

# Incidence and Risk Factors for Diarrhea Following Kidney Transplantation and Association With Graft Loss and Mortality

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**Background:** Gastrointestinal complications after kidney transplantation are associated with inferior graft outcomes. We examined the incidence, risk factors, and outcomes of posttransplantation diarrhea.

**Study Design:** Historic cohort study.

**Setting & Participants:** We examined first kidney transplant recipients in the United States from 1995 to 2002, with follow-up through December 2002. Recipients of multiple organs were excluded. We limited our study population to Medicare beneficiaries.

**Predictors:** Recipient, donor, and transplant characteristics were ascertained by means of US Renal Data System database inquiry.

**Outcomes:** Incidence of diarrhea, graft loss, and death after transplantation. First episodes of diarrhea after transplantation were ascertained by using *International Classification of Disease, Ninth Revision, Clinical Modification* codes using Medicare billing data. Cause of diarrhea was classified as infectious or not and according to specific cause. Graft loss and death were ascertained from the date of the first diarrhea episode.

**Results:** We enrolled 41,442 patients. Mean follow-up was  $758 \pm 399$  days. We observed 7,103 diarrhea cases and 8,104 graft losses (4,201 deaths). The 3-year cumulative incidence of diarrhea was 22%, with 18% diagnosed as noninfectious diarrhea with an unspecified cause. Using multivariate Cox proportional hazards analysis, factors associated with increased risk of unspecified noninfectious diarrhea were female sex (hazard ratio [HR], 1.40; 95% confidence interval, 1.33 to 1.48), type 1 diabetes (HR, 1.20; 95% confidence interval, 1.06 to 1.37), and regimens containing tacrolimus and mycophenolate mofetil (HR, 1.37; 95% confidence interval, 1.28 to 1.46). Unspecified noninfectious diarrhea was associated with increased risk of graft failure (HR, 2.13; 95% confidence interval, 1.98 to 2.28) and patient death (HR, 2.04; 95% confidence interval, 1.85 to 2.24).

**Limitations:** Use of claims data to ascertain patient characteristics and events; inability to make causal inference based on retrospective designs.

**Conclusions:** Regimens containing tacrolimus and mycophenolate mofetil were associated with increased risk of noninfectious diarrhea. Episodes of noninfectious diarrhea doubled the hazard of graft loss and patient death.

*Am J Kidney Dis* 51:478-486. © 2008 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Kidney transplantation; graft survival; diarrhea; gastrointestinal complications; US Renal Data System.

Kidney transplantation is the treatment of choice in patients with end-stage renal disease. Although kidney transplantation outcomes have greatly improved and renal allograft survival exceeds 90% at 1 year posttransplantation,<sup>1</sup> medical complications after transplantation are common, ranging from mild symptoms to life-threatening conditions.<sup>2</sup> Certain medical

complications are associated with adverse posttransplantation outcomes, including graft loss.<sup>3</sup> In particular, we previously showed gastrointestinal (GI) complications posttransplantation to be associated independently with poor graft outcomes.<sup>4</sup> Among GI complications, diarrhea is very common.<sup>5</sup> The incidence of diarrhea ranged from 13% to 38% for regimens containing cyclo-

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Received April 26, 2007. Accepted in revised form November 19, 2007. Originally published online as doi: 10.1053/j.ajkd.2007.11.013 on January 31, 2008.

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0272-6386/08/5103-0018\$34.00/0

doi:10.1053/j.ajkd.2007.11.013

sporine and mycophenolate mofetil (MMF)<sup>6-10</sup> and 29% to 64% for regimens with tacrolimus and MMF.<sup>11,12</sup> To assess the impact of diarrhea on kidney transplantation outcomes, we conducted this retrospective study of a large cohort of recent kidney transplant recipients by using Medicare claim data in the US Renal Data System (USRDS). The objectives of this study are to quantify the risk of diarrhea, identify clinically relevant risk factors, and estimate the impact of this complication on such posttransplantation outcomes as graft loss and patient survival. Because the cause of diarrhea can be infectious, noninfectious, or both, we categorized diarrhea into groups and studied them accordingly.

## METHODS

### Study Design, Setting, and Population

In this historic cohort study, we included all first renal allograft recipients who underwent transplantation between January 1, 1995, and December 31, 2002, and were reported to the Organ Procurement Transplant Network Registry and the USRDS with a functioning graft at the time of discharge from the transplantation hospitalization. We limited the study population to those who had Medicare as their primary insurance provider. We excluded all patients receiving a multiorgan transplant or undergoing retransplantation and those with inconsistent coding for immunosuppression regimens at discharge. The Institutional Review Board of Saint Louis University (St Louis, MO) approved the study protocol.

### Variables of Interest and Measurement

#### Definition of Diarrhea

*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9 CM) codes contained in Medicare billing data supplied by the USRDS were used to identify transplant recipients with diarrhea. Both Medicare inpatient and outpatient services claims (part A and B) were used. Because of the large number of diagnoses and heterogeneous causes of diarrhea, we classified patients in 5 subgroups according to whether the specific causes of diarrhea were identified and whether they were infectious in origin by using the following *International Classification of Diseases, Ninth Revision* codes: other and unspecified diarrhea: 558.9, 787.91, and 564.5; unspecified infectious diarrhea: 009.x; ulcerative colitis: 556.x; other noninfectious causes: 579.8, 558.3, 306.4, 558.2, 564.4, and 579.1; and specified infectious cause: 001.x, 004.1, 008.xx, 006.x, 007.x, 120.2, 121.5, 121.6, 126.1, 127.2, 127.3, 127.5, and 128.8.

#### Outcomes Associated With Diarrhea

The primary outcome was graft failure, identified by return to dialysis therapy, retransplantation, or death. Secondary outcomes were patient death and death-censored graft loss as reported in the USRDS and United Network for Organ Sharing (UNOS) registers.

### Baseline Demographic and Clinical Characteristics

Baseline recipient factors as reported in the USRDS and UNOS registers included age, sex, race, ethnicity, body mass index, causes of end-stage renal disease, duration of dialysis therapy before transplantation, smoking habit, alcohol abuse, functional limitation, history of diabetes, hypertension, cerebrovascular disease, peripheral vascular disease, congestive heart failure, angina pectoris, arrhythmia, chronic obstructive pulmonary disease, and preceding myocardial infarction and donor factors, including age, race, ethnicity, living/deceased status, hypertension, drug abuse, body mass index, diabetes, and smoking habit. Transplant factors included cytomegalovirus (CMV) seropairing, degree of HLA matching, delayed graft function, and reactive antibody panel (peak panel reactive antibody > 80%). Maintenance immunosuppressive regimens were ascertained at baseline by using UNOS discharge data. Regimen groups were mutually exclusive.

### Statistical Analysis

#### Cumulative Incidence of Diarrhea

Incidences of diarrhea were calculated by using the product-limit method. The administrative claim with the earliest clinical visit for each type of diagnosis defined the event date so that each patient was counted only once in the analysis. Because patients experienced different types of diarrhea during the study period, diarrhea diagnosis categories were not mutually exclusive. We did not examine the temporality of dual diagnosis.

#### Risk Factors for Diarrhea

We used multivariate Cox proportional hazards analysis to obtain estimates of risk of developing diarrhea (hazard ratios [HRs] and 95% confidence intervals) controlling for the baseline recipient, donor, and transplant-related characteristics listed. To correct violations of the proportional hazards assumption, we tested all time-interaction terms and retained in the final model only those with *P* less than 0.001. We considered *P* less than 0.05 to be statistically significant.

#### Outcomes Associated With Diarrhea

We used multivariate Cox proportional hazards analysis with diarrhea as a time-varying covariate to obtain estimates of the risk of primary outcomes (HRs and 95% confidence intervals) according to known confounding factors. We included all variables listed as possible confounders in the model of graft loss. We censored death and all-cause graft failure on 3 years posttransplantation (the time patients lose Medicare coverage) and on the last possible claim date (December 31, 2002). We also censored all-cause graft failure on death in the death-censored graft failure models. We censored our diarrhea diagnosis variables on 3-year posttransplantation follow-up, last possible claim, and outcome.

Because diarrhea diagnosis may be an incidental event during a hospitalization for other unrelated causes, the risk of poor outcomes associated with diarrhea could be overestimated by our analyses. To estimate the magnitude of this possible bias, we performed a sensitivity analysis with the conservative assumption that all diarrhea cases that occurred

during a hospitalization were misclassified. Thus, diarrhea cases were categorized as hospitalized or not hospitalized according to their status at the moment of first diagnosis. A multivariate Cox proportional hazard analysis was used to assess the risk of graft loss, including hospitalized and nonhospitalized diarrhea as time-varying covariates. Adjustments of HR estimates are provided for all covariates listed.

In a reduced model including all the mentioned variables, we verified the validity of the proportional hazards assumption testing with time interactions, and violations of the proportionality assumption were corrected by retaining significant time interactions in the final model. In the full model, we also included interaction terms between different types of diarrhea to adjust for the possible confounding effect of more than 1 type of diarrhea occurring in the same patient. We used a stepwise approach to limit final models to include only time interactions with *P* less than 0.001 and cross-interactions with *P* less than 0.05, an inclusion level for variable selection that protects against negative confounding factors. However, a thorough analysis of multiple diarrhea type interaction is beyond the objectives of this study. All results were tested for interference caused by collinearity. SAS for Windows, version 9 (SAS Institute, Cary, NC), was used for all statistical analyses.

## RESULTS

### Characteristics of the Sample

We identified 42,257 eligible Medicare beneficiaries who received their first renal allograft during the study period. Of them, 815 had multiple inconsistent immunosuppression regimen prescriptions in the UNOS discharge record and were excluded from analysis. Baseline characteristics of study subjects are listed in Table 1. The majority of patients were white, non-Hispanic, men, and older than 45 years. The 3 most common causes of end-stage renal disease were diabetes, hypertension, and glomerulonephritis. Almost 80% received the organ from a deceased donor. About three quarters of patients had hypertension, 16.2% were obese, 3.1% were smokers, and 0.6% were alcohol abusers. A history of cardiovascular diseases, such as chronic heart failure (6.9%), myocardial infarction (1.5%), and peripheral vascular disease (6.3%), was present in a minority of cases (data not shown). MMF-based regimens were the most prescribed in the overall sample. Almost 25% of subjects were discharged with immunosuppression schemas not classifiable in the 4 most represented regimens; of them, 1,872 (4.5%) were missing values for this variable.

**Table 1. Demographic and Clinical Characteristics of Study Sample at Baseline**

	Study Sample	
	No. of Patients	%
Women	16,491	39.8
Age (y)		
<18	1,029	2.5
18-29	4,539	11.0
30-44	11,395	27.5
45-60	14,808	35.7
>60	9,671	23.2
Race		
White	26,373	63.6
Black	12,424	30.0
Other	2,645	6.4
Hispanic	5,652	13.6
Cause of end-stage renal disease		
Type 1 diabetes	4,990	12.0
Type 2 diabetes	5,815	14.0
Hypertension	9,352	22.6
Polycystic kidney disease	2,807	6.8
Glomerulonephritis	8,133	19.6
Other	5,025	12.1
Unknown	5,320	12.8
Immunosuppression		
Cyclosporine + MMF	14,988	36.2
Tacrolimus + MMF	10,026	24.2
Cyclosporine + azathioprine	5,954	14.4
Tacrolimus + azathioprine	623	1.5
Other regimen	7,979	19.3
Missing	1,872	4.5
Induction therapy	19,193	46.3
Steroids	36,608	93.2
mTOR inhibitors	2,848	6.9

Note: N = 41, 442.

Abbreviations: MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

### Incidence of Diarrhea

There were 7,103 cases of diarrhea during the study period. The cumulative incidence of all types of diarrhea increased during the 3 years after kidney transplantation (Table 2). Compared with all other categories of diarrhea, the cumulative incidence of unspecified noninfectious diarrhea was the highest during the whole study period. At 3 years posttransplantation, the incidence of unspecified noninfectious diarrhea was 19.0% (95% confidence interval, 18.5% to 19.4%), whereas the type of diarrhea with the next highest incidence, ulcer-

**Table 2. Categories of Diarrhea**

Diarrhea Group	No. of Cases at 3 Years	Incidence (%)		
		1 Year	2 Years	3 Years
Overall	7,103	11.5 (11.1-11.8)	17.5 (17.0-17.9)	22.6 (22.1-23.1)
Other and unspecified diarrhea	5,871	9.0 (8.9-9.2)	14.4 (14.2-14.6)	19.0 (18.7-19.2)
Unspecified infectious diarrhea	510	0.8 (0.7-0.8)	1.2 (1.2-1.3)	1.7 (1.6-1.8)
Ulcerative colitis	946	1.8 (1.7-1.9)	2.3 (2.3-2.4)	2.9 (2.8-3.0)
Other noninfectious causes	132	0.2 (0.2-0.2)	0.3 (0.3-0.4)	0.4 (0.4-0.5)
Specified infectious cause	677	0.9 (0.9-1.0)	1.6 (1.5-1.7)	2.3 (2.2-2.4)

*Note:* Values expressed as percent (95% confidence interval) unless noted otherwise. Definition, frequency, and cumulative incidence of diarrhea during 3 years after kidney transplantation.

ative colitis, was at 2.9% (95% confidence interval, 2.7% to 3.1%).

### Independent Risk Factors for Diarrhea

Independent clinical correlates of diarrhea are listed in Table 3. After controlling for potential confounders, women and those with diabetes were at greater risk of diarrhea. HLA mismatch was associated with unspecified diarrhea. White recipients and those with a longer dialysis history were at greater risk of unspecified noninfectious diarrhea. CMV-seronegative patients receiving a kidney from a CMV-positive donor were at greater risk of noninfectious and unspecified infectious diarrhea than all other combinations of recipient and donor CMV serological test results.

Type of maintenance immunosuppression also affected risk of diarrhea. Compared with patients receiving cyclosporine and MMF, those receiving cyclosporine and azathioprine had a lower risk of developing unspecified noninfectious diarrhea (HR, 0.90), whereas risk increased in patients prescribed tacrolimus with both MMF (HR, 1.37) and azathioprine (HR, 1.22). Discharge regimens containing mammalian target of rapamycin inhibitors were associated with a slight increase in risk of unspecified noninfectious diarrhea.

### Outcomes After Diarrhea

Hazards of graft loss, death, and death-censored graft loss after adjustment for a variety of clinically important risk factors for all categories of diarrhea are listed in Table 4. All types of diarrhea significantly increased the risk of graft loss in the full model (HR range, 1.31 to 2.73). After controlling for the confounding effect of more than 1 diarrhea type occurring in the same

patient, risks of graft loss, death, and death-censored graft loss were unchanged or increased for each diarrhea type compared with the reduced model.

Unspecified noninfectious diarrhea, the most commonly diagnosed form of diarrhea, doubled the risk of graft failure, death, and death-censored graft failure. Other factors with a significant impact on graft outcomes included donor age and recipient race, cause of end-stage renal disease, HLA mismatch, duration of dialysis therapy before transplantation, CMV status, delayed graft function, and such recipient comorbidities as cerebrovascular diseases, congestive heart failure, and angina pectoris. Finally, patients receiving tacrolimus with MMF had a lower risk of graft loss compared with those prescribed regimens containing azathioprine (not shown).

### Sensitivity Analysis

Effects of diagnosis setting on graft loss are listed in Table 5. Among those patients diagnosed with diarrhea in the outpatient setting (nonhospitalized group), all types of diarrhea remained an independent risk factor for graft loss (HR range, 1.53 to 2.72).

## DISCUSSION

This study of Medicare claims data indicates that the cumulative 3-year posttransplantation incidence of diarrhea was 22%. More than 80% of patients had a diagnosis of the unspecified noninfectious type, and almost half the cases first occurred in the first posttransplantation year. This temporal pattern is consistent with the dynamics of transplant-related complications.<sup>4,13</sup> Most importantly, posttransplantation diarrhea

Table 3. Factors Associated With Various Types of Diarrhea

	Noninfectious			Infectious	
	Not Specified (n = 5,871; 14.2%)	Ulcerative Colitis (n = 946; 2.3%)	Other Specified (n = 132; 0.3%)	Not Specified (n = 510; 1.2%)	Specified (n = 677; 1.6%)
Female sex	<b>1.40 (1.33-1.48)</b>	<b>1.33 (1.17-1.52)</b>	<b>1.52 (1.07-2.16)</b>	<b>1.31 (1.9-1.56)</b>	<b>1.40 (1.20-1.64)</b>
Recipient age (y)					
<18	1.07 (0.90-1.28)	0.79 (0.47-1.34)	1.13 (0.31-4.17)	<b>2.02 (1.43-2.87)</b>	0.89 (0.45-1.77)
18-29	Reference	Reference	Reference	Reference	Reference
30-44	0.97 (0.88-1.06)	0.82 (0.65-1.03)	1.72 (0.88-3.34)	<b>0.70 (0.55-0.89)</b>	0.88 (0.64-1.21)
45-60	0.91 (0.83-1.00)	0.87 (0.69-1.10)	1.53 (0.77-3.06)	<b>0.64 (0.49-0.82)</b>	0.93 (0.68-1.28)
>60	1.03 (0.93-1.14)	1.16 (0.91-1.49)	1.05 (0.47-2.33)	<b>0.61 (0.46-0.82)</b>	1.10 (0.78-1.56)
Recipient race					
White	Reference	Reference	Reference	Reference	Reference
Black	<b>0.91 (0.85-0.98)</b>	0.98 (0.83-1.16)	1.12 (0.70-1.79)	0.89 (0.70-1.13)	<b>0.73 (0.59-0.91)</b>
Other	<b>0.83 (0.73-0.93)</b>	0.83 (0.61-1.11)	1.28 (0.63-2.63)	1.14 (0.79-1.65)	<b>0.67 (0.46-0.99)</b>
Recipient body mass index					
Normal	Reference	Reference	Reference	Reference	Reference
Overweight	<b>0.91 (0.85-0.97)</b>	0.88 (0.75-1.04)	0.86 (0.55-1.35)	0.98 (0.78-1.22)	0.97 (0.79-1.18)
Obese	<b>0.92 (0.85-0.99)</b>	0.87 (0.72-1.06)	0.76 (0.44-1.31)	1.03 (0.80-1.33)	1.12 (0.89-1.40)
Cause of end-stage renal disease					
Type 1 diabetes	<b>1.20 (1.06-1.37)</b>	1.25 (0.90-1.75)	<b>4.24 (1.70-10.61)</b>	<b>1.69 (1.08-2.65)</b>	1.22 (0.83-1.80)
Type 2 diabetes	0.93 (0.81-1.06)	1.20 (0.86-1.67)	2.10 (0.78-5.70)	1.13 (0.71-1.81)	1.02 (0.67-1.54)
Hypertension	<b>0.84 (0.76-0.93)</b>	1.07 (0.82-1.39)	1.10 (0.51-2.38)	1.28 (0.90-1.82)	0.95 (0.70-1.27)
Polycystic kidney disease	0.91 (0.81-1.04)	0.77 (0.53-1.11)	1.12 (0.43-2.94)	1.02 (0.64-1.62)	1.06 (0.74-1.52)
Glomerulonephritis	<b>0.87 (0.79-0.96)</b>	1.12 (0.86-1.44)	1.45 (0.71-2.96)	1.12 (0.79-1.59)	0.93 (0.71-1.21)
Other	Reference	Reference	Reference	Reference	Reference
Unknown	0.92 (0.83-1.02)	<b>1.32 (1.01-1.73)</b>	1.15 (0.52-2.57)	1.35 (0.93-1.95)	1.04 (0.78-1.40)
Recipient diabetes	<b>1.13 (1.03-1.25)</b>	1.26 (1.00-1.60)	0.65 (0.32-1.33)	1.01 (0.73-1.40)	1.02 (0.74-1.39)
CMV status					
Donor <sup>-</sup> /recipient <sup>-</sup>	Reference	Reference	Reference	Reference	Reference
Donor <sup>-</sup> /recipient <sup>+</sup>	0.97 (0.88-1.07)	1.04 (0.81-1.32)	1.02 (0.55-1.90)	1.19 (0.86-1.67)	0.86 (0.66-1.12)
Donor <sup>+</sup> /recipient <sup>-</sup>	<b>1.24 (1.13-1.36)</b>	<b>1.28 (1.00-1.63)</b>	1.19 (0.64-2.20)	<b>1.44 (1.03-2.01)</b>	1.09 (0.84-1.40)
Donor <sup>+</sup> /recipient <sup>+</sup>	1.05 (0.96-1.14)	1.08 (0.86-1.35)	0.87 (0.48-1.56)	1.05 (0.77-1.44)	0.91 (0.72-1.15)
CMV undiagnosed	1.07 (0.96-1.19)	1.13 (0.85-1.49)	1.28 (0.64-2.56)	<b>1.48 (1.03-2.14)</b>	0.95 (0.70-1.29)
HLA match					
No mismatch	<b>0.87 (0.79-0.96)</b>	1.02 (0.81-1.29)	1.07 (0.58-1.99)	<b>0.68 (0.47-0.99)</b>	0.78 (0.58-1.05)
No DR mismatch	0.96 (0.90-1.02)	0.99 (0.85-1.16)	1.28 (0.85-1.92)	0.88 (0.70-1.09)	0.88 (0.73-1.07)
DR mismatch	Reference	Reference	Reference	Reference	Reference
Discharge immunosuppressive regimen					
MMF + cyclosporine	Reference	Reference	Reference	Reference	Reference
Azathioprine + cyclosporine	<b>0.90 (0.82-0.99)</b>	0.96 (0.77-1.19)	<b>2.00 (1.13-3.54)</b>	0.99 (0.72-1.35)	1.05 (0.82-1.34)
MMF + tacrolimus	<b>1.37 (1.28-1.46)</b>	0.91 (0.76-1.08)	1.00 (0.61-1.62)	<b>1.44 (1.14-1.81)</b>	<b>1.25 (1.01-1.54)</b>
Azathioprine + tacrolimus	<b>1.22 (1.00-1.48)</b>	0.75 (0.43-1.30)	1.64 (0.50-5.35)	1.57 (0.87-2.83)	1.14 (0.68-1.93)
Other	1.08 (1.00-1.17)	0.73 (0.59-0.90)	1.48 (0.88-2.49)	1.19 (0.91-1.55)	1.17 (0.93-1.48)
Steroids	0.92 (0.81-1.03)	1.03 (0.74-1.44)	0.97 (0.45-2.08)	0.99 (0.65-1.51)	1.45 (0.94-2.23)
mTOR inhibitors	<b>1.15 (1.02-1.30)</b>	1.08 (0.79-1.49)	0.90 (0.43-1.89)	0.86 (0.55-1.35)	1.01 (0.67-1.50)
Induction therapy	0.99 (0.94-1.04)	1.00 (0.88-1.15)	0.73 (0.51-1.05)	1.16 (0.97-1.39)	1.11 (0.94-1.29)
Recipient alcoholic	<b>1.29 (0.93-1.79)</b>	1.53 (0.72-3.26)	NA	0.70 (0.17-2.84)	0.36 (0.05-2.59)

