Nocardiosis in renal transplant patients

Maya Gibson [1], Nianlan Yang,[2,3] Jennifer L Waller,[2] Lufei Young,[4] Wendy B Bollag,[5] Mufaddal Kheda,[1] Azeem Mohammed,[1] Stephanie L Baer [1,6]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jim-2021-001783).

[1]Department of Medicine, Augusta University Medical College of Georgia, Augusta, Georgia, USA
[2]Department of Biostatistics and Epidemiology, Augusta University, Augusta, Georgia, USA
[3]Department of Biostatistics, The University of Alabama at Birmingham, Birmingham, Alabama, USA
[4]College of Nursing, Augusta University, Augusta, Georgia, USA
[5]Department of Dermatology, Medical College of Georgia, Augusta, Georgia, USA
[6]Infection Control and Epidemiology, Augusta VA Medical Center, Augusta, Georgia, USA

Correspondence to
Dr Stephanie L Baer, 1 Freedom Way (235), Augusta, GA 30904, USA; stephanie.baer@va.gov

Accepted 20 July 2021
Published Online First 23 August 2021

To cite: Gibson M, Yang N, Waller JL, *et al*. *J Investig Med* 2022;**70**:36–45.

ABSTRACT

Renal transplant patients are immunosuppressed and are at increased risk of opportunistic infections, including *Nocardia* infection. In renal transplant patients, information on the incidence and risk factors associated with nocardiosis is limited. To address the incidence and risk factors associated with nocardiosis in a large renal transplant population, we used the US Renal Data System (USRDS). Sequelae of allograft failure or rejection after infection were also examined. Demographics, clinical risk factors, *Nocardia* diagnosis, and allograft failure following *Nocardia* infection were queried in USRDS renal transplant patients using International Classification of Diseases, Ninth Revision (ICD-9) codes in billing claims and Centers for Medicare and Medicaid Services Form 2728. Generalized linear models were used to determine the risk factors associated with nocardiosis, and Cox proportional hazards models were used to examine the association of risk factors with graft failure among patients with *Nocardia* infection. Of 203,233 renal transplant recipients identified from 2001 to 2011, 657 (0.32%) were diagnosed with *Nocardia* infection. Pneumonia was the most frequent presentation (15.2%), followed by brain abscess (8.4%). Numerous factors associated with increased *Nocardia* infection included age >65 years (OR=2.10, 95% CI 1.71 to 2.59), history of transplant failure (OR=1.28, CI 1.02 to 1.60) or history of rejection (OR=4.83, CI 4.08 to 5.72), receipt of a deceased donor transplant (OR=1.23, CI 1.03 to 1.46), and treatment with basiliximab (OR=1.25, CI 1.00 to 1.55), cyclosporine (OR=1.30, CI 1.03 to 1.65), tacrolimus (OR=2.45, CI 2.00 to 3.00), or thymoglobulin (OR=1.89, CI 1.59 to 2.25). In patients with nocardiosis administration of antithymocyte globulin (HR=2.76), chronic obstructive pulmonary disease (HR=2.47), and presentation of *Nocardia* infection with brain abscess (HR=1.85) were associated with an increased risk of graft failure. This study provides new information to enhance early recognition and targeted treatment of nocardiosis in renal transplant patients.

Significance of this study

What is already known about this subject?

- The reported incidence of *Nocardia* infection in solid transplant recipients is 0.4%–3.6%.
- Risk factors associated with nocardial infection include cytomegalovirus viremia, steroid use, and calcineurin inhibitors.
- Pulmonary infection presentation is the most common manifestation of nocardiosis in renal transplant patients.

What are the new findings?

- Of renal transplant recipients from 2001 to 2011, there is 0.32% incidence of nocardiosis within the United States.
- The most common presentations of *Nocardia* infection in this cohort were pneumonia (14%) and brain abscess (8%).
- Administration of basiliximab, cyclosporine, tacrolimus, or thymoglobulin was associated with an increased risk of nocardial infection.
- Administration of antithymocyte globulin and presentation of *Nocardia* infection with brain abscess were associated with an increased risk of graft failure.

How might these results change the focus of research or clinical practice?

- Nocardial infection is a rare infection in renal transplant patients which may present as pneumonia and/or brain abscess.
- Many of the common immunosuppressants are associated with an increased risk of this opportunistic infection as are age 65+ at initial transplant, history of transplant failure, history of transplant rejection, or receipt of a transplant from a deceased donor.

INTRODUCTION

Renal transplant recipients are by necessity immunosuppressed and are at a significantly increased risk of opportunistic infections, such as *Nocardia* infection. This bacterium is a Gram-positive filamentous rod which is rarely known to cause infection, with a reported incidence of 0.4%–3.6% in solid organ transplant recipients.[1–3] A retrospective cohort study in 1989 of 94 renal transplant patients with *Nocardia* infection at a single center described various presentations: pulmonary (88%), cutaneous (20%), central nervous system (7%), and septic arthritis (7%).[4] Nocardiosis may mimic the presentation

Table 1 Descriptive statistics, n (%), overall and by *Nocardia* infection in 203,233 ESRD transplant patients

			Nocardia infection	
Variable	**Level**	Overall N=**203,233**	**Yes** n=**657 (0.3%)**	**No** n=**202,576 (99.7%)**
Demographic variables				
Age at transplant	65+	26,863 (13.2)	115 (17.5)	26,748 (13.2)
	<65	176,370 (86.8)	542 (82.5)	175,828 (86.8)
Race	Black	50,814 (25.0)	163 (24.8)	50,651 (25.0)
	Other	11,418 (5.6)	39 (5.9)	11,379 (5.6)
	White	141,001 (69.4)	455 (69.3)	140,546 (69.4)
Gender	Female	81,004 (39.9)	260 (39.6)	80,744 (39.9)
	Male	122,229 (60.1)	397 (60.4)	121,832 (60.1)
Ethnicity	Hispanic	25,719 (12.7)	86 (13.1)	25,633 (12.6)
	Non-Hispanic/unknown	177,514 (87.3)	571 (86.9)	176,943 (87.4)
Transplant-related variables				
Donor type	Cadaver	139,308 (68.6)	487 (74.1)	138,821 (68.5)
	Living	63,925 (31.5)	170 (25.9)	63,755 (31.5)
History of graft failure	Yes	87,034 (42.8)	442 (67.3)	86,592 (42.7)
	No	116,199 (57.2)	215 (32.7)	115,984 (57.3)
History of kidney rejection	Yes	56,130 (27.6)	398 (60.6)	55,732 (27.5)
	No	147,103 (72.4)	259 (39.4)	146,844 (72.5)
Antithymocyte	Yes	8211 (4.0)	26 (4.0)	8185 (4.0)
	No	195,022 (96.0)	631 (96.0)	194,391 (96.0)
Azathioprine	Yes	39,979 (19.7)	164 (25.0)	39,815 (19.6)
	No	163,254 (80.3)	493 (75.0)	162,761 (80.4)
Basiliximab	Yes	35,279 (17.4)	103 (15.7)	35,176 (17.4)
	No	167,954 (82.6)	554 (84.3)	167,400 (82.6)
Cyclosporine	Yes	38,399 (18.9)	170 (25.9)	38,229 (18.9)
	No	164,834 (81.1)	487 (74.1)	164,347 (81.1)
Everolimus	Yes	959 (0.5)	*	*
	No	202,274 (99.5)	*	*
Infliximab	Yes	13 (0.0)	*	*
	No	203,220 (100.0)	*	*
Muromonab	Yes	17,925 (8.8)	84 (12.8)	17,841 (8.8)
	No	185,308 (91.2)	573 (87.2)	184,735 (91.2)
Mycophenolate	Yes	151,580 (74.6)	513 (78.1)	151,067 (74.6)
	No	51,653 (25.4)	144 (21.9)	51,509 (25.4)
Prednisone	Yes	192,456 (94.7)	630 (95.9)	191,826 (94.7)
	No	10,777 (5.3)	27 (4.1)	10,750 (5.3)
Rituximab	Yes	1675 (0.8)	*	*
	No	201,558 (99.2)	*	*
Sirolimus	Yes	34,103 (16.8)	97 (14.8)	34,006 (16.8)
	No	169,130 (83.2)	560 (85.2)	168,570 (83.2)
Steroid	Yes	193,552 (95.2)	635 (96.7)	192,917 (95.2)
	No	9681 (4.8)	22 (3.3)	9659 (4.8)
Tacrolimus	Yes	140,896 (69.3)	503 (76.6)	140,393 (69.3)
	No	62,337 (30.7)	154 (23.4)	62,183 (30.7)
Thymoglobulin	Yes	64,678 (31.8)	242 (36.8)	64,436 (31.8)
	No	138,555 (68.2)	415 (63.2)	138,140 (68.2)
Clinical diagnosis				
Asthma	Dx	14,579 (7.2)	49 (7.5)	14,530 (7.2)
	No Dx	188,654 (92.8)	608 (92.5)	188,046 (92.8)
Cytomegalovirus	Dx	14,038 (6.9)	66 (10.0)	13,972 (6.9)
	No Dx	189,195 (93.1)	591 (90.0)	188,604 (93.1)
COPD	Dx	19,507 (9.6)	67 (10.2)	19,440 (9.6)
	No Dx	183,726 (90.4)	590 (89.8)	183,136 (90.4)

Continued

Table 1 Continued

Variable	Level	Overall N=203,233	*Nocardia* infection Yes n=657 (0.3%)	*Nocardia* infection No n=202,576 (99.7%)
Diabetes	Dx	89,929 (44.3)	313 (47.6)	89,616 (44.2)
	No Dx	113,304 (55.7)	344 (52.4)	112,960 (55.8)
Hepatitis B	Dx	2937 (1.5)	*	*
	No Dx	200,296 (98.5)	*	*
Hepatitis C	Dx	10,711 (5.3)	26 (4.0)	10,685 (5.3)
	No Dx	192,522 (94.7)	631 (96.0)	191,891 (94.7)
HIV	Dx	831 (0.4)	*	*
	No Dx	202,402 (99.6)	*	*
Granulomatous disease	Dx	24 (0.1)	*	*
	No Dx	203,209 (99.1)	*	*
Tobacco	Dx	38,559 (19.0)	119 (18.1)	38,440 (19.0)
	No Dx	164,674 (81.0)	538 (81.9)	164,136 (81.0)

Antithymocyte globulin refers to horse origin globulin (Atgam) and thymoglobulin is rabbit antithymocyte globulin.
*Per USRDS regulations, data for variables with frequencies of 10 or less must be suppressed to prevent potential identification of individuals.
COPD, chronic obstructive pulmonary disease; Dx, diagnosis; ESRD, end-stage renal disease; USRDS, US Renal Data System.

of other opportunistic pathogens such as fungi. Infection occurs around 2 months to 2 years after renal transplant.[1 5] Previously reported comorbidities or medications associated with *Nocardia* infection include cytomegalovirus viremia, steroid use, and calcineurin inhibitors.[6–8]

Diagnosis of *Nocardia* infection often requires an invasive procedure such as bronchoscopy or biopsy to obtain a stainable specimen or culture. Misdiagnosis may arise due to structural similarities to *Actinomyces*. However, unlike *Actinomyces*, *Nocardia* will appear as a partially acid-fast filamentous rod on Kinyoun stain. Common sites of *Actinomyces* infection include the oral cavity, digestive tract, female reproductive tract, thoracic cavity, or musculoskeletal system. A study by Rousseau *et al*[9] estimates the prevalence of actinomycosis in renal transplant patients to be 0.02%.

