Clinical Infectious Diseases

MAJOR ARTICLE

Nocardia Infections in Hematopoietic Cell Transplant Recipients: A Multicenter International Retrospective Study of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation

Diana Averbuch,[1,a] Julien De Greef,[2,a] Amelie Duréault,[3,a] Lotus Wendel,[4] Gloria Tridello,[5] David Lebeaux,[6,7] Malgorzata Mikulska,[8] Lidia Gil,[9] Nina Knelange,[4] Tsila Zuckerman,[10] Xavier Roussel,[11] Christine Robin,[12] Alienor Xhaard,[13] Mahmoud Aljurf,[14] Yves Beguin,[15] Amandine Le Bourgeois,[16] Carmen Botella-Garcia,[17] Nina Khanna,[18] Jens Van Praet,[19] Nicolaus Kröger,[20] Nicole Blijlevens,[21] Sophie Ducastelle Leprêtre,[22] Aloysius Ho,[23] Damien Roos-Weil,[24] Moshe Yeshurun,[25,26] Olivier Lortholary,[27,28] Arnaud Fontanet,[29,30] Rafael de la Camara,[31] Julien Coussement,[32,33,b] Johan Maertens,[34,b] and Jan Styczynski[35,b], European Study Group for Nocardia in Hematopoietic Cell Transplantation

[1]Pediatric Infectious Diseases, Faculty of Medicine, Hebrew University of Jerusalem, Hadassah Medical Center, Jerusalem, Israel; [2]Department of Internal Medicine and Infectious Diseases, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium; [3]Centre d'Infectiologie Necker Pasteur, Hôpital Necker-Enfants Malades, Assistance Publique - Hôpitaux de Paris, Université Paris Descartes, Paris, France; [4]European Society for Blood and Marrow Transplantation (EBMT) Data Office, Leiden, The Netherlands; [5]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; [6]Université de Paris, Paris, France; [7]Service de Microbiologie, Unité Mobile d'Infectiologie, Assistance Publique - Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France; [8]Division of Infectious Diseases, University of Genoa and Ospedale Policlinico San Martino, Genoa, Italy; [9]University of Medical Sciences, Poznan, Poland; [10]Rambam Medical Center, Haifa, Israel; [11]Hematology Department, University Hospital of Besançon, Besançon, France; [12]Henri Mondor University Hospital, Creteil, France; [13]Hematology-Transplantation, Hospital St-Louis, Paris Diderot University, Paris, France; [14]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [15]Centre Hospitalier Universitaire of Liège and University of Liège, Liège, Belgium; [16]Centre Hospitalier Universitaire Nantes, Nantes, France; [17]Centre Hospitalier Universitaire Bordeaux, Bordeaux, France; [18]Division of Infectious Diseases and Hospital Epidemiology, University and University Hospital of Basel, Basel, Switzerland; [19]Department of Nephrology and Infectious Diseases, Algemeen Ziekenhuis Sint-Jan Brugge-Oostende, Brugge, Belgium; [20]Department of Stem Cell Transplantation, University Medical Center, Hamburg, Germany; [21]Radboud University Medical Center, Nijmegen, The Netherlands; [22]Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France; [23]Singapore General Hospital, Singapore; [24]Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France; [25]Institution of Hematology, Rabin Medical Center, Petah Tikva, Israel; [26]Sacker School of Medicine, Tel Aviv University, Tel Aviv, Israel; [27]Paris University, Necker Pasteur Center for Infectious Diseases and Tropical Medicine IHU Imagine, Necker Enfants Malades University Hospital, Paris, France; [28]National Reference Center for Invasive Mycoses and Antifungals, Molecular Mycology Unit, CNRS UMR 2000, Institut Pasteur, Paris, France; [29]Institut Pasteur, Emerging Diseases Epidemiology Unit, Global Health Department, Paris, France; [30]Pasteur-Cnam risques infectieux et émergents Unit, Conservatoire National des Arts et Métiers, Paris, France; [31]Hospital de la Princesa, Madrid, Spain; [32]Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Australia; [33]National Centre for Infection in Cancer, Peter MacCallum Cancer Centre, Melbourne, Australia; [34]Department of Hematology, Universitaire Ziekenhuizen Leuven, Leuven, Belgium; and [35]Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland

Background. Nocardiosis is rare after hematopoietic cell transplantation (HCT). Little is known regarding its presentation, management, and outcome in this population.

Methods. This retrospective international study reviewed nocardiosis episodes in HCT recipients (1/1/2000–31/12/2018; 135 transplant centers; 33 countries) and described their clinical, microbiological, radiological, and outcome characteristics.

Results. We identified 81 nocardiosis episodes in 74 allo- and 7 auto-HCT recipients. Nocardiosis occurred a median of 8 (IQR: 4–18) months post-HCT. The most frequently involved organs were lungs (70/81; 86%) and brain (30/81; 37%); 29 (36%) patients were afebrile; 46/81 (57%) had disseminated infections. The most common lung imaging findings were consolidations (33/68; 49%) or nodules (32/68; 47%); brain imaging findings were multiple brain abscesses (19/30; 63%). Ten of 30 (33%) patients with brain involvement lacked neurological symptoms. Fourteen of 48 (29%) patients were bacteremic. *Nocardia farcinica* was the most common among molecularly identified species (27%; 12/44). Highest susceptibility rates were reported to linezolid (45/45; 100%), amikacin (56/57; 98%), trimethoprim-sulfamethoxazole (57/63; 90%), and imipenem (49/57; 86%). One-year and last follow-up (IQR: 4–42.5 months) all-cause mortality were 40% (32/81) and 52% (42/81), respectively. In the multivariable analysis, underlying disease not in complete remission (HR: 2.81; 95% CI: 1.32–5.95) and prior bacterial infection (HR: 3.42; 95% CI: 1.62–7.22) were associated with higher 1-year all-cause mortality.

Conclusions. Nocardiosis is a late post-HCT infection usually manifesting as a pulmonary disease with frequent dissemination, brain infection, and bacteremia. Brain imaging should be performed in HCT recipients with nocardiosis regardless of neurological symptoms. Overall mortality is high.

Keywords. nocardiosis; hematopoietic cell transplantation; central nervous system infection; mortality.

Received 21 July 2021; editorial decision 23 September 2021; published online 1 October 2021.

