# *Clostridium difficile* Infection Is Associated With Poor Outcomes in End-Stage Renal Disease

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**Objective:** To investigate the association of *Clostridium difficile* infection (CDI) with the outcomes of hospitalized patients with end-stage renal disease (ESRD).

**Methods:** We extracted all adult cases with a discharge diagnosis of ESRD or CDI from the United States Nationwide Inpatient Sample 2009 database. Outcome variables (mortality, length of hospital stay [LOS], and hospitalization charges), demographic information, and comorbidity data were collected. Data were evaluated by univariate and multiple regression analyses.

**Results:** We identified 184,139 cases with ESRD of which 2.8% had CDI. Comparison of patients with ESRD + CDI to those with only ESRD revealed in-hospital mortality (13.2% vs 5.3%; $P < 0.001$), LOS (17.3 vs 7.1 days; $P < 0.001$), and charges ($124,846 vs $56,663; $P < 0.001$) to be more than 2-fold greater. In the ESRD cohort (ESRD only and ESRD + CDI), CDI was independently associated with greater mortality (adjusted odds ratio, 2.15; 95% CI, 2.07–2.24; $P < 0.001$), longer LOS (mean difference, 9.4 days; 95% CI, 9.2–9.5; $P < 0.001$), and higher charges (mean difference, $62,824; 95% CI, 61,615–64,033; $P < 0.001$).

**Conclusions:** *Clostridium difficile* infection is associated with significantly worse outcomes in hospitalized patients with ESRD.

**Key Words:** *Clostridium difficile* infection, end-stage renal disease, hospital charges, length of stay, mortality, Nationwide Inpatient Sample (NIS) database

(*J Investig Med* 2012;60: 529–532)

*Clostridium difficile* infection (CDI) is a leading cause of nosocomial diarrhea[1] and is associated with significant morbidity and mortality in hospitalized individuals.[2] During the past few years, multiple studies have demonstrated a complex interrelationship between this infection and chronic diseases. Several disorders including cancer, organ transplantation, and inflammatory bowel disease have been shown to confer an increased risk of acquiring CDI.[3] Moreover, these disorders might predispose patients to the development of more severe CDI (eg, fulminant colitis). Similarly, CDI seems to be associated with worse overall outcomes in patients with a preexisting significant disease burden as recently reported for cirrhosis.[4]

Chronic kidney disease (CKD) is one of the most common chronic medical conditions affecting the general population; in the United States, this disease affects approximately 13% of adults.[5] Despite the impact of CKD on the health of the population, the relationship of CDI and this disorder is not well understood. Data from individual, but not all, single-center studies suggest that patients with CKD are at an increased risk of acquiring CDI and have greater mortality associated with this infection.[6–8] Recently, Eddi et al[9] demonstrated that only a subset of patients with CKD, those with end-stage renal disease (ESRD), is at an increased risk of acquiring CDI (odds ratio [OR], 2.60; 95% CI, 1.25–5.41; $P = 0.0165$). However, the clinical implications of CDI in the ESRD population have not been thoroