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Risk Factors for Nontuberculous Mycobacteria Infections in Solid Organ Transplant Recipients: A Multinational Case-Control Study

Carlos Mejia-Chew,[1] Peggy L. Carver,[2] Sasinuch Rutjanawech,[1] Luis F. Aranha Camargo,[3] Ruan Fernandes,[3] Sara Belga,[4] Shay-Anne Daniels,[4] Nicolas J. Müller,[5] Sara Burkhard,[5] Nicole M. Theodoropoulos,[6] Douwe F. Postma,[7] Pleun J. van Duijn,[8] María Carmen Fariñas,[9,10] Claudia González-Rico,[9,10] Jonathan Hand,[11] Adam Lowe,[11] Marta Bodro,[12] Elisa Vanino,[13,14] Ana Fernández Cruz,[15] Antonio Ramos,[15] Mateja Jankovic Makek,[16] Ribal Bou Mjahed,[17] Oriol Manuel,[17] Nassim Kamar,[18] Antonia Calvo-Cano,[19] Laura Rueda Carrasco,[19] Patricia Muñoz,[20] Sara Rodríguez,[20] Sandra Pérez-Recio,[21] Núria Sabé,[21] Regino Rodríguez Álvarez,[22] José Tiago Silva,[23,24] Alessandra Mularoni,[25] Elisa Vidal,[26] Juana Alonso-Titos,[27] Teresa del Rosal,[28] Annika Y. Classen,[29,30] Charles W. Goss,[1] Mansi Agarwal,[1] and Francisco López-Medrano[23,24]; on behalf of the EMOTE study group

[1]Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA; [2]College of Pharmacy, The University of Michigan, Ann Arbor, Michigan, USA; [3]Hospital Israelita Albert Einstein, São Paulo, Brazil; [4]Division of Infectious Diseases, Department of Medicine, The University of British Columbia Faculty of Medicine, Vancouver, Canada; [5]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Switzerland; [6]Department of Medicine, Division of Infectious Diseases & Immunology, UMass Chan Medical School, Worcester, Massachusetts, USA; [7]Department of Internal Medicine and Infectious Diseases, University Medical Center Groningen, The Netherlands; [8]Department of Clinical Microbiology, University Medical Center Groningen, The Netherlands; [9]Infectious Diseases Service, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Spain; [10]CIBERINFEC (CB21/13/00068), ISCIII, Madrid, Spain; [11]Department of Infectious Diseases, Ochsner Medical Center, New Orleans, Louisiana, USA; [12]Hospital Clinic Barcelona, Spain; [13]Infectious Diseases Unit, IRCCS Policlinico Sant'Orsola, University of Bologna, Italy; [14]Infectious Diseases Unit, Ravenna Hospital, AUSL Romagna, Italy; [15]Internal Medicine Department, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; [16]University Hospital Center Zagreb, University of Zagreb School of Medicine, Croatia; [17]Lausanne University Hospital (CHUV), University of Lausanne, Switzerland; [18]Department of Nephrology and Organs Transplantation, Toulouse Rangueil University, INSERM UMR 1291, Toulouse Institute for Infectious and Inflammatory Disease (Infinity), Paul Sabatier University, Toulouse, France; [19]Infectious Disease Department, University Hospital Badajoz, Badajoz, Spain; [20]Hospital Gregorio Marañón, Madrid, Spain; [21]Tuberculosis Unit, Department of Infectious Diseases, Bellvitge University Hospital Bellvitge University Hospital-Bellvitge Biomedical Research Institute (IDIBELL), University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain; [22]Hospital Universitario Cruces, Barakaldo, Spain; [23]Unit of Infectious Diseases, University Hospital 12 de Octubre, Instituto de Investigación del Hospital 12 de Octubre (imas12), School of Medicine, Universidad Complutense, Madrid, Spain; [24]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC; CB21/13/00009), Instituto de Salud Carlos III, Madrid, Spain; [25]IRCC-ISMETT, Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo, Italy; [26]Infectious Diseases Service, Reina Sofia University Hospital, Madrid, Spain; [27]Nephrology Department, Hospital Regional Universitario de Málaga, Málaga, Spain; [28]Pediatric Infectious and Tropical Diseases Department, Hospital Universitario La Paz, Madrid, Spain; [29]Faculty of Medicine and University Hospital Cologne, Department I for Internal Medicine, University of Cologne, Cologne, Germany; and [30]German Centre for Infection Research (DZIF), partner site Bonn-Cologne, Cologne, Germany

Background. Risk factors for nontuberculous mycobacteria (NTM) infections after solid organ transplant (SOT) are not well characterized. Here we aimed to describe these factors.

Methods. Retrospective, multinational, 1:2 matched case-control study that included SOT recipients ≥12 years old diagnosed with NTM infection from 1 January 2008 to 31 December 2018. Controls were matched on transplanted organ, NTM treatment center, and post-transplant survival greater than or equal to the time to NTM diagnosis. Logistic regression on matched pairs was used to assess associations between risk factors and NTM infections.

Results. Analyses included 85 cases and 169 controls (59% male, 88% White, median age at time of SOT of 54 years [interquartile range {IQR} 40–62]). NTM infection occurred in kidney (42%), lung (35%), heart and liver (11% each), and pancreas transplant recipients (1%). Median time from transplant to infection was 21.6 months (IQR 5.3–55.2). Most underlying comorbidities were evenly distributed between groups; however, cases were older at the time of NTM diagnosis, more frequently on systemic corticosteroids and had a lower lymphocyte count (all $P < .05$). In the multivariable model, older age at transplant (adjusted odds ratio [aOR] 1.04; 95 confidence interval [CI], 1.01–1.07), hospital admission within 90 days (aOR, 3.14; 95% CI, 1.41–6.98), receipt of antifungals (aOR, 5.35; 95% CI, 1.7–16.91), and lymphocyte-specific antibodies (aOR, 7.73; 95% CI, 1.07–56.14), were associated with NTM infection.

Conclusions. Risk of NTM infection in SOT recipients was associated with older age at SOT, prior hospital admission, receipt of antifungals or lymphocyte-specific antibodies. NTM infection should be considered in SOT patients with these risk factors.

Keywords. nontuberculous mycobacteria; solid organ transplant; risk factors; NTM.

Nontuberculous mycobacteria (NTM) are environmental microorganisms that cause pulmonary, extrapulmonary, or disseminated disease [1]. The incidence of NTM pulmonary disease (NTM-PD), the most common presentation, has been increasing in the last decades [2, 3]. In many countries, prevalence of NTM-PD has surpassed that of tuberculosis [4].

In solid organ transplant (SOT) recipients the use of immunosuppressant's to prevent graft rejection, pose a particular increased risk of infection [5, 6]. Although NTM infections in SOT are thought to be rare, the true incidence is unknown due to the lack of mandatory reporting for NTM. The estimated frequency of NTM infection in SOT varies by the transplanted organ, highest in lung (0.46–14%), followed by heart (0.24–2.8%), kidney (0.16–0.38%), and liver recipients (0.04%) [7, 8]. There are no estimates for pancreatic or small bowel recipients [9].

Furthermore, distinguishing between colonization and infection is often difficult. In a single-center study over a 10-year period, 1.5% of SOT recipients had positive cultures, but 82% of those NTM isolates represented colonization; hence, only 0.26% had disease [10]. Knoll et al found that airway colonization in lung transplant was not associated with decreased median post-transplant survival [11].

Risk factors for NTM infection in SOT recipients are not well characterized. A case-control study found that lung transplant recipients and those with biopsy-proven acute rejection were at highest risk of NTM disease [12]. Katsolis et al, looking exclusively at lung transplant recipients, found increased risk of disease in those with underlying cystic fibrosis, receipt of anti-thymocyte globulin, and NTM infection before transplant [13]. Another study of lung transplant recipients found that almost a quarter had pre-transplant infection with the same NTM species [14]. Prior infection was also described by Huang et al as a risk factor for infection following transplantation, as well as receipt of a single lung transplant [15]. Shah et al found increased risk of NTM infection after lung transplantation in Black Americans and patients with high-risk cytomegalovirus (CMV) mismatch [8]. Because previous studies have been single center, limited to lung transplant recipients or a particular NTM species, the aim of this multinational study was to describe the clinical characteristics and risk factors for developing NTM infections after SOT.

METHODS

Study Design and Setting

Retrospective, multinational, 1:2 matched case-control study including SOT recipients diagnosed with NTM infection between 1 January 2008 and 31 December 2018. We established a multisite collaboration with 25 centers from 10 countries in Europe and America to study the epidemiology, clinical characteristics, management, and outcomes of transplant recipients with NTM disease (EMOTE study). All sites followed research regulations and obtained approval from their local institutional review board. Personal health information collected was compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and European General Data Protection Regulation (GDPR) data privacy laws; hence, informed consent was waived.

Participants

We included patients ≥12 years of age who had received a SOT prior to the NTM infection and met the case definition. NTM-PD needed to fulfil clinical, radiological, and microbiological diagnostic criteria recommended by guidelines during the study period [16, 17]. NTM-PD was also established if the managing physician considered treatment was warranted based on positive cultures. Extrapulmonary disease required at least 1 positive culture deemed clinically relevant and meriting therapy. Systemic disease required involvement of ≥2 noncontiguous organs. For each case we selected 2 controls matched on (1) same transplanted organ in the same institution as the case; (2) no NTM disease up to the date of inclusion; (3) had survived at least as long as the case had prior to the NTM diagnosis.

Variables and Definitions

Date of diagnosis was the collection date of the culture(s) that met case definition (ie, index date). For controls, a corresponding date was chosen based of their matched case's date of diagnosis (ie, if NTM infection develops 500 days post-transplantation, the control's "index date" is 500 days after transplantation). We collected demographic characteristics, comorbidities in the year prior to the index date, transplant characteristics (underlying disease leading to transplantation, date of transplant, donor age, and post-transplant need for intensive care unit [ICU] admission, mechanical ventilation, renal replacement therapy, CMV disease, and organ rejection), concomitant infections, and laboratory data (white blood cell count, neutrophil and lymphocyte counts, platelets, hemoglobin, hematocrit, creatinine, transaminases, total bilirubin, lactate dehydrogenase); closest to the index date but limited to 6 months prior to or after that date. We also collected use of immunosuppressive therapy, hospitalizations, receipt of chemotherapy or radiotherapy; all within 90 days of the index date; a period based on previous data linking risk of NTM disease to acute organ rejection and aimed at identifying augmented immunosuppression. Concomitant infection was defined as a clinical syndrome with supporting microbiological data and warranting therapy. Age at transplant and age at diagnosis refer to the age of the patient at the time of SOT and at the time NTM infection diagnosis, respectively.

For cases, we recorded clinical symptoms, microbiological characteristics (NTM species and susceptibilities, smear positivity, pathology biopsy results, time to culture positivity, number of positive cultures, and specimen source). Abiding GDPR rules, date of transplant was time zero and all other events were captured as time in days from it.

Data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based software platform electronic data capture tools, hosted at Washington University in St. Louis, Missouri, USA, and protected by its server's firewalls [18].

Statistical Analysis

To assess between-group differences in demographics, transplant characteristics, comorbidities, risk factors, concomitant infections, and laboratory values we used bivariate conditional regression, conditional on matched pairs. To identify risk factors for NTM disease, we used a multivariable conditional logistic-regression approach. Variables were selected using a forward-stepwise approach with entry criteria of $P < .10$, and variables were retained for P values $< .05$. Variables with $> 5\%$ missing data were not considered for inclusion in the multivariable models. Additionally, clinically important variables supported by previous studies and a priori expectations (underlying lung disease and lymphocyte count) were included in all models. Lymphocyte count was an exploratory variable considered relevant to include given the biological plausibility of well-described increased risk of NTM infection in those with poor T-cell function, and higher risk of pulmonary reinfection in those with lymphopenia [5, 19]. All statistical tests were 2-tailed, and P values $< .05$ were considered significant. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

We included 85 cases of NTM infection from 10 Spanish (n = 19), 4 American (n = 37), 3 Swiss (n = 7), 2 Italian (n = 3), 1 Brazilian (n = 6), 1 Canadian (n = 5), 1 Dutch (n = 4), 1 French (n = 2), and 1 Croatian (n = 2) centers; and 169 matched controls. For 1 case, only 1 control was available. Overall, 59% of the participants were male, 88% were White, and median age at transplant was 54 years (interquartile range [IQR] 40–62). The most frequent organ transplanted was kidney (42%), followed by lung (35%), heart (11%), liver (11%), and pancreas (1%). Distribution of demographic and transplant characteristics were similar between groups except for older age at the time of transplant (58 vs 52 years; $P = .009$) and time of NTM diagnosis (61 vs 55 year; $P = .014$) in cases compared to the controls (Table 1). Comorbidities were similarly distributed between groups apart from cancer (11.8% vs 4.1%; $P = .029$) that was significantly more frequent in the cases (Table 1).

Characteristics of NTM Infections in SOT Recipients

The most common NTM species isolated in SOT were *Mycobacterium avium* complex (MAC) (n = 27, 31.7%), *Mycobacterium abscessus* complex (MABSC) (n = 18, 21.2%), and *Mycobacterium fortuitum* (n = 9, 10.5%) (Table 2 and Supplementary Table 1). The number of NTM infections in SOT due to slowly growing mycobacteria (SGM) and rapidly growing mycobacteria (RGM) was similar (56% vs 44%, respectively), and the most common sites of NTM infection were pulmonary (n = 49, 57.6%), skin and soft tissues (n = 18, 21.2%), endovascular and disseminated disease (n = 14, 16.5%), and other (n = 4, 4.7%). In those with endovascular and disseminated disease (n = 14), organ involvement included the lungs (n = 8), the gastrointestinal tract (n = 7), lymph nodes (n = 3), endovascular (n = 4), bone and joint (n = 2), and skin and soft tissues (n = 2); only 1 case had a central-line associated bloodstream infection due to an RGM. Other sites of infection included one case each of mediastinitis, empyema, colitis, and kidney allograft infection (Table 2). The majority of those with pulmonary NTM (n = 49) were diagnosed with specimens obtained through bronchoscopy (n = 38, 77%). In those with disseminated disease (n = 14), only 5 (35%) had positive blood cultures. Overall, 46% of specimens tested had acid-fast bacilli on smears and NTM polymerase chain reaction (PCR) DNA sequencing was done in 34% of the samples.

Median [IQR] time from transplant to infection was 21.6 months [5.3–55.2] and was longer in kidney and liver (34.7 months [17.0–64.0] and 21.6 months [7.0–64.0], respectively) than in lung or heart recipients (11.3 months [4.2–31.0] and 3.5 months [2.9–67.1], respectively). For extrapulmonary NTM, median [IQR] time to diagnosis was longer than for pulmonary disease (30.6 months [9.4–61.8] vs 20.2 months [4.6–51.0], respectively), but similar between SGM and RGM (Figure 1). Only 11 (13%) cases had a prior positive culture that was considered colonization, but none of the NTM species identified were the same species that caused disease.

The most common symptoms in patients with pulmonary NTM were cough (68%), dyspnea (39%), fever (35%), and fatigue (30%). In patients with extrapulmonary NTM infection, almost half (46%) had skin lesions, and only 25% had fever. However, although fever was frequent in those with disseminated disease (n = 10/14, 71%), only 1 case had skin lesions (7%). Most patients with extrapulmonary disease (60%) had protean clinical manifestations that varied by site of infection.

Risk Factors for NTM Disease

Compared to the controls, cases had more hospitalizations (32% vs 18%; $P = .006$) and were more commonly diagnosed with another infection (36% vs 5%; $P < .001$) in the previous 90 days. Among those with a concomitant infection, pneumonia (32% vs 11%; $P < .001$) and urinary tract infection (11% vs 3%; $P = .016$) were significantly more frequent in cases than in controls (Supplementary Table 2). In cases, the most frequent concomitant infection was fungal (15%), followed by bacterial (13%), and viral (8%). At the time of diagnosis, cases were more frequently receiving systemic corticosteroids (85% vs 75%; $P = .027$) and had a lower median lymphocyte count compared to controls ($0.8–10^3/\mu L$ vs $1.2–10^3/\mu L$; $P < .001$). Use of other immunosuppressant's within 90 days and suspected or confirmed organ rejection prior to the diagnosis was not different between cases and controls (Table 1). Underlying reasons

Table 1. Baseline Characteristics of Solid Organ Transplant Recipients With Nontuberculous Mycobacterial Disease and Their Matched Controls

Clinical Characteristics	Cases n = 85 (%)	Controls n = 169 (%)	OR (95% CI)[a]	P Value[b]
Demographic characteristics				
Median [IQR] age at diagnosis in years	61 [47–66]	55 [43–64]	1.03 (1.01–1.06)	.014
Female sex	35 (41)	68 (40)	1.06 (.59–1.89)	.843
White race	72/82 (88)	136/155 (88)	.62 (.23–1.65)	.512
Transplant characteristics				
Type of solid organ transplantation[c]				
Heart	9 (11)	18 (11)	…	…
Lung	30 (35)	60 (36)	…	…
Kidney	36 (42)	72 (43)	…	…
Liver	9 (11)	17 (10)	…	…
Pancreas	1 (1)	2 (1)	…	
Median [IQR] age at transplant in years	58 [44–63]	52 [39–61]	1.03 (1.01–1.06)	.009
Median [IQR] number of transplants	1 [1–1]	1 [1–1]	1.71 (.78–3.75)	.181
Median [IQR] donor age in years	43.5 [26–56]	38 [23–50]	1.02 (.99–1.05)	.147
Median [IQR] length of post-transplant ICU stay in days	3 [0–9]	2 (0–6)	1.03 (1.00–1.05)	.077
Post-transplant renal replacement therapy	12/82 (15)	20/161 (12)	1.37 (.59–3.17)	.463
Post-transplant mechanical ventilation	32/79 (41)	62/156 (40)	1.12 (.44–2.82)	.813
CMV serological status				
D−/R −	17/72 (24)	26/127 (21)	1.09 (.48–2.45)	.836
D+/R +	22/72 (31)	39/127 (31)	1.07 (.53–2.17)	.856
D−/R +	14/72 (19)	22/127 (17)	1.32 (.57–3.09)	.518
D+/R −	19/72 (26)	40/127 (32)	.72 (.35–1.48)	.374
Post-transplant CMV disease	18 (2)	24 (14)	1.70 (.83–3.48)	.143
Median [IQR] viral load in copies/ml	1486 [780–29°000]	24°437 [6033–90°500]	1.00 (.99–1.0)	.409
Median [IQR] time to CMV disease in days	106 [29–239]	131 [42–227]	1.00 (.999- 1.0001)	.998
Comorbidities[d]				
Obesity (BMI ≥30 Kg/m^2)	13 (15)	21 (12)	1.38 (.59–3.22)	.462
Diabetes mellitus	27 (32)	55 (33)	.96 (.53–1.72)	.881
Hypertension	37 (44)	80 (47)	.82 (.44–1.52)	.532
Chronic kidney disease	36 (42)	58 (34)	1.64 (.85–3.15)	.139
Congestive heart failure	13 (15)	15 (9)	2.62 (.93–7.33)	.067
Cardiac arrhythmia	10 (12)	13 (8)	1.61 (.67–3.85)	.284
Chronic lung disorders	16 (19)	20 (12)	1.91 (.87–4.18)	.107
Pulmonary circulation disorders	5 (6)	5 (3)	2.19 (.58–8.36)	.249
Gastroesophageal disease	15 (18)	25 (15)	1.3 (.6–2.81)	.505
End-stage liver disease	5 (6)	5 (3)	4.59 (.5–42.4)	.179
Cancer	10 (12)	7 (4)	3.12 (1.12–8.65)	.029
Autoimmune disease	12 (14)	12 (7)	2.5 (.95–6.61)	.064
Risk factors within 90 days of index date				
Concomitant infections	31 (36)	9 (5)	25.85 (6.15–108.65)	<.001
Hospital admission	27 (32)	31 (18)	2.84 (1.34–6.01)	.006
ICU admission	9 (11)	16 (9)	1.5 (.34–6.7)	.596
Use of PPIs or H2-RAs	54 (64)	117 (69)	.71 (.38–1.33)	.288
Immunosuppression at the time of diagnosis[e]				
Calcineurin inhibitor	70 (82)	141 (83)	.94 (.42–2.13)	.890
Mycophenolate	59 (69)	118 (70)	.96 (.48–1.9)	.907
mTor inhibitor	10 (12)	13 (8)	1.96 (.66–5.85)	.228
Systemic corticosteroids	72 (85)	126 (75)	3.11 (1.14–8.49)	.027
Average prednisone dose in mg, median [IQR][f]	10 [5–15]	5 [5–15]	1.01 (.99–1.03)	.244
Lymphocyte-specific antibodies[g]	8 (9)	11 (7)	3.35 (.59–18.88)	.171
Organ rejection prior to the index date[h]	16 (19)	26 (16)	1.39 (.63–3.07)	.416
Median [IQR] days from rejection to index date	214 [78.5–685.5]	985.5 (262–3215)	1.0 (.99–1)	.47
Concomitant infections at the time of diagnosis				
Bacterial	11 (13)	2 (1)	10.85 (2.42–48.71)	.002
Fungal	13 (15)	5 (3)	20.54 (2.64–159.75)	.004

