, μg/mL, No. (%) | Intermediate MIC, μg/mL, No. (%) | Resistant MIC, μg/mL, No. (%) |
|---------------------------------------------|----------------------------------|----------------------------------|-------------------------------|
| Amikacin                                    | ≤16, 60 (93.8)                   | 32, 4 (6.2)                      | ≥64, 0 (0)                    |
| Amoxicillin/clavulanic acid                 | ≤8/4, 0 (0)                      | 16/5 (12.2)                     | ≥32/16, 36 (87.8)            |
| Azithromycin†                                | ≤128, 42 (95.5)                 | 256, 0 (0)                      | ≥512, 2 (4.5)                |
| Cefotaxin                                    | ≤16, 22 (34.4)                  | 32–64, 39 (60.9)                | ≥128, 3 (4.7)                |
| Ciprofloxacin                               | ≤1, 1 (1.6)                     | 2, 0 (0)                        | ≥4, 63 (98.4)                |
| Clarithromycin                              | ≤2, 60 (93.8)                   | 4, 0 (0)                        | ≥8, 4 (6.2)                  |
| Clindamycin†                                | ≤2, 51 (100)                    | 2, 0 (0)                        | ≥4, 0 (0)                    |
| Doxycycline‡                                 | ≤1, 7 (12.3)                    | 8, 0 (0)                        | ≥16, 50 (87.7)               |
| Imipenem                                    | ≤4, 22 (34.4)                   | 8, 33 (51.5)                    | ≥16, 9 (14.1)                |
| Kanamycin                                    | ≤16, 36 (100)                   | 32, 0 (0)                       | ≥64, 0 (0)                   |
| Linezolid                                    | ≤8, 28 (43.8)                   | 16, 13 (20.3)                   | ≥32, 23 (35.9)               |
| Moxifloxacin                                 | ≤1, 4 (6.2)                     | 2, 0 (0)                        | ≥4, 60 (93.8)                |
| Tigecycline                                  | ≤2, 57 (89.1)                   | 4, 3 (4.7)                      | ≥4, 4 (6.2)                  |
| Tobramycin                                   | ≤4, 32 (50)                     | 8, 4 (6.2)                      | ≥24, 23 (35.9)               |
| Trimethoprim/sulfamethoxazole                | ≤32, 0 (0)                      | NA, 0 (0)                       | ≥64, 64 (100)                |

Abbreviations: MIC, minimum inhibitory concentration; NA, not available. †Forty-four were tested for azithromycin sensitivity.
‡Fifty-one isolates tested for clofazimine susceptibility.
§Fifty-seven isolates were tested for doxycycline sensitivity.
∥Thirty-six isolates only were tested for kanamycin sensitivity.

injury (OR, 3.4; 95% CI, 0.9–18; P = .04), and COPD (OR, 3.1; 95% CI, 1.04–10.8; P = .04) showed significant association with treatment failure (Table 5).

**DISCUSSION**

Our study describes the short-term outcomes of a large cohort of hospitalized patients with *M. abscessus* complex infections in Miami, Florida, and differs from previous studies analyzing long-term outcomes such as treatment failure among outpatients with *M. abscessus* complex infections [13–15]. To our knowledge, this is the largest case series of *M. abscessus* complex infections over a 4-year period described in the literature.

Thus far, *M. abscessus* complex has been considered the most pathogenic of the rapidly growing mycobacteria, accounting for approximately 65% to 80% of lung disease caused by such, and most likely to cause pulmonary infections in patients with underlying lung disease such as cystic fibrosis [1–3, 16–21]. In our study, the most frequent source of *M. abscessus* complex infections was respiratory (57.4%), similar to previous studies [1–3, 16, 17]. *M. abscessus* complex is known to cause infections in immunocompromised hosts [22–26]. Redelman-Sidi et al. reported 44 cases of *M. abscessus* complex over a 10-year period at a large cancer center in New York [22]; Candido et al. reported 30/129 patients with cystic fibrosis with NTM pulmonary infections over a 4-year period in Brazil [23]. Longworth et al. recently reported 15 cases of *M. abscessus* out of 34 (44%) NTB infections in solid organ transplant recipients over a 7.5-year period [24], and Knoll et al. reported 5/53 (9.4%) cases of *M. abscessus* complex in 53 transplant recipient patients who had 1 or more cultures positive for NTM over 15 years [25]. Smaller cases series of *M. abscessus* complex have been reported by others [26–28]. In our cohort, 20/108 (19%) patients were solid organ transplant recipients (kidney, lung, and liver being the most common); 34 (31.5%) patients were on immunosuppressive therapy. However, organ transplant was not associated with treatment failure among the patients with respiratory infections, which could be due to the small number of patients included in our cohort.

Our study identified a high rate of early treatment failure among hospitalized patients who developed infections with *M. abscessus* group strains. Risk factors highly associated with early treatment failure were presence of disseminated infection, resistance to clarithromycin, intravenous amikacin treatment receipt, acute kidney injury, and prosthetic device, followed by prior transplantation and immunosuppressive therapy use. The significant treatment failure associated with clarithromycin resistance is concordant with other publications. Park et al. demonstrated higher disease progression and worse treatment outcome in pulmonary *M. abscessus* isolates that harbored the erythromycin ribosome methyltransferase (erm) (41) gene [13]. Koh et al. showed that 92% of antibiotic treatment failure defined as recurrence or persistence of positive culture after 12-month treatment for *M. abscessus* pulmonary infections was caused by different *M. abscessus* genotype coinfections [14]. A negative conversion at 12 months of treatment completion was significantly higher in *M. abscessus* isolates of the C28 sequevar, smooth colonies, and those susceptible to clarithromycin [14]. Our subgroup multivariate analysis revealed a significantly lower rate of treatment failure if treated with macrolide (Table 5). The clarithromycin resistance association with treatment failure could not be assessed in this subgroup of patients given that the number of resistant strains to macrolide was low.
among the respiratory infections (2.8%) (Table 5). Despite the high in vitro susceptibility rates of our M. abscessus complex isolates to amikacin, treatment with this antibiotic was associated with a statistically significantly higher failure (Table 4). A plausible explanation is that aminoglycoside-induced renal toxicity was also high in our patients treated with intravenous amikacin (60%) (Table 3).

South Florida was shown to be a highly significant spatial cluster for pulmonary nontuberculous infections in the United States [10]. Possible theories to explain the difference in the number
### Table 4. Bivariate and Multivariate Analysis of Risk Factors for Early Failure of Treatment of *Mycobacterium abscessus* Complex Infections

| Risk Factor                                      | Early Failure to Treatment (n = 36), No. (%) | No Early Failure to Therapy (n = 72), No. (%) | Bivariate Analysis, OR (95% CI) | Bivariate Analysis, P Value | Multivariate Analysis, OR (95% CI) | Multivariate Analysis, P Value |
|--------------------------------------------------|---------------------------------------------|-----------------------------------------------|----------------------------------|--------------------------------|-----------------------------------|----------------------------------|
| **Age, y**                                       |                                             |                                               |                                  |                                |                                   |                                  |
| 18–40                                            | 9 (25)                                      | 24 (33.3)                                     | Ref.                             | -                              | Ref.                              | -                                |
| 41–65                                            | 14 (38.9)                                   | 29 (40.3)                                     | 1.3 (0.5–3.5)                    | .62                            | 1.01 (0.4–2.9)                    | .67                              |
| >65                                              | 13 (36.1)                                   | 19 (26.4)                                     | 1.8 (0.6–5.2)                    | .26                            | 1.4 (0.5–4.2)                     | .34                              |
| **Gender**                                       |                                             |                                               |                                  |                                |                                   |                                  |
| Female                                           | 20 (55.6)                                   | 37 (51.4)                                     | 1.18 (0.5–2.9)                  | .84                            | 0.9 (0.4–2.1)                     | .78                              |
| Male                                             | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Race**                                         |                                             |                                               |                                  |                                |                                   |                                  |
| Caucasian                                        | 12 (33.3)                                   | 22 (30.6)                                     | Ref.                             | Ref.                           | Ref.                              | Ref.                            |
| Hispanic                                         | 15 (41.7)                                   | 26 (36.1)                                     | 1.1 (0.4–2.7)                   | .9                             | 0.8 (0.5–2)                      | .81                              |
| African American                                 | 8 (22.2)                                    | 19 (26.4)                                     | 0.8 (0.3–2.3)                   | .64                            | 0.5 (0.2–2.6)                    | .6                               |
| Other                                            | 1 (2.8)                                     | 5 (6.9)                                       | 0.4 (0.04–3.5)                  | .38                            | 0.3 (0.03–2.9)                   | .41                              |
| **Diabetes mellitus**                            |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Malignancy**                                   |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **HIV**                                          |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **COPD**                                         |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Bronchiectasis**                               |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Autoimmune disease**                           |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Site of positive culture**                     |                                             |                                               |                                  |                                |                                   |                                  |
| Respiratory                                      | 13 (36.1)                                   | 23 (31.9)                                     | Ref.                             | Ref.                           | Ref.                              | Ref.                            |
| Blood                                            | 4 (11.1)                                    | 9 (12.5)                                      | 0.8 (0.2–3)                      | .72                            |                                   |                                  |
| Soft tissue                                      | 2 (5.6)                                     | 8 (11.1)                                      | 0.4 (0.08–2.4)                  | .35                            |                                   |                                  |
| Bone                                             | 1 (2.8)                                     | 2 (2.8)                                       | 0.9 (0.07–10.7)                 | .9                             |                                   |                                  |
| Abdominal                                        | 4 (11.1)                                    | 2 (2.8)                                       | 3.5 (0.6–22)                    | .17                            |                                   |                                  |
| **Disseminated infection**                       |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Organ transplant**                             |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Within 1 y of the infection**                  |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **After 1 y of *M. abscessus* infection**         |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Immunosuppressive therapy**                    |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Central line**                                 |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Line or prosthetic device removal**            |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Received prosthetic device**                   |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Recent surgery (in the past 6 mo)**            |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Acute kidney injury**                          |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Chronic kidney disease**                       |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Dialysis**                                     |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Abnormal imaging result**                      |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Antibiotic therapy receipt**                   |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Intravenous amikacin treatment receipt**       |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Clarithromycin resistance**                    |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Macrolide treatment receipt**                  |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Infectious diseases consult**                  |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Discontinuation of antibiotics before 4 wk due to side effect** | | | | | | |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |
| **Received surgical intervention**                |                                             |                                               |                                  |                                |                                   |                                  |
| Male                                              | 16 (44.4)                                   | 35 (48.6)                                     |                                   |                                |                                   |                                  |

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; IV, intravenous; NP, not possible to calculate; OR, odds ratio; Ref, reference group.

*Means significant association.

Six out of 23 patients who were treated with IV amikacin failed treatment early vs 4 out of 52 patients who did not fail treatment early who received IV amikacin.

Three out of 10 total patients who failed treatment among the 64 *M. abscessus* isolates that were tested for antibiotic susceptibility were clarithromycin resistant vs 1 out of 54 patients who did not fail treatment who had clarithromycin-resistant *M. abscessus* complex.

Twenty out of 23 patients who failed treatment were treated with macrolide (clarithromycin or azithromycin) vs 51 out of 52 patients who did not fail treatment who were treated with macrolide.
of infections compared with other regions in the United States include the warm tropical climate and water colonization [9]. 

*M. abscessus* are organisms that have the ability to survive and proliferate in habitats that they share with humans, such as drinking water [9]. Although chlorine is the most commonly used disinfectant to treat drinking water in the United States [29], it has been reported that the Miami-Dade County Water and Sewer department use monochloramine (http://www.miamidade.gov/water/water-supply-treatment.asp#3). Most communities use either chlorine or chloramines and switch back and forth between these products at different times of the year or for operational reasons [29]; there is evidence that bacterial communities shift during water disinfection, and mycobacteria have been found to increase during monochloramine treatment [30]. Furthermore, Donohue et al. showed that there are statistically significant higher levels of NTM in nonchlorinated than in chlorinated tap water [31]. Unlike the *M. abscessus* complex outbreak linked to hospital tap water at a tertiary care hospital in Durham, North

### Table 5. Bivariate Subgroup Analysis of Risk Factors for Early Treatment Failure in Patients With *M. abscessus* Complex Respiratory Infections

| Risk Factor                                      | Early Failure to Treatment (n = 19), No. (%) | No Early Failure to Therapy (n = 40), No. (%) | Bivariate Analysis, OR (95% CI) | Multivariate Analysis, OR (95% CI) | P Value | P Value |
|--------------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------|-----------------------------------|---------|---------|
| Age, y                                           |---------------------------------------------|---------------------------------------------|---------------------------------|-----------------------------------|---------|---------|
| 18–40                                            | 6 (31.6)                                   | 11 (27.5)                                  | Ref.                            | Ref.                              | .72     | -       |
| 41–65                                            | 6 (31.6)                                   | 17 (42.5)                                  | 0.6 (0.2–2.5)                   | 0.5 (0.2–2.1)                     | .6      | -       |
| >65                                              | 7 (36.8)                                   | 12 (30)                                    | 1.1 (0.2–4.1)                   | 0.9 (0.2–3.5)                     | .7      | -       |
| Gender                                           |                                            |                                            |                                 |                                   | .71     | -       |
| Female                                           | 9 (47.4)                                   | 21 (52.5)                                  | 0.8 (0.2–2.4)                   | 0.7 (0.2–2.1)                     | .7      | -       |
| Male                                             | 10 (52.6)                                  | 19 (47.5)                                  |                                 |                                   |         |         |
| Race                                             |                                            |                                            |                                 |                                   | .26     | -       |
| Caucasian                                        | 10 (52.6)                                  | 10 (25)                                    | Ref.                            | Ref.                              | .7      | -       |
| Hispanic                                         | 6 (31.6)                                   | 17 (42.5)                                  | 0.3 (0.1–1.2)                   | 0.2 (0.3–1.5)                     | .2      | -       |
| African American                                 | 2 (10.5)                                   | 9 (22.5)                                   | 0.21 (0.04–1.2)                 | 0.18 (0.1–1.4)                    | .12     | -       |
| Other                                            | 1 (5.3)                                    | 4 (10)                                     | 0.25 (0.02–2.6)                 | 0.2 (0.08–2.1)                    | .3      | -       |
| Diabetes mellitus                                | 5                                           | 8                                          | 1.3 (0.4–4.6)                   |                                   | .4      | -       |
| Malignancy                                        | 4                                           | 6                                          | 1.4 (0.4–5.6)                   | 1.3 (0.5–4)                       | .56     | -       |
| HIV                                              | 6                                           | 8                                          | 1.6 (0.5–5.2)                   | 1.4 (0.6–10)                      | .4      | -       |
| COPD                                             | 10                                          | 6                                          | 3.5 (1.1–11.1)                  | 3.1 (1.0–10.8)                    | .04     | -       |
| Cystic fibrosis                                  | 5                                           | 4                                          | 2.6 (0.6–10.9)                  | 2.1 (0.7–9.4)                     | .24     | -       |
| Bronchiectasis                                   | 6                                           | 6                                          | 2.1 (0.6–7.4)                   | 1.8 (0.7–6.8)                     | .3      | -       |
| Interstitial lung disease                        | 2                                           | 3                                          | 1.4 (0.2–9.1)                   | 1.3 (0.3–8.4)                     | .6      | -       |
| GERD                                             | 3                                           | 4                                          | 1.6 (0.3–7.8)                   | 1.4 (0.5–6.4)                     | .5      | -       |
| Presence of second site of infection             | 3 (15.8)                                   | 0 (0)                                      | NP                             | 0.04*                            | NP      | 0.05    |
| Organ transplant                                 | 5 (26.3)                                   | 5 (12.5)                                   | 2.5 (0.5–12.6)                  |                                   | .2      | -       |
| Immunosuppressive therapy                        | 14 (73.7)                                  | 24 (60)                                    | 1.8 (0.5–7.9)                   |                                   | .2      | -       |
| Central line                                     | 1 (5.3)                                    | 3 (75)                                     | 0.7 (0.02–9.3)                  | 0.75                              | -       | -       |
| Line or prosthetic device removal                 | 1 (5.3)                                    | 1 (2.5)                                    | 2.1 (0.02–165.17)               |                                   | .6      | -       |
| Prosthetic device                                 | 14 (73.7)                                  | 9 (22.5)                                   | 9.6 (2.4–42.4)                  | <.001*                            | 8.1 (2.3–33) | <.001* |
| Recent surgery                                    | 5 (26.3)                                   | 6 (15)                                     | 2.02 (0.4–9.4)                  |                                   | .3      | -       |
| AKI                                              | 6 (31.6)                                   | 4 (10)                                     | 4.12 (0.8–22.8)                 | 3.4 (0.9–18)                      | .04*    | -       |
| ESRD                                             | 1 (5.3)                                    | 4 (10)                                     | 0.5 (0.01–5.6)                  |                                   | .5      | -       |
| Dialysis                                         | 1 (5.3)                                    | 1 (2.5)                                    | 2.1 (0.02–165.17)               |                                   | .6      | -       |
| Intravenous amikacin treatment receipt           | 3 (75)                                     | 10 (31.3)                                  | 6.6 (0.4–361.8)                 | 5.6 (0.5–268.4)                   | .08     | -       |
| Clarithromycin resistance                        | 1 (7.7)                                    | 0 (0)                                      | NP                             | 0.17                              | -       | -       |
| Macrolide treatment receipt                      | 10 (30.3)%                                 | 3 (100)%                                   | 0 (0–0.6)                      | 0.14 (0.01–0.5)                   | .02*    | -       |
| Antibiotic therapy                               | 13 (68.4)                                  | 23 (57.5)                                  | 1.6 (0.4–6.2)                   |                                   | .42     | -       |
| Infectious diseases consult                      | 8 (42.1)                                   | 11 (27.5)                                  | 1.9 (0.5–6.9)                   |                                   | .26     | -       |
| Discontinuation of antibiotics                   | 5 (26.3)                                   | 15 (37.5)                                  | 0.6 (0.1–2.2)                   |                                   | .39     | -       |
| Treatment measures other than antibiotics        | 16 (84.2)                                  | 36 (90)                                    | 0.6 (0.09–4.6)                  |                                   | .52     | -       |

Abbreviations: AKI, acute kidney injury; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; NP, not possible to calculate; OR, odds ratio.

*Statistically significant.

Ten out of 33 patients with *M. abscessus* complex lung infections who received macrolide had early treatment failure vs 3 patients who did not receive macrolides out of 3 who had early treatment failure.
Carolina [32], the characteristics of the identified cases included in our study failed to fulfill the criteria for an outbreak as the number of reported cases yearly has remained almost the same throughout the 4 years of our study at all the sites of infection; our cases were not clustered in a particular area or hospital unit, nor were they related to a specific procedure or patient population.

Other risk factors previously associated with treatment failures or worst outcomes include macrolide resistance through the inducible erm (41) gene, including failure of achieving or maintaining culture conversion [14, 15, 33, 34]. In our study, clarithromycin and amikacin were the most likely antimicrobials to be susceptible in vitro, and all our tested M. abscessus isolates for macrolide susceptibility had MICs for clarithromycin determined before and after an extended 2-week incubation with clarithromycin to evaluate the presence of an active erm (41) gene. Our high susceptibility rates to macrolides among our M. abscessus isolates could be due to the predominance of M. abscessus subsp. massiliense in our isolates, which appears to be more susceptible to macrolides than M. abscessus sensu stricto and M. bolletii [34]. This contrasts with previous studies describing constitutive macrolide resistance between 2.7% and 28.6% and inducible resistance in 65% to 68.8% of M. abscessus complex isolates [35–37].

In our study, we found a high proportion of fluoroquinolone resistance, confirming the results of a study by Maurer et al. that evaluated the in vitro activities of all generations of quinolones for clinical and reference rapidly growing mycobacteria and found gyrA and gyrB mutations responsible for an intrinsic low level of resistance to quinolones in mycobacteria [33]. However, other rapidly growing mycobacteria species showed distinct susceptibilities to this class of antimicrobials and patterns of mutations, contrary to what has been traditionally defined, suggesting that other mechanisms of resistance, different from gyrA or gyrB mutations, may also be involved in resistance to high levels of quinolones [38].

Of the isolates tested, more were susceptible to amikacin (93.8%) than any other antibiotic. Some studies suggest that chromosomally encoded drug-modifying enzymes play an important role in the lack of aminoglycoside bactericidal activity against rapidly growing mycobacteria [29], but the clinical significance is unknown. Few studies have evaluated the synergy between 2 antibiotics against M. abscessus [39, 40]. The in vitro combination of clofazimine and amikacin shows a significant synergistic activity [41]. A study by Huang et al. in Taiwan reported synergy between tigecycline and clarithromycin but an antagonistic activity between tigecycline and amikacin [39].

Although our study found decreased susceptibilities to imipenem and cefoxitin in vitro, the use of either of those 2 agents remains the backbone of combination treatment of M. abscessus group infections. A French study showed that most of the M. abscessus isolates were moderately susceptible or immediately resistant to cefoxitin and imipenem, with the MIC distributions for cefoxitin and imipenem very close to the breakpoints [40]. Another study showed that M. abscessus produces a clavulanate-insensitive broad-spectrum β-lactamase that limits the in vivo efficacy of β-lactams, except cefoxitin and, to a lower limit, imipenem [42]. Epidemiological cutoff values for wild-type strains should be determined to improve the interpretation of MICs for clinical strains. Similarly, studies are warranted to further understand the correlation between the in vitro and the in vivo activity of the antibiotics against these organisms. The paucity of bactericidal antibiotics to treat these organisms in addition to the immune state of the hosts affected by these infections could explain, in some cases, the poor therapeutic outcomes of M. abscessus group infections [33].

The strengths of our study include the high number of cases over a 4-year period within 2 hospitals and, to our knowledge, the largest case series to date. The inclusion of multiple sources of infections, a high proportion of immunocompromised and immunocompetent patients, and the comprehensive review of potential risk factors were associated with early treatment failure in M. abscessus group infections. Our study also has limitations, including the retrospective design, analysis of a specialized hospitalized population in a single urban area, and the unavailability of subspecies information and molecular typing. Short-term outcome is another limitation to be considered. Our number of deaths is probably underestimated because some patients might have been lost to follow-up. Unfortunately, there is no consensus definition of M. abscessus complex infection treatment failure, which is clinically relevant and needed in the near future. In addition, the antimicrobial susceptibilities of M. abscessus group are not routinely done locally by our microbiology laboratories but are sent out based upon the treating physician’s request; therefore, in vitro synergistic antimicrobial activity against M. abscessus group is seldom reported. Nonetheless, we believe our study is an important contribution to the literature relevant to health care providers who encounter infections with nontuberculous mycobacteria worldwide.

In conclusion, M. abscessus complex can lead to severe infections with high morbidity and mortality. We describe our experience in Miami, the antimicrobial susceptibility trends and risk factors that correlated with worse outcomes. Future studies are needed to better understand the causes of high prevalence in South Florida and develop efforts to prevent and optimize the management of these multidrug-resistant infections.

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