Title

Increased Incidence of Nocardial Infections in an Era of Atovaquone Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients

Journal

Transplantation and Cellular Therapy, 24(8)

ISSN

2666-6375

Authors

Molina, Alfonso
Winston, Drew J
Pan, Darren
et al.

Publication Date

2018-08-01

DOI

10.1016/j.bbmt.2018.03.010

COVER LETTER

Corresponding Author:

Drew J. Winston, MD, Room 42-121 CHS Department of Medicine, UCLA Center for Health Sciences, Los Angeles, CA. 90095: phone number:_____, fax number: _____, e-mail: dwinston@mednet.ucla.edu

Category of Manuscript:

Rapid Communication

All authors have reviewed the manuscript, agree with its contents, and consent to its submission to BBMT:

x	x
Alfonso Molina	Drew J. Winston, MD
x	x
Darren Pan, MD	Gary J. Schiller, MD

HIGHLIGHTS

1. **Nocardiosis after allogeneic stem cell transplant is a late-onset complication.**

   (82 characters with spaces)
2. **Observed an increased incidence of nocardiosis with use of atovaquone**

   prophylaxis. (85 characters with spaces)
3. **Avoid prophylaxis with atovaquone or pentamidine for *Pneumocystis jiroveci*.**

   (78 characters with spaces)
4. **Trimethoprim-sulfamethoxazole is superior for *Pneumocystis jiroveci***

   prophylaxis. (83 characters with spaces)

Note: Highlights are a short collection of bullet points that convey the core findings and provide readers with a quick textual overview of the article. These three to five bullet points describe the essence of the research (e.g. results or conclusions) and highlight what is distinctive about it.

Highlights will be displayed in online search result lists, the contents list and in the online article, but will not (yet) appear in the article PDF file or print.

Specifications:

- Include 3 to 5 highlights.
- There should be a maximum of 85 characters, including spaces, per highlight.
- Only the core results of the paper should be covered.

TITLE PAGE

Increased Incidence of Nocardial Infections in an Era of Atovaquone Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients

Alfonso Molina, Drew J. Winston, MD, Darren Pan, MD, Gary J. Schiller, MD.

David Geffen School of Medicine, University of California, Los Angeles; Division of Hematology-Oncology, Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, California

Key words: Nocardial infection, atovaquone prophylaxis, stem cell transplantation

Correspondence: Drew J. Winston, MD, Room 42-121 CHS Department of Medicine, UCLA Center for Health Sciences, Los Angeles, CA. 90095: e-mail: dwinston@mednet.ucla.edu

FINANCIAL DISCLOSURE STATEMENT

Conflicts of Interests:

Alfonso: none

Dr. Winston:

Dr. Schiller:

Darren:

ABSTRACT

Nocardial infections have been rare after allogeneic hematopoietic stem cell transplantations (HSCT). We report 10 recent cases of late-onset nocardiosis (mean time of onset of 448 days after transplantation) primarily in patients on high doses of corticosteroids for graft-versus-host disease (GVHD). All 10 patients had pulmonary infection caused by *Nocardia* species susceptible to trimethoprim-sulfamethoxazole (TMP-SMX). At time of diagnosis, 8 of 10 patients were not receiving TMP-SMX for prophylaxis of *Pneumocystis jiroveci* pneumonia (PJP) (7 on atovaquone, 1 on intravenous pentamidine). After the initiation of atovaquone prophylaxis for PJP in place of TMP-SMX for many UCLA allogeneic HSCT patients in 2012, the incidence of nocardial infections increased more than tenfold from 0.17% (1 case in 575 patients from 2000 to 2011) to 2.2% (9 cases in 411 patients from 2012 to 2017). While there were no deaths directly related to nocardial infection treated primarily with TMP-SMX, overall mortality was 40%. Based on this experience, the use of atovaquone for PJP prophylaxis in place of TMP-SMX may be associated with an increased risk for previously rare nocardial infections after allogeneic HSCT.