Note: Values expressed as hazard ratio (95% confidence interval). Independent risk factors for diarrhea after kidney transplantation; associations between recipient, donor, and graft-related baseline characteristics and risk of developing diarrhea. All significant associations at  $P < 0.05$  level are printed in bold type.

Abbreviations: CMV, cytomegalovirus; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

**Table 4. Impact of Diarrhea on Transplant Outcomes**

Type of Diarrhea	Graft Failure	Death-Censored Graft Failure	Patient Death
<b>Model 1</b>			
Unspecified noninfectious	<b>2.04 (1.90-2.19)</b>	<b>2.04 (1.86-2.24)</b>	<b>2.15 (1.97-2.35)</b>
Nonspecified infection	<b>1.62 (1.35-1.94)</b>	<b>1.45 (1.12-1.88)</b>	<b>1.93 (1.57-2.36)</b>
Ulcerative colitis	<b>1.30 (1.12-1.51)</b>	1.06 (0.84-1.33)	<b>1.50 (1.26-1.79)</b>
Specified noninfectious	1.42 (0.96-2.11)	1.36 (0.80-2.31)	<b>2.33 (1.57-3.47)</b>
Specified infection	1.21 (0.99-1.47)	1.21 (0.93-1.57)	1.14 (0.87-1.49)
<b>Model 2</b>			
Unspecified noninfectious	<b>2.13 (1.98-2.28)</b>	<b>2.06 (1.88-2.26)</b>	<b>2.04 (1.85-2.24)</b>
Nonspecified infection	<b>2.37 (1.77-3.19)</b>	<b>1.46 (1.13-1.89)</b>	<b>2.65 (1.84-3.82)</b>
Ulcerative colitis	<b>1.31 (1.13-1.52)</b>	1.03 (0.82-1.30)	<b>1.50 (1.25-1.80)</b>
Specified noninfectious	<b>2.73 (1.64-4.54)</b>	<b>2.66 (1.37-5.18)</b>	<b>3.19 (1.65-6.14)</b>
Specified infection	<b>1.67 (1.28-2.17)</b>	1.21 (0.93-1.57)	<b>1.84 (1.30-2.62)</b>

*Note:* Independent effect of different types of diarrhea on graft outcomes during a 3-year follow-up period. Values expressed as hazard ratio (95% confidence interval). Hazard ratios adjusted for recipient and donor transplant-related characteristics as described in Methods section. Model 1 adjusted for time interactions. Model 2 adjusted for time interaction and interaction between different types of diarrhea. Time interactions not statistically significant at the 0.001 level and cross-interaction terms not statistically significant at the 0.05 level were eliminated from the final model. All significant associations at  $P < 0.05$  level are printed in bold type.

doubled the risk of graft loss, patient death, and death-censored graft survival.

