Mycobacterium genavense Infections in Immunocompromised Patients Without HIV: Case Series of Solid Organ Transplant Patients and Literature Review

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Background. Mycobacterium genavense infection is rare and can occur in immunocompromised patients without human immunodeficiency virus (HIV).

Methods. We describe 2 cases of M genavense infection in solid organ transplant (SOT) recipients, and we performed a literature review of immunocompromised patients without HIV.

Results. Fifty-two cases are reported. Predisposing factors were receipt of SOT (40.4%) and autoimmune disease (36.5%). Infection was disseminated in 86.5% of cases. Organs involved were lymph nodes (72.3%), gastrointestinal tract (56.5%), lung (35.5%), and bone marrow (28.8%). Most patients were treated with at least 3 antimycobacterial agents (98%), with a clinical cure achieved in 54.9%. In multivariate analysis, lack for cure was associated with age of the time infection (odds ratio [OR], 15.81 [95% confidence interval (CI), 2.92–152.93]; P = .011) and positive bone marrow culture (OR, 1.05 [95% CI, 1.01–1.12]; P = .042).

Conclusions. Mycobacterium genavense infection is a rare and generally disseminated disease with a poor prognosis. Optimal treatment regimen and its duration remain to be defined.

Keywords. HIV uninfected; immunocompromised; Mycobacterium genavense; solid organ transplant.

Mycobacterium genavense is an opportunistic nontuberculous mycobacterium first described by Böttger et al in 1992 in a patient infected with human immunodeficiency virus (HIV) [1]. This slow-growing mycobacterium has been isolated in tap water and in wild and domestic animals (birds, rabbits, cats, ferrets, snakes, etc) [2–7]. It has also been shown to colonize the gastrointestinal tract of healthy humans [8]. The pathogenesis of M genavense infection is not known, probably due to the lack of an animal model of infection and patients infected. According to most authors, transmission to humans occurs following oral ingestion from contaminated water or close contact with infected animals. It has been isolated from nonsterile sites, such as lung secretions or gastric fluid, and it is difficult to assess, especially in immunocompetent patients, when M genavense should be considered colonization or infection.

However, this mycobacterium mainly infects immunocompromised patients, particularly those with HIV infection, and might be responsible for 3.9%–12.8% of nontuberculous mycobacterial (NTM) infections in some cohorts of people living with HIV (PLWH) with a poor prognosis [9, 10]. Since the era of antiretroviral therapy (ART), M genavense infection is less frequently identified in PLWH. Following its description, it has been also described in immunocompromised patients without HIV, especially in solid organ transplant (SOT) recipients, patients on immunosuppressive therapy for autoimmune disease, patients who received allogeneic stem cell transplantation, patients with lymphoproliferative malignancies, and patients with a primary immunodeficiency [11–14]. Regardless of the immunodeficiency, symptoms of M genavense infections seem to be similar to those caused by the Mycobacterium avium complex (abdominal pain, lung involvement, diarrhea, lymphadenopathy, fever, pancytopenia, and hepatosplenomegaly) [9, 10, 15]. This organism is difficult to culture due to its slow growth in liquid media and failure to grow in solid media. Definitive identification requires mainly molecular techniques or, in a rare case, matrix-assisted laser desorption/ionization–time of flight mass spectrometry [11, 16–18]. The aim of this review was to assess the clinical, microbiological, and prognostic features of M genavense infection in immunocompromised patients without HIV and to determine risk factors associated with not being cured.
MATERIALS AND METHODS

Patient Selection
First, we report 2 cases of disseminated M genavense infection in renal transplant recipients occurring in our institution. Patients gave their informed consent to use their clinical and biological data for publication, and this case series was conducted in accordance with the 1964 Helsinki Declaration.

We then performed a systematic review of the literature from the first case of M genavense infection described in 1992 to December 2021 via an electronic search of PubMed, Science Direct, and the Cochrane Library using the keywords “Mycobacterium” AND “genavense” (Medical Subject Headings). We also reviewed reference lists of included papers to identify unpublished data and studies missed by our search. No language or age constraints were applied to the search.

Articles were selected for review if their titles or abstracts suggested that they reported individual or group data from immunocompromised patients without HIV with a diagnosis of M genavense infection. Articles were excluded if patients had HIV infection, they were not immunocompromised, or if the immunodeficiency was not identified. Conference papers, case reports, case series, and cohort studies were included. Special attention was paid to avoid the inclusion of duplicated cases within meeting abstracts, case reports, or articles.

Definition
A patient was included when a M genavense infection was confirmed by molecular identification or culture from a positive or negative sample for acid-fast bacilli (AFB) on direct examination. The disease was considered disseminated when signs or symptoms involving 2 or more organs or systems were detected and/or M genavense was isolated from blood, bone marrow (BM), or other organs. Pulmonary localization required the isolation of the organism from the respiratory tract (from at least 2 separate expectorated sputum samples or positive culture from at least 1 bronchial wash or lavage or transbronchial or lung biopsy) in association with imaging anomalies (nodules, infiltrate, cavitary opacities, etc) and pulmonary symptoms (cough, dyspnea, etc), as recommended by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), the European Respiratory Society, and the European Society of Clinical Microbiology and Infectious Diseases [15, 19, 20]. For nonpulmonary infections analyzed in this review, a clinically relevant infection was defined as a positive AFB or culture or molecular detection of M genavense with clinical signs in accordance with the isolation site and, if applicable, consistent radiological findings. Patients were considered cured if they were asymptomatic, were not undergoing treatment, and were alive.

Data Extraction
For each included patient, the following information was extracted from the study: year of publication; demographic characteristics of the patient, type of immunodeficiency; treatment and duration of immunosuppression; clinical, laboratory, and radiologic features; method for identifying M genavense; antimycobacterial therapy and other therapeutic management strategies; presence of immune reconstitution inflammatory syndrome (IRIS); clinical outcome (cured, dead, alive with chronic symptoms, or improved but remained under treatment); and follow-up.

Statistical Analysis
Continuous variables are presented as median and interquartile range and categorical variables as frequency and percentage. For univariate and multivariate analyses, patients were classified into 2 categories, cured or not being cured, including dead patients, patients alive with chronic symptoms, or patients with an improvement of symptoms but still under treatment at the time of publication. In the univariate analysis, patients were compared for the risk of not being cured using Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. In the multivariate analysis, we used a logistic regression model to assess the association between the risk of not being cured and factors with a P value < .20 in the univariate analysis. All analyses were 2-sided, and P < .05 was considered statistically significant. Statistical analyses were performed using R studio software version 3.6.3 (R Development Core Team, 2019).

Literature Review
The search of the PubMed, Science Direct, and Cochrane Library databases provided 734 citations. After the exclusion of duplicates and articles with titles and abstracts that did not meet the inclusion criteria, 51 full-text articles were assessed for eligibility. Eighteen articles were excluded, and 33 were included, mostly case reports (Figure 1). Since the first case of M genavense infection in an immunocompromised patient without HIV was published in 1997 by Bogdan et al [21], 52 cases (including our 2 patients) of M genavense infection in immunocompromised patients without HIV have been described [11–14, 21–48] (Table 1). The majority of reports are case reports or case series, with the largest series including 9 cases in the study by Hoeffsloot et al [43].

Case 1
A 50-year-old man was admitted in September 2015 for fever, night sweats, fatigue, weight loss, and abdominal pain. He had undergone a preemptive renal transplant in 2007 for polycystic renal disease (PKD). Maintenance immunosuppressive treatment consisted of 150 mg of mycophenolate mofetil (MMF) per day, 1 g of ciclosporine per day, and 10 mg of prednisone per day. At admission, physical examination revealed a distended abdomen that was mildly tender to palpation and hepatomegaly due to PKD. No lymphadenopathy was found. Blood tests showed an increased C-reactive protein (CRP) level (135 mg/L) and a creatinine level of 175 µmol/L (stable for a few months). The CD4+
T-lymphocyte count (737 cells/µL) and BM examination with cellular immunophenotyping were normal. Viral (cytomegalovirus and Epstein-Barr virus polymerase chain reaction [PCR]) and bacterial (blood culture and urine culture) analyses were negative. The computed tomography (CT) scan revealed liver PKR and mesenteric and retroperitoneal lymph nodes (LNs). Gastroscopy and colonoscopy were normal. Fluorodesoxyglucose positron emission tomography (PET)/CT revealed hypermetabolic cervical, mediastinal, and subclavicular LNs in addition to abdominal LNs. Cervical LN biopsy showed numerous AFB. No argument for lymphoma was reported based on histology and flow cytometry immunophenotyping. The mycobacteriology laboratory performed 16S ribosomal RNA (rRNA) gene sequencing to identify *M. genavense*. The direct molecular test enabled immediate treatment of the patient in November 2015 with a combination of ethambutol, clarithromycin, and rifampicin. After 4 months of incubation, a mycobacterial culture (mycobacteria growth indicator tube [MGIT]) of the LN was also positive for *M. genavense* (identification with molecular hybridization DNA-STRIP, Hain Lifescience), but antibiotic susceptibility was not able to be performed due to insufficient growth in subculture. After 24 months of treatment, the clinical symptoms had partially resolved, CRP levels were still increased at approximately 50 mg/L, and PET/CT scans showed the persistence of hypermetabolic disseminated LNs. Rifampicin was discontinued, and clofazimine and bedaquiline were added in November 2017. MMF was stopped and the cyclosporine dose was decreased. Unfortunately, he developed side effects of treatment with a prolonged QT interval that was exacerbated by clarithromycin and bedaquiline and corneal deposits due to clofazimine, leading to a recurrent discontinuation periods of 2 weeks of the antituberculosis treatment. Five months later, the patient’s medical condition worsened, with a recurrence of night sweats and fever. Intestinal symptoms were also exacerbated with diarrhea and malabsorption syndrome and weight loss. Control CT showed that the sizes of most enlarged abdominal and mediastinal LNs had increased. In April 2018, treatment was changed to oral clarithromycin, ethambutol, moxifloxacin, and intravenous amikacin and rifampicin. Interferon gamma (IFN-γ) (85 µg 3 times a week) was added, and cyclosporine was stopped in April 2018. Amikacin was discontinued in June 2018 because of ototoxicity. Symptoms rapidly improved with normalization of CRP levels. One year later, PET/CT scans showed a partial response with the persistence of some hypermetabolic LNs, leading to the cessation of IFN-γ. Antituberculosis treatments were continued for an additional 12 months. No sign of *M. genavense* infection relapse was observed 2 years after the end of treatment. PET/CT scans showed mesenteric fibrotic LNs, considered as sequelae of the infection.

**Figure 1.** Flowchart of literature review from 1992 to 2021. Abbreviation: PLWH, people living with HIV.
### Table 1. Literature Review of Reported Cases of *Mycobacterium genavense* in Immunocompromised Patients Without HIV, 1992–2021