[a]D. A., J. D. G., and A. D. contributed equally.

[b]J. C., J. M., and J. S. contributed equally.

Previous presentation: The partial results of this study were presented orally at the 47th virtual Annual EBMT Conference, 2021.

Correspondence: D. Averbuch, Pediatric Infectious Diseases, Faculty of Medicine, Hebrew University of Jerusalem, Hadassah Medical Center, Jerusalem, Israel (adiana@hadassah.org.il).

Clinical Infectious Diseases® 2022;75(1):88–97

https://doi.org/10.1093/cid/ciab866

Nocardia spp. are environmental gram-positive bacilli that may cause infection in humans. Because inhalation is the most common *Nocardia* spp. acquisition route, the lung is the most frequently involved organ. Dissemination to the brain, skin, soft tissues, and/or other body sites is common [1].

While *Nocardia* infection (nocardiosis) may occur in previously healthy people, most of those infected are immunocompromised, with solid-organ transplant (SOT) recipients being

the most affected [2]. Solid-organ transplant recipients with nocardiosis have been the subject of several studies in recent years [1, 3, 4], but very little is known regarding the disease in hematopoietic cell transplant (HCT) recipients.

Available reports indicate that nocardiosis is rare after HCT, occurring in 0.3–1.7% of allogeneic (allo-) and 0.2% of autologous (auto-) HCT recipients [5–7]. Since 2000, 1 multicenter case series (10 patients with hematological malignancies) [8], 7 small single-center HCT case series [5, 6, 9–13], and 1 retrospective analysis of 112 cases, including 16 HCT recipients [14], have been published.

The current international retrospective study aims to clarify the characteristics and outcome of nocardiosis in HCT recipients.

METHODS

Study Objectives

Our primary objective was to describe the clinical, radiological, and microbiological characteristics of nocardiosis in HCT recipients.

Secondary objectives were as follows: (1) assessing all-cause mortality at 1 year after nocardiosis and (2) determining factors associated with 1-year all-cause mortality.

Study Design and Settings

This was an international retrospective study supported by the Infectious Diseases Working Party (IDWP) of the European Society for Blood and Marrow Transplantation (EBMT). Demographic and HCT-related data were obtained using the EBMT database. Data on nocardiosis episodes were collected using a dedicated case report form (see Supplementary Appendix and Supplementary Table 1 for details including data collected and definitions used [3, 4, 15]).

Inclusion Criteria

Adults (≥18 years of age) and children meeting the following criteria were eligible: (1) allo- or auto-HCT history, (2) *Nocardia* spp. isolation in a clinical sample after start of HCT conditioning, (3) suggestive clinical and/or radiological nocardiosis signs, and (4) diagnosis made between 1 January 2000 and 31 December 2018.

Microbiology

Diagnosis required *Nocardia* growth in a clinical sample. *Nocardia* identification at the genus level required 1 of the following methods, performed on bacterial colonies:

1. Molecular identification (ie, gene sequencing);
2. Matrix-assisted laser desorption/ionization time-of flight spectrometry (MALDI-TOF); or
3. Typical bacterial colonies growth (dry chalky-white appearance, buff or pigmented, waxy cerebriform colonies) in association with suggestive microscopy (partial acid-fast–stained gram-positive branching filamentous organisms).

Identification at the species level required the amplification and sequencing of a gene fragment coding for the 16S ribosomal RNA or *hsp65* [2].

Antibiotic susceptibility testing (AST) was performed by local laboratories. The method of testing was recorded. Pathogens classified as in vitro "resistant" or "intermediate" were considered as "resistant." Only susceptibility to antibiotics for which Clinical and Laboratory Standards Institute (CLSI) breakpoints are available is reported [16].

Statistical Analysis

Clinical, radiological, laboratory, treatment, and outcome data were described for the first episode of nocardiosis. Continuous data are presented as median (interquartile range [IQR]). Categorical data are presented as numbers and percentage of total. One-year all-cause survival was assessed using the Kaplan-Meier estimator and compared between groups using log-rank tests. To identify factors associated with 1-year all-cause survival, a univariate Cox regression model was used. Variables with a P value less than .05 on univariable analysis were included in a multivariable Cox regression model. A bilateral P value less than .05 was considered statistically significant. All analyses were performed using the statistical software SAS version 9.4 (SAS Institute).

RESULTS

Participating Centers and Included Patients

We invited 587 EBMT centers to participate, and 135 of 587 agreed (representing 33 countries). The highest response rate was in Belgium, France, and Israel (29/81 centers [36%] compared with 106/506 centers [21%] in the 30 remaining countries) (Supplementary Table 2). Among the 135 participating centers, 99 of 135 centers reported having no cases and 36 of 135 centers reported at least 1 case. In 19 of 33 countries, all 26 centers (27 337 HCTs performed during the study period) reported no cases. In the 14 of 33 other countries, 73 centers reported no cases (77 178 HCTs performed); and 36 centers reported 81 nocardiosis cases including 57 cases from 19 Belgian, French, and Israeli centers (36 126 HCTs performed) and 24 cases from 17 centers from 11 other countries (28 036 HCTs performed).

Supplementary Figure 1 presents the distribution of nocardiosis cases according to the year of diagnosis; 4 were children. Most patients were allo-HCT recipients (74/81; 91%). The most common underlying disease was acute leukemia (25/81; 31%). None of the patients were severely neutropenic at diagnosis of nocardiosis; 47% were severely lymphocytopenic. Half of the patients had comorbidities, mainly underlying pulmonary disease (17/81; 21%) and diabetes mellitus (11/81; 14%) (Table 1).

Table 1. Patient Characteristics

Patient Characteristics	Total, n (%)
Number of patients	81 (100)
Male	58 (72)
Age at HCT, median (range), y	50.2 (1.2–71.1)
Children (<18 y)	4 (5)
Underlying disease	
Acute myeloid leukemia	18 (22)
Acute lymphoblastic leukemia	7 (9)
Myelodysplastic/myeloproliferative + chronic myeloid leukemia	9 (24)
Lymphoma	16 (20)
Plasma cell disorders	11 (14)
Chronic lymphocytic leukemia	7 (9)
Others	3 (4)
Type of HCT	
Allogeneic	74 (91)
Autologous	7 (9)
Chronological number of the most recent HCT for this patient	
First	57 (70)
Second or more	24 (30)
Source of stem cells	
Bone marrow/cord blood	15/1 (20)
Peripheral blood	65 (80)
HLA match type (n = 74)	
Matched related	31 (42)
Matched unrelated	25 (34)
Mismatched	18 (24)
Conditioning (n = 80): myeloablative (vs non-myeloablative)	44 (55)
Acute GVHD at the time of nocardiosis (n = 69)	12 (17)
Chronic GVHD at the time of nocardiosis (n = 72)	31 (43)
Antilymphocyte agents any time before nocardiosis (as antithymocyte globulin, antilymphocyte globulin, alemtusumab)	48 (59)
Within 12 months before nocardiosis	33 (41)
Immune suppressive medications at the time of nocardiosis (n = 80)	69 (86)
Steroids	58 (73)
<1 mg/kg/d	42 (53)
≥1 mg/kg/d	10 (12)
Dose unknown	6 (8)
Tacrolimus	23 (29)
Cyclosporine	22 (28)
Mycophenolate mofetil	12 (15)
Others	8 (10)
Two or more immune suppressive drugs	42 (52)
Underlying disease status after HCT at the time of nocardiosis (n = 78)	
Continued complete remission	59 (76)
Never in complete remission/relapse/progression	19 (24)
Comorbidities at the time of nocardiosis	41 (51)
Pulmonary disease	17 (21)
Diabetes mellitus	11 (14)
Renal disease	6 (7)
Solid tumor	4 (5)
Other	22 (27)
Trimethoprim-sulfamethoxazole prophylaxis at nocardiosis diagnosis (n = 79)	33 (42)

Abbreviations: GVHD, graft versus host disease; HCT, hematopoietic cell transplantation.

Nocardiosis Presentation

Nocardiosis occurred at a median of 8 (IQR: 4–18) months following HCT (Figure 1). The most frequently involved organs were lungs (70/81; 86%) and brain (30/81; 37%) (Table 2). Most infections were disseminated (46/81; 57%). One-third of the patients were afebrile.

Lung imaging was performed in 75 of 81 (93%) patients (computed tomography [CT] scan in 66 patients, fluorodeoxyglucose–positron emission tomography–CT [FDG-PET-CT] in 1 patient, and X-ray only in 8 patients). Lung lesions were observed in 68 of 75 (91%) cases. The most frequently reported lesions were consolidations (n = 33, 49%) and nodules (n = 32, 47%); among nodules, 19 of 32 (59%) were cavitated.

Brain imaging was performed in 59 of 81 patients: CT scan in 36 of 59 (61%) and magnetic resonance imaging (MRI) in 38 of 59 (64%) cases. In 30 cases (51%), results were abnormal. The most common brain imaging finding was multiple brain abscesses (n = 19, 63%). Among 35 patients who had brain imaging despite having no neurological abnormalities on clinical examination, the presence of brain abscess(es) was detected in 10 of 35 cases (29%), meaning that 10 of 30 (33%) of patients with brain involvement were without neurological symptoms. Brain involvement generally occurred in the setting of disseminated infection (27/30; 90%).

A total of 16 of 81 (20%) patients had concomitant microbiologically documented infection(s), including bacteremia (6/81), other bacterial infection (4/81), invasive fungal disease (3/81), cytomegalovirus disease (1/81), or respiratory viral infection (4/81) (see details in Supplementary Table 3).

Microbiological Characteristics

Blood cultures were collected in 48 (59%) patients; 14 (29%) of them had *Nocardia* bacteremia and 3 of these 14 patients (all with central venous catheter (CVC) at diagnosis of nocardiosis) had an isolated bacteremia (ie, without any other site involved).

Other procedures most commonly performed to diagnose nocardiosis were bronchoalveolar lavage (BAL), sputum culture, and brain and lung biopsy (Supplementary Table 4).

The microbiological identification method was reported in 77 of 81 cases (95%). Specifically, molecular biology was performed in 44 of 81 cases (54%), allowing identification at the species level. The remaining cases were identified using either MALDI-TOF (28/81; 35%) or identification of typical colonies with suggestive microscopy (5/81; 6%), and were therefore reported as *Nocardia* spp. *Nocardia farcinica* was the most frequent species (27%; 12/44) (Figure 2). The proportion of brain (6/12 [50%] vs 7/32 [22%]; $P = .1$) and skin/soft tissue/muscle involvement (4/12 [33%] vs 2/32 [6%]; $P = .04$) was higher in infections caused by *N. farcinica* than in those due to other species.

The AST (Supplementary Table 5) was performed by E-test BioMérieux (n = 37; 46%), broth microdilution (n = 9; 11%), or

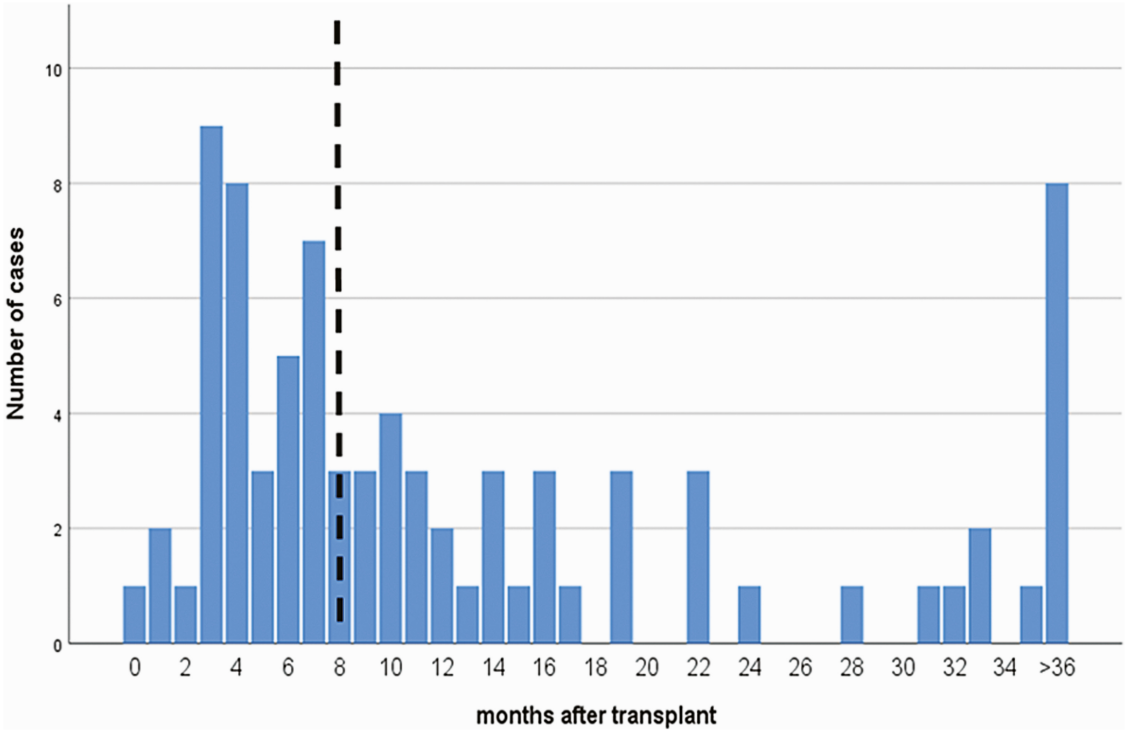

Figure 1. Distribution of the time (in months) between hematopoietic cell transplantation and the occurrence of nocardiosis. The dashed line represents the median time point (8 months).

another method (n = 3; 4%); in 23 cases (28%) the method was not reported and in 9 cases (11%) susceptibility was not reported. All 45 tested isolates were found to be susceptible to linezolid, 56 of 57 (98%) to amikacin, 57 of 63 (90%) to trimethoprim-sulfamethoxazole (TMP-SMX), and 49 of 57 (86%) to imipenem. Thirty-three (42%) of 79 patients were receiving TMP-SMX prophylaxis at the time of nocardiosis. The proportion of TMP-SMX–resistant pathogens was 4 of 25 (16%) among patients who received TMP-SMX prophylaxis at the time of nocardiosis, as compared with 2 of 36 (6%) among those who did not.

Management of Nocardiosis

Antibiotic therapy data were available in 80 patients (Supplementary Table 6). One patient did not receive treatment for an ulcerative skin lesion and recovered following reduction in immune suppression. The most frequently used drugs were TMP-SMX (54/79; 68%), imipenem (36; 46%), and amikacin (35; 44%). Drug-related adverse events were recorded in 27 of 80 patients (34%), leading to drug discontinuation in 18 of 80 patients (23%) (Supplementary Table 7). Treatment duration was known for 72 of 80 treated patients: 49 patients completed antibiotic therapy (median duration: 7 months; IQR: 3.5–12 months), 20 patients died before antibiotic cessation, and 3 patients were still on antibiotics at last follow-up (range: 4–10 months).

Among the 3 patients who had isolated *Nocardia* bacteremia, 2 had infections that were probably CVC–related, with persistence of bacteremia until line removal (at days 7 and 9). However, catheter tip cultures remained negative, differential time-to-positivity was not measured, and semiquantitative/quantitative cultures were not performed. One of these 2 patients received 4.5 months of antibiotic treatment and died 5.5 months after treatment cessation (death not attributed to nocardiosis); the second patient received 10 months of antibiotic treatment and was alive and cured at last follow-up. The third patient had 2 days of *Nocardia* bacteremia and was cured without line removal (unknown duration of antimicrobial therapy).

After completion of anti–*Nocardia* therapy, 14 patients received secondary TMP-SMX prophylaxis (low-dose TMP-SMX in 12 patients, and 800/160 mg/day in 2 patients). Sixteen patients underwent a surgical procedure for treatment of nocardiosis.

Outcome of Nocardiosis

One-year all-cause mortality was 40% (32/81). The median time to death in these patients was 2.5 months (IQR: 1–6 months). In 11 (14%) patients (10 following allo-HCT and 1 following auto-HCT) who developed nocardiosis a median of 7 (range: 2–35) months after HCT, death was attributed to nocardiosis.

The median duration of follow-up for the entire cohort was 18 months (IQR: 4–42.5 months). At last follow-up, all-cause mortality was 52% (42/81).

Significant or approaching significance parameters associated with 1-year all-cause mortality are presented in Supplementary

Table 2. Nocardiosis Episode Characteristics

Episode Characteristics	Total	Allo-HCT	Auto-HCT
Number (%) of patients	81 (100)	74 (100)	7 (100)
Time in days from onset of symptoms to the day of diagnosis (n = 70), median (IQR)	12 (5.00–23.25)	12.0 (5.0–22.0) (n = 65)	7.0 (7.0–45.5) (n = 5)
Time in months from HCT to onset of symptoms or (if unavailable) to the day of diagnosis: median (IQR)	8.0 (4–18)	8.0 (4–17.25)	7.0 (1–39.0)
Involved organs, n (%)			
Localized disease	35 (43)	32 (43)	3 (43)
Lung	27 (33)	24 (32)	3 (43)
Brain	3 (4)	3 (4)	0
Skin/soft tissue/muscle	3 (4)	3 (4)	0
Joint or bone	2 (3)	2 (3)	0
Disseminated disease	46 (57)	42 (57)	4 (57)
Lung	43 (53)	41 (55)	2 (29)
Brain	27 (33)	25 (34)	2 (29)
Skin/soft tissue/muscle	9 (11)	9 (12)	0
Joint or bone	3 (4)	3 (4)	0
Others[a]	8 (10)	8 (11)	0
Bacteremia	14/48 (29)	12/44 (27)	2/4 (50)
Clinical signs, n (%)			
Fever >38°C	52 (64)	48 (65)	4 (57)
Respiratory signs	54 (67)	50 (68)	4 (57)
Cough/sputum production	38 (47)	35 (47)	3 (43)
Dyspnea	23 (28)	21 (28)	2 (29)
Chest pain	17 (21)	15 (20)	2 (29)
Others[b]	9 (11)	9 (12)	0
Neurological signs	24 (29)	21 (28)	3 (43)
Headache	12 (15)	9 (12)	3 (43)
Confusion	5 (6)	5 (7)	0
Seizures	5 (6)	5 (7)	0
Other neurological signs[c]	12 (15)	12 (16)	0
Other signs			
Asthenia	17 (21)	16 (22)	1 (14)
Skin/soft tissue/muscle lesion	12 (15)	12 (16)	0
Others[d]	23 (28)	22 (28)	1 (14)
Hospitalization in the intensive care unit due to nocardiosis, n (%)	20 (25)	19 (26)	1 (14)
Imaging, n (%)			
Type of lung involvement (n = 68)			
Lung consolidation	33 (49)	31/63 (49)	2/5 (40)
Nodules	32 (47)	30/63 (48)	2/5 (40)
Nodules with cavitation	19 (28)	18/63 (29)	1/5 (20)
Pleural effusion	10 (15)	9/63 (14)	1/5 (20)
Interstitial syndrome	5 (7)	4/63 (6)	1/5 (20)
Other types[e]	6 (9)	6 /63 (10)	0
Lobes involved (n = 58)			
One lobe involved	20 (35)	19/54 (35)	1/4 (25)
Multilobar involvement	38 (65)	35/54 (65)	3/4 (75)
Bilateral involvement	31 (54)	28/54 (52)	3/4 (75)
Type of brain abscess (n = 30), n (%)			
Single lesion	11 (37)	10/28 (36)	1/2 (50)
Multiple lesions	19 (63)	18/28 (64)	1/2 (50)
Bilateral involvement	9 (30)	8/28 (29)	1/2 (50)
Infections that occurred concomitant or before nocardiosis,[f] n (%)			
Bacterial infection	31 (38)	27 (37)	4 (57)
Bacteremia concomitant to nocardiosis	6 (7)	5 (7)	1 (14)
Bacteremia before nocardiosis	14 (17)	13 (18)	1 (14)
Other bacterial infections concomitant with nocardiosis	4 (5)	4 (5)	0 (0)

Table 2. Continued

Episode Characteristics	Total	Allo-HCT	Auto-HCT
Other bacterial infections before nocardiosis	11 (14)	9 (12)	2 (29)
Invasive fungal disease	18 (22)	16 (22)	2 (28)
During nocardiosis	3 (4)	2 (3)	1 (14)
Before nocardiosis	15 (18)	14 (19)	1 (14)
Cytomegalovirus reactivation within 6 m before nocardiosis (n = 77)	29 (38)	29/71 (41)	0/6 (0)
Epstein-Barr virus reactivation within 6 m before nocardiosis (n = 63)	16 (25)	15 (25)	1 (25)
Outcome, n (%)			
Relapse (n = 64)	3 (5)	3/57 (5)	0/7
Mortality 1 y after nocardiosis	32 (40)	31 (42)	1 (14)
Mortality at the last follow-up	42 (52)	39 (53)	3 (43)

Abbreviations: Allo, allogeneic; Auto, autologous; GVHD, graft versus host disease; HCT, hematopoietic cell transplantation; IQR, interquartile range.

[a]Other organs included (n = 8 patients): liver (n = 4), spleen (n = 2), and one each of sinuses, lymph nodes, oral lesion, spinal cord, pancreas, and kidneys.

[b]Other respiratory complaints: acute respiratory distress (n = 5), hemoptysis (n = 4).

[c]Other neurological signs included: paresis (n = 4), ataxia (n = 3), facial nerve paralysis (n = 2), behavioral changes (n = 2), vomiting (n = 1), and one each of blurred vision, drowsiness, speech disturbances, gate disturbances, tremor, and anosmia.

[d]Other signs included: weight loss (n = 6), arthritis (n = 4), chills (n = 3), abdominal pain (n = 3), limb pain and/or swelling (n = 3), hypoxia (n = 2), and one each of neck swelling, back pain, diarrhea, lymphadenopathy local, septic shock, sweating, syncope, ageusia, hypotension, dysphagia, and renal failure.

[e]Others: abscess (n = 3), one each of atelectasis, lymph node mediastinum, tree-in-bud infiltrations.

[f]Additional details on infections that occurred concomitant or before nocardiosis are provided in Supplementary Table 3.

Table 8. In univariable and multivariable analyses, not being in continued complete remission of the underlying disease and prior bacterial infection were significantly associated with mortality (Table 3; Figure 3). Age, gender, underlying disease and its status at HCT, presence of comorbidities, HCT number, stem cell source, HLA matching, conditioning, acute or chronic graft-versus-host disease (GVHD) at the time of nocardiosis, immune suppressive medication number, lung or brain involvement, bacteremia, disseminated disease, lymphopenia and *Nocardia* species were not associated with 1-year mortality.

Among the 64 patients who completed antimicrobial therapy, 3 (5%) experienced nocardiosis relapse (Supplementary Table 9).

Comparison of Early and Late Nocardiosis (≤24 vs >24 Months Post-HCT)

We compared 66 of 81 (82%) early with 15 of 81 (18%) late post-HCT nocardiosis cases. Median time from symptom onset to diagnosis was shorter in early than in late cases (9 [IQR: 5–20] days vs 26 [10–45] days; $P = .03$). Use of antilymphocyte agents (as antithymocyte globulin, antilymphocyte globulin, alemtuzumab) was more frequent in patients with early than in those with late nocardiosis (42/64 [66%] vs 5/15 [33%]; $P = .02$). The proportions of disseminated disease (40/66 [61%] vs 6/15 [40%]) and brain involvement (27/66 [41%] vs 3/15 [20%]) were higher in patients with early compared with late nocardiosis, but these differences were not statistically significant ($P = .1$ for both comparisons). There were no other statistically significant differences in terms of clinical presentation, imaging findings, previous infections, relapse, and mortality.

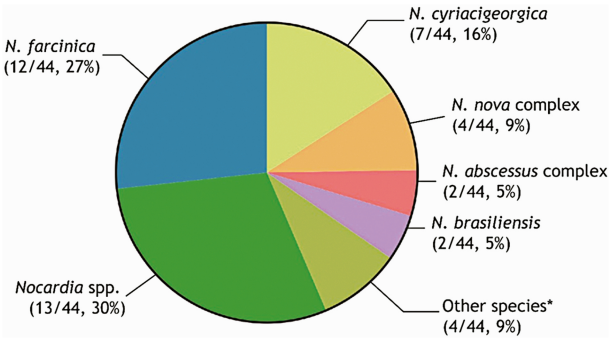

Figure 2. Distribution of *Nocardia* species (for 44/81 isolates identified by molecular method). Other species: 1 each of *N. paucivorans*, *N. veterana*, *N. mexicana*, and *N. shimofuesnsis*/*shigoensis*.

DISCUSSION

This multinational retrospective study of nocardiosis is the largest performed in HCT patients to date. We present clinical, radiological, microbiological, treatment, and outcome data for 81 HCT recipients with nocardiosis. Nocardiosis after HCT is rare, although severe infection, with 40% mortality at 1 year after diagnosis, directly attributed to the infection in 11 patients (14%).

The 7 single-center case series reported since 2000 each comprise 5 to 15 nocardiosis cases among adults following allo-HCT [5, 6, 9–13]. A review of 50 cases in adults after allo-HCT—these case series and others—has recently been published [10]. In addition, a retrospective study recently compared nocardiosis between 67 immunocompromised (including 16 HCT recipients) and 45 immunocompetent patients [14].

We found nocardiosis to be a late post-HCT complication, with a median time of 8 months after transplantation. This is a shorter interval than for SOT recipients, in whom nocardiosis

Table 3. Factors Significantly Associated With 1-Year All-Cause Mortality

Patient Characteristics	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Underlying disease status after HCT at the time of nocardiosis (n = 78)		.005		.01
Continued complete remission	1.00			
Never in complete remission/relapse/progression	2.91 (1.38–6.13)		2.81 (1.32–5.95)	
Presence of bacterial infection (within 3 months prior to nocardiosis or during nocardiosis)		.003		.001
No	1.00			
Yes	2.91 (1.43–5.90)		3.42 (1.62–7.22)	

Abbreviations: CI, confidence interval; HCT, hematopoietic cell transplantation; HR, hazard ratio.

is generally diagnosed after the first post-transplantation year [3, 12]. In line with this finding, and as observed elsewhere, none of the patients in our study were neutropenic at the time of nocardiosis [14]. Supporting the importance of T-cell immunity in preventing nocardiosis [2, 13], half our patients were lymphocytopenic, 73% received steroids, 60% had acute or chronic GVHD at the time of infection, and 41% had received an antilymphocyte agent within 1 year before nocardiosis. Nocardiosis appears to be mainly a concern for allo-HCT patients, with only a few following auto-HCT reported in our study as well as in the literature [17].

As seen in other populations [1, 14], lung nocardiosis was the most common type of infection in HCT recipients. In our study, lung consolidations and nodules were almost equally reported in about half the patients, with most nodules being cavitated. Diagnostically, this association between nocardiosis and lung nodules is important because such nodules in allo-HCT recipients often suggest invasive mold infection. Another important observation is that one-third of our patients were afebrile at presentation. Thus, even in afebrile patients, presence of late post-HCT lung consolidations or nodules should prompt investigation for nocardiosis. Bronchoalveolar lavage was frequently performed with high yield, but sputum examination was positive in 43% of cases, indicating that this simple examination should be performed as a complementary test whenever possible or when BAL is contraindicated.

Brain involvement was frequent in our study. It was found in almost 40% of patients, a rate higher than in previous reports looking at SOT recipients and other immunocompromised hosts [3, 14]. Previously published studies were often too small (and/or included non-HCT patients) to provide a precise estimate of the brain involvement frequency in HCT patients with nocardiosis. Notably, asymptomatic brain involvement was frequent in our cohort, with detection of brain abscess(es) in 29% of patients who underwent brain imaging despite having no neurological manifestations. The frequency of brain involvement may thus probably have been underestimated because not all patients had brain imaging. Asymptomatic brain involvement, previously described in a non-HCT setting [3], emphasizes the importance of systematic brain imaging in immunocompromised patients with nocardiosis.

Disseminated disease was more frequent in our study (57%) than in SOT patients (42.7%) [3] or in a heterogenous immunocompromised patient cohort (27%) [14]. Forty-two percent of allo-HCT patients were receiving TMP-SMX anti-*Pneumocystis* prophylaxis at the time of nocardiosis. This rate is higher than in previous HCT studies (23% in a recent literature review [10]) and appears to substantiate that low-dose TMP-SMX does not effectively prevent nocardiosis after HCT. Although some researchers have suggested that TMP-SMX prophylaxis may reduce nocardiosis risk after HCT [11], evidence from case-control studies suggests that low-dose TMP-SMX (≤800/160 mg, 3 times per week) does not prevent nocardiosis in SOT recipients [3, 18]. Its effect on nocardiosis risk in HCT recipients requires further study.

Optimal management of nocardiosis has not been determined for HCT recipients. Its treatment is challenging due to antibiotic toxicity (eg, myelotoxicity), resistance, and unknown efficacy of different agents. As in other studies, TMP-SMX was frequently part of the treatment protocol, followed by imipenem and amikacin, and TMP-SMX resistance was infrequent [10, 11, 14]. One-third of patients developed side effects attributed to antibiotics, some of which led to treatment discontinuation—a finding consistent with limited tolerance reported in other series [6, 12].

Available data suggest that patients with nocardiosis have a greater mortality risk than control HCT patients [7]. Case series found an overall mortality rate of 40–70%, with nocardiosis being the cause of death in 0–33% of infected patients [5, 6, 9–12, 14]. Similarly, in our study, 40% of patients died within 1 year of nocardiosis diagnosis; in 14%, death was attributed to nocardiosis. Identifying variables associated with poor outcome may be of major interest in this population. In our study, 1-year mortality was associated with not being in continued complete remission of the underlying disease and prior bacterial infection.

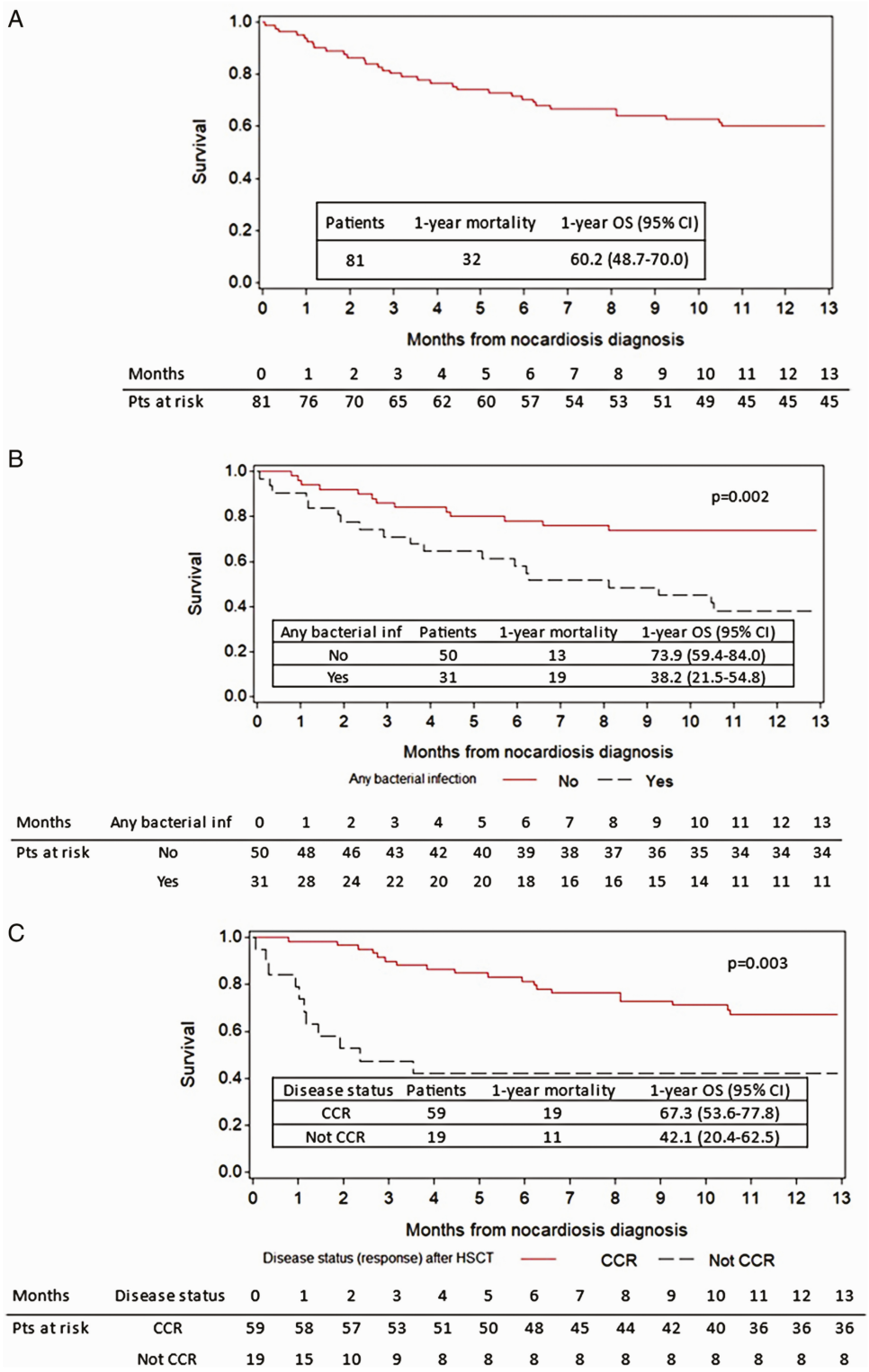

Figure 3. Survival curves 1 year after nocardiosis diagnosis. The Kaplan-Meier curves are presented up to 1 year after nocardiosis diagnosis. Comparison between the groups in panels (*B*) and (*C*) was performed using log-rank test. *A*, Survival curve in all patients. *B*, Survival curves in patients in continued complete remission and in those not in continued complete remission of the underlying disease. *C*, Survival curves in patients with and without bacterial infections before or during nocardiosis. Abbreviations: CCR, continued complete remission; CI, confidence interval; inf, infection; OS, overall survival; Pts, patients.

Our study has several limitations. First, it is retrospective, and some data are missing. We were unable to determine the effects of interventions (eg, therapy duration, drugs used, combination vs monotherapy) on 1-year survival because of the retrospective study design, treatment protocol heterogeneity, significant missing data regarding isolate susceptibility, and the

therapy timing. Second, species distribution data were limited, with molecular identification performed in only 44 isolates. Third, AST was not performed in a substantial proportion of isolates. Moreover, agents for which CLSI breakpoints are not determined were frequently used. This underscores the importance of further studies to define the best treatment strategies and enable distinct standardized treatment recommendations.

Last, although considerable effort was invested in exhaustive reporting of nocardiosis in participating centers, no conclusions concerning overall nocardiosis incidence in HCT recipients can be drawn, since a significant proportion of contacted centers did not respond. The number of nocardiosis cases and response rate were higher in Belgium, France, and Israel compared with other countries. Significant heterogeneity in response rates (with more respondents coming from the countries where the study coordinators are from) is common in multicenter European studies [3,19]. In the future, similar studies should ideally have a more balanced representation and coordinators in each participating country. Other potential explanations for the differences observed between countries in terms of numbers of cases include differences in patients' characteristics, immune suppression, post-transplantation TMP-SMX prophylaxis, and methods used to diagnose nocardiosis.

Our study, nevertheless, has important strengths. Comprising the largest cohort of HCT recipients with nocardiosis during the past 20 years, it enabled a summary of microbiological, clinical, imaging, and outcome data, and highlighted specific features useful for managing this infrequent complication. In particular, we demonstrated the importance of brain imaging in all HCT patients with nocardiosis, irrespective of neurological signs or symptoms. This is the first study that enabled multivariable analysis of factors associated with 1-year mortality following nocardiosis.

Conclusions

In this large retrospective international cohort, we found that nocardiosis is a late post-HCT infection that usually manifests as a pulmonary disease with frequent dissemination and brain involvement. Overall mortality is high. Underlying disease status and concurrent infections appear to play key roles in prognosis.

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

Acknowledgments. Study group members: M. Arat, Florence Nightingale Sisli Hospital, Instanbul, Turkey; I. W. Blau, Campus Virchow Klinikum CVK, Berlin, Germany; D. Bron, Institut Jules Bordet, Brussels, Belgium; K. Carlson, Department of Hematology, University Hospital, Uppsala, Sweden; M. Collin, Nordern Centre for Bone Marrow Transplantation Freeman Hospital—Adult HSCT Unit, Newcastle, United Kingdom; C. Cordonnier, Hôpital Henri Mondor, Creteil, France; A. Ganser, Hannover Medical School, Hannover, Germany; B. Gruhn, Department of Pediatrics, Jena University Hospital, Jena, Germany; C. Junghanss, Universitaet Rostock, Rostock, Germany; T. Marchand, Centre Hospitalier Universiteire de Rennes, Rennes, France; S. Martin, Robert-Bosch-Krankenhaus, Stuttgart, Germany; G. A. Milone, Azienda Ospedaliera Universitaria Policlinico—San Marino, Catania, Italy; A. Nagler, Chaim Sheba Medical Center, Tel Hashomer, Israel; S. Pagliuca, St-Louis Hospital, Paris, France; R. Ram, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; J. M. Ribera, ICO-Hospital Germans Trias i Pujol, Josep Carreras Research Institute, Badalona, Spain; J. de la Serna, Hospital Univ. 12 de Octubre, Madrid, Spain; M. Stamouli, Attikon University General Hospital, Athens, Greece; A. Villate, Service d'Hématologie et Thérapie Cellulaire, Centre Hospitalier Universitaire de Tours Université de Tours, Tours, France.

Potential conflicts of interest. All outside this study: D. A. received consulting fees from Takeda, Pfizer; payment for lectures from GSK; M. M. received personal fees for lectures from Pfizer, Gilead, MSD, and Janssen and for board meetings from Pfizer; N. K received research grants from Neovii, Jazz, Celgene, and Riemser, and honoraria from Neovii, Sanofi, Jazz, Celgene, Riemser, and Gilead; R. d. l. C. received consulting fees from Clinigen (03/2018, Foscarnet CMV treatment), Janssen (11/2018, Lumicitabine RSV in Immunocompromised Patients; 01/2019, Antiviral for RSV Respiratory Virtual Advisory Board), Roche (11/2019; Diagnostics Needs in Infectious Diseases in Immunocompromised Patients), and IQONE (11/2019, Foscarnet Viral Infections in Stem Cell Transplantation); honoraria for presentations for conferences/seminars from MSD, Gilead, Pfizer, Astellas, Novartis; payment for expert testimony from Astellas (cytomegalovirus vaccine in allogeneic HSCT patients); support for attending the European Hematology Association annual meeting from Janssen, and attending American Society for Blood and Marrow Transplantation meeting from MSD; participation in a Data Safety Monitoring Board or Advisory Board GSK (Herpes zoster subunit [HZ/su] vaccine; member of the Independent Data Monitoring Committee); J. C. participated in the advisory board of Sanofi (payment made to J. C.). J. D. G. received consulting fees from Menarini. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Margalit I, Lebeaux D, Tishler O, et al. How do I manage nocardiosis? Clin Microbiol Infect **2021**; 27:550–8.
2. Lafont E, Conan PL, Rodriguez-Nava V, Lebeaux D. Invasive nocardiosis: disease presentation, diagnosis and treatment—old questions, new answers? Infect Drug Resist **2020**; 13:4601–13.
3. Coussement J, Lebeaux D, van Delden C, et al; European Study Group for Nocardia in Solid Organ Transplantation. Nocardia infection in solid organ transplant recipients: a multicenter European case-control study. Clin Infect Dis **2016**; 63:338–45.
4. Lebeaux D, Freund R, van Delden C, et al. Outcome and treatment of nocardiosis after solid organ transplantation: new insights from a European study. Clin Infect Dis **2017**; 64:1396–405.
5. Daly AS, McGeer A, Lipton JH. Systemic nocardiosis following allogeneic bone marrow transplantation. Transpl Infect Dis **2003**; 5:16–20.
6. Mansi L, Daguindau E, Saas P, et al. Diagnosis and management of nocardiosis after bone marrow stem cell transplantation in adults: lack of lymphocyte recovery as a major contributing factor. Pathol Biol **2014**; 62:156–61.
7. van Burik JA, Hackman RC, Nadeem SQ, et al. Nocardiosis after bone marrow transplantation: a retrospective study. Clin Infect Dis **1997**; 24:1154–60.
8. Cattaneo C, Antoniazzi F, Caira M, et al. Nocardia spp infections among hematological patients: results of a retrospective multicenter study. Int J Infect Dis **2013**; 17:e610–4.
9. Shannon K, Pasikhova Y, Ibekweh Q, Ludlow S, Baluch A. Nocardiosis following hematopoietic stem cell transplantation. Transpl Infect Dis **2016**; 18:169–75.
10. Kurosawa S, Sekiya N, Doki N, et al. The emergence of rare nocardiosis following allogeneic hematopoietic stem cell transplantation in the era of molecular taxonomy. Int J Infect Dis **2019**; 89:154–62.
11. Molina A, Winston DJ, Pan D, Schiller GJ. Increased incidence of nocardial infections in an era of atovaquone prophylaxis in allogeneic hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant **2018**; 24:1715–20.

12. Hemmersbach-Miller M, Stout JE, Woodworth MH, Cox GM, Saullo JL. Nocardia infections in the transplanted host. Transpl Infect Dis **2018**; 20:e12902.
13. Roussel X, Daguindau E, Berceanu A, et al. Altered thymic CD4+ T-cell recovery after allogeneic hematopoietic stem cell transplantation is critical for nocardiosis. Curr Res Transl Med **2019**; 67:135–43.
14. Steinbrink J, Leavens J, Kauffman CA, Miceli MH. Manifestations and outcomes of nocardia infections: comparison of immunocompromised and nonimmunocompromised adult patients. Medicine **2018**; 97:e12436.
15. European Society of Blood and Marrow Transplantation. Med-AB forms manual (a guide to the completion of the EBMT HSCT Med-AB forms). Available at: https://www.ebmt.org/sites/default/files/2018-03/MED-AB%20Forms%20Manual.pdf. Accessed 21 February 2019.
16. Woods GL, Brown-Elliott BA, Conville PS, et al. Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes. 2nd edition. Wayne (PA): Clinical and Laboratory Standards Institute; Report No.: M24-A2. **2011**.
17. Chouciño C, Goodman SA, Greer JP, Stein RS, Wolff SN, Dummer JS. Nocardial infections in bone marrow transplant recipients. Clin Infect Dis **1996**; 23:1012–9.
18. Peleg AY, Husain S, Qureshi ZA, et al. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. Clin Infect Dis **2007**; 44:1307–14.
19. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the infectious diseases working party of the European bone marrow transplantation group. Clin Infect Dis **2017**; 65:1819–28.