Table 1. Continued

Clinical Characteristics	Cases n = 85 (%)	Controls n = 169 (%)	OR (95% CI)[a]	P Value[b]
Viral	7 (8)	3 (2)	4.67 (1.21–18.05)	.026
Other	2 (2)	1 (1)	4 (.36–44.11)	.258
Laboratory values at the time of diagnosis				
Median [IQR] white blood cell count (10^3/μL)	6.29 (4.42–8.35)	5.915 (4.5–8.6)	.98 (.90–1.07)	.669
Median [IQR] neutrophil count (10^3/μL)	3.91 (2.6–6.5)	4 (2.8–6.38)	1.0 (.90–1.11)	.956
Median [IQR] lymphocyte count (10^3/μL)	.8 (.45–1.19)	1.2 (.79–1.7)	.25 (.12–.54)	<.001
Median [IQR] aspartate aminotransferase (U/L)	26.5 (19–34.5)	22 (16–27)	1.00 (.99–1.01)	.485
Median [IQR] alanine aminotransferase (U/L)	24 (18.5–34.5)	21 (15–31)	1.01 (.99–1.02)	.245

Abbreviations: BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; D, organ donor; ICU, intensive care unit; IQR, interquartile range; H2-RAs, histamine H2 receptor antagonists; mTOR, mechanistic target of rapamycin; OR, odds ratio; PPIs, proton pump inhibitors; R, organ recipient.

[a]OR and 95% CI from bivariate conditional regression, conditional on matched pairs.

[b]P value from Type 3 Wald tests.

[c]Transplant type was a matching variable for cases and controls.

[d]Limited to comorbidities with a frequency >5 in at least one of the groups.

[e]received within the 90 days prior to the index date.

[f]Doses of different corticosteroids were converted to the equivalent prednisone dose in mg.

[g]This included basiliximab (n = 12) or alemtuzumab (n = 4), rituximab (n = 1), and anti-thymocyte globulin (n = 2).

[h]Suspected or confirmed organ rejection.

for transplantation and other laboratory values at the time of diagnosis did not differ significantly (Supplementary Table 3 and Table 1).

In the multivariable conditional logistic-regression model, factors associated with a higher likelihood of NTM infection after SOT included receipt of lymphocyte-specific antibodies (adjusted odds ratio [aOR], 7.73; 95% confidence interval [CI], 1.07–56.14; P = .043), receipt of antifungals (aOR, 5.35; 95% CI, 1.7–16.91; P = .004), and prior hospitalization (aOR 3.14; 95% CI, 1.41–6.98; P = .005); all within 90 days of the NTM diagnosis.