| Author, Publication Year [Reference] | Sex | Age | Organ(s) Involved | Immunosuppression Type (Duration of IS Treatment Before Infection) | Microbiologic Findings | Treatment | Outcome |
|-------------------------------------|-----|-----|-------------------|---------------------------------------------------------------|-----------------------|-----------|---------|
| Bogdan et al, 1997 [21]             | M   | 72  | Lung, spleen, kidney, BM disorder | B-cell CLL, CTX, AZA (7 mo) | AFB in BM, spleen, kidney, lung | Postmortem diagnosis | Death |
| Krebs et al, 2000 [22]              | F   | 67  | BM, LN (cervical, inguinal, mediastinal), and SPM | CTX, azathioprine (120 mo) | AFB on BM, Positive blood cultures at 43 d, positive BM cultures at 7 and 20 d | CLR, EMB, RFB (6 mo) | Cured |
| Léautez et al, 2000 [23]            | F   | 38  | Skin and soft tissue | Sarcoïdosis, No treatment | AFB on pus, Positive pus culture within 6 mo and positive PCR | CLR, EMB, CPX (12 mo) | Cured at 14 mo follow-up |
| Ndorimpa et al, 2003 [24]           | M   | 18  | LN, abdominal tumor | Primary T-cell quantitative and qualitative deficiency | AFB on LN | Postmortem diagnosis | Death |
| Le Berre et al, 2004 [25]           | F   | 45  | BM, LN, SPM, GI tract, urine | Renal transplant (42 mo) | AFB and positive PCR on BM and urine | CLR, EMB, LVX (22 mo) | Cured at 12 mo after treatment |
| Nurmohamed et al, 2007 [26]         | M   | 67  | Abdominal LN, lung, SPM, urine, GI tract | Renal transplant, CTX, MMF, cyclosporine (7 mo) | AFB and positive culture in BM, Positive PCR in BM, peritoneal fluid, sputum, and urine | RFB, EMB, CLR, OFX | Death |
| de Lastours et al, 2008 [27]        | M   | 37  | Digestive tract, abdominal LN | Heart transplant, CTX, MMF, tacrolimus (7 mo) | AFB and positive culture on intestinal biopsy, Positive PCR on intestinal biopsy and blood | CLR, AMK, EMB, MOX, clofazimine (18 mo) | Cured |
| Daum et al, 2008 [28]               | F   | 28  | Digestive tract, liver | SLE, MMF, AZA, cyclosporine (18 mo) | AFB and PCR positive on duodenal biopsy | Not available >15 mo | Cured |
| Dumouchel-Champagne et al, 2009 [29]| M   | 72  | BM, abdominal LN, SPM | Sarcoïdosis, CTX (6 mo) | AFB and positive PCR on BM | RFB, AZM, CPX (5 mo) | Death |
| Lorenzen et al, 2009 [30]           | M   | 52  | BM, abdominal and supraclavicular LN | Myasthenia, CTX, AZA (48 mo) | AFB and positive culture and PCR on duodenal biopsy | RFB, AZM, EMB, MOX changed to IV MOX, SM, INH, EMB, AMK, and oral RFB and AZM | Improved but remains on treatment |
| Lu et al, 2009 [32]                 | M   | 56  | GI tract, abdominal LN | Allogeneic HSCT, CTX, tacrolimus, budesonide (21 mo) | AFB and positive culture and PCR on duodenal biopsy | RFB, CLR, CIP (24 mo) | Cured |
| Sharifian et al, 2009 [33]          | M   | 39  | GI tract, abdominal LN | Myasthenia, CTX, AZA, cyclosporine | Positive PCR on duodenal biopsy | RIF, CLR, MOX, EMB | Cured |
| Escapa et al, 2010 [34]             | M   | 67  | GI tract, abdominal LN | Renal transplant, CTX, AZA (18 mo) | AFB on intestinal and positive culture on stool | CLR, EMB, LVX | Cured |
| Doggett & Strasfeld, 2011 [35]      | M   | 64  | Lung, mediastinal and abdominal LN, BM | Renal transplant, CTX, MMF, tacrolimus (36 mo) | AFB and positive PCR on LN, Positive blood culture on blood and BM and positive PCR on MB | AZM, RFB, MOX, EMB (12 mo) | Cured |
| Rammaert et al, 2011 [36]           | M   | 44  | Culture and positive PCR on sputum | Renal transplant, CTX, MMF, tacrolimus (36 mo) | | CLR, RFB, MOX, EMB (>24 mo) | Cured |
| Charles et al, 2011 [37]            | M   | 63  | SPM, hepatomegaly, abdominal LN, lung, intestinal tract | Liver transplant, CTX, MMF, tacrolimus (24 mo) | AFB on LN and sputum, Positive PCR | RIF, CLR, EMB, INH | Died |
|               | F   | 37  | SPM, hepatomegaly, abdominal LN, intestinal tract | Heart transplant, CTX, MMF, tacrolimus (28 mo) | AFB on intestinal biopsy and abdominal LN, Positive PCR | CLR, AMK, EMB, MXF | Cured |
|               | F   | 41  | Intestinal tract, BM, urine, hepatomegaly, mediastinal and abdominal LN | Renal transplant, CTX, MMF, tacrolimus (39 mo) | AFB on urine, liver, jejunal, and BM biopsy, Positive PCR | CLR, AMK, EMB, CIP | Cured |
|               | M   | 72  | Urine, BM, SPM, pleural effusion | Sarcoïdosis, CTX (9 mo) | AFB on urine, BM and spleen, Positive PCR | RIF, EMB, INH | Died |
| Author, Publication Year | Patient Age/ Sex | Organ(s) Involved | Microbiologic Findings | Treatment | Outcome |
|--------------------------|------------------|-------------------|------------------------|-----------|---------|
| Santos et al, 2014 [37]  | 32/F | No treatment | Skin and soft tissue abscess | AFB on pus, Positive PCR | RIF, EMB, CLR | Cured |
| Guitard et al, 2012 [37] | 56/M | Heart transplant, MMF, cyclosporine (96 mo) | BM, abdominal and mediastinal LN, duodenum | AFB on BM, mediastinal LN and duodenal LN biopsy, PCR positive on duodenal and LN | RFB, CLR, AMK, EMB, MOX (12 mo), Reduced IS therapy, Stopped MMF | Improved, remained on treatment |
| Lhuiller et al, 2012 [38] | 43/F | Lung transplant, MMF, tacrolimus (84 mo) | Mediastinal LN, lung | AFB, culture, and PCR positive on sputum | CLR, EMB, AMK | Cured |
| Lorensen et al, 2012 [39] | 52/M | Lung transplant | Lung and pleural effusion, abdominal LN, intestinal tract | AFB on lung and colon and LN biopsy, Positive culture on stool | RIF, CLR, CIP | Unknown |
| Potjewijd et al, 2012 [39] | 43/F | IL-12/IL-23 receptor deficiency | BM, cervical and abdominal LN, hepatomegaly, SPM | AFB on LN and BM, Positive culture on blood and sputum, PCR positive on LN, BM, blood, and sputum | RIF, EMB, CLR (18 mo) | Cured |
| Tassone et al, 2013 [40] | 35/F | Heterozygous mutations of β1 subunit of IL-12 receptor gene, Autoimmune hepatitis | BM, liver, abdominal LN, duodenum, ascites | AFB on BM, liver, LN, and duodenal biopsy, Positive PCR on liver biopsy | RFB, CLR, MOX (27 mo), + INF-γ, Stopped IS therapy | Improved, remained on treatment |
| Nambi et al, 2014 [41] | 51/F | Seronegative arthritis | Mediastinal, cervical, supraclavicular, abdominal LN, lung, subcutaneous nodules | AFB and positive PCR on subcutaneous nodules and LN | RFB, AMK, MOX, AZM (24 mo) | Cured |
| Santos et al, 2014 [42] | 66/M | Renal transplant (48 mo) | Intestinal tract, lung | AFB, positive PCR and culture on stool | CLR, EMB, LVX | Cured |
| 28/F | HSCT (12 mo) | Intestinal tract, BM, lung | AFB on stool and BM, Positive culture on blood, stool, and BM | RIF, CLR, EMB (6 mo) | Died |
| 52/F | Heart transplant (72 mo) | Intestinal tract, BM, lung, and pleural effusion, splenomegaly, abdominal LN, liver | AFB on lung biopsy, Positive culture on blood and sputum, Positive PCR on stool, BM, spleen, and sputum | RIF, EMB, PZA, LVX (5 mo) | Died |
| Hoeslloot et al, 2013 [43] | 7/F | Hyper-IgE syndrome | Intestinal tract, lung | Positive PCR on stool | RIF, EMB, CLR, LVX | Cured |
| 55/M | Renal transplant (48 mo) | Skin and soft tissue abscess | AFB on pus, Positive PCR | RIF, EMB, CLR (18 mo) | Cured |
| 57/M | Sarcoïdosis | Lung | INNO-LIPA Mycobacteria v2 or 16S PCR positive on lung biopsy and sputum | RIF, CLR, MOX | Improved, remained on treatment |
| 63/M | Non-Hodgkin lymphoma, Chemotherapy with rituximab (3 mo) | Disseminated, BM | INNO-LIPA Mycobacteria v2 or 16S PCR positive on BM | RIF, EMB, CLR | Improved, remained on treatment |
| 73/F | Renal transplant | Disseminated, LN | INNO-LIPA Mycobacteria v2 or 16S PCR positive on LN | RIF, EMB, PZA, INH (1 mo) | Died |
| 54/F | Liver transplant, CTX, AZA (228 mo) | Disseminated, digestive tract, BM, mediastinal LN | INNO-LIPA Mycobacteria v2 or 16S PCR positive on blood, stool, BM | RIF, EMB, CLR (12 mo) | Chronic symptoms, remained on long-term treatment |
| 57/M | Interstitial nephritis with granuloma, CTX, cyclophosphamide | Disseminated, lung | INNO-LIPA Mycobacteria v2 or 16S PCR positive on sputum | RIF, EMB, CLR (14 mo) | Died |
| 42/M | Idiopathic CD4+ lymphopenia | Disseminated, BM | INNO-LIPA Mycobacteria v2 or 16S PCR positive on BM | RIF, EMB, CLR | Chronic symptoms, remained on long-term treatment |
| 72/M | Sarcoïdosis | CTX, AZA | Disseminated, BM | INNO-LIPA Mycobacteria v2 or 16S PCR positive on BM | RIF, EMB, CLR | Died |
| 43/M | IL-12 receptor deficiency | Disseminated, BM, cervical LN, lung | INNO-LIPA Mycobacteria v2 or 16S PCR positive on BM, sputum, cervical LN | RIF, EMB, CLR | Chronic symptoms, remained on long-term treatment |
### Table 1. Continued

| Author, Publication Year [Reference] | Patient Age/ Sex | Immunosuppression Type (Duration of IS Treatment Before Infection) | Organ(s) Involved | Microbiologic Findings | Treatment | Outcome |
|-------------------------------------|------------------|---------------------------------------------------------------|------------------|------------------------|-----------|---------|
| Renoult et al, 2013 [44]           | 48/M             | Renal and pancreatic transplant                              | Lung, mediastinal and abdominal LN, ascites, duodenum       | AFB and positive culture on duodenal biopsy                 | RFB, CLR, MXF (13 mo) | Died    |
| Mahmood et al, 2018 [13]           | 51/M             | Renal transplant                                              | Right knee arthroplasty                                     | Positive culture and PCR on knee arthroplasty              | RFB, CLR, CIP, clofazimine (24 mo) | Cured   |
| Asakura et al, 2017 [45]           | 66/F             | Idiopathic CD4+ lymphopenia                                    | Digestive tract, mediastinal and abdominal LN, renal mass    | Positive culture and PCR on blood and LN                  | RFB, CLR, MOX (7 mo) | Died    |
| Coelho et al, 2017 [12]            | 13/M             | H SCT                                                         | Abdominal LN, lung, liver, kidney, digestive tract          | AFB on LN and BAL                                          | RFB, AZM, EMB, CIP (12 mo) | Cured   |
| Ombelet et al, 2016 [46]           | 47/M             | Renal and heart transplant                                    | Supraclavicular, mediastinal, and abdominal LN              | AFB and positive PCR on LN                                 | RFB, CLR, AMK, EMB, MOX (13 mo) | Cured   |
| Gonzalez-Granado et al, 2019 [14]  | 3/M              | NF-kB1 deficiency                                             | Digestive tract, BM                                         | Positive PCR BM and gut                                   | RIF, CLR, EMB, LVX (24 mo) | Cured   |
| Grunebaum et al, 2020 [51]         | 22/F             | Adenosine deaminase deficiency                                 | Digestive tract                                             | AFB on stool and intestinal biopsy                         | RIF, AZM, CIP (12 mo) | Cured   |
| Hosoda et al, 2020 [47]            | 73/M             | RA, CTX, MTX (72 mo)                                          | Lung, mediastinal LN                                        | AFB on sputum and BAL fluid                               | RIF, CLR, EMB (>12 mo) | Cured   |
| Ito et al, 2020 [48]               | 53/M             | EBV-positive LPD                                              | Mediastial, abdominal, and inguinal LN                      | AFB and positive PCR on sputum                             | RIF, CLR, EMB (17 mo) | Cured   |
| Case 1                             | 50/M             | Renal transplant CTX, MMF, cyclosporine (84 mo)               | Digestive tract, disseminated LN,                           | AFB on supraclavicular LN                                  | ETM, CLR, RIF (24 mo) | Chronic |
|                                     |                  |                                                               |                                                              | Positive culture and PCR on LN                             | changed to ETM, CLR, RIF, MOX (14 mo) | symptoms, on treatment |
|                                     |                  |                                                               |                                                              |                                                                  | INF-γ (12.0 mo 3 times per wk) |                   |
|                                     |                  |                                                               |                                                              |                                                                  | Stopped MMF and tacrolimus |                   |
| Case 2                             | 37/F             | Renal transplant                                              | LN, digestive tract, ascites, pleural effusion, liver,      | AFB on BM, sputum, urine, colon, duodenal and cutaneous     | RIF, MOX, CLR, LNZ | Chronic |
|                                     |                  |                                                               |                                                              | biopsy                                                     | Stopped MMF and tacrolimus | symptoms, on treatment |
|                                     |                  |                                                               |                                                              | Positive culture and PCR on BM                             |                                                                     |                   |

Abbreviations: AFB, acid-fast bacilli; AMK, amikacin; AZA, azathioprin; AZM, azithromycin; BAL, bronchoalveolar lavage; BM, bone marrow; CIP, ciprofloxacin; CLL, chronic lymphocytic leukemia; CLR, clarithromycin; CPX, ciprofloxacin; CTX, corticosteroid; EMB, ethambutol; EBV, Epstein-Barr virus; F, female; GI, gastrointestinal; H SCT, hemato poetic stem cell transplant; IFN-γ, interferon gamma; IL, interleukin; INH, isoniazid; IRIS, immune reconstitution inflammatory syndrome; IS, immunosuppressive; IV, intravenous; LN, lymph node; LNZ, linezolid; LPD, lymphoproliferative disease; LVX, levofloxacin; M, male; MMF, mycophenolate mofetil; MOX, moxifloxacin; MTX, methotrexate; OFX, ofloxacin; PCR, polymerase chain reaction; PZA, pyrazinamid; RA, rheumatoid arthritis; RFB, rifabutin; RIF, rifampicin; SLE, systemic lupus erythematosus; SM, spectinomycin; SPM, splenomegaly; TNF-α, tumor necrosis factor alpha.

**Case 2**

A 37-year-old woman was admitted in April 2020 for fever, night sweats, diarrhea, weight loss, abdominal pain, cough, and erythema nodosum. She had undergone 3 renal transplants (1987, 1990, and 2010) for Denys-Drash syndrome. Maintenance immunosuppressive treatment consisted of tacrolimus, MMF, and prednisone. Blood tests revealed anemia (6.6 g/dL), neutropenia (910 cells/µL), and inflammatory syndrome (CRP level of 109 mg/L). The CD4+ T-lymphocyte count was 174 cells/µL. An analysis of BM showed that sputum, urine, colon, duodenal, and cutaneous biopsies were positive for AFB. The BM culture was positive 5 months later, and *M. genavense* was identified with a molecular technique (hsp65 PCR). Gastroscopy revealed inflammation of the duodenum, and colonoscopy was normal except for the presence of a polypl in the sigmoid colon. A CT scan showed bilateral pleural effusion, mesenteric and retroperitoneal LNs, splenomegaly, hepatomegaly, ascites, and jejunoileitis. PET/CT scans confirmed
previous results with hypermetabolic abdominal LNs. The patient successively received (1) rifampicin, clarithromycin, and ethambutol (April to May 2020); (2) rifampicin, ethambutol, amikacin, and azithromycin because of digestive intolerance to clarithromycin (May 2020 to June 2020); (3) rifampicin, azithromycin, and clofazimine due to the ototoxicity of amikacin and visual alteration induced by ethambutol (June 2020 to July 2020); and (4) rifampicin, azithromycin, moxifloxacin, and linezolid (from July 2020), and MMF and tacrolimus were discontinued. Diarrhea rapidly resolved, but she still had a febrile peak several times a week. The PET/CT scan performed in October 2020 showed a worsening of the diseases with an increased number and size of LNs (mediastinal, mesenteric, and retroperitoneal), a new sigmoid colon hypermetabolic signal, stability of pleural effusion, and an increased hypermetabolic signal of the BM and spleen. A new colonoscopy revealed diffuse adenomatous polyposis and adenocarcinoma of the sigmoid. She underwent a left colectomy in April 2021. A diagnosis of IRIS was suspected based on the worsening condition after MMF and tacrolimus discontinuation. Corticosteroids were started, but she became dependent on this treatment. Because of corticosteroid-dependent IRIS, treatment with an anti–tumor necrosis factor alpha (TNF-α) antibody was initiated. After 2 injections, symptoms of IRIS were resolved. In March 2022 she was still receiving antimicobacterial treatment for the persistence of digestive chronic symptoms.

**Patient Demographics and Characteristics of Infection**

**Patient Demographics**

Patient characteristics are summarized in Supplementary Data 1 and 2. The median age of patients was 51 years (range, 3–80 years) with a male preponderance (sex ratio, 1.6). The most common underlying immunosuppressions were SOT (21/52 [40.4%]), autoimmune disease (19/52 [36.5%]), hematological disorder (6/52 [11.5%]), and primary immunodeficiency (PID) (6/52 [11.5%]). Five cases of PID and 1 case of autoimmune disease (neutralizing anti–IFN-γ autoantibodies) were revealed by this mycobacterial infection, whereas immunosuppression was already diagnosed in the other patients. Thirty-four patients received immunosuppressive (IS) therapy (34/46 [73.9%]) with a median duration before the diagnosis of mycobacterial infection of 39 months (range, 1–228 months). The most frequent IS treatments were corticosteroids (n = 31 [67.4%]), MMF (n = 15 [32.6%]), and tacrolimus (n = 10 [21.7%]). A total of 31 (67.4%) reported patients received >1 IS treatment.

**Clinical Features**

Infection was limited to the skin and soft tissue in 2 patients, lung in 3 patients, diffuse intestinal bowel in 1 patient, and bone and joint involvement in 1 patient [11, 13, 23, 43, 47, 51].

**Mycobacterium genavense** infection was mainly disseminated (45/52 [86.5%]). The main organs involved were LN (3/474 [72.3%]), gastrointestinal tract (26/46 [56.5%]), lung (16/45 [35.5%]), liver and spleen (17/47 [36.2%]), and BM (15/52 [28.8%]) (Supplementary Data 1). The median blood CD4+ count was 143 cells/µL (range, 2–285 cells/µL). Radiological examinations of pulmonary disease showed nodes (9/16) with cavitation in 3 patients, alveolar and interstitial infiltrates (2/16), pleural effusion (2/16), bronchiolar inflammation (1/16), and bronchial mass (1/16) [11, 12, 21, 31, 36, 38, 41–43, 47].

**Diagnosis**

*Mycobacterium genavense* grew in culture after the collection of samples from 23 patients (23/43 [53.4%]) with a median delay of 7 weeks (range, 1.5–30 weeks). The culture was positive in liquid media for 8 patients [23, 26, 32, 42] and in solid media for 3 patients [13, 23]. Data were not available for the other cases. Antibiotic susceptibilities were assessed for isolates from 3 patients [34, 42]. All isolates were susceptible to rifampicin and streptomycin; 1 isolate was susceptible to pyrazinamide, and 1 was susceptible to ethambutol. Two isolates were resistant to isoniazid. Mycobacterial growth in cultures was reported from different samples, including blood (n = 7), digestive tract (n = 8), BM (n = 6), sputum (n = 3), or LN (n = 2). AFB were mainly identified in stool/intestinal biopsy (n = 17), LN (n = 15), or BM (n = 15) samples. Histological findings of mycobacterial infection were reported in 11 patients [11/36 [30.5%]]. *Mycobacterium genavense* was identified with molecular techniques (16S rRNA, rpoB, or hsp65 gene analysis, gene sequencing, or reverse hybridization of amplicons of the inter-16S-23S rRNA polymorphic spacer region) in 51 of 52 (98%) patients (Supplementary Data 2).

**Treatments and Outcomes**

Most patients were treated with at least 3 antimycobacterial drugs (48/49 [98%]), with a clinical cure achieved in 54.9% of patients (28/51) (Supplementary Data 1). Clarithromycin or azithromycin was used in drug regimen therapy in 93.9% of patients (49/51), rifampicin or rifabutin in 79.6% of patients (39/49), ethambutol in 75.5% of patients (37/49), and fluoroquinolones in 65.2% of patients (32/49) (Supplementary Data 1). Two patients did not receive mycobacterial treatment because the diagnosis was postmortem, and treatment was not reported for 1 patient. Data for the treatment duration were available for 29 patients, which ranged from 1 to 48 months with a median duration of 13 months. Despite the use of different antimycobacterial strategies, the medical condition worsened for 3 patients, and IFN-γ was initiated, leading to an improvement of symptoms in all patients [25, 40]. One patient received IFN-γ therapy at doses up to 200 µg/m², 1 received a dose of 100 µg 3 times weekly, and our patient received a dose of 85 µg 3 times weekly for 1 year. Two patients developed IRIS due to a...
were systemic lupus erythematosus (SLE) and renal transplant. The CD4⁺ counts were 17 cells/µL and 174 cells/µL, respectively. The symptoms of 5 patients improved but they remained under treatment, and 4 patients experienced chronic symptoms and were not considered cured. Fourteen patients died (27.5%), and 2 patients had a recurrence of M genavense infection 21 months and 4 years after complete remission [22, 51].

Univariate and Multivariate Analyses of Risk Factors Associated With Not Being Cured

According to the univariate analysis, age, sex, underlying immunosuppressive conditions (SOT, hematological disorders, or autoimmune/PID disease), duration of IS treatment before infection, and number of antimycobacterial treatments were not associated with an increased risk of remission failure. In the multivariate analysis, BM involvement and age were associated with a risk of not being cured (odds ratio [OR], 15.81 [95% confidence interval {CI}, 2.92–152.93]; P = .005 and OR, 1.05 [95% CI, 1.01–1.12]; P = .042, respectively) (Table 2).

DISCUSSION

NTM consists of >190 distinct species of ubiquitous environmental organisms that are often found in soil and water [52]. Annual prevalence of NTM infection in the United States ranges from 1.4 to 13.9 per 100,000 persons and seems to increase from 2.5% to 8% per year [53]. In a snapshot of the NTM species distribution in 30 countries across 6 continents (n = 20,182 patients), M avium complex was the most frequent mycobacteria (47%), followed by Mycobacterium gordonae (11%) and Mycobacterium xenopi (8%), with important differences in geographical distribution [54]. Mycobacterium abscessus and Mycobacterium fortuitum were the most frequently isolated rapidly growing mycobacteria (RGM) worldwide with the highest prevalence in East Asia (up to 27% of NTM) [54]. However incidence of M abscessus, the most commonly identified NTM species responsible for severe respiratory and skin and mucosal infections, has increased during the last decade in Western Hemisphere countries, especially in patients with cystic fibrosis [53, 55].

Estimated prevalence of NTM infection in SOT is between 0.16% and 4.4% and the causative species varies by the type of organ transplant [56]. For example, RGM represents approximatively 40% of NTM infection of renal transplant recipients and 10% of heart and lung transplant recipients [56]. Mycobacterium genavense is a rare and slow-growing group III NTM leading to infection in immunocompromised hosts [1, 11, 43, 57]. The prevalence of M genavense infection in PLWH in a Swiss cohort, but before the introduction of ART, was 12.8% of NTM infections [9]. In this review, we focused on immunocompromised hosts without HIV. We reported 52 cases of M genavense infection in this population. As expected, SOT was the most frequent underlying immunocompromised condition (n = 21 [40.4%]), followed by autoimmune disease (n = 19 [36.5%]), but none of these immunodeficiencies were associated with an increased risk of not being cured. In this population, 73.9% of patients received at least 1 immunosuppressive therapy with a median time to infection of 39 months (range, 1–228 months). However, even in SOT or hematopoietic stem cell transplant (HSCT) recipients, M genavense is a rare cause of NTM infection [55, 56, 58]. Immunodeficiency was revealed by M genavense infection in 6 patients. Four patients were diagnosed with interleukin 12 (IL-12)/IFN-γ pathway disorders (1 with a neutralizing anti–IFN-γ autoantibody and 3 with IL-12 receptor deficiency) [39, 40, 43, 45]. Immunity against intracellular pathogens such as mycobacteria depends on an effective cell-mediated immune response. Susceptibility to mycobacterial disease is also associated with IL-12/interleukin 23/IFN-γ impairment [59–61]. Dendritic cells and macrophages phagocytize mycobacterial pathogens through innate pattern recognition receptors, especially Toll-like receptors (TLRs) 2 and 4. Activation of these TLRs induces the production of IL-12 and TNF-α. IL-12 stimulates IFN-γ production by natural