Diarrhea is a common complication in kidney transplant recipients. Immunosuppressive agents are known to make transplant recipients susceptible to infectious diarrhea.<sup>14</sup> They also can cause direct injury to the GI tract, resulting in noninfectious diarrhea.<sup>15</sup> In clinical trials evaluating the effects of immunosuppression, the incidence of diarrhea ranged from 16% to 64%, depending on the regimen and duration of the study.<sup>6-12</sup> Our estimate is in the lower bound of that range. In our study, we used claims data to ascertain diarrhea, which likely accounts for the lower incidence observed in our study compared with

previous clinical trials. Claims tend to capture more severe cases or cases in which treatment is sought, whereas clinical trials generally have a greater capture rate of less severe complications.

The cause of diarrhea may include infectious and noninfectious causes and can be multifactorial.<sup>5,14</sup> Differentiation between infectious versus noninfectious causes of posttransplantation diarrhea includes the presence of fever, leukocytosis, leukocytes in stools, and specific imaging or endoscopic findings.<sup>5</sup> The incidence of unspecified noninfectious diarrhea increased from 9.0% in the first year to 19.0% in the third year after transplantation. The cumulative incidence of the other types of diarrhea remained low for

**Table 5. Diagnosis Setting and Risk of Graft Loss**

Type of Diarrhea	Diagnosis Setting	Absolute Frequency at 3 y	Hazard Ratio (95% confidence interval)
Unspecified noninfectious	Nonhospitalized	5,064	2.13 (1.97-2.29)
	Hospitalized	807	2.10 (1.80-2.45)
Unspecified infectious	Nonhospitalized	482	2.66 (1.96-3.60)
	Hospitalized	28	2.22 (1.15-4.29)
Ulcerative colitis	Nonhospitalized	863	1.30 (1.11-1.53)
	Hospitalized	83	1.16 (0.74-1.82)
Specified noninfectious	Nonhospitalized	120	1.52 (1.00-2.32)
	Hospitalized	12	41.25 (10.21-166.72)
Specified infection	Nonhospitalized	497	1.56 (1.12-2.17)
	Hospitalized	180	2.71 (1.70-4.31)

*Note:* Risk of graft loss associated with a diarrhea episode occurred during a hospitalization. Hazard ratios adjusted for recipient and donor transplant-related characteristics as described in Methods section.

the duration of the study. We found medical claims for specific causes of infectious diarrhea in about 2% of kidney transplant recipients during the 3-year follow-up, and about 40% of cases occurred within the first year. The diagnosis of specific causes of infectious diarrhea requires positive identification of the responsible organisms. The true incidence of specific types of diarrhea is not well documented, and confirmation of the specific causes can be difficult. The proportion of patients diagnosed as infectious in our sample was 17%, which is less than that previously reported in a small case series of 108 patients with severe diarrhea.<sup>16</sup> One possible explanation for this difference is that some mild infections may have gone unrecognized in our sample and been classified as unspecified noninfectious diarrhea cases. In addition, time from transplantation at the time of enrollment in the mentioned case series ranged from 1 to 258 months, whereas we observed patients along a narrower time frame (36 months posttransplantation). In our sample, the incidence of infectious diarrhea increased by 29 times during the follow-up period versus a 13-times increase in cumulative incidence of noninfectious diarrhea. It therefore is possible that longer follow-up would have allowed us to observe a larger proportion of infectious cases.

One of the objectives of the study is to identify clinical correlates of posttransplantation diarrhea. We found female sex was associated with an increase in incidences of all types of diarrhea. Transplant recipients with type 1 diabetes were at risk of noninfectious diarrhea, which may be caused in part by the presence of diabetic autonomic neuropathy involving the GI tract.<sup>17</sup> We also found that CMV-naïve serostatus in recipients of organs from CMV-seropositive donors is associated with increased risk of unspecified noninfectious diarrhea and unspecified infectious diarrhea. Valganciclovir and ganciclovir used to prevent CMV infection are associated with diarrhea and could in part explain the greater incidence of diarrhea in this group.<sup>18</sup> It also is possible that a fraction of unspecified noninfectious diarrhea was directly caused by CMV visceral dissemination, which is prone to underascertainment in routine examinations.<sup>19</sup> However, Maes et al<sup>16</sup> reported that only 7% of patients affected by severe diarrhea had a diagnosis of CMV infection by means of histological examina-

tion, and only 4.5% responded to intravenous ganciclovir (10- to 24-day treatment course). Based on these data, only a small fraction of misdiagnosed CMV cases could have biased our results, even assuming the unrealistic hypothesis that all CMV colitis cases were erroneously classified under the unspecified noninfectious group.

Finally, according to previous research, we found that regimens based on MMF and tacrolimus were associated with a greater incidence of infectious and unspecified noninfectious diarrhea. However, the lack of follow-up data about treatment regimens and dosage did not allow us to account for regimen changes and examine the dose-response relationship of immunosuppression exposure and diarrhea incidence.

We and others previously showed that overall GI complications were associated with an increased risk of graft loss.<sup>4,20,21</sup> In this study, irrespective of the underlying cause, infectious or noninfectious, specific or nonspecific, diarrhea was associated with an increased risk of graft loss and patient death.

Patients with a diagnosis of unspecified noninfectious diarrhea had a 2-fold increased risk of graft failure, death-censored graft failure, and death. It is possible that diarrhea is an incidental event in the course of hospitalization for other unrelated causes or the consequence of severe medical conditions. In this case, the medical condition leading to hospitalization (instead of the diagnosis of diarrhea itself) could be the risk factor detected, and our findings reflect the increased likelihood of diarrhea being diagnosed during a hospitalization rather than a true association. However, these concerns are partially discounted because even cases of diarrhea diagnosed in outpatient settings were associated with a significant greater risk of graft loss. Nonetheless, even in outpatient settings, diarrhea can result from the treatment of severe concurrent diseases (eg, antibiotics, chemotherapy, and radiotherapy) or be a manifestation of systemic conditions that can be detrimental to graft outcomes per se. We could not verify this hypothesis in our study. However, recent findings suggested that less than 20% of severe diarrhea cases in kidney transplant patients remained unexplained after an infectious cause was systematically searched for and treated and immunosuppression dose was decreased.<sup>16</sup>

The combination of tacrolimus and MMF is one of the most effective immunosuppressive

regimens despite the high incidence of GI complications. However, the presence of posttransplantation diarrhea often is associated with a subsequent decrease in MMF dose. In addition, we previously found an association between GI complications and poor adherence to treatment protocols. In the same study, poorly adherent patients faced a greater risk of graft loss.<sup>22</sup> Dose reductions or discontinuation may result in inadequate immunosuppression and lead to worse graft and patient survival rates. We previously showed that MMF dose reduction or discontinuation after any type of GI event was associated with increased risk of graft loss.<sup>23</sup> Thus, dose reductions or discontinuation of immunosuppressive drugs should be avoided when possible, and identification of specific causes of diarrhea, even paucisymptomatic forms, should be pursued because the inflammatory response impairment in kidney transplant recipients can mask symptoms.<sup>24</sup> As shown by Maes et al,<sup>16</sup> aggressive and systematic diagnostic management can avoid decreasing the immunosuppression dose in almost 50% of patients with severe diarrhea.

In addition, diarrhea has detrimental effects on quality of life. It recently was reported that patient-reported diarrhea symptoms were associated with impaired quality of life, with the latter becoming more impaired the more severe the GI symptoms.<sup>25</sup> Preliminary data suggest that changes in immunosuppressive therapy could improve GI symptom burden and increase GI-specific health-related quality of life in patients experiencing GI symptoms, including diarrhea.<sup>26,27</sup>

There are several limitations to this study. First, the definition of diarrhea varies and claims data may be subject to coding bias and error. It is likely that we underestimated the incidence of diarrhea. Second, we did not examine the Medicare claim report before transplantation. Because diarrhea can be a chronic illness, it is possible that some of these diarrhea claims may not be of new onset or specific to the transplantation setting. For example, although we found an increase in the diagnosis of ulcerative colitis during the study period, new-onset ulcerative colitis after transplantation is a rare phenomenon caused by concurrent immunosuppression therapy. Third, we included in our analysis only Medicare beneficiaries. Differences and similarities of Medicare beneficiaries compared with the general

kidney transplant population were discussed elsewhere.<sup>3</sup> Medicare beneficiaries compared with the general kidney transplant population are slightly older, less educated, more likely to be African American, and have a greater burden of comorbid conditions (obesity and hepatitis C infection) and larger number of HLA mismatches. Finally, although we provided evidence of a detrimental effect of diarrhea on transplantation outcomes, we cannot prove the causal relationship between the two. A study of events and/or intervention after diarrhea is crucial to address factors that may explain the adverse outcomes. Given that some immunosuppressive agents are associated with diarrhea, examination of medication changes after diarrhea and adherence/compliance to immunosuppressive agents after diarrhea could shed new light on the clinical management of patients with diarrhea. Other additional factors may impact on the association between diarrhea and decreased graft and patient survival. Additional studies would be able to investigate whether an added effect exists. The nature of these relationships is beyond the scope of this study.

However, registry data offer real-world descriptions of clinical practices and are relatively free from investigator bias. Also, we provided relatively complete follow-up of all Medicare beneficiaries receiving a kidney transplant in the United States between 1995 and 2002 with a wide set of clinically relevant covariates. Results from retrospective population-based studies can help generate well-founded scientific hypotheses, offer guidance for the management of patients, and contribute to set public health priorities.