Older age was associated with 4% higher likelihood of NTM disease (aOR 1.04; 95% CI, 1.01–1.07; P = .013) and 8% higher likelihood when limited to those with extrapulmonary disease (aOR 1.08; 95% CI, 1.02–1.15; P = .008). In those with extrapulmonary disease, the multivariable model identified receipt of antivirals within 90 days as a factor increasing the likelihood of NTM infection (aOR 56.86; 95% CI, 1.58–2043.41; P = .027). In the multivariable analysis limited to patients with pulmonary disease, hospital admission and prior receipt of antibacterial and antifungal therapy were associated with a higher likelihood of NTM disease (Table 3).

When lymphocyte count was included in the models, higher lymphocyte count was associated with a 75% lower likelihood of NTM disease (95% CI, .12–.55; P < .001), and this association remained significant in the pulmonary (aOR 0.29; 95% CI, .09–.9; P = .032) and extrapulmonary models (aOR 0.28; 95% CI, .1–.84; P = .023) (Table 3 and Supplementary Figure 1).

Pulmonary and Extrapulmonary NTM Disease

In subgroup analysis limited to extrapulmonary NTM disease (n = 36), comorbidities, risk factors, demographic and transplant characteristics were similarly distributed between cases and controls. Compared to controls, cases had been more frequently hospitalized (28% vs 13%; P = .041) or diagnosed with other infections (25% vs 7%; P = .016) within 90-days of the NTM disease diagnosis, explaining the higher use of antibacterial (66% vs 28%; P < .001) and antiviral therapies (37% vs 15%; P = .015) seen (Supplementary Table 4).

Those with pulmonary disease (n = 49) were more likely to have a concomitant fungal infection (24% vs 5%, OR 9.86; 95% CI, 2.17–44.72; P < .001) or diagnosed with pneumonia (45% vs 14%, OR 7.67; 95% CI, 2.58–22.79; P < .001), 90 days prior to the NTM diagnosis (Supplementary Table 5).

Overall, at the time of diagnosis, median lymphocyte count was lower in patients with both pulmonary (0.9 vs 1.2–10^3/μL; P = .016) and extrapulmonary disease (0.7 vs 1.21–10^3/μL; P = .009) than controls (Supplementary Tables 4 and 5).

DISCUSSION

To the best of our knowledge, this is the first multinational and largest study to explore risk factors for NTM infection in SOT population. NTM infection was significantly associated with older age at the time of transplant, receipt of lymphocyte-specific antibody therapy, prior hospital admission and receipt of antifungal therapy; all within 90 days of the diagnosis. In the general population, older age is a predictor of poor prognosis for NTM-PD [20]; however, this has not been previously described as a risk factor in SOT. Hospitalization and receipt of antifungal therapy within 90 days are likely markers of both delayed NTM disease and/or misdiagnosis; however, 15% of the cases did have a concomitant fungal infection. Delayed diagnosis is common in NTM-PD, yet poorly characterized in the general population

Table 2. Clinical and Microbiological Characteristics of Nontuberculous Mycobacterial Disease in Solid Organ Transplant Recipients

Characteristics	Overall n = 85 (%)	Lung n = 30 (%)	Kidney n = 36 (%)	Liver n = 9 (%)	Heart n = 9 (%)	Pancreas n = 1 (%)
			Transplant Type			
Rapid growing mycobacteria	37 (44)	18 (60)	10 (28)	5 (56)	3 (33)	1 (100)
Mycobacterium abscessus complex	18	12	2	1	2	1
Mycobacterium chelonae	8	2	4	1	1	…
Mycobacterium fortuitum	9	3	3	3	…	…
Mycobacterium mucogenicum	2	1	1	…	…	…
Slow growing mycobacteria	48 (56)	12 (40)	26 (72)	4 (44)	6 (67)	…
Mycobacterium avium complex	27	9	11	3	4	…
Mycobacterium kansasii	8	…	6	…	2	…
Mycobacterium genavense	5	…	5	…	…	…
Mycobacterium haemophilum	2	…	2	…	…	…
Mycobacterium xenopi	1	1	…	…	…	…
Mycobacterium marinum	1	…	1	…	…	…
Mycobacterium celatum	1	…	…	1	…	…
Mycobacterium parascrofulaceum	1	…	1	…	…	…
Mycobacterium scrofulaceum	1	1	…	…	…	…
Mycobacterium gordonae	1	1	…	…	…	…
Site of NTM infection						
Pulmonary	49 (58)	26 (87)	12 (33)	5 (56)	5 (56)	1 (100)
Skin and soft tissue	18 (21)	2 (7)	11 (31)	2 (22)	3 (33)	0
Endovascular and disseminated disease	14 (21)	0	11 (31)	2 (22)	1 (11)	0
Other[a]	4 (5)	2 (7)	2 (6)	0	0	0
Median number of positive cultures [IQR]	1 [1–2]	1 [1–2]	1 [1–2]	2 [1–2]	1 [1–1.5]	3
Median time from transplant to culture positivity in months [IQR]	21.6 [5.3–55.2]	11.3 [4.2–31.0]	34.7 [17.0–64.0]	21.6 [3.5–69.6]	3.5 [2.9–67.1]	27.3

Abbreviations: IQR, interquartile range; NTM, nontuberculous mycobacteria.