Mortality among renal transplant recipients with non-disseminated nocardiosis ranges between 15% and 20%, while it is considerably higher, at 50%–60%, for disseminated infection.[1 5] Retrospective studies suggest that early diagnosis of nocardiosis and timely treatment with antibiotics may significantly reduce mortality among renal transplant patients.[5] However, several antibiotics used to treat *Nocardia* infection either affect the pharmacokinetics of immunosuppressive medicines or are nephrotoxic. *Nocardia* is not often covered by empiric antibiotics for undifferentiated fever, pneumonia, or rash. Therefore, understanding the risk factors associated with nocardiosis following renal transplant may help clinicians determine the best strategy for more expedient diagnosis and treatment.

Currently there is no reported study of nocardiosis within the United States renal transplant population. This study aims to examine the overall frequency of *Nocardia* diagnosis, the different presentations of this infection, and the associated immunosuppressive regimens, comorbidities, and risk factors associated with a diagnosis of *Nocardia* infection. Allograft failure or rejection after nocardiosis was also investigated.

METHODS

Study cohort

A retrospective cohort study design was used to examine the incidence, time to infection, demographic, and clinical risk factors associated with individuals diagnosed with *Nocardia* infection among the renal transplant cohort in the United States Renal Data System (USRDS).[10] The USRDS is a large federal data set containing demographic data, hospital, and physician/supplier claims on all Medicare-funded patients with end-stage renal disease (ESRD) in the United States on their initiation of dialysis. The database contains demographic characteristics, dialysis claims, transplant and treatment history, hospitalization events, physical/supplier services, comorbidity condition, and mortality data. All ESRD transplant patients aged 18 or older without missing data on sex, race, ethnicity, or hospital claims data were considered for inclusion in the study sample. Patients who received a pre-emptive transplant prior to dialysis were excluded as they are not in the database. This study examined the incidence of *Nocardia* infection, risk factors associated with *Nocardia* infection, presentations of *Nocardia* infection, and time to graft failure following a *Nocardia* infection.

Nocardia infection

To determine whether ESRD transplant patients had a *Nocardia* infection, International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for nocardiosis (039.1, 039.8, and 039.9) were used. All *Nocardia* infections after an initial transplant were included. *Nocardia* and *Actinomyces* share the same ICD-9 code, so the presentation of *Nocardia* infection was analyzed using clinical presentation ICD-9 codes for pneumonia, brain abscess, bacteremia, cellulitis/abscess, cutaneous nodules, and nodular pneumonia. Diagnoses with codes for lumpy jaw (039.2), Madura foot (039.4), and cutaneous infection (039.0) were excluded as these presentations are usually associated with *Actinomyces* infection. To account for time at risk of infection, the number of person-years at risk was determined from the time of the first transplant to the time of first *Nocardia* diagnosis, or to the last known follow-up date for

Table 2 Simple and final adjusted relative risk from GLIM of risk factors for *Nocardia* infection in 203,233 ESRD transplant patients

		Simple models		Final adjusted model			
Risk factor	**Level**	**RR**	**95% CI**	**P value**	**aRR**	**95% CI**	**P value**
Demographic variables							
Sex	Female vs male	0.96	0.82 to 1.13	0.6291	–		–
Race	Black vs white	1.08	0.90 to 1.30	0.2721	–		–
	Other vs white	1.29	0.92 to 1.82		–		–
Ethnicity	Hispanic vs non-Hispanic	1.06	0.85 to 1.34	0.5886	–		–
Age at transplant	65+ vs <65	2.27	1.86 to 2.78	<0.0001	2.10	1.71 to 2.59	<0.0001
Transplant-related variables							
History of transplant failure	Yes vs no	1.39	1.14 to 1.71	0.0015	1.28	1.02 to 1.6	0.0326
History of rejection	Yes vs no	3.27	2.8 to 3.82	<0.0001	4.83	4.08 to 5.72	<0.0001
Donor type	Cadaver vs living	1.46	1.23 to 1.74	<0.0001	1.23	1.03 to 1.46	0.0224
Antithymocyte	Yes vs no	0.81	0.55 to 1.2	0.2899	–		–
Azathioprine	Yes vs no	0.86	0.72 to 1.02	0.0880	0.73	0.58 to 0.92	0.0069
Basiliximab	Yes vs no	1.12	0.91 to 1.38	0.2910	1.25	1 to 1.55	0.0455
Cyclosporine	Yes vs no	0.97	0.81 to 1.15	0.7066	1.30	1.03 to 1.65	0.0257
Everolimus	Yes vs no	0.36	0.05 to 2.55	0.3050	–		–
Muromonab	Yes vs no	1.06	0.84 to 1.33	0.6354	–		–
Mycophenolate	Yes vs no	1.30	1.08 to 1.57	0.0052	–		–
Prednisone	Yes vs no	1.94	1.32 to 2.85	0.0008	–		–
Rituximab	Yes vs no	3.23	1.73 to 6.02	0.0002	1.81	0.96 to 3.4	0.0660
Sirolimus	Yes vs no	0.84	0.68 to 1.05	0.1244	0.65	0.52 to 0.8	0.0001
Steroid	Yes vs no	2.10	1.37 to 3.21	0.0006	–		–
Tacrolimus	Yes vs no	2.24	1.87 to 2.68	<0.0001	2.45	2 to 3	<0.0001
Thymoglobulin	Yes vs no	2.04	1.74 to 2.39	<0.0001	1.89	1.59 to 2.25	<0.0001
Clinical diagnoses							
Cytomegalovirus	Dx vs no Dx	1.41	1.09 to 1.82	0.0080	–		–
COPD	Dx vs no Dx	0.98	0.76 to 1.26	0.8711	0.78	0.6 to 1.02	0.0653
Diabetes	Dx vs no Dx	1.18	1.02 to 1.38	0.0306	0.86	0.73 to 1.01	0.0650
Hepatitis B	Dx vs no Dx	0.92	0.48 to 1.78	0.8054	–		–
Hepatitis C	Dx vs no Dx	0.70	0.48 to 1.04	0.0784	0.56	0.38 to 0.84	0.0045
Asthma	Dx vs no Dx	0.99	0.74 to 1.32	0.9345	–		–
Tobacco	Dx vs no Dx	0.93	0.76 to 1.13	0.4545	0.74	0.6 to 0.91	0.0038

Antithymocyte globulin refers to horse origin globulin (Atgam) and thymoglobulin is rabbit antithymocyte globulin.
aRR, adjusted risk ratio; COPD, chronic obstructive pulmonary disease; Dx, diagnosis; ESRD, end-stage renal disease; GLIM, generalized linear model; RR, risk ratio; USRDS, US Renal Data System.

subjects without a *Nocardia* diagnosis. The person-years at risk were then used in the statistical modeling.

Risk factors associated with *Nocardia* infection

Demographic variables including race, ethnicity, mode of dialysis, and access type at initiation of dialysis were obtained from the Centers for Medicare and Medicaid Services (CMS) Form 2728, which is completed on initiation of dialysis. Transplant-related comorbidities and clinical risk factors were determined using procedure (current procedural terminology, CPT) and diagnosis (ICD-9) codes, and documentation of prescription of immunosuppression regimen medications was available in the transplant database. All CPT and ICD-9 codes used in this study are listed in online supplemental table 2. Transplant-related risk factors included age at transplant, donor type, history of rejection requiring at least one kidney transplant, and history of transplant failure. No limitation was placed on the number of previous kidney transplants. Immunosuppressive medications were evaluated within the database; however, the time of initiation and dosage are not made available. The medications reviewed included prescriptions for steroids, mycophenolate, cyclosporine, tacrolimus, sirolimus, prednisone, antithymocyte globulin (Atgam, Pfizer), azathioprine, everolimus, muromonab, basiliximab, rabbit antithymocyte globulin (thymoglobulin), rituximab, and infliximab. Comorbidities included the diagnosis code for cytomegalovirus, HIV, diabetes, hepatitis B, hepatitis C, granulomatous disease, chronic obstructive pulmonary disease (COPD), asthma, and tobacco use occurring after the initiation of dialysis but prior to *Nocardia* infection. Diagnosis of cytomegalovirus was defined as a diagnosis code after transplant and before the *Nocardia* diagnosis (or last follow-up date for controls). The risk factors are listed in online supplemental table 1.

The number of person-years at risk was calculated from the time of initial transplant to the time of the first *Nocardia* diagnosis (for those with a diagnosis), or to the last known follow-up date (date of death or last claim date) for controls.

Risk factors associated with increased graft failure in transplant patients with *Nocardia* infection

Among patients with nocardial infection, graft failure was defined as a diagnosis code occurring in patients who

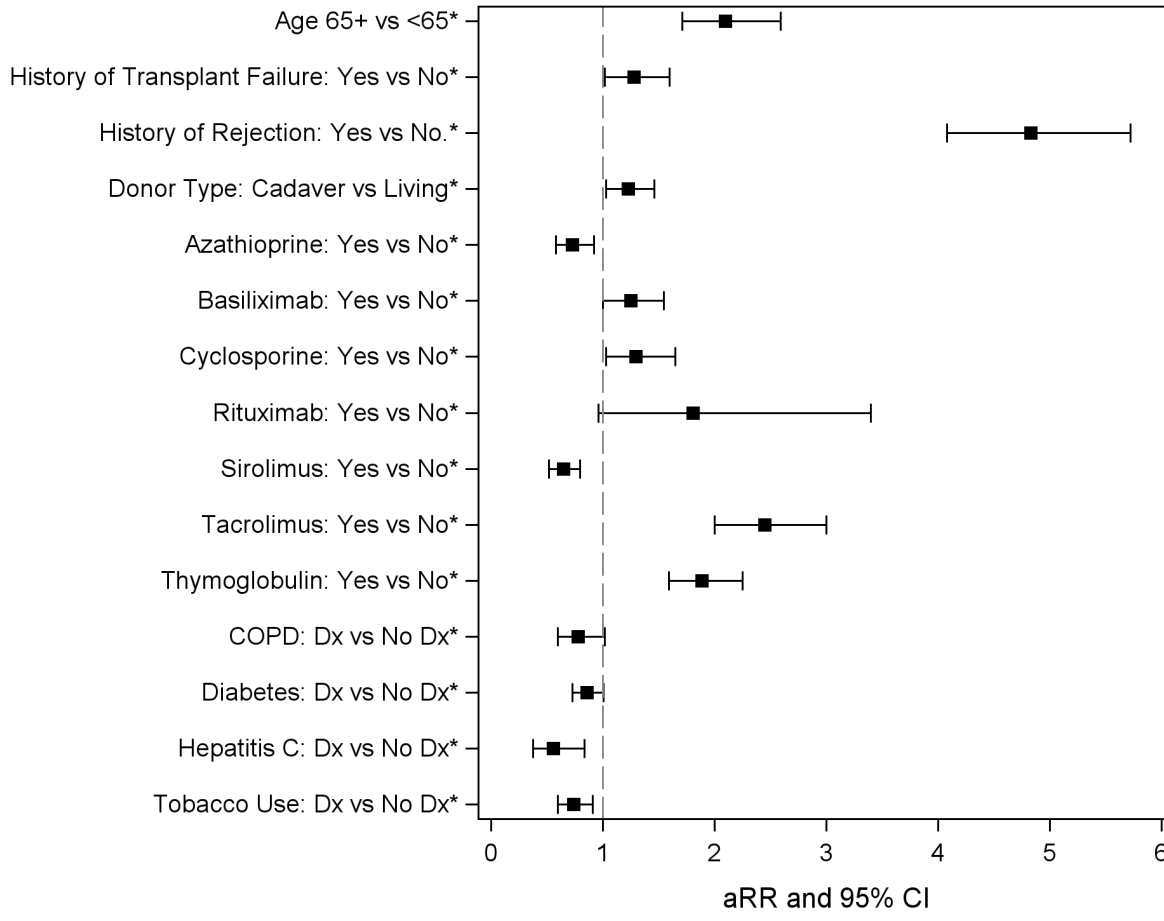

Figure 1 aRR and 95% CI from the final adjusted model for *Nocardia* infection among patients with end-stage renal disease. *Statistical significance. COPD, chronic obstructive pulmonary disease.

experienced a graft failure within 6 months from the time of *Nocardia* infection diagnosis. The reason 6 months was chosen for follow-up was to attempt to isolate the association of the infection or any adverse effect of its treatment on graft failure. Subjects with premature graft failure, defined as having graft failure occur within 14 days of transplant, were excluded (n=105). Time to graft failure was calculated as the number of days between the *Nocardia* infection diagnosis and the graft failure diagnosis code, or 183 days (or 6 months) for those who did not have a graft failure or whose failure occurred after 183 days. In the cohort with *Nocardia* infection, mortality was low enough the data is not reportable due to the data privacy constraints of the database.

Statistical analysis

All statistical analyses were performed using SAS V.9.4 and statistical significance was assessed using an alpha level of 0.05. Descriptive statistics for demographic, transplant-related risk factors, and clinical diagnoses were determined overall and by *Nocardia* diagnosis. χ^2 or t-tests were used to examine preliminary differences between those with and without *Nocardia* infection. To examine the association of risk factors with *Nocardia* infection, a generalized linear model (GLIM) was used incorporating person-years at risk. Each GLIM assumed a binomial distribution of the outcome measure, logit link, and used the natural log of the number of person-years at risk as an offset parameter to estimate the OR for *Nocardia* infection. Each risk factor was examined in a simple model and the crude OR was estimated along with 95% CI. All risk factors were then entered into a comprehensive full GLIM, and a backward model building strategy was used to arrive at the comprehensive final model. Starting with the full model, the most non-significant variable was removed from the model. The Akaike's information criterion (AIC) and −2Log likelihood (−2LL) test were used to determine whether the reduced model fit is as good as the previous model. A lower AIC and non-statistically significant −2LL test indicated whether the reduced model was as good as the previous model. If the reduced model was not as good as the previous model, the variable was re-entered in the model and the next most non-significant variable was examined for removal. The final model included any variable that was statistically significant and/or needed in the model using the model building criteria. Adjusted OR and the corresponding 95% CI are presented for the final models.

For graft failure within 6 months after *Nocardia* infection, a Cox proportional hazards (CPH) analysis was used to investigate the effect of various demographic,

Table 3 Descriptive statistics, n (%), overall and by graft failure in 552 patients with *Nocardia* infection

Variable	Level	Overall	Graft failure within 183 days post *Nocardia* infection	
			Yes n=87 (15.8%)	No n=465 (84.2%)
Demographic variables				
Ethnicity	Hispanic	74 (13.41)	*	*
	Non-Hispanic	478 (86.59)	*	*
Race	Black	134 (24.28)	15 (17.24)	119 (25.59)
	Other	31 (5.62)	*	*
	White	387 (70.11)	*	*
Sex	Female	210 (38.04)	33 (37.93)	177 (38.06)
	Male	342 (61.96)	54 (62.07)	288 (61.94)
Age at transplant	65+	102 (18.48)	13 (14.94)	89 (19.14)
	<65	450 (81.52)	74 (85.06)	376 (80.86)
Transplant-related risk factors				
Donor type	Cadaver	410 (74.28)	64 (73.56)	346 (74.41)
	Living	142 (25.72)	23 (26.44)	119 (25.59)
History of transplant failure	Yes	90 (16.30)	*	*
	No	462 (83.70)	*	*
Kidney rejection	Yes	385 (69.75)	50 (57.47)	335 (72.04)
	No	167 (30.25)	37 (42.53)	130 (27.96)
Antithymocyte	Yes	24 (4.35)	*	*
	No	528 (95.65)	*	*
Azathioprine	Yes	130 (23.55)	17 (19.54)	113 (24.30)
	No	422 (76.45)	70 (80.46)	352 (75.70)
Basiliximab	Yes	87 (15.76)	18 (20.69)	69 (14.84)
	No	465 (84.24)	69 (79.31)	396 (85.16)
Cyclosporine	Yes	139 (25.18)	18 (20.69)	121 (26.02)
	No	413 (74.82)	69 (79.31)	344 (73.98)
Everolimus	Yes	*	*	*
	No	*	*	*
Infliximab	Yes	*	*	*
	No	*	*	*
Muromonab	Yes	66 (11.96)	*	*
	No	486 (88.04)	*	*
Mycophenolate	Yes	444 (80.43)	68 (78.16)	376 (80.86)
	No	108 (19.57)	19 (21.84)	89 (19.14)
Prednisone	Yes	534 (96.74)	*	*
	No	18 (3.26)	*	*
Rituximab	Yes	*	*	*
	No	*	*	*
Sirolimus	Yes	81 (14.67)	*	*
	No	471 (85.33)	*	*
Steroid	Yes	537 (97.28)	*	*
	No	15 (2.72)	*	*
Tacrolimus	Yes	431 (78.08)	70 (80.46)	361 (77.63)
	No	121 (21.92)	17 (19.54)	104 (22.37)
Thymoglobulin	Yes	204 (36.96)	27 (31.03)	177 (38.06)
	No	348 (63.04)	60 (68.97)	288 (61.94)
Clinical diagnosis				
Cytomegalovirus	Dx	58 (10.51)	12 (13.79)	46 (9.89)
	No Dx	494 (89.49)	75 (86.21)	419 (90.11)
COPD	Dx	55 (9.96)	15 (17.24)	40 (8.60)
	No Dx	497 (90.04)	72 (82.76)	425 (91.40)
Diabetes	Dx	268 (48.55)	45 (51.72)	223 (47.96)
	No Dx	284 (51.45)	42 (48.28)	242 (52.04)