| Characteristic                      | Not Cured (n = 23) | Cured (n = 28) | Value |
|-------------------------------------|-------------------|---------------|-------|
| Age, y, median (IQR)                | 56.00 (45.00–64.50) | 44.50 (37.00–55.25) | .068  |
| Female sex                          | 10 (43.5)         | 10 (35.7)     | .782  |
| Immunodeficiency                    |                   |               | .999  |
| Solid organ transplant              | 8 (34.8)          | 12 (42.9)     |       |
| Hematological disorder              | 2 (8.7)           | 4 (14.3)      |       |
| Autoimmune disease and primary immunodeficiency | 13 (56.5) | 12 (42.9) |       |
| Duration of IS treatment before infection, (months), median (IQR) | 48.00 (8.75–102.00) | 39.00 (28.00–60.00) | .871  |
| Positive blood culture              | 3 (13.0)          | 5 (17.9)      | .933  |
| Digestive tract                    | 10 (58.8)         | 15 (53.6)     | .973  |
| Lymph node                         | 15 (83.3)         | 21 (75.0)     | .762  |
| Lung                               | 4 (25.0)          | 9 (32.1)      | .876  |
| Bone marrow                        | 13 (61.9)         | 7 (25.0)      | .021  |
| Antimycobacterial therapy, No. of treatments | 2               | 3             | .933  |
|                                    | 15 (71.4)         | 14 (51.9)     |       |
|                                    | 4 (19.0)          | 10 (37.0)     | .373  |
|                                    | 1 (4.8)           | 2 (7.4)       |       |
|                                    | 1 (4.8)           | 0 (0.0)       |       |
| Fluoroquinolones                   | 12 (57.1)         | 19 (70.4)     | .518  |
| Ethambutol                         | 14 (66.7)         | 23 (89.2)     | .243  |
| Macrolide and rifampicin regimen    | 4 (19.0)          | 9 (33.3)      | .437  |

Data are presented as No. (%) unless otherwise indicated. Abbreviations: IQR, interquartile range; IS, immunosuppressive.
killer cells and stimulates the differentiation of specific Th1 cells, which also produce IFN-γ. In synergy with TNF-α, IFN-γ activates infected macrophages, a major effector mechanism of cell-mediated immunity [39, 59, 62]. Some patients who seem apparently healthy may be predisposed to mycobacterial infections due to Mendelian susceptibility to mycobacterial disease or another inherited or acquired adult-onset immunodeficiency [60, 63]. Immune screening, especially of the IL-12/IFN-γ pathway, should be performed in these supposedly “healthy” patients.

This review reports that the infection was mainly disseminated (86.5%) and preferentially involved LNs, gastrointestinal tract, lung, and BM, which was associated with a worse prognosis in univariate and multivariate analyses. The median duration of IS therapy prior to M genavense infection was 39 months (range, 1–228 months), which is higher than other NTM infections reported in SOT recipients (ranging from 4.2 months in HSCT patients to 30 months in patients with heart transplants) [58]. The mean delay between SLE or rheumatoid arthritis (RA) diagnosis and NTM infection was 9.3 ± 5.8 years and 6.7 ± 4.3 years, respectively [64, 65]. Compared to this review, NTM infection in patients with autoimmune disease or SOT is more localized than disseminated. In patients with SLE, disseminated NTM infection occurs in 0.09% of patients and ranges from 0 to 18.2% in patients living with RA [64–67]. For SOT patients, disseminated NTM infection is common but is the second mode of presentation in renal transplant recipients and the third most common presentation in heart and lung transplant recipients [58].

Wetzstein et al performed a literature review of all cases of M genavense infection (PLWH and patients without HIV) [68]. They included 233 patients, most of them living with HIV (n = 171 [76.7%]). They did not perform subgroup analysis to compare PLWH versus immunocompromised patients without HIV regarding clinical or biological characteristics, treatment, and mortality. Our retrospective cohort only concerns immunocompromised patients without HIV and compared to their literature review, which mainly includes PLWH (76.7%), we found a different clinical presentation. Pulmonary involvement and LN infiltration seem to be more frequent in immunocompromised patients without HIV (35.5% vs 9.5%–12.6% and 72.3% vs 48.6%, respectively) as well as BM involvement, which is not reported in their literature review. Gastrointestinal tract involvement and hepatosplenomegaly seem to be similar between the 2 populations [68].

The diagnosis of M genavense infection remains a challenge for physicians because of the absence of specific symptoms and difficulties in culturing the organism [9–11, 17, 20, 69]. For all mycobacterial analyses, culture should include solid and broth (liquid) media for the detection and enhancement of growth. The system mainly used for liquid media is the nonradiometric MGIT, which contains a modified Middlebrook 7H9 broth in conjunction with a fluorescence quenching–based oxygen sensor to detect mycobacterial growth. Standard solid media such as Lowenstein-Jensen agar or Middlebrook 7H10 and 7H11 media fail to support M genavense growth. Solid media must be supplemented with Mucobactin J, and the incubation period should be at least 12 weeks for both culture media [10, 17, 20, 70]. A direct examination of samples showed AFB in 94.4% of cases (42/44), and despite adequate liquid and solid media culture, M genavense grew slowly after the collection of samples from 23 of 43 patients (53.4%) with a median delay of 7 weeks (range, 1.5–30 weeks). Culture was positive in liquid media for 8 patients and in solid media for 3 patients, but identification required molecular techniques in 98% of patients. These results are similar to previous studies on PLWH with a positive culture detected in 30%–50% of cases [10, 11, 70]. Molecular techniques, such as amplification and sequencing of the 16S rRNA, hsp65, or rpoB genes or reverse hybridization of amplicons of the inter-16S-23S rRNA polymorphic spacer region, are frequently used before the culture becomes positive, especially for immunocompromised patients with a positive AFB smear and negative PCR for Mycobacterium tuberculosis [16, 20, 69–73]. However, these techniques may be directly performed on samples (eg, blood, LN, intestinal biopsy, sputum, BM), regardless of the result of the AFB smear. Direct molecular biological methods might better identify M genavense infection and improve the prognosis.

Because of the extreme fastidiousness of M genavense to growth, the optimal regimen and duration for this infection have not been established. Available data regarding drug susceptibilities suggested that most isolates are susceptible to rifampicins, streptomycin, fluoroquinolones, amikacin, and macrolides [17, 19, 20, 34, 42, 69]. Most isolates are resistant to ethambutol and isoniazid, and one-third of isolates are resistant to clofazimine [42, 69]. In the literature review, most treatment regimens were based on at least a combination of 3 treatments, which often included macrolides (93.9%), rifampicins (79.6%), ethambutol (75.5%), and fluoroquinolones (62.5%). In the study by Charles et al [11], most patients (with or without HIV) were treated with a combination of rifabutin, clarithromycin, and ethambutol. However, the correlation between in vitro susceptibility and clinical outcomes has not been determined. Multidrug therapy (at least 3), including macrolides, seems to be more effective [15, 68]. Unfortunately because of its fastidious difficulty to grow and its rarity, no data are available regarding resistance mechanisms. Molecular methods (such as whole genome sequencing or multiplex PCR) could help to identify drug resistance and its mechanisms, such as for M tuberculosis [74]. However, there is no publication available for M genavense.