In conclusion, posttransplantation diarrhea was frequent, and the most common type was of unspecified noninfectious origin. This type of diarrhea was associated with increased risk of graft loss, patient death, and death-censored graft survival. Immunosuppressive regimens based on tacrolimus and MMF combined were associated with a greater incidence of unspecified noninfectious type of diarrhea. Additional modifiable factors also were associated with an increased risk of diarrhea. Our findings provide the rationale for studies uncovering the underlying cause, describing the natural history, and evaluating the relationship of diarrhea with the incidence of graft loss.

## ACKNOWLEDGEMENTS

Data reported here were supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government.

*Support:* This study was supported in part by a grant to Dr Schnitzler from the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) K25-DK-02916-03. Dr Lentine is supported by a grant from the NIDDK, K08-0730306.

*Financial Disclosure:* Dr Schnitzler received financial support from Novartis Pharma AG to conduct this study.

## REFERENCES

- Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D: Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 342:605-612, 2000
- Adams PL: Long-term patient survival: Strategies to improve overall health. *Am J Kidney Dis* 47:S65-S85, 2006 (suppl 2)
- Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ: Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 3:178-185, 2003
- Hardinger KL, Brennan DC, Lowell J, Schnitzler MA: Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. *Transpl Int* 17:609-616, 2004
- Ponticelli C, Passerini P: Gastrointestinal complications in renal transplant recipients. *Transpl Int* 18:643-650, 2005
- Sollinger HW: Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation* 60:225-232, 1995
- The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group: A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 61:1029-1037, 1996
- Mathew TH: A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: Results at three years. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. *Transplantation* 65:1450-1454, 1998
- European Mycophenolate Mofetil Cooperative Study Group: Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 345:1321-1325, 1995
- European Mycophenolate Mofetil Cooperative Study Group: Mycophenolate mofetil in renal transplantation: 3-Year results from the placebo-controlled trial. *Transplantation* 68:391-396, 1999
- Miller J, Mendez R, Pirsch JD, Jensik SC: Safety and efficacy of tacrolimus in combination with mycophenolate mofetil (MMF) in cadaveric renal transplant recipients. FK506/MMF Dose-Ranging Kidney Transplant Study Group. *Transplantation* 69:875-880, 2000
- Squifflet JP, Backman L, Claesson K, et al: Dose optimization of mycophenolate mofetil when administered with a low dose of tacrolimus in cadaveric renal transplant recipients. *Transplantation* 72:63-69, 2001
- Chang HR, Lin CC, Lian JD: Early experience with enteric-coated mycophenolate sodium in de novo kidney transplant recipients. *Transplant Proc* 37:2066-2068, 2005
- Helderman JH, Goral S: Gastrointestinal complications of transplant immunosuppression. *J Am Soc Nephrol* 13:277-287, 2002
- Ducloux D, Ottignon Y, Semhoun-Ducloux S, et al: Mycophenolate mofetil-induced villous atrophy. *Transplantation* 66:1115-1116, 1998
- Maes B, Hadaya K, de Moor B, et al: Severe diarrhea in renal transplant patients: Results of the DIDACT Study. *Am J Transplant* 6:1466-1472, 2006
- Feldman M, Schiller LR: Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 98:378-384, 1983
- Paya C, Humar A, Dominguez E, et al: Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 4:611-620, 2004
- Kambham N, Vij R, Cartwright CA, Longacre T: Cytomegalovirus infection in steroid-refractory ulcerative colitis: A case-control study. *Am J Surg Pathol* 28:365-373, 2004
- Pelletier RP, Akin B, Henry ML, et al: The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. *Clin Transplant* 17:200-205, 2003
- Tierce JC, Porterfield-Baxa J, Petrilla AA, Kilburg A, Ferguson RM: Impact of mycophenolate mofetil (MMF)-related gastrointestinal complications and MMF dose alterations on transplant outcomes and healthcare costs in renal transplant recipients. *Clin Transplant* 19:779-784, 2005
- Takemoto S, Pinsky B, Lentine K, Bunnapradist S, Burroughs T, Schnitzler M: Poor immunosuppression adherence: Associated factors and possible consequences. In: World Transplant Congress 2006 Poster Abstracts. *Am J Transplant* 6 Suppl 2: 488, 2006
- Bunnapradist S, Lentine KL, Burroughs TE, et al: Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. *Transplantation* 82:102-107, 2006
- Rubin RH: Gastrointestinal infectious disease complications following transplantation and their differentiation from immunosuppressant-induced gastrointestinal toxicities. *Clin Transplant* 15:S11-S22, 2001 (suppl 4)
- Ekberg H, Kyllonen L, Madsen S, Grave G, Solbu D, Holdaas H: Increased prevalence of gastrointestinal symptoms associated with impaired quality of life in renal transplant recipients. *Transplantation* 83:282-289, 2007
- Bolin P, Tanriover B, Lynn M, et al: Significant improvement of GI-symptoms burden in African-American transplant recipients after conversion to EC-MPS. *Transplantation* 82:S514-S515, 2006 (suppl 2)
- Chan L, Mulgaonkar S, Walker R, Arns W, Ambuhl P, Schiavelli R: Patient-reported gastrointestinal symptom burden and health-related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. *Transplantation* 81:1290-1297, 2006