Continued

Table 3 Continued

Variable	Level	Overall	Graft failure within 183 days post *Nocardia* infection	
			Yes n=87 (15.8%)	No n=465 (84.2%)
Hepatitis B	Dx	*	*	*
	No Dx	*	*	*
Hepatitis C	Dx	23 (4.17)	*	*
	No Dx	529 (95.83)	*	*
HIV	Dx	*	*	*
	No Dx	*	*	*
Granulomatous disease	Dx	*	*	*
	No Dx	*	*	*
Asthma	Dx	40 (7.25)	*	*
	No Dx	512 (92.75)	*	*
Tobacco	Dx	102 (18.48)	19 (21.84)	83 (17.85)
	No Dx	450 (81.52)	68 (78.16)	382 (82.15)

Antithymocyte globulin refers to horse origin globulin (Atgam) and thymoglobulin is rabbit antithymocyte globulin.
*Per USRDS regulations, data for variables with frequencies of 10 or less must be suppressed to prevent potential identification of individuals.
COPD, chronic obstructive pulmonary disease; Dx, diagnosis; USRDS, US Renal Data System.

transplant-related, or clinical risk factor variables on the time from transplant to graft failure using a similar model building strategy as before. Adjusted HR and 95% CI were determined for the final model.

Before multivariable modeling for both *Nocardia* infection as an outcome and for graft failure as an outcome, variance inflation factors between all potential risk factors were examined. All variance inflation factors were <5, indicating no multicollinearity between risk factors.

RESULTS

Descriptive statistics

Of the 203,233 patients with ESRD with data available for evaluation in the USRDS transplant population between 2001 and 2011, 657 (0.32%) were diagnosed with *Nocardia* infection. Table 1 shows the descriptive statistics for ESRD transplant patients. Of all the transplant patients, 60% were male, nearly 70% were white and 25% black, 13% were Hispanic, and 13% were aged 65 or older at the time of initial transplant. About 70% received their transplant from a deceased donor and 42% had a history of graft failure.

Risk factors associated with *Nocardia* infection

Table 2 and figure 1 show the final adjusted OR for risk factors associated with *Nocardia* infection.

Age 65+ at initial transplant (OR=2.10, CI 1.59 to 2.25), history of transplant failure (OR=1.28), history of transplant rejection (OR=4.83), receipt of a transplant from a deceased donor (OR=1.23), or receipt of various immunosuppressant drug therapies including tacrolimus (OR=2.45, CI 2.00 to 3.00) and thymoglobulin (OR=1.89, CI 1.59 to 2.25) were associated with increased risk of *Nocardia* infection. Immunosuppressants with weaker association with increased risk included basiliximab (OR=1.25, CI 1.00 to 1.55) and cyclosporine (OR=1.30, CI 1.03 to 1.65). Receipt of azathioprine (OR=0.73) or receipt of sirolimus (OR=0.65), or a diagnosis of COPD (OR=0.78), diabetes (OR=0.86), or hepatitis C (OR=0.56), and tobacco use (OR=0.74) were associated with a decreased risk of *Nocardia* infection.

Risk factors associated with graft failure within 6 months after *Nocardia* infection

Of all the transplant patients, 87,034 (42.82%) experienced graft failure. Patients with a diagnosis of *Nocardia* infection showed a higher percentage of graft failure at any time (67.28% vs 42.75% with and without *Nocardia*, respectively) as well as a history of kidney rejection (60.58% vs 27.25% with and without *Nocardia*, respectively).

A subcohort was used to study the presentation of *Nocardia* infection and the possible associated risk of graft failure within 183 days (roughly 6 months) to account for appropriate post-transplant follow-up; patients with graft failure occurring after 183 days were excluded and 552 patients with *Nocardia* infection were included. Among those with *Nocardia* infection, nearly 16% experienced graft failure. Demographic statistics of this cohort were comparable with patients with risk factors for *Nocardia* infection, as mentioned above (table 3).

Pneumonia was the most frequent presentation of *Nocardia* infection (n=78/552, 14.13%), followed by brain abscess (n=43/552, 7.79%). A few patients presented with infections in more than one system. Table 4 and figure 2 show the final adjusted HR from the CPH model of risk factors associated with graft failure.

Antithymocyte globulin (HR=2.76), COPD (HR=2.47), and presentation of *Nocardia* infection with brain abscess (HR=1.85) were significantly associated with increased risk of graft failure. A history of graft failure (HR=0.41) and a history of kidney rejection (HR=0.52) were significantly associated with a decreased risk of graft failure.

DISCUSSION

To date, there has been no cumulative study that evaluated the risk factors for nocardiosis in renal transplant patients within the USUnited States. Our study used the USRDS,

Table 4 Simple and final adjusted HR from CPH of risk factors for graft failure in 552 patients with *Nocardia* infection