[a]Other sites of infection included one case each of mediastinitis, empyema, colitis, and kidney allograft infection.

[21, 22], and it might impact outcomes as those with NTM-PD who achieve microbiological eradication after six months of therapy have lower mortality risk [23].

Although 1 of the diagnostic criteria for NTM-PD in current guidelines is the exclusion of an alternative diagnosis [24], these criteria have not been validated in SOT recipients. In SOT, a myriad of infections can occur due to the net state of immunosuppression, and fungal infections, commonly aspergillosis, are well-known to increase morbidity and mortality in this population [25], potentially leading to misdiagnosis. Additionally, *Mycobacterium avium* complex and *Aspergillus* species coinfection has been previously reported [26]. Epidemiologically, environmental co-exposure for fungi and Mycobacteria and clinically use of immunosuppressive therapy, are shared risks for both diseases in SOT. This might explain the association of increased of NTM infection and receipt of antifungal therapy seen in this study.

Although, therapy with lymphocyte-specific antibodies in this study included almost exclusively basiliximab or alemtuzumab, which are commonly used as induction therapy and to treat cell-mediated allograft rejection, we found no increased risk of NTM infection in those with prior acute organ rejection, unlike previously described in another study [12]. Nonetheless,

the increased likelihood of NTM disease with these agents in the multivariable model is supported by the finding of higher lymphocyte counts being associated with a lower likelihood of NTM disease in the bivariate analysis, and in the predetermined entry multivariable model, where it remained the only factor significantly associated with NTM disease. This finding is biologically plausible, given the increased risk of NTM infection in those with poor T-cell function like severe combined immunodeficiency, advanced human immunodeficiency virus infection, and kidney and liver transplant recipients [27–29].

In keeping with findings from other studies where the median onset of NTM infection in transplant recipient varied widely [12, 30], in this study time to infection ranged from 6 days to 27 years. The higher incidence of lung infection seen compared to other organs is in keeping with the epidemiology of NTM disease in the general population, where around 75% cases are pulmonary [31, 32]. Although over half of those patients with disseminated NTM infection had evidence of lung involvement, none of the lung transplant recipients were diagnosed with disseminated disease, similar to that seen by Huang and colleagues [15]. Furthermore, no case of isolated NTM lymphadenitis was reported, consistent with previous studies that found
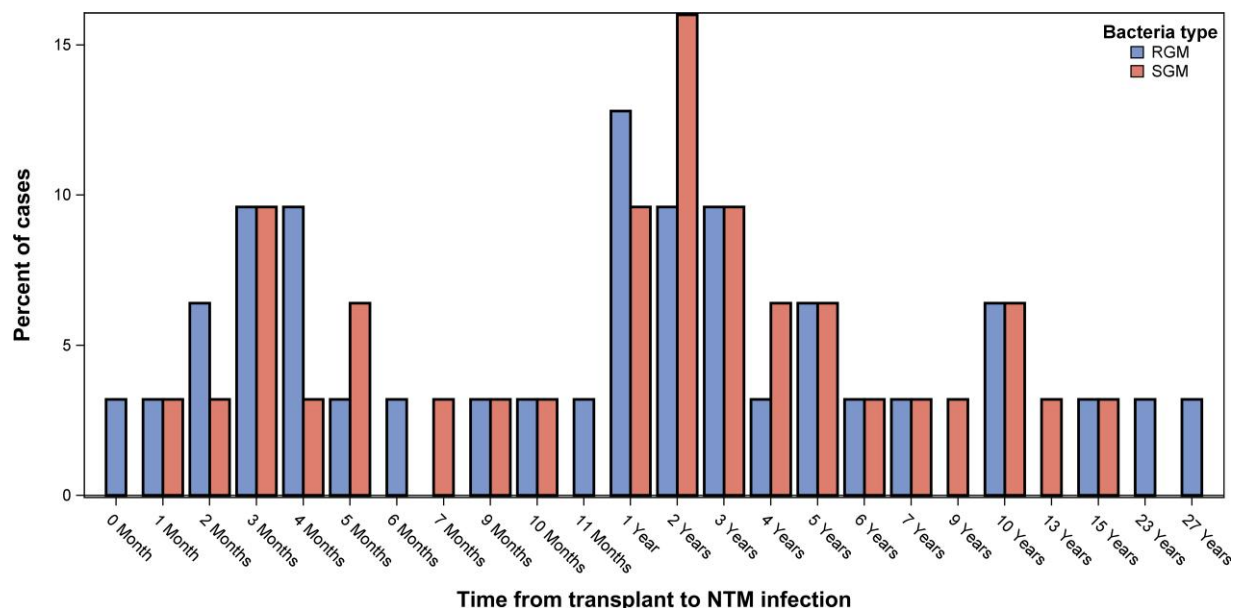
Figure 1. Time from transplant to infection by type of nontuberculous mycobacteria. Abbreviations: NTM, nontuberculous mycobacteria; RGM, rapidly growing mycobacteria; SGM, slow growing mycobacteria.

