# *Clostridium difficile* infection in dialysis patients

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## ABSTRACT

*Clostridium difficile* infection (CDI) is the most common cause of nosocomial diarrhea. Patients with end-stage renal disease (ESRD) may be at increased risk for CDI. Patients with ESRD with CDI have increased mortality, longer length of stay, and higher costs. The present studies extend these observations and address associated comorbidities, incidence of recurrence, and risk factors for mortality. We queried the United States Renal Data System (USRDS) for patients with ESRD diagnosed with CDI, and assessed for the incidence of infection, comorbidities, and mortality. The records of 419,875 incident dialysis patients from 2005 to 2008 were reviewed. 4.25% had a diagnosis of a first CDI. In the majority of patients with CDI positive, a hospitalization or ICU stay was documented within 90 days prior to the diagnosis of CDI. The greatest adjusted relative risk (aRR) of CDI was present in patients with HIV (aRR 2.68), age ≥65 years (aRR 1.76), and bacteremia (aRR 1.74). The adjusted HR (aHR) for death was 1.80 in patients with CDI. The comorbidities demonstrating the greatest risk for death in dialysis patients with CDI included age ≥65 years and cirrhosis (aHR 2.28 and 1.76, respectively). Recurrent CDI occurred in 23.6%, was more common in Caucasians, and in those who were older. CDI is a common occurrence in patients with ESRD, with elderly patients, patients with HIV positive, and bacteremic patients at highest risk for infection. Patients with CDI had nearly a twofold increased risk of death.

### Significance of this study

**What is already known about this subject?**

- *Clostridium difficile* is the most common cause of nosocomial diarrhea.
- Patients with end-stage renal disease (ESRD) with *C. difficile* infection (CDI) have increased mortality.
- Patients with ESRD with CDI have longer length of stay and higher costs.

**What are the new findings?**

- The majority of patients with ESRD with CDI had an ICU or hospital admission within 90 days of the diagnosis.
- The greatest risk of CDI in ESRD is in patients with HIV, age >65 years, and bacteremia.
- The HR for death in patients with ESRD with CDI was 1.80.
- Recurrent CDI occurs in 23.6% of patients with ESRD with a first CDI.

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

- This study identifies those patients at increased risk for CDI. Some of the typical risk factors for recurrent infection do not appear to apply to the ESRD population, presumably due to the similarities between the inpatient setting and dialysis center environments. Outpatient transmission in dialysis units may play a role; thus, efforts to prevent the spread of *C. difficile* in these venues may be justified.

## INTRODUCTION

*Clostridium difficile* infection (CDI) is the most common cause of nosocomial diarrhea.[1] Risk factors for CDI include inpatient hospitalizations and antibiotic therapy, the latter of which promotes overgrowth of the toxin producing bacterium and the development of mucosal infection.[2] Other factors associated with increased risk of CDI include: increasing age, severity of underlying disease, non-surgical gastrointestinal (GI) procedures, antiulcer medications, and the presence of a nasogastric tube.[3]

Patients with end-stage renal disease (ESRD) may also be at increased risk for CDI due to repeated hospitalizations, impaired host defenses from uremia, recurrent infection requiring frequent antibiotic use, and a recognized increased risk of colonization with the bacterium.[4]

In a review of the United States Nationwide Inpatient Sample 2009 database, patients with ESRD with CDI were shown to have increased mortality, longer length of stay, and higher costs when compared to ESRD alone.[5] This work demonstrated the importance of CDI in ESRD, but lacked information on associated comorbidities, incidence of recurrence, and relevant risk factors for mortality. To address these questions, we queried the United States Renal Data System (USRDS) for patients with ESRD diagnosed with CDI and assessed for the incidence of infection, occurrence of comorbidities, and associated mortality.

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## METHODS

### Study cohort

The USRDS is a deidentified database that includes physician/supplier claims and vital statistics on all patients with ESRD in the USA.[6] Demographic information for this work was obtained from the USRDS patient information data set, and comorbidities were defined by ICD-9 billing codes from claims submitted to Medicare, or the latest version of the form CMS-2728.

A retrospective analysis of all patients with ESRD above 18 years of age whose incident date of dialysis was between 2005 and 2008 was conducted. Patients were excluded if form CMS-2728 had incomplete information about vascular access type on first dialysis, or if their record contained a version of the form that lacks this information (prior to 2005).