INTRODUCTION

Nocardia spp. is an aerobic, gram-positive bacterium commonly found in the soil, water, and air [1]. Infection occurs primarily by inhalation and thus usually causes respiratory symptoms with radiographic evidence of pneumonia. In severe cases, hematogenous dissemination to other organs can occur, causing cutaneous nodules, brain abscesses or other visceral disease. Nocardiosis has been an uncommon infection among allogeneic hematopoietic stem cell transplantation (HSCT) recipients. An incidence of 0.3% to 1.7% has been reported in allogeneic HSCT patients [2-6]. The preferred agent for treatment of most nocardial infections is trimethoprim-sulfamethoxazole (TMP-SMX) [1]. When used for prophylaxis of *Pneumocystis jiroveci* pneumonia (PJP) following HSCT, it is believed that TMP-SMX can also be efficacious as prevention of nocardial infections [4, 5, 7].

At the UCLA Medical Center, nocardiosis has been rare in HSCT patients. However, in recent years, we have seen a significant rise in the incidence of nocardiosis in patients following allogeneic HSCT. In this article, we report a possible association between the use of atovaquone in place of TMP-SMX for PJP prophylaxis and an increased incidence of nocardial infections following allogeneic HSCT.

METHODS

A retrospective review of patient's medical records and UCLA Clinical Microbiology Laboratory culture results was performed to identify allogeneic HSCT recipients with a diagnosis of nocardiosis between January 1, 2000 and August 30, 2017. Baseline patient characteristics, underlying disease, allograft type, conditioning regimen,

pre-transplant and donor CMV serology, immunosuppressive agents, and GVHD status were collected. The clinical features of *Nocardia* infection and PJP prophylaxis at the time of diagnosis were also included in this review. The diagnosis of nocardiosis was made based on at least one culture of respiratory secretions or blood positive for *Nocardia* from a patient with clinical features of *Nocardia* infection not explainable by other causes.

All *Nocardia* isolates were identified in the UCLA Clinical Microbiology Laboratory. Prior to 2013, a 7H11 solid media was used to recover *Nocardia* from clinical specimens [8]. From 2013 to the present, a buffered-charcoal yeast extract media was used to enhance recovery of *Nocardia* from cultures [9]. All cultures were held for 3 at least weeks and examined daily for growth. Before 2013, *Nocardia* susceptibility testing was performed by an outside reference laboratory (Quest Diagnostics Infectious Disease, Inc., 33608 Ortega Highway, Bldg. B-West Wing, San Juan Capistrano, CA 92675-2042). After 2013, *Nocardia* susceptibility testing was performed at the UCLA Clinical Microbiology Laboratory. *Nocardia* susceptibility testing was performed in the both settings, using broth microdilution trays. After inoculation of organisms, these trays are incubated for 72 hours and then read per standard antimicrobial susceptibility testing protocols to determine minimum inhibitory concentrations (MICs) [10]. CLSI M24-A2 susceptibility breakpoints are used [11].

RESULTS

Patient Characteristics

A total of 10 cases of nocardiosis were identified in allogeneic HSCT recipients at

the UCLA Medical Center in a 17-year period between 2000 and 2017 (Table 1). The majority of patients were men (7 of 10). The median age was 42 years (range 15 – 63 years). Except for one patient with myelofibrosis, all patients had underlying leukemia (7 patients) or lymphoma (2 patients). Eight patients had received matched-related donor allografts, and 2 patients had matched unrelated donor allografts. The source of stem cells was peripheral blood in 6 patients and bone marrow in 4 patients. There were no cord-blood transplant recipients with nocardial infection. The pre-transplant conditioning regimen was myeloablative in 7 patients and non-myeloablative in 3 patients.

Seven patients had a history of acute and/or chronic graft-versus-host disease (GVHD) after allogeneic HSCT (6 chronic GVHD, 2 acute GVHD). Four patients had active chronic GVHD at the time of diagnosis of nocardial infection. All 10 patients were on immunosuppressive drugs for prevention or treatment of GVHD when nocardial infection occurred. Six of 10 patients were receiving a combination of tacrolimus and prednisone, one received prednisone alone, one received tacrolimus alone, and one received tacrolimus plus prednisone and methotrexate. Among the 8 patients on prednisone, the median daily prednisone dose was 55 mg (range 25 - 100 mg), with seven of 8 patients receiving ≥ 40 mg per day. The median daily tacrolimus dose was 2.25 mg (range 1.5 - 4 mg).