		Simple models			Final adjusted model		
Risk factor	**Level**	**HR**	**95% CI**	**P value**	**aHR**	**95% CI**	**P value**
Demographic variables							
Sex	Female vs male	0.98	0.64 to 1.51	0.9287	–		–
Race	Black vs white	0.61	0.35 to 1.07	0.0835	–		–
	Other vs white	0.68	0.25 to 1.88	0.4612	–		–
Ethnicity	Hispanic vs non-Hispanic	0.82	0.43 to 1.59	0.5581	–		–
Age at transplant	65+ vs <65	0.78	0.43 to 1.4	0.3986	0.63	0.34 to 1.15	0.1309
Transplant-related variables							
History of transplant failure	Yes vs no	0.43	0.2 to 0.93	0.0317	0.41	0.18 to 0.91	0.0280
History of rejection	Yes vs no	0.56	0.36 to 0.85	0.0067	0.52	0.33 to 0.80	0.0032
Donor type	Cadaver vs living	0.98	0.61 to 1.58	0.9444	–		–
Antithymocyte	Yes vs no	1.68	0.73 to 3.85	0.2212	2.76	1.16 to 6.55	0.0213
Azathioprine	Yes vs no	0.79	0.47 to 1.35	0.3903			
Basiliximab	Yes vs no	1.43	0.85 to 2.4	0.1789	1.51	0.89 to 2.59	0.1299
Cyclosporine	Yes vs no	0.78	0.47 to 1.32	0.3552	–		–
Muromonab	Yes vs no	0.75	0.36 to 1.54	0.4282	–		–
Mycophenolate	Yes vs no	0.85	0.51 to 1.41	0.5294	–		–
Prednisone	Yes vs no	3.08	0.43 to 22.14	0.2630	–		–
Sirolimus	Yes vs no	0.56	0.27 to 1.17	0.1229	0.54	0.26 to 1.14	0.1046
Steroid	Yes vs no	0.79	0.25 to 2.49	0.6846	–		–
Tacrolimus	Yes vs no	1.15	0.67 to 1.95	0.6132	–		–
Thymoglobulin	Yes vs no	0.74	0.47 to 1.17	0.1972	–		–
Clinical diagnoses							
Cytomegalovirus	Dx vs no Dx	1.42	0.77 to 2.62	0.2550	1.73	0.92 to 3.23	0.0937
COPD	Dx vs no Dx	2.05	1.18 to 3.58	0.0113	2.47	1.40 to 4.35	0.0018
Diabetes	Dx vs no Dx	1.16	0.76 to 1.76	0.4979	–		–
Hepatitis C	Dx vs no Dx	1.50	0.61 to 3.71	0.3752	–		–
Asthma	Dx vs no Dx	0.61	0.22 to 1.67	0.3387	0.50	0.18 to 1.38	0.1815
Tobacco	Dx vs no Dx	1.27	0.77 to 2.12	0.3508	–		–
Clinical presentation of *Nocardia* infection							
Pneumonia	Dx vs no Dx	1.29	0.75 to 2.22	0.3548	–		–
Brain abscess	Dx vs no Dx	2.03	1.12 to 3.65	0.0189	1.85	1.02 to 3.36	0.0437
Bacteremia	Dx vs no Dx	1.87	0.59 to 5.92	0.2867	–		–

Antithymocyte globulin refers to horse origin globulin (Atgam) and thymoglobulin is rabbit antithymocyte globulin.
aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; CPH, Cox proportional hazards; Dx, diagnosis; USRDS, US Renal Data System.

which encompasses all patients with ESRD and thus qualify for Medicare, providing a large sample size to analyze our clinical question. Our investigation confirms that older age, transplantation of deceased donor kidney, and/or therapy with tacrolimus, corticosteroids, and thymoglobulin are associated with increased risk of infection. It is important to note that trimethoprim-sulfamethoxazole is used as prophylaxis against *Nocardia*. However, it has not been proven to provide reliable protection against nocardiosis.[11]

Prior to our study, no study to our knowledge has evaluated the risk factors for graft failure in patients who have been infected with *Nocardia*. The cohort of patients who were diagnosed with *Nocardia* infection showed a higher percentage of graft failure at any time and in addition had more previous diagnoses of kidney rejection when compared with transplant patients without *Nocardia* diagnosis. After the *Nocardia* diagnosis, patients with prescriptions for antithymocyte globulin or with a diagnosis of COPD were associated with an increased risk of graft failure. This is similar to existing evidence that suggests patients with ESRD with a diagnosis of COPD or after a renal transplant carry a greater risk of infection, death, and repeated hospitalization, which increase the risk for graft failure.[12] Additionally, if nocardial infection presented as a brain abscess, there was an association with an increased risk for graft failure. The association with graft failure could be due to the severity of the infection, the nature of the therapy required, or the emphasis on decreasing immunosuppression due to severe infection.

Surprisingly, having a history of graft failure or a history of kidney rejection, which was 40%–60% prevalent in the cohort with nocardiosis, was associated with a decreased risk of graft failure. We speculate that the explanation might be due to increased physician and/or patient attention to their immunosuppressive regimen in patients with past graft failure. It could also be a result of other confounding variables not accounted for in the database, confounders in the multivariate model which when adjusted for had a stronger association than *Nocardia*, or a limitation introduced by limiting the cohort to only patients with *Nocardia* infection or limiting the follow-up to 6 months.

