Incidence and risk factors for mucormycosis in renal transplant patients

Melissa Rachel Downey ,[1] Varsha Taskar,[1] Daniel F Linder,[2] Stephanie L Baer ,[1,3] Jennifer L Waller,[2] Wendy B Bollag,[1,4,5] Mufaddal Kheda,[1] Azeem Mohammed,[1] Sandeep Padala[1]

ABSTRACT

Background Renal transplant patients are at increased risk for mucormycosis. Diabetes, neutropenia, deferoxamine therapy, and immunosuppressive medications have been associated with increased risk of mucormycosis in studies of solid organ transplant recipients. To focus on renal transplant patients, the US Renal Data System (USRDS) was queried to determine the incidence and risk factors for mucormycosis.

Methods All renal transplant patients in the USRDS from 1988 to 2015 were queried for a diagnosis of mucormycosis after the first transplant date using ICD-9 and ICD-10 codes. The International Classification of Diseases (ICD) codes, which currently exist in the ninth and tenth revisions, are a global system of classification used to code diagnoses, procedures, and symptoms. We defined proven mucormycosis by a histopathologic or fungal stain procedure code within 7 days of the diagnosis code. Logistic regression controlling for person-years at risk was used to examine demographic and clinical diagnosis risk factors for mucormycosis.

Results Of the 306,482 renal transplant patients, 222 (0.07%) had codes consistent with proven mucormycosis. The incidence of mucormycosis increased from 1990 to 2000 (peak 17.6 per 100,000 person-years) and subsequently demonstrated more variability. Hispanic ethnicity (OR=1.45), age 65 years or greater (OR=1.64), other or black race compared with white race (OR=1.96 and 1.74), cadaver or other donor type (OR=2.41), and receiving tacrolimus (OR=2.09) were associated with increased risk. Comorbidities associated with decreased risk of mucormycosis included female sex (OR=0.68), iron overload (OR=0.56), and receiving mycophenolate mofetil (OR=0.67) or azathioprine (OR=0.53).

Conclusions In renal transplant patients, age, deceased donor graft transplant, tacrolimus administration, race other than white, and Hispanic ethnicity were associated with increased risk of mucormycosis. Unexpectedly, iron overload was protective. Mucormycosis is a rare infection in renal transplant patients which should be considered in patients with the above risk factors after more common infections have been ruled out.

Significance of this study

What is already known about this subject?

- Renal transplant patients are at high risk for opportunistic infections including mucormycosis.
- Mucormycosis is a rare, lethal fungal infection that has increased in incidence over the last several decades.
- Diabetes, neutropenia, deferoxamine therapy, and immunosuppressive medications have been previously identified as risk factors for mucormycosis.

What are the new findings?

- A formal study investigating risk factors and incidence of mucormyocis in renal transplant patients has not been conducted prior to this study.
- Much of the previous information was reliant on case studies and meta-analysis.
- This study unexpectedly identified decreased association between iron overload and the development of mucormycosis.
- This study identified tacrolimus as a risk factor for mucormycosis, which is inconsistent with the previous literature.

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

- Increased understanding of risk factors for mucormycosis may permit increased identification of this fungal infection in in renal transplant patients.

INTRODUCTION

Renal transplant patients are inherently at high risk for a wide variety of opportunistic infections that are bacterial, viral, or fungal in nature due to the necessary immunosuppression. Of note, the incidence of mucormycosis has increased over the last decade not only in immunocompromised patients but also in immunocompetent patients. The Transplant-Associated Infection Surveillance Network found that mucormycosis comprised 2% of invasive fungal infections in organ transplant patients from 2001 to 2006.[1] Additionally, current estimates suggest that 0.2%–1.2% of renal transplant patients develop mucormycosis.[2]

Mucormycosis, a rare infection attributed to fungi, such as *Mucor*, *Rhizomucor*, and *Rhizopus* which belong to the class *Zygomycetes*, has a high

For numbered affiliations see end of article.

Correspondence to
Dr Stephanie L Baer, Augusta University, Augusta, GA 30904, USA;
stephanie.baer@va.gov

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mortality rate.[3] Agents of mucormycosis are typically found in decaying matter such as old bread.[3] *Zygomycetes* primarily gain entry to the body via inhaled spores which germinate and form hyphae in the host. However, other avenues of infection include ingestion of contaminated food and direct skin contact or inoculation by trauma. Once the infection has been established, the host frequently has tissue necrosis from blood vessel invasion and thrombosis formation.

Fungal infections, due to their infrequency and similarity of presentation to that of other infections such as mycobacteria, are often difficult to detect and diagnose. Compounding this difficulty, fungi are frequent contaminants or common human colonists irrelevant to the current infection. This difficulty in detection and diagnosis has led to the development of protocols to define fungal infections as possible, probable, or proven to facilitate standardization of mycologic research. A diagnosis of a proven fungal infection requires histologic identification of the fungus in biopsy or culture of the specimen extracted from a disease site or otherwise typically sterile site.[4] Relative to other invasive fungal infections, mucormycosis is 10-fold to 50-fold less frequent than invasive fungal infections such as aspergillosis.[5] Despite the rare incidence, *Zygomycetes* have emerged as increasingly significant pathogens in the last decade because of the resulting lethality as opportunistic pathogens.[3]

While mucormycosis in renal transplant patients is relatively rare, the outcomes associated with this invasive fungal infection are extremely dismal. Overall, the mortality rate attributed to mucormycosis varies from 33% to 54%.[3 6 7] The mortality rate is heavily dependent on the patient's underlying medical conditions, the site of infection, risk factors, and strain of fungus.[3] Of note, Song *et al*'s review of 174 cases found that over the past 50 years, the incidence of mucormycosis in renal transplant recipients is increasing.[8]

While Roden *et al*'s review of 929 case studies identified diabetes, neutropenia, deferoxamine use, immunosuppression, and allogeneic stem cell/organ transplantation as risk factors for mucormycosis, a formal study has not been conducted focusing only on renal transplant patients.[9] To address this gap in medical knowledge, the US Renal Data System (USRDS), a national Medicare data system that collects information on all patients with chronic kidney disease and end-stage renal disease (ESRD) in the USA, was queried. This study seeks to determine the incidence and the risk factors for diagnosis of mucormycosis in renal transplant patients in the USA. Increased understanding of risk factors for mucormycosis will permit more relevant screening and earlier diagnosis/therapy which may potentially reduce morbidity and mortality.

MATERIALS AND METHODS

All ESRD transplant patients age 18 or older without missing data on sex, race, ethnicity, or hospital claims data were included in the study sample.

Outcome variable

From this sample, hospital claims, physician supplier claims, and detailed claims data were queried for a diagnosis of mucormycosis following the first transplant date using an ICD-9 code of 117.7 or an ICD-10 code of B46.9. In order to validate that these diagnosis codes were representative of a true diagnosed infection, we required that the medical records also contain the procedure code that would be needed to recover the fungi from the infected site to allow definition of the infection as proven. Thus, we defined proven mucormycosis as a histopathologic procedure code of 88304, 88305, or 88307 or a Gram stain for fungal organisms code of 88312 within 7 days of the mucormycosis diagnosis.

Risk factors

Demographic variables, transplant-related risk factors, and relevant clinical diagnoses were obtained from the CMS Form-2728 or the USRDS patient, transplant, transplant follow-up data, hospital claims, physician supplier claims, or detailed claims files using procedure (CPT) and diagnosis (ICD-9 or ICD-10) codes. The Centers for Medicare & Medicaid Services (CMS) codes are a system of codes used to identify diagnoses and procedures for participants of Medicare and Medicaid. The Current Procedural Terminology (CPT) codes are a system of codes used by qualified healthcare professionals to identify medical procedures. Demographic data included age at transplant (≤ 65 or >65), gender, race, and ethnicity. Transplant-related risk factors included donor type, as well as mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, prednisone, anti-thymocyte, azathioprine, everolimus, muromonab, basiliximab, thymoglobulin, rituximab, and infliximab use. Clinical diagnoses codes considered as potential risk factors occurred at any time and included diabetes, iron overload, HIV, leukopenia, bacteremia, septicemia, chronic liver disease, and total parenteral nutrition. A diagnosis code of cytomegalovirus was included if it occurred after transplant and before the mucormycosis diagnosis (or last follow-up date for controls).

The number of person-years at risk was calculated as the time of transplant to the time of the first mucormycosis diagnosis for those with the diagnosis or to the last known follow-up date or death among those without the diagnosis.

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 diagnosis were determined overall and by mucormycosis.

To examine the association of risk factors with mucormycosis, logistic regression was used controlling for the person-years at risk. Each risk factor was examined in a simple model and the crude OR was estimated along with the 95% CI. An offset parameter of the natural log of the person years at risk was used in all models. All risk factors were then entered into a comprehensive full exact conditional logistic regression model and a backward model building strategy was used to arrive at the final model. Starting with the full model, the least 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 the data as well as the previous model. A lower AIC and non-statistically significant −2LL test indicated whether the reduced model fit the data as well as the previous model. If the reduced model did not fit as well as the previous model, the variable was re-entered in the model and the next least significant variable was examined for possible removal. The

Table 1 Descriptive statistics (n (%)) overall and by mucormycosis

Variable	Level	Overall (N=306,460)	Yes N=222 (0.07%)	No N=306,238 (99.93%)
Demographics				
Sex	Female	121,031 (39.5)	69 (31.1)	120,962 (39.5)
	Male	185,429 (60.5)	153 (68.9)	185,276 (60.5)
Race	Black	77,974 (25.4)	75 (33.8)	77,899 (25.4)
	White	209,190 (68.3)	124 (55.9)	209,066 (68.3)
	Other	19,296 (6.3)	23 (10.4)	19,273 (6.3)
Ethnicity	Hispanic	42,673 (13.9)	37 (16.7)	42,636 (13.9)
	Non-hispanic	263,787 (86.1)	185 (83.3)	263,602 (86.1)
Age at transplant	65+	43,470 (14.2)	33 (14.9)	43,437 (14.2)
	≤65	262,990 (85.8)	189 (85.1)	262,801 (85.8)
Age at transplant*		48.2 (14.1)	48.7 (13.2)	48.2 (14.1)
Person-years at risk*		8.0 (6.4)	2.2 (3.8)	8.0 (6.4)
Transplant-related risk factors				
Donor type	Cadaver/other	222,437 (72.6)	190 (85.6)	222,247 (72.6)
	Living	84,023 (27.4)	32 (14.4)	83,991 (27.4)
Mycophenolate mofetil	Yes	189,561 (61.9)	139 (62.6)	189,422 (61.9)
	No	116,899 (38.1)	83 (37.4)	116,816 (38.2)
Cyclosporine	Yes	117,581 (38.4)	83 (37.4)	117,498 (38.4)
	No	188,879 (61.6)	139 (62.6)	188,740 (61.6)
Tacrolimus	Yes	206,898 (67.5)	158 (71.2)	206,740 (67.5)
	No	99,562 (32.5)	64 (28.8)	99,498 (32.5)
Sirolimus	Yes	38,858 (12.7)	27 (12.2)	38,831 (12.7)
	No	267,602 (87.3)	195 (87.8)	267,407 (87.3)
Prednisone	Yes	285,035 (93.0)	207 (93.2)	284,828 (93.0)
	No	21,425 (7.0)	15 (6.8)	21,410 (7.0)
Anti-thymocyte	Yes	<11†	<11	<11
	No	<11	<11	<11
Azathioprine	Yes	70,906 (23.1)	44 (19.8)	70,862 (23.1)
	No	235,554 (76.9)	178 (80.2)	235,376 (76.9)
Everolimus	Yes	<11	<11	<11
	No	<11	<11	<11
Muromomab	Yes	26,981 (8.8)	27 (12.2)	26,954 (8.8)
	No	279,479 (91.2)	195 (87.8)	279,284 (91.2)
Basiliximab	Yes	49,259 (16.1)	33 (14.9)	49,226 (16.1)
	No	257,201 (83.9)	189 (85.1)	257,012 (83.9)
Belatacept	Yes	<11	<11	<11
	No	<11	<11	<11
Clinical diagnoses				
Diabetes	Diagnosis	79,810 (26.0)	64 (28.8)	79,746 (26.0.)
	No diagnosis	226,650 (74.0)	158 (71.2)	226,492 (740)
Iron overload	Diagnosis	55,637 (18.2)	25 (11.3)	55,612 (18.2)
	No diagnosis	250,823 (81.9)	197 (88.7)	250,626 (81.8)
Cytomegalovirus	Diagnosis	<11	<11	<11
	No diagnosis	<11	<11	<11
HIV	Diagnosis	<11	<11	<11
	No diagnosis	<11	<11	<11
Leukopenia	Diagnosis	25,628 (8.4)	20 (9.0)	25,608 (8.4)
	No diagnosis	280,832 (91.6)	202 (91.0)	280,630 (91.6)
Bacteremia	Diagnosis	<11	<11	<11
	No diagnosis	<11	<11	<11
Septicemia	Diagnosis	41,098 (13.4)	26 (11.7)	41,072 (13.4)
	No diagnosis	265,362 (86.6)	196 (88.3)	265,166 (86.6)
Chronic liver disease	Diagnosis	<11	<11	<11
	No diagnosis	<11	<11	<11
Total parenteral nutrition	Diagnosis	(0.0)	0 (0.0)	0 (0.0
	No diagnosis	306,460 (100.0)	222 (100.0)	306,238 (100.0)

*Values are expressed as mean (SD).
†<11—at least on cell had less than 11 subjects; per the Center for Medicare Services guidelines, these data cannot be reported.

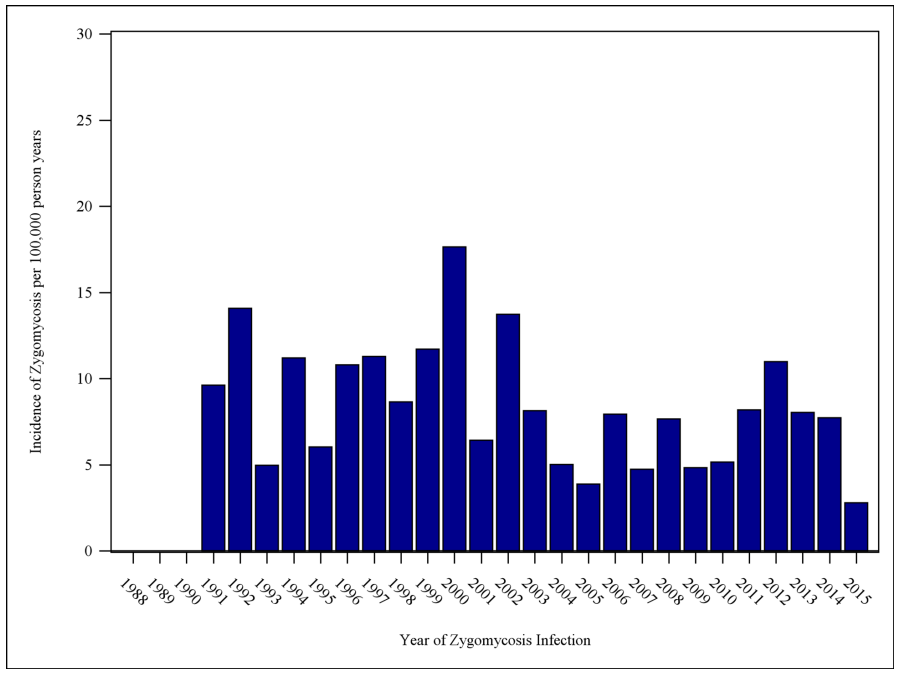

Figure 1 Annual incidence per 100,000 person-years of mucormycosis in US Renal Data System renal transplant patients from 1988 to 2015.

final model included any variable that was statistically significant and/or needed in the model using the model building criteria. The adjusted OR and corresponding 95%CI are presented for the final model.

RESULTS

Of the 448,037 transplant patients, 306,460 patients had complete data and met all criteria for inclusion in the study sample. The total number of subjects with a diagnosis of proven mucormycosis was n=222 (0.07%). Table 1 provides the descriptive statistics on all variables overall and by mucormycosis diagnosis. Overall, the study population was mostly male, white, non-Hispanic, and less than or equal to 65 years of age. The mean age at transplant was 48.2 years and the average person-years at risk was 8.0. Of the 306,460 transplant patients included in this study, 222 (0.07%) had a proven diagnosis of mucormycosis. The demographics of the subset with proven mucormycosis closely resembled the overall population in that they were mostly male, white, non-Hispanic, and less than or equal to 65 years of age. In those with proven mucormycosis, the mean age at transplant was 48.7 years and the average person-years at risk was 2.2.

The annual incidence of mucormycosis is shown in figure 1. The incidence of mucormycosis per 100,000 person-years increased from 1990 until 2000 where it peaked with 17.6 cases of mucormycosis per 100,000 persons. After 2000, the incidence displayed more variability.

The final logistic regression model controlling for person-years at risk is shown in table 2. Female sex (OR=0.68, 95%CI 0.51 to 0.90), other race compared with white race (OR=0.51, 95%CI 0.33 to 0.80), mycophenolate mofetil (OR=0.67, 95%CI 0.50 to 0.90) and azathioprine (OR=0.53, 95%CI 0.37 to 0.78) use, and iron overload (OR=0.56, 95%CI 0.37 to 0.85) were associated with a decreased risk of mucormycosis. Hispanic ethnicity (OR=1.45, 95%CI 1.00 to 2.09), age 65 years or greater (OR=1.64, 95%CI 1.12 to 2.39), other or black race compared with white race (OR=1.96, 95%CI 1.25 to 3.06 and OR=1.74, 95%CI 1.28 to 2.35, respectively), cadaver or other donor type (OR=2.41, 95%CI 1.65 to 3.52), and receipt of tacrolimus (OR=2.09, 95%CI 1.51 to 2.91) were associated with an increased risk of meeting the proven mucormycosis definition. Figure 2 provides the forest plot of adjusted OR for the final logistic regression model.

DISCUSSION

Out of 306,460 renal transplant patients that were included in the study, 222, or 0.07%, had codes consistent with this study's definition of proven mucormycosis. The lower observed prevalence was likely due to the fact that only renal transplant patients were included, as well as the application of a very strict definition of proven mucormycosis, which eliminated patients without both diagnosis and procedural codes consistent with the diagnosis. This estimate of prevalence is lower than in other studies of solid organ transplants which noted 0.2%–1.2%.[2] In the current study, the incidence of mucormycosis appeared to peak in 2000. This shift in epidemiology of infection might be attributable to changes in immunosuppression or prophylaxis protocols applied after transplant such as with the approval of posaconazole in 2006 by the Food and Drug Administration (FDA) which is a federal organization responsible for ensuring the safety and efficacy of products including medications.

In this USRDS cohort, age greater than 65, receipt of deceased donor renal transplant graft, receipt of tacrolimus, race other than white, and Hispanic ethnicity were associated with increased risk of mucormycosis. Tacrolimus has been shown in recent cohorts from 2009 and 2013 to reduce the incidence of mucormycosis. One of these studies found tacrolimus to increase the levels

Table 2 Simple and final adjusted relative risk from matched sample on mucormycosis