All patients were receiving prophylactic agents for prevention of PJP at the time of the diagnosis of nocardial infection. Seven of 10 patients were taking daily atovaquone (1500 mg), two were receiving TMP-SMX, and one had received monthly intravenous pentamidine (180 mg). Both patients on TMP-SMX prophylaxis received 800-160 mg three times daily on Saturday and Sunday only.

Clinical Features of Nocardiosis

The mean time from day of allogeneic HSCT to diagnosis of nocardial infection was 449 days (range 116 - 806 days) (Table 2). Nine of 10 patients had only pulmonary nocardiosis, while one patient had both pulmonary infection and brain abscesses. Other bacterial, fungal and/or viral concomitant organisms were found in the respiratory cultures of 30% of the patients. Atypical mycobacteria were the most common other organisms, which were frequently of uncertain clinical significance.

The median absolute neutrophil count among patients was 4.1 $x10^3/\mu L$ (range 2.6 $x10^3/\mu L$ – 11.8 $x10^3/\mu L$) and the median absolute lymphocyte count was 5.9 $x10^3/\mu L$ (range 0.1 $x10^3/\mu L$ - 18.8 $x10^3/\mu L$). Lymphopenia (less than 500 lymphocytes/1μL) was present in 2 patients. CMV infection (viremia) within the 2 weeks prior to diagnosis of *Nocardia* infection was present in 2 patients. *Nocardia* species causing infections included *N. cyriacigeorica* (3 cases), *N. farcinica* (2 cases), *N. veterana* (2 cases), and unspecified *Nocardia* (3 cases). All 10 *Nocardia* isolates were sensitive to TMP-SMX.

TMP-SMX was the drug used for treatment of nocardial infection in 8 patients. Other drugs (amoxicillin-clavulanate, minocycline and doxycycline) were used in two other patients with an allergy to TMP-SMX. Nocardial infection resolved in 6 patients. Nocardial infections in four other patients were stable when the patients expired from other causes. Overall mortality was 40% (4 of 10 patients) but no deaths were attributed to nocardial infection.

Incidence of Nocardial Infection and Use of Atovaquone Prophylaxis after Allogeneic HSCT by Transplant Year

986 patients underwent allogeneic HSCT at UCLA Medical Center between 2000

and 2017. Ten patients were diagnosed with nocardiosis between 2000 and 2017. The use of atovaquone instead of TMP-SMX for PJP prophylaxis for a variety of reasons was started in 2012 and progressively increased over the next 4 years. Prior to 2012, there was only 1 case of nocardial infection in 575 allogeneic HSCT patients (0.17%). From 2012 to 2017, when the use of atovaquone prophylaxis became more frequent, the incidence of nocardial infection increased more than tenfold from 0.17% (1 case in 575 patients) to 2.2% (9 cases in 411 patients). Atovaquone was primarily used in place of TMP-SMX to avoid myelosuppression and cytopenias.

DISCUSSION

In contrast to fungal, viral, and other bacterial infections, nocardiosis has been a relatively uncommon opportunistic infection in stem cell transplant recipients. Indeed, except for two small case series of nocardial infections published in the 1990's and two case series published more recently in 2003 and 2016, most cases of nocardiosis in stem cell transplant recipients reported in the literature have been isolated case reports [2 – 5]. In 1997, Van Burik et al., reported only 22 nocardial infections among 879 patients receiving allogeneic stem cell transplants (an incidence of 0.3%) at three transplant centers over 25 years. Similarly, Choucino et al., in 1996 and Daly et al., in 2003 both reported a 1.7% incidence of nocardial infection among patients receiving allogeneic stem cell transplants at Vanderbilt University and Princess Margaret Hospital in Toronto, respectively. In 2016, Shannon et al., described 15 cases of nocardiosis following allogeneic stem cell transplantation between 2003 and 2013 at the Moffitt Cancer Center in Florida. While the reasons for this very low incidence of nocardiosis in stem cell

transplant recipients have been debated, it has been speculated that the use of TMP-SMX for prevention of PJP may also reduce the risk for nocardial infection [4, 5, 7]. Human immunodeficiency virus (HIV) – infected patients given prophylactic TMP-SMX on a daily basis also have a very low rate of nocardiosis [12]. Nonetheless, some transplant recipients develop nocardial infection despite receiving prophylactic TMP-SMX on a intermittent basis, suggesting that the dosage of prophylactic TMP-SMX as well as other factors may influence the risk for nocardial infections [6].