Wetzstein et al found, before and after the exclusion of PLWH before the ART era, that survival was significantly worse in patients without a macrolide-containing regimen [68].
In our cohort, a treatment regimen with macrolide was reported in 93.9% of patients (n = 46/49); therefore, in our analysis no antimicrobial regimen (number, duration, or combination) was associated with a better outcome. The ATS/IDSA, European Respiratory Society, and European Society of Clinical Microbiology and Infectious Diseases guidelines recommend a combination of azithromycin, rifampicin, and ethambutol and, in case of intolerance or drug resistance, moxifloxacin, amikacin, or clofazimine [15]. The optimal duration is also not established, but treatment should be continued until at least 12 months postconversion to culture negative to complete the treatment regimen [15, 20]. In this literature review, the median duration of treatment was 13 months (range, 1–48 months), but data were available for only 29 patients (range, 1–48 months), and an important part of the management of this infection is to reduce immunosuppression to restore immunity. Among patients receiving IS therapy, 44.3% stopped or reduced the treatment. Two patients developed IRIS. Physicians should be aware of this complication in patients who require an important reduction in immunosuppressive therapy, and a progressive reduction should be preferred. Despite the use of different multidrug therapies, the conditions of 3 patients worsened and they received IFN-γ in addition to antimycobacterial therapy. This therapy improved symptoms in all patients. As previously described, IL-12 and IFN-γ are necessary for clearing M genavense infection [61]. IFN-γ treatment might help to improve the immune response and symptoms, especially in patients with an IFN-γ deficiency. However, only limited data are available on the role of IFN-γ treatment in the treatment of tuberculosis or NTM infection. In a randomized, double-blind, placebo-controlled study, 32 patients were treated with either intramuscular IFN-γ and antimycobacterial therapy or antimycobacterial therapy and placebo for NTM pulmonary infection. The overall response in the IFN-γ group was significantly higher than that in the antimycobacterial therapy–alone group (72.2% vs 37.5% complete responders, respectively). A total of 11.1% of patients in the IFN-γ–treated group died compared with 35.7% of patients in the control group [75]. In a pilot study, 8 patients were treated with IFN-γ for multidrug-resistant tuberculosis in addition to antibiotics, leading to a reduction in lesion sizes and negative sputum smears and cultures [76]. Its prescription should be discussed with a reference center for mycobacterial infection to evaluate the benefit/risk balance of this treatment due to a risk of iatrogenic IRIS and should be limited to patients who are not responding well to therapy. In PLWH, a low CD4 count (< 500 cells/μL) is a major risk factor for IRIS, and IFN-γ is discussed as having an important pathogenic role [77]. In SOT recipients and other immunocompromised patients without HIV, the IRIS prevalence is not known, but posttransplant IRIS is rare and remains poorly studied. Thus, risk factors for IRIS in this population have not been established, and management is based on IRIS treatment in PLWH [49, 50].

**Mycobacterium genavense** infection has a poor prognosis in this population, with a mortality rate of approximately 30%. However, we are not always able to report whether death is a direct consequence of *M genavense* infection. In PLWH, before the era of ART, the median survival after *M genavense* infection ranged from 6.3 to 10.7 months and the mortality rate was estimated to be 89.9% after 24 months. In the most recent literature review, 5-year mortality for PLWH after the introduction of ART was 39.3%. Survival improved substantially because of the combination of ART and antimycobacterial therapy [68]. In Mahmood and colleagues’ systematic review in 2017 (n = 44), they found no correlation between mortality and age, underlying immunosuppressive disease, disseminate disease, or drug management in univariate analysis, and no multivariate analysis was performed [13]. However, in our updated review compared to Mahmood et al. (n = 52 [-18%]), age and BM involvement were associated with a failure of complete remission in the multivariate analysis. These results confirmed what we suspected: Elderly patients with BM involvement reflecting the importance of disseminated disease are difficult to treat and to cure.

Our study has several limitations. First, most patients were derived from case reports, and data were missing for some patients, especially the outcomes. Indeed, some patients experienced chronic symptoms or were still receiving treatment when the case report was published, and we do not know the final outcome. Consequently, for our analysis, we chose a composite criteria: complete remission versus nonremission, including death; chronic symptoms; and improved symptoms but remaining under treatment. This composite criteria might introduce bias, and some patients with chronic symptoms or with an improvement of symptoms could be in complete remission or die. The 2 patients with a postmortem diagnosis were included in the analysis to show the difficulty in diagnosing this disease. But it could also induce a bias because these 2 patients increased the rate of not being cured while they did not have “a chance” to receive an appropriate treatment. There is also risk of publication bias in this literature review mainly composed of case series/reports, where only complicated cases of *M genavense* or patients with poor outcomes/or positive outcomes with novel therapies are likely to be published. Furthermore, this literature review does not provide information on the prevalence of *M genavense* infection in patients without HIV, and thus we only conclude that infection is rare. Because of nonconsensual guidelines for treatment, the antimycobacterial regimen varied between patients, and we were unable to determine if one regimen or duration was associated with complete remission.

**CONCLUSIONS**

*Mycobacterium genavense* infection is a rare cause of mycobacterial infection in immunocompromised patients without HIV.
Compared to other NTM infections in this population, this disease is mainly disseminated with frequent involvement of the digestive tract and BM, with a poor prognosis. The optimal treatment regimen and its duration remain to be established, but IS therapy must be decreased. Mycobacterium genavense infection should be considered in the differential diagnosis of mycobacteria detected with AFB staining but not with culture, even in patients without known evidence of immunodeficiency. IFN-γ might be discussed for patients without an improvement despite treatment with antitycobacterial therapy.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors. A.B. and R.C. analyzed data and drafted the report. All authors read and approved the final report.

Potential conflicts of interest. The authors: No reported conflicts.

Notes

Author contributions. A.B., S.D., A.T.-L., C.D., and R.V. collected data. A.B. and R.C. analyzed data and drafted the report. All authors read and approved the final report.

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