		Simple models			Final adjusted model		
Risk factor	**Level**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Demographic variables							
Sex	Female vs male*	0.66	0.50 to 0.88	0.0046	0.68	0.51 to 0.90	0.0075
Race	Black vs white*	1.84	1.38 to 2.46	<0.0001	1.74	1.28 to 2.35	0.0002
	Other race vs white*	2.10	1.35 to 3.28		1.96	1.25 to 3.06	
Ethnicity	Hispanic vs non-Hispanic*	1.29	0.91 to 1.87	0.1570	1.45	1.00 to 2.09	0.0498
Age group	65+ vs ≤ 65	1.86	1.28 to 2.69	0.0010	1.64	1.12 to 2.39	0.0107
Transplant-related variables							
Donor type	Cadaver/other vs living*	2.58	1.77 to 3.75	<0.0001	2.41	1.65 to 3.52	<0.0001
Mycophenolate mofetil	Yes vs no*	1.02	0.77 to 1.33	0.9115	0.67	0.50 to 0.90	0.0081
Cyclosporine	Yes vs no*	0.58	0.44 to 0.76	<0.0001			
Tacrolimus	Yes vs no*	2.11	1.58 to 2.82	<0.0001	2.09	1.51 to 2.91	<0.0001
Sirolimus	Yes vs no*	0.89	0.59 to 1.33	0.5630			
Azathioprine	Yes vs no*	0.48	0.35 to 0.67	<0.0001	0.53	0.37 to 0.78	0.0012
Muromomab	Yes vs no*	1.02	0.68 to 1.52	0.9329	1.47	0.95 to 2.28	0.0850
Basiliximab	Yes vs no*	1.24	0.85 to 1.79	0.2604			
Clinical diagnoses							
Diabetes	Diagnosis vs no Diagnosis*	1.26	0.94 to 1.69	0.1160			
Iron overload	*Diagnosis vs no Diagnosis*	0.67	0.44 to 1.01	0.0577	0.56	0.37 to 0.85	0.0063
Leukopenia	Diagnosis vs no Diagnosis*Dx vs no Dx*	1.29	0.81 to 2.04	0.2783			
Septicemia	Diagnosis vs no Diagnosis*Dx vs no Dx*	0.81	0.54 to 1.22	0.3110			

*Asterisk indicates the referent group.

of prophylactic posaconazole, therefore proposing a mechanism of this effect.[10 11] The cases in this study cohort span from 1990 to 2015; therefore, the effect of combined tacrolimus with posaconazole prophylaxis may have been diluted by earlier cases. The review summarizing published clinical cases by Roden and colleagues identified multiple risks for mucormycosis among these cases, including diabetes and neutropenia, which were not found to be independent risks in the current cohort.[9] Increased clinical suspicion for mucormycosis in susceptible patients with the aforementioned risk factors may be beneficial in expediting both diagnosis and treatment

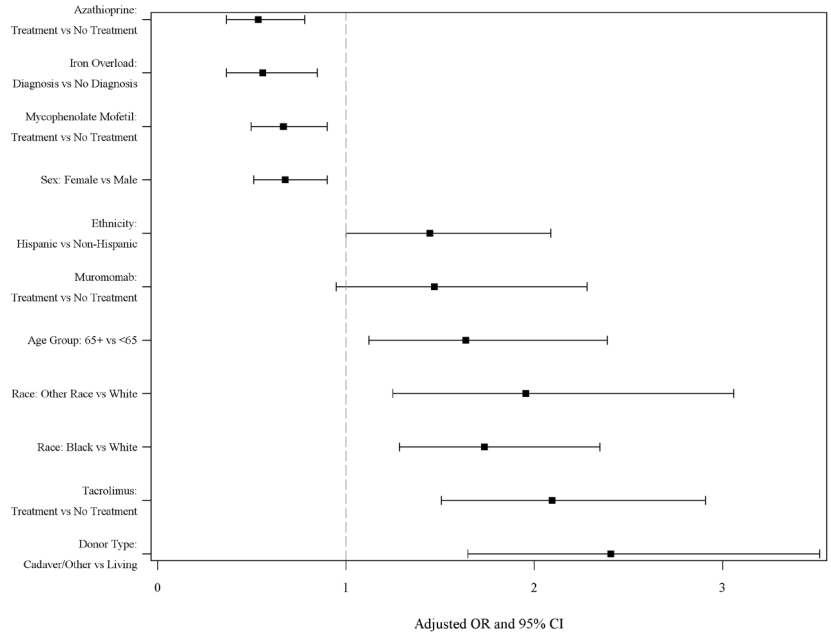

Figure 2 Forest plot for risk factors for mucormycosis diagnosis among renal transplant patients in the USA from 1988 to 2015.

with the goal of lowering morbidity and mortality in these patients.

The risk factors associated with decreased risk of mucormycosis included receipt of azathioprine or mycophenolate mofetil, a diagnosis of iron overload, and female gender. The aforementioned review by Roden *et al* identified deferoxamine therapy as a risk factor for mucormycosis. Unexpectedly, our study identified a diagnosis of iron overload as protective against mucormycosis in this cohort. We attribute this finding to potential aggressive medical management of recognized iron overload, to perhaps a unique effect of iron in renal patients, or to a coding artifact.

The limitations of this study are many due to the nature of querying administrative and hospital claims data for the USA only. A major limitation of this study was our reliance on accurate recording and reporting of ICD-9 and ICD-10 codes by physicians and hospitals. The USRDS does not contain laboratory data to provide additional confirmation of the diagnosis of proven mucormycosis. For example, cytomegalovirus (CMV), a genus of herpesviruses, viremia or antigenemia data are not available, only the diagnosis code. In addition, our queries concerning immunosuppressive agents and prophylaxis regimens were limited for simplicity and due to concerns regarding lack of relevant data availability in the USRDS for the years that were queried. Future studies delving into prophylaxis regimens would be of interest. Finally, the definition of mucormycosis chosen was influenced by guidelines set by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group. This strict definition of proven infections likely resulted in the exclusion of numerous infections due to lack of both diagnosis and procedural codes. However, this narrow definition still allowed for a robust number of infections while giving more certainty to the validity of the cohort containing patients with proven mucormycosis infections for analysis. Despite these limitations, our query represents the largest of its kind in renal transplant patients. Furthermore, the strength of using a nationwide database to study rare infections such as mucormycosis is that due to their rarity a prospective study is not feasible without being prohibitively expensive and logistically futile.

In summary, mucormycosis is one of the rarest and most lethal opportunistic infections in renal transplant patients. The current study showed that in US renal transplant patients from 1988 to 2015, risks associated with proven mucormycosis infection included age greater than 65, receipt of deceased donor renal transplant graft, administration of tacrolimus, race other than white race, and being of Hispanic ethnicity. These observations should be used to consider mucromycosis in the differential of difficult to diagnose or treat infections in renal transplant patients.

Author affiliations
[1]Medicine, Medical College of Georgia, Augusta, Georgia, USA
[2]Population Health Sciences, Augusta University, Augusta, GA, USA
[3]Hospital Epidemiology, Charlie Norwood VA Medical Center, Augusta, GA, USA
[4]Dermatology, Medical College of Georgia, Augusta, Georgia, USA
[5]Medicine, Charlie Norwood VA Medical Center, Augusta, GA, USA

Twitter Stephanie L Baer @StephanieBaerMD

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The USRDS study protocol was deemed 'non-human subjects research' by the Augusta University Institutional Review Board (AUIRB #1363391-1). As per USRDS guidelines, no patient consent was required. The manuscript was reviewed by the USRDS and the National Institute of Diabetes and Digestive and Kidney Diseases and determined to fulfill USRDS privacy requirements.

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Data availability statement Data are available upon reasonable request. The data analyzed in this article are available in the USRDS Database, at https://www.usrds.org/for-researchers/simple-data-requests/, and can be accessed by submitting a Simple Data Request form.

ORCID iDs
Melissa Rachel Downey http://orcid.org/0000-0003-2294-6043
Stephanie L Baer http://orcid.org/0000-0002-7871-755X

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