Similar to the previous case series, we found that nocardiosis after allogeneic HSCT is usually a late onset infection (mean time of onset of 449 days after transplantation) and is frequently associated with GVHD (7 of 10 patients) and ongoing immunosuppressive therapy with high doses of corticosteroids (8 of 10 patients). Pulmonary infection was the most common initial clinical presentation (9 of 10 patients), which is also consistent with previous reports in stem cell transplant recipients. Disseminated infection was relatively uncommon in our patients (one patient had both pneumonia and brain abscesses) but was reported more frequently in previous publications [2 – 5]. Central nervous system lesions (mostly brain abscesses) are the common manifestation of disseminated infection. Thirty percent of our highly immunosuppressed patients also had other organisms (most common atypical mycobacteria) isolated from their respiratory secretions during their clinical course, which were frequently of uncertain clinical significance and not always treated. Similar concomitant organisms have also been noted in other previous reports of nocardiosis in allogeneic HSCT [2 – 5].

When the UCLA stem cell transplant program was started in the 1970's, a

protocol using high dose trimethoprim (240 mg) – sulfamethoxazole (1200 mg) every 8 hours on two consecutive days of each week was developed for prevention of PJP [12]. This intermittent scheduled of high-dose TMP-SMX prophylaxis was designed to potentially reduce the risk of cytopenia associated with daily TMP-SMX prophylaxis in patients receiving methotrexate for prevention of GVHD, while still providing effective prophylaxis against PJP. Subsequent experience with this intermittent schedule of TMP-SMX at UCLA, at other transplant centers, and in HIV-infected patients has confirmed the efficacy and safety of intermittent TMP-SMX for prevention PJP [13]. Nevertheless, when studies demonstrated the efficacy of atovaquone (1500 mg daily) for prevention of PJP in both HIV-infected patients and in transplant recipients intolerant of TMP-SMX [13 – 15], there was an increased use of atovaquone prophylaxis in UCLA allogeneic HSCT starting in 2012 (Table 3). During this period of increasing atovaquone prophylaxis to avoid cytopenia associated with TMP-SMX, we observed a 10-fold increase in the incidence of nocardial infections. Indeed, 8 of out 10 patients (80%) with nocardial infection were on either atovaquone (7 patients) or intravenous pentamidine (one patient) when they developed infection. Two patients on intermittent TMP-SMX prophylaxis still developed nocardiosis, although they may not have been compliant with their medications. Sixty to 80% of the patients in previous studies of nocardiosis after allogeneic HSCT were also not taking TMP-SMX prophylaxis [2 – 5]. Thus, while the role of TMP-SMX in prevention of nocardiosis after transplantation may not be entirely clear, these combined data suggest that TMP-SMX does have some protective effect.

The total absence of any cases of nocardial infection in UCLA allogeneic stem cell transplant from 2000 to 2011 followed by a significant increase with the use of

atovaquone prophylaxis caused us to look for other contributing factors. Except for a greater number of cord-blood stem cell transplants in recent years, the types of stem cell transplants and immunosuppressive regimens did not change significantly. Furthermore, none of our nocardial infections occurred in a cord-blood stem cell transplant recipient. All UCLA stem cell transplant patients have been closely followed by the same experienced transplant infectious disease specialist (DJW) for the past 42 years for infectious complications. Thus, it is unlikely that any significant number of nocardial infections would have been overlooked. In 2013, the UCLA Clinical Microbiology Laboratory began using buffered-charcoal yeast extract media to enhance recovery of *Nocardia* in culture [9]. While this change in culture technique may have contributed to easier recovery of *Nocardia* from cultures of clinical specimens, we began seeing more cases of nocardiosis even before this change in culture method.

Before 1990, most *Nocardia* strains causing infection were reported as *Nocardia asteroides.* Subsequently, by using new molecular tools, it was found that many species were inaccurately identified [1]. It has now become apparent that nocardial infections are caused by multiple species, each with its own antimicrobial susceptibility pattern [1, 6, 16]. Thus, identification of *Nocardia* species and antimicrobial susceptibility testing are recommended to guide therapy. All of our *Nocardia* isolates causing infection were sensitive to TMP-SMX and 9 of 10 isolates were also sensitive to imipenem. All 8 nocardial infections treated with trimethoprim-sulfamethoxazole and 2 other infections treated with other antimicrobial agents either resolved or were stable on therapy. The therapy was well tolerated. Nonetheless, 4 of 10 patients (40%) expired from causes unrelated to nocardial infection. The overall mortality rates in the previous published case

series of nocardiosis after allogeneic HSCT ranged from 53% to 70%, although nocardial attributable mortality was much less.

In conclusion, nocardial infection after allogeneic HSCT is a late-onset complication frequently associated with GVHD and increased immunosuppressive therapy with corticosteroids. The infection most commonly involves the lung, but may also disseminate to the central nervous system and cause brain abscesses. Treatment with TMP-SMX is usually effective. Although nocardiosis has been very uncommon after allogeneic HSCT, we observed an increased incidence of nocardiosis during an era of increased atovaquone prophylaxis for prevention of PJP. Consequently, we have re-emphasized the use of TMP-SMX for PJP prophylaxis in our allogeneic HSCT patients by returning to our older protocol of high-dose TMP-SMX (240 mg of trimethoprim – 1200 mg of sulfamethoxazole three times daily on two consecutive days of each week) in all patients not allergic to sulfa drugs [12]. If a patient develops significant neutropenia or thrombocytopenia on TMP-SMX, the drug is temporarily stopped and then restarted at the same dose after recovery of the cytopenia with or without the administration of growth factors. Unless a patient is totally intolerant of TMP-SMX, prophylaxis with atovaquone or pentamidine is avoided. A similar strategy for prevention of PJP has been suggested in published guidelines [7].

ACKNOWLEDGMENTS

Should we acknowledge Dr. Omai Garner from the Clinical Microbiology Laboratory for his help with the culturing and susceptibility methods portion of the manuscript?

Note: Authors must disclose any primary financial relationship with a company that has a direct financial interest in the subject matter or products discussed in the submitted manuscript, or with a company that produces a competing product. These relationships (such as honoraria, ownership of stock, patents, or consulting fees) and any direct support of research by a commercial company will be included in the Acknowledgements section of the published article.

REFERENCES

1. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ, Jr. Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbial Rev. 2006; 259-282.

2. Van Burik JA, Hackman RC, Nadeem SQ, et al. Nocardiosis after bone marrow transplantation: a retrospective study. Clin Infect Dis 1997; 24: 1154-1160.

3. Choucino C, Goodman SA, Greer JP, et al. Nocardial infections in bone marrow transplant recipients. Clin Infect Dis 1996; 26; 1012-1019

4. Daly AS, Mcgeer A, Lipton JH. Systemic nocardiosis following allogeneic bone marrow transplantation. Transpl Infect Dis 2003; 5: 16-20

5. Shannon K, Pasikhova Y Ibekweh Q, Ludlow S Baluch A. Nocardiosis following hematopoietic stem cell transplantation. Transpl infect Dis 2016; 18: 169-175

6. Lebeauy D, Morelon E, Suarez F, et al. Nocardiosis in transplant recipients. Eur J Clin Microbial Infect Dis 2014; 33: 689-702.

7. Tomblynn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantations recipients: a global perspective. Biol Blood Marrow Transplant 2009; 15: 1143-1238.

8. Conville, Patricia S. and Witebsky, Frank G. Aerobic Actinomycetes In: Versalovic, James and Carroll, Karen C. and Funke, Guido and Jorgensen, James H. and Landry, Marie Louise and Warnock, David W. Manual of Clinical Microbiology. 10th edition. Washington DC: ASM Press; 2011 p. 459-471

9. Vickers RM, Rihs JD, Yu VL. Clinical demonstration of isolation of *Nocardia asteroides* on buffered charcoal-yeast extract media. J Clin Microbial 1992; 30:227-228

10. Wallace RJ Jr, Septimus EJ, Musher DM, Martin RR. Disk diffusion susceptibility testing of *Nocardia* species. J Infect Dis 1977; 135: 568-576

11. Clinical and Laboratory Standards Institute Performance standards for antimicrobial susceptibility testing. Document M100-S21. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.

12. Winston, DJ, Gale RP, Meyer DV, Young LS. Infectious complications of human bone marrow transplantation. Medicine 1979; 58: 1-31

13. Rodriguez M, Fishman JA. Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. Clin Microbial Rev. 2004; 17: 770-782

14. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for prevention of *Pneumocystis carin;* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides or both. N Engl J Med 1998; 339: 1889-1895.

15. Colby C, McAfee SL, Sackstein R, et al. A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole for *Pneuomocystis carini* pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1999; 24: 897-902.

16. Wang HL, Seo YH, LaSala PR, Tarrand JJ, Han XY. Nocardiosis in 132 patients with cancer. Microbiological and clinical analyses. Am J Clin Path 2014; 142: 513-523

TABLES

Table 1. Characteristics of Patients with Nocardial Infection

Characteristic	Patient									
	1	2	3	4	5	6	7	8	9	10
Age (years)	54	15	52	52	30	36	38	30	63	45
Gender	M	F	F	M	F	M	M	M	M	M
Underlying Malignancy	AML	ALL	AML	LYM	LYM	ALL	MF	AML	CML	AML
Allograft Type	MRD PBSC	MRD PBSC	MRD PBSC	MUD PBSC	MRD PBSC	MRD BM	MUD BM	MRD PBSC	MRD BM	MRD BM
Conditioning Regimen	MAC	MAC	MAC	RIC	MAC	MAC	MAC	RIC	RIC	MAC
Pre-Transplant CMV Serology	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Positive	Positive	Negative
Donor CMV Serology	UNK	UNK	Negative	Negative	Positive	Positive	Negative	Positive	Negative	Negative
GVHD Prophylaxis	PDN TAC	PDN	PDN TAC	PDN TAC	TAC	TAC	PDN TAC	PDN TAC	PDN TAC	PDN TAC MTX
PJP Prophylaxis	ATQ	PI	ATQ	TMP-SMX	ATQ	TMP-SMX	ATQ	ATQ	ATQ	ATQ
PJP Prophylaxis Dose	1,500 mg daily	180 mg monthly	1,500 mg daily	800-160 mg TID Sat/Sun	1,500 mg daily	800-160 mg TID Sat/Sun	1,500 mg daily	1,500 mg daily	1,500 mg daily	1,500 mg daily
aGVHD Max Grade	-	-	-	-	Grade 3	-	-	Grade 3	-	-
aGVHD Treatment	-	-	-	-	TAC	-	-	PDN TAC BUD	-	-
cGVHD Severity	Mild	-	Mild	Mild	Mild	-	-	-	Mild	Moderate
cGVHD Treatment	TAC AZM	-	TAC PDN MMF	TAC BUD MEP	TAC PDN AZM	-	-	-	DEX RTX ECP	TAC PDN MMF

Abbreviations: **aGVHD**, acute graft-versus-host disease; **ALL**, acute lymphoblastic leukemia; **AML**, acute myeloid leukemia; **ATQ**, atovaquone; **AZM**, azithromycin; **BM**, bone marrow; **BUD**, budesonide; **CML**, chronic myeloid leukemia; **cGVHD**, chronic graft-versus-host disease; **DEX**, dexamethasone; **ECP**, extracorporeal photopheresis; **F**, female; **LYM**, lymphoma; **MAC**, myeloablative conditioning; **M**, male; **MEP**, methylprednisolone; **MF**, myelofibrosis; **MMF**, mycophenolate; **MRD**, matched-related donor; **MTX**, methotrexate; **MUD**, matched-unrelated donor; **PBSC**, peripheral blood stem cell; **PDN**, prednisone; **PI**, pentamidine; **PJP**, *Pneumocystis jirovecii* pneumonia; **RIC**, reduced intensity conditioning; **RTX**, rituximab; **TAC**, tacrolimus; **TMP-SMX**, trimethoprim-sulfamethoxazole; **UNK**, unknown

Table 2. Clinical Features of *Nocardia* Diagnosis

Characteristic	Patient									
	1	2	3	4	5	6	7	8	9	10
Site of Infection	PUL	PUL	PUL	PUL	PUL	PUL	PUL	PUL	PUL	Brain
Days From Transplant	806	162	618	604	525	457	493	116	194	523
PJP Prophylaxis	ATQ	PI	ATQ	TMP-SMX	ATQ	TMP-SMX	ATQ	ATQ	ATQ	ATQ
ANC ($x10^3/\mu L$)	7.5	3.1	4.1	11.8	2.6	3.7	8.7	5.4	4.0	2.9
Lymphocyte Count ($x10^3/\mu L$)	16.2	7.4	4.4	4.0	13.8	18.8	3.6	0.4	13.9	0.1
CMV Load (copies/mL)	37,080	NEG	NEG	NEG	137	NEG	NEG	301	137	NEG
***Nocardia* Species**	*N. cyria-cigeorica*	*N. farcinica*	*N. veterana*	*N. veterana*	UND	UND	*N. cyria-cigeorica*	UND	*N. cyria-cigeorica*	*N. farcinica*
Species MIC (μg/mL)										
AMK	1 (S)	<0.5 (S)	<0.5 (S)	<0.5 (S)	-	<0.5 (S)	1 (S)	-	<0.5 (S)	<0.5 (S)
IMP	1 (S)	1 (S)	<0.2 (S)	<0.2 (S)	1 (S)	<0.2 (S)	1 (S)	0.5 (S)	2 (S)	-
LZD	-	4 (S)	<0.5 (S)	1 (S)	-	1 (S)	2 (S)	2 (S)	2 (S)	-
TMP-SMX	<1/20 (S)	<1/20 (S)	<1/20 (S)	<1/20 (S)	<1/20 (S)	<1/20 (S)	<1/20 (S)	<1/20 (S)	<1/20 (S)	<1/20 (S)
Concomitant Organisms	-	-	-	-	*A. indulans*	*R. aquatilis*, *P. agglo-merans*, *M. chelonae*, Rhinovirus	-	-	MAC	-
Nocardia Treatment	TMP-SMX	MIN, AMC	TMP-SMX	TMP-SMX	DOX, AMC	TMP-SMX	TMP-SMX	TMP-SMX	TMP-SMX	TMP-SMX
Treatment Duration (days)	1	367	154	397	513	136	183	105	121	24
Outcome	Death, infection stable	Infection resolved	Infection resolved	Infection resolved	Infection resolved	Death, infection stable	Infection resolved	Death, infection stable	Infection resolved	Death, infection stable
Cause of Death	ARF, Aspiration PNA	-	-	-	-	ARF, PNA	-	Intra-cranial bleed	-	ARF, Sepsis

Abbreviations: **AMC**, amoxicillin-clavulanate; **AMK**, amikacin; **ANC**, absolute neutrophil count; **ARF**, acute respiratory failure; **ATQ**, atovaquone; **DOX**, doxycycline; **IMP**, imipenem; **LZD**, linezolid; **MAC**, mycobacterium avium complex; **MIC**, minimal inhibitory concentration, **MIN**, minocycline; **NEG**, negative; **PI**, pentamidine; **PNA**, pneumonia; **PJP**, *Pneumocystis jirovecii* pneumonia; **PUL**, pulmonary; **S**, susceptible; **TMP-SMX**, trimethoprim-sulfamethoxazole; **UND**, undetermined

Table 3. Time of Nocardial Infection and Use of Atovaquone Prophylaxis after Allogeneic HSCT by Transplant Year

Transplant Year	No. of Allogeneic HSCT Patients	No. of *Nocardia* Infections	No. of Patients on Atovaquone for PJP Prophylaxis
2000	40	0	0
2001	41	0	0
2002	35	0	0
2003	42	0	0
2004	51	0	0
2005	48	0	0
2006	40	0	0
2007	57	0	0
2008	54	0	0
2009	51	0	0
2010	66	0	0
2011	50	1	0
2012	52	1	8
2013	71	0	9
2014	80	0	19
2015	81	6	34
2016	73	1	37
2017	54	1	12
Total	986	10	119
2000 - 2011	575	1	0
2012 - 2017	411	9	119

Abbreviations: **HSCT**, hematopoietic stem cell transplantation; **PJP**, *Pneumocystis jirovecii* pneumonia