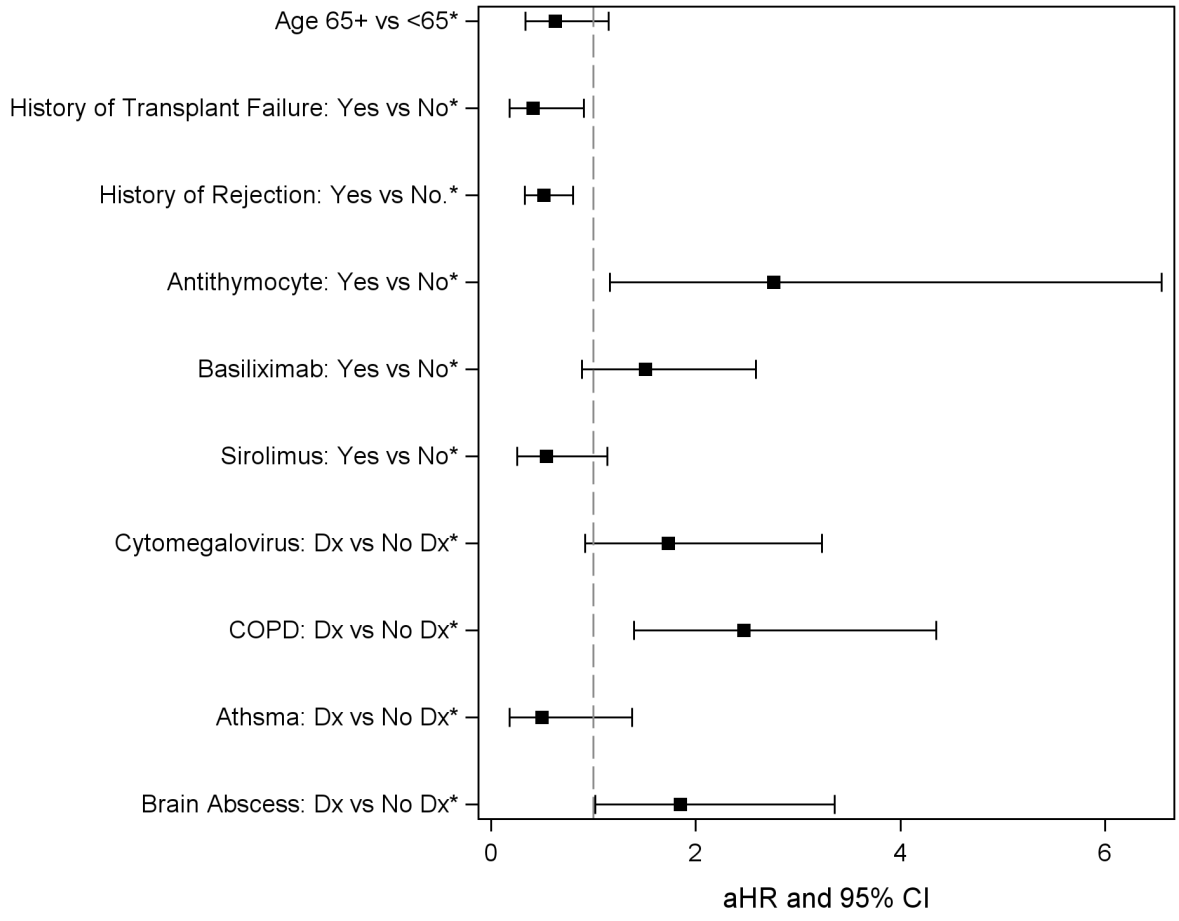

Figure 2 HR and 95% CI from the final adjusted model for graft failure among patients with *Nocardia* diagnosis. *Statistical significance. CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease.

Our study demonstrates a lower occurrence of *Nocardia* infection (0.3%) than the values reported in previous studies,[1–3 5] despite the fact that the ICD-9 codes used do not necessarily discriminate between a diagnosis of *Nocardia* or *Actinomyces* infection. Thus, limitations of this study include the nature of the USRDS data set, with all diagnoses inferred from billing codes submitted to Medicare or taken from CMS Form 2728, and the fact that *Nocardia* and *Actinomyces* share the same diagnostic ICD-9 code. To improve diagnostic reliability, an ICD-9 code for lumpy jaw, Madura foot, and cutaneous infection were excluded as these presentations are usually associated with *Actinomyces* infection. Another limitation is the lack of clinical-level data in the USRDS necessary to confirm an infection of *Nocardia*. Also part of the limitation of using an administrative database, the medication data queried did not include the details of timing, medication use as induction or maintenance therapy, and no patient compliance data were available. Due to the USRDS being a database of dialysis patients, those patients who received a pre-emptive transplant prior to initiation of dialysis were not available in the data set for this analysis. Although this study had its limitations, it used the largest available database of renal transplant patients in the United States, thereby providing a large cohort of patients and increasing the strength of the study.

The results from this data set provide evidence that encourages clinicians to suspect *Nocardia* infection, particularly in the presence of certain risk factors, in the assessment of pneumonia or brain abscesses in renal transplant patients. However, additional studies are required to further evaluate the timing of infection after renal transplant and to identify appropriate prophylaxis regimens to prevent nocardiosis and/or transplant failure after infection.

Twitter Stephanie L Baer @StephanieBaerMD

Acknowledgements This work was supported with resources provided by the Charlie Norwood VA medical center.

Contributors All authors have contributed to the preparation of this manuscript.

Funding The study is supported by the Augusta University Medical Scholars Program (MG), a grant from Dialysis Clinic (MK, JLW, and AM), and the Translational Research Program of the Department of Medicine, Augusta University.

Disclaimer The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US Government. The contents do not represent the views of the Department of Veterans Affairs or the US Government.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Augusta University Institutional Review Board has determined that this research qualifies as non-human subjects research as the data set includes no identifiable data. The data reported here have been supplied by the US Renal Data System (USRDS).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Maya Gibson http://orcid.org/0000-0001-7546-8052
Stephanie L Baer http://orcid.org/0000-0002-7871-755X

REFERENCES

1 Wilson JW. Nocardiosis: updates and clinical overview. *Mayo Clin Proc* 2012;87:403–7.
2 Queipo-Zaragozá JA, Broseta-Rico E, Alapont-Alacreu JM, *et al*. Nocardial infection in immunosuppressed kidney transplant recipients. *Scand J Urol Nephrol* 2004;38:168–73.
3 Centers of Disease Control and Prevention. Nocardiosis 2013. *Atlanta: U.S. Department of Health and Human Services* 2015.
4 Wilson JP, Turner HR, Kirchner KA, *et al*. Nocardial infections in renal transplant recipients. *Medicine* 1989;68:38–57.
5 Clark NM, AST Infectious Diseases Community of Practice. *Nocardia* in solid organ transplant recipients. *Am J Transplant* 2009;9 Suppl 4:S70–7.
6 Yu X, Han F, Wu J, *et al*. *Nocardia* infection in kidney transplant recipients: case report and analysis of 66 published cases. *Transpl Infect Dis* 2011;13:385–91.
7 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.
8 Srinivas KV, Freigoun OS, Rabie A, *et al*. Cerebral nocardiosis in a renal transplant recipient: a case report. *Saudi J Kidney Dis Transpl* 2000;11:583–6.
9 Rousseau C, Piroth L, Pernin V, *et al*. Actinomycosis: an infrequent disease in renal transplant recipients? *Transpl Infect Dis* 2018;20:e12970.
10 Collins AJ, Foley RN, Chavers B, *et al*. Us renal data system 2013 annual data report. *Am J Kidney Dis* 2014;63:A7.
11 Majeed A, Beatty N, Iftikhar A, *et al*. A 20-year experience with nocardiosis in solid organ transplant (SOT) recipients in the southwestern United States: a single-center study. *Transpl Infect Dis* 2018;20:e12904.
12 Couchoud C, Béchade C, Bemrah A, *et al*. Chronic respiratory disease: an unrecognized risk factor in dialysis. *Nephrology Dialysis Transplantation* 2017;32:2118–25.