### Outcome variables

The primary outcome was CDI, which was determined using an ICD-9 diagnosis code of 008.45. The first episode of CDI was used for patients who had more than one listing of the diagnosis. Recurrent CDI (rCDI) was defined as having a second CDI at least 15 days following the first episode of CDI and no more than 1 year afterwards. The outcome used in survival analyses was time to death from the initiation of dialysis.

### Covariates

Clinical covariates were selected based on presumed risk factors for CDI and included, in addition to demographics, (1) medical or surgical conditions necessitating potential antibiotic therapy, that is, decubitus ulcer, diverticulitis, bacteremia, osteomyelitis, or urinary tract infection (UTI); (2) potentially immunosuppressed states, that is, diabetes mellitus (DM), leucopenia, autoimmune diseases, HIV infection, or history of a kidney transplant; (3) diagnoses with potential for bowel breach, that is, GI bleeding, laparotomy, or duodenal ulcer; and (4) history of intensive care unit (ICU) or other hospital admission in the previous 90 days. Cirrhosis was included as an indicator of advanced liver disease. Each covariate was considered in the analysis if the diagnosis code was present at or before the date of the first diagnosis of CDI. Vascular access type used at the initiation of dialysis was taken from form 2728.

### Analyses

Descriptive analyses were performed comparing patients with and without a diagnosis of CDI. Mean and SD for continuous variables, and frequencies for categorical variables, were calculated. Bivariate analyses using generalized linear regression assuming an underlying binomial distribution of the outcome were performed for each covariate to determine its crude risk of CDI. Multivariable analyses were conducted using backward elimination of non-significant variables to determine adjusted risks. Survival analyses to determine time to death among patients with ESRD with CDI was conducted using the Cox proportional hazards regression model. None of the variables were time dependent. Analyses were conducted at an $\alpha$ level of 0.05 using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

## RESULTS

### Characteristics of the study population

These studies analyzed the records of 419,875 incident dialysis patients from 2005 to 2008. During this period, all patients had a current CMS-2728 form and at least one hospitalization from which ICD-9 diagnosis codes and hospitalization information were taken. From this group, 17,853 (4.25%) patients had a diagnosis of a first CDI.

Table 1 summarizes the characteristics of all patients, as well as those with a diagnosis of CDI. CDI was less common in men and black race, and more frequent in Caucasians. When compared to the entire population, vascular catheter use for dialysis access was more common in patients with CDI (72.06% vs 69.73%, for CDI vs the entire population, respectively). Hospitalization (60.3%) or ICU stay (78.7%) was documented within 90 days prior to the diagnosis of CDI in the majority of patients with CDI.

### Risk factors for CDI

Table 2 summarizes several risk factors, and the unadjusted and adjusted relative risks (aRRs), for the development of CDI. Over 9% of patients with HIV, UTI, GI bleeding, osteomyelitis, and diverticulitis had a diagnosis of CDI.

Using multivariable analysis with a model adjusting for all significant covariates, the greatest RR of CDI was present in patients with HIV (RR 2.68), age ≥65 years (RR 1.76), and bacteremia (RR 1.74). Ten additional conditions associated with an elevated RR for CDI included pneumonia, rheumatoid arthritis, infection with hepatitis C virus (HCV), duodenal ulcer, diverticulitis, osteomyelitis, laparotomy, GI bleeding, UTI, and DM, with the aRR ranging from 1.25 to 1.54. Hispanic ethnicity and black race were associated with a decreased risk of CDI infection (aRR 0.76 and 0.75, respectively).

### Outcomes and survival analysis

A greater percentage of patients with CDI died when compared to the entire cohort (68.78% vs 42.01%, respectively) and underwent colectomy (0.60% vs 0.07%, respectively) (table 3). The adjusted HR (aHR) for death was 1.80 in patients with CDI.

The comorbidities demonstrating the greatest risk for death in patients with CDI included age ≥65 years and cirrhosis (aHR 2.28 and 1.76, respectively). Eight additional conditions were associated with an elevated aHR for death:

**Table 1** Characteristics of the study populations (%)

| Variable | All patients | CDI positive |
|---|---|---|
| Age ≥65 years | 210,405 (50.1) | 12,081 (67.6) |
| Male sex | 234,617 (55.9) | 9092 (50.9) |
| Black race | 122,035 (29.1) | 4292 (24.0) |
| Caucasian | 274,645 (65.4) | 12,947 (72.5) |
| AV fistula | 47,732 (11.4) | 1192 (6.7) |
| AV graft | 14,181 (3.4) | 530 (3.0) |
| Dialysis catheter | 293,192 (69.8) | 12,864 (72.1) |
| Inpatient events 90 days prior to *C. difficile* diagnosis | | |
| ICU stay | NA | 10,771 (60.3) |
| Hospitalization | NA | 14,047 (78.7) |

AV, arteriovenous; CDI, *Clostridium difficile* infection; ICU, intensive care unit.

**Table 2** Comorbidities associated with *C. difficile* colitis

| | All patients | | *C. difficile* infection | | | | Unadjusted association 95% CI | | | Adjusted association* 95% CI | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Absent | | Present | | | | | | | |
| | Count | Per cent | N | Per cent | N | Per cent | RR | Lower | Upper | RR | Lower | Upper |
| HIV | 3481 | 0.83 | 3143 | 90.29 | 338 | 9.71 | 2.31 | 2.08 | 2.56 | 2.68 | 2.40 | 2.99 |
| ≥65 years | 210,405 | 50.11 | 198,324 | 94.26 | 12,081 | 5.74 | 2.08 | 2.02 | 2.15 | 1.76 | 1.70 | 1.82 |
| Bacteremia | 80,305 | 19.13 | 73,192 | 91.14 | 7113 | 8.86 | 2.80 | 2.72 | 2.88 | 1.74 | 1.68 | 1.80 |
| Diabetes | 168,129 | 40.04 | 157,420 | 93.63 | 10,709 | 6.37 | 2.24 | 2.18 | 2.31 | 1.54 | 1.49 | 1.59 |
| UTI | 41,234 | 9.82 | 37,346 | 90.57 | 3888 | 9.43 | 2.54 | 2.45 | 2.63 | 1.44 | 1.38 | 1.49 |
| GI bleeding | 26,495 | 6.31 | 24,066 | 90.83 | 2429 | 9.17 | 2.34 | 2.24 | 2.44 | 1.42 | 1.35 | 1.48 |
| Osteomyelitis | 10,838 | 2.58 | 9838 | 90.77 | 1000 | 9.23 | 2.24 | 2.11 | 2.38 | 1.35 | 1.27 | 1.44 |
| Laparotomy | 1992 | 0.47 | 1830 | 91.87 | 162 | 8.13 | 1.92 | 1.65 | 2.22 | 1.33 | 1.14 | 1.55 |
| Diverticulitis | 9690 | 2.31 | 8783 | 90.64 | 907 | 9.36 | 2.27 | 2.13 | 2.41 | 1.32 | 1.23 | 1.41 |
| Duodenal ulcer | 4540 | 1.08 | 4135 | 91.08 | 405 | 8.92 | 2.12 | 1.93 | 2.33 | 1.30 | 1.18 | 1.43 |
| HCV | 9594 | 2.28 | 8942 | 93.20 | 652 | 6.80 | 1.62 | 1.50 | 1.75 | 1.27 | 1.17 | 1.39 |
| Rheumatoid arthritis | 3412 | 0.81 | 3157 | 92.53 | 255 | 7.47 | 1.77 | 1.57 | 1.99 | 1.25 | 1.11 | 1.41 |
| Pneumonia | 50,131 | 11.94 | 45,967 | 91.69 | 4164 | 8.31 | 2.24 | 2.17 | 2.32 | 1.25 | 1.20 | 1.29 |
| Hispanic | 57,027 | 13.58 | 55,150 | 13.72 | 1877 | 10.51 | 0.76 | 0.72 | 0.79 | 0.76 | 0.72 | 0.79 |
| Black race | 122,035 | 29.06 | 117,743 | 29.29 | 4292 | 24.04 | 0.75 | 0.73 | 0.78 | 0.75 | 0.73 | 0.78 |

*These variables were statistically significant in the final model and the RR is adjusted for all other variables in the final model. The full model also included: cirrhosis, colostomy, endocarditis, esophageal reflux, esophagitis, gastric ulcer, hemodialysis, hepatitis B viral infection, incident date of dialysis, incision of chest wall or pleural cavity, kidney transplant, leucopenia, pancytopenia, peritoneal dialysis, and urosepsis.
GI, gastrointestinal; HCV, hepatitis C virus; UTI, urinary tract infection.

duodenal ulcer, leucopenia, HCV, UTI, urosepsis, laparotomy, GI bleeding, and HIV, with aHRs ranging from 1.09 to 1.39. The year of incident dialysis also represented a risk for death in patients with CDI, with a significant increase in years 2007 and 2008.

Kidney transplant, Hispanic ethnicity, and peritoneal dialysis were associated with a decreased aHR for death (aHR 0.13, 0.65, and 0.66, respectively). Five other conditions were associated with a decreased HR for mortality and included osteomyelitis, esophagitis, esophageal reflux, diverticulitis, black race, and peritoneal dialysis, with aHRs ranging from 0.95 to 0.72.