it to be rare in the absence of disseminated infection [30, 33]. Similarly, yield of mycobacterial blood cultures in disseminated disease was slightly lower than previously reported in in people with human immunodeficiency virus (HIV) [34].

This study has several limitations. First, there is a risk of misclassification of some variables (eg, pneumonia) that could have overlapped with the outcome of NTM diagnosis, potentially leading to erroneous associations of increased risk. To

Table 3. Multivariable Conditional Regression Models of Risk Factors Significantly Associated With Nontuberculous Mycobacterial Disease, Pulmonary, and Extrapulmonary, in Solid Organ Transplant Recipients

Multivariable models with stepwise selection[a]

	Any NTM Disease (n = 249)		NTM Pulmonary Disease (n = 145)		NTM Extrapulmonary Disease (n = 106)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age at transplant	1.04 (1.01–1.07)	.013	…		1.08 (1.02–1.15)	.008
Chronic lung/pulmonary circulation disorder[b]	…		2.23 (.81–6.14)	.12	…	
Lymphocyte-specific antibodies	7.73 (1.07–56.14)	.043	…		…	
Prior antibacterials	…		5.35 (1.83–15.66)	.002	6.71 (1.72–26.22)	.006
Prior antifungals	5.35 (1.7–16.91)	.004	5.25 (1.33–20.75)	.018	…	
Prior antivirals	…		…		0 56.86 (1.58–2043.41)	.027
Prior hospital admission[c]	3.14 (1.41–6.98)	.005	0.33 (1.12–.93)	.035	…	
Secondary models[d]						
…	Any NTM Disease (n = 185)		NTM Pulmonary Disease (n = 128)		NTM Extrapulmonary Disease (n = 57)	
…	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Lymphocyte count (10³/µL)	0.25 (.12–.54)	<.001	0.29 (.09–.9)	.032	0.28 (.1–.84)	.023
Chronic lung/pulmonary circulation disorder[b]	…		1.56 (.46–5.29)	.473	…	
Prior antibacterials	…		3.63 (1.24–10.64)	.019	…	

Abbreviations: CI, confidence interval; NTM, nontuberculous mycobacteria; OR, odds ratio.

[a]Models were generated using a stepwise selection approach with entering in all variables that had ≤5% missing data. Variables were entered into the model with P < .1 and remained in the model if P < .05. OR, 95% CI, and P values are shown only for variables that were included in the final models.

[b]Chronic lung disease/pulmonary circulation disorder was included into the NTM pulmonary disease models.

[c]Includes all admissions within 90 days of the NTM infection diagnosis.

[d]Models had lymphocyte count included.

minimize this we removed such variables from the multivariable model. Due to the multisite study design there is a risk of diagnostic access bias; thus, we addressed this by using matched pairs from the same center. In addition, despite being the largest case series of NTMs in SOT, the number of patients is still relatively small, likely reflecting the low incidence of NTM infection after SOT [7], especially when strict diagnostic criteria are applied [10]. It could also be due to lack of outbreaks during the study period at the participating centers. However, it might represent under diagnosis of NTM infection due to a low index of suspicion. The study design did not allow us to calculate incidence rates. Moreover, the inclusion of multiple centers from several countries reflects a wide environmental epidemiology and broad scope of medical management. Finally, missing data might have limited the precision of the estimates and increased the likelihood of bias. However, to minimize potential bias that can result from analyzing variables with high rates of missingness, we only considered variables with <5% missing data in the multivariable models, with the exception of lymphocyte count.

In conclusion, this is the first multinational study describing clinical characteristics and risk factors for NTM after SOT. Risk of NTM infection after SOT was associated with older age at the time of transplant, and hospital admission, receipt of antifungals or lymphocyte-specific antibodies; all within 90 days of the diagnosis. Higher risk of NTM disease in those with lymphopenia warrants further investigation. Our study provides relevant information to clinicians about the context in which NTM infection occurs. An international prospective NTM registry in SOT could help identify predictors to establish an early diagnosis for these uncommon infections.

Supplementary Data

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

Notes

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