### Recurrent CDI

Of all patients surveyed with an initial CDI, rCDI occurred in 23.6%. Table 4 summarizes the risk factors associated with rCDI.

When compared to patients without a recurrence, rCDI was more common in Caucasians and those who were older. The aRR of rCDI was increased in patients with HIV and age of starting dialysis. Neither number of hospital days nor admissions in the 90 days before rCDI were associated with an increased risk.

## DISCUSSION

The results of this study demonstrate that CDI occurs in over 4% of incident dialysis patients, and is associated with an increased HR for death by 80%. Using multivariable analysis, we determined that CDI was more common in Caucasians, women, the elderly, and was associated with other infectious conditions. The RR of developing CDI was highest in patients with HIV (aRR 2.68) and in those with age ≥65 years at ESRD diagnosis (aRR 1.76). Bacteremia, diabetes, UTI, and GI bleeding also carried significant risk. Over 78% of patients with CDI positive had a hospital admission in the 3 months prior to CDI diagnosis, and when compared to patients with CDI negative, there was a nearly 10-fold increase in the incidence of colectomy. Taken together, these data demonstrate that elderly hospitalized patients with ESRD are at risk for CDI similar to the general population. However, the data also indicate specific risk factors for CDI in patients with ESRD, including 13 comorbidities with an increase in the aRR for CDI. Many of these conditions were also associated with an increased risk of death.

When compared to the general population, patients with ESRD may be at increased risk for the development of CDI due to more frequent hospitalization. In this regard, patients with ESRD averaged 1.73 admissions per patient year in 2012.[6] In contrast and for calendar year 2009, the general population averaged 0.11 admissions per patient year.[7] Thus, the known association between CDI and hospitalization is readily applicable to patients with ESRD.

In the present study, HIV infection conferred the greatest increase in RR for the development of CDI, with a 2.6-fold increase over patients with HIV negative. The explanation for this finding is not clear from our data; however, we would speculate that patients with HIV on dialysis remain relatively immunosuppressed compared to patients with HIV negative and/or may experience more hospitalizations, infectious complications, or increased exposure to antibiotics.[8]

The current study showed that from 2005 to 2008, there was a yearly increase in the aHR for death in patients with CDI positive and CDI negative, with patients with CDI positive exhibiting a numerically greater increase. The explanation for this trend is not clear from our data; however, one possibility is that older, sicker patients were being referred for dialysis therapy in 2007 and 2008. In the patients with CDI positive, the recognition of BI/

**Table 3** Outcomes and aHR of death in dialysis patients with *C. difficile* colitis

| | All patients | | *C. difficile* | | | |
|---|---|---|---|---|---|---|
| | | | Absent | | Present | |
| Outcomes | Count | Per cent | N | Per cent | N | Per cent |
| Died | 176,681 | 42.01 | 164,402 | 40.89 | 12,279 | 68.78 |
| Colectomy | 403 | 0.1 | 296 | 0.07 | 107 | 0.6 |
| **HR of death** | | | | | | |
| | | | 95% CI | | | |
| | HR | | Lower | | Upper | |
| Increased risk for mortality* | | | | | | |
| | 1.8 | | 1.77 | | 1.83 | |
| *C. difficile* colitis | | | | | | |
| ≥65 years | 2.28 | | 2.25 | | 2.3 | |
| Cirrhosis | 1.76 | | 1.71 | | 1.81 | |
| HIV | 1.39 | | 1.32 | | 1.46 | |
| GI bleeding | 1.31 | | 1.29 | | 1.33 | |
| Laparotomy | 1.25 | | 1.18 | | 1.33 | |
| Urosepsis | 1.18 | | 1.16 | | 1.19 | |
| UTI | 1.14 | | 1.12 | | 1.16 | |
| HCV | 1.13 | | 1.1 | | 1.17 | |
| Leucopenia | 1.124 | | 1.055 | | 1.198 | |
| Duodenal ulcer | 1.085 | | 1.045 | | 1.127 | |
| Year of first ESRD service | | | | | | |
| 2005 | 1.00 | | NA | | NA | |
| 2006 | 1.07 | | 1.03 | | 1.12 | |
| 2007 | 1.36 | | 1.29 | | 1.43 | |
| 2008 | 1.74 | | 1.63 | | 1.85 | |
| Decreased risk for mortality* | | | | | | |
| Osteomyelitis | 0.946 | | 0.921 | | 0.972 | |
| Esophagitis | 0.906 | | 0.874 | | 0.939 | |
| Esophageal reflux | 0.811 | | 0.799 | | 0.824 | |
| Diverticulitis | 0.746 | | 0.724 | | 0.767 | |
| Black | 0.723 | | 0.715 | | 0.731 | |
| PD | 0.656 | | 0.641 | | 0.672 | |
| Hispanic | 0.652 | | 0.641 | | 0.662 | |
| Kidney transplant | 0.133 | | 0.124 | | 0.142 | |

*Each covariate was present at or after the start of dialysis.
aHR, adjusted HR; ESRD, end-stage renal disease; GI, gastrointestinal; HCV, hepatitis C virus; PD, peritoneal dialysis; UTI, urinary tract infection.

**Table 4** aRR for recurrent *C. difficile* colitis*

| | | 95% CI* | | |
|---|---|---|---|---|
| Variable | aRR | Lower | Upper | p Value |
| Race: black vs white | 0.98 | 0.97 | 0.99 | <0.01 |
| Race: other vs white | 1.00 | 0.97 | 1.02 | <0.01 |
| Age at incident ESRD: ≥65 vs <65 | 1.02 | 1.01 | 1.03 | <0.01 |
| Bacteremia/sepsis | 0.98 | 0.96 | 0.99 | <0.01 |
| Urosepsis | 1.02 | 1.00 | 1.03 | 0.0426 |
| Diabetes | 1.01 | 1.00 | 1.02 | 0.0269 |
| Hepatitis C | 0.97 | 0.95 | 0.99 | 0.0268 |
| HIV | 1.05 | 1.02 | 1.08 | <0.01 |
| Number of hospital days prior to rCDI | 1.002 | 1.000 | 1.004 | 0.0146 |
| Hospitalization 90 days prior to rCDI | 1.01 | 1.00 | 1.02 | <0.01 |

*These variables comprised the final model and the aRR is adjusted for all other variables in the model. The full model included gender, race, age, dialysis type, incident year of dialysis, bacteremia, bacteremia+sepsis, diverticulitis, osteomyelitis, kidney transplant, peritonitis, pneumonia, UTI, urosepsis, candida colonization, cirrhosis, decubitus ulcer, diabetes, duodenal ulcer, endocarditis, esophagitis, esophageal reflux, gastric ulcer, gastrointestinal hemorrhage, glomerulonephritis, hepatitis C infection, HIV, lupus, methicillin-resistant staphylococcus aureus (MRSA) infection, peripheral vascular disease (PVD), rheumatoid arthritis, chest wall or pleural cavity incision, total parenteral nutrition (TPN), any ICU stay, number of hospitalizations 90 days before rCDI, and number of admissions 90 days before rCDI.
aRR, adjusted relative risk; ESRD, end-stage renal disease; ICU, intensive care unit; rCDI, recurrent CDI.

NAP1/027 (NAP1) in the early 2000s may have also contributed to the increase in risk of death. Originating in Canada, NAP1 is recognized to be a more virulent strain of *C. difficile*, producing increased amounts of toxins A, B, and a third, binary toxin.[9]

The present study also assessed risk factors for rCDI in ESRD. Risk factors for rCDI in the general population include increasing age, initial disease severity, and hospital exposure.[10] In our query, HIV carried the greatest RR for recurrent infection, similar to initial CDI. Unlike the general population, neither hospital admissions nor hospital days were associated with an increase in risk. We would speculate that this may be related to the epidemiological similarities between dialysis units and the inpatient setting with respect to exposure to healthcare-associated infection, close association with other patients, and access to common healthcare providers.

Our studies augment and extend the work of Pant *et al*.[5] In this regard, we confirmed the increased risk of mortality. In addition, we showed several risk factors for infection, and demonstrated factors responsible for an increased risk of death, including older age and cirrhosis.

The present work is based on a query of the USRDS data set. This database contains patient-specific data on essentially all patients with ESRD treated in the USA. All diagnoses and procedures were inferred from billing codes submitted to Medicare or extracted from form 2728 and are not the result of actual medical documentation. The size of the data set and the ability to capture data from every hemodialysis patient in the country may offset these limitations.

In summary, CDI is a common occurrence in patients with ESRD, with elderly patients and patients with HIV positive at highest risk with an increased risk of death. Finally, some of the typical risk factors for recurrent infection do not appear to apply to the ESRD population, presumably due to the similarities between the inpatient setting and dialysis center environments.

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**Competing interests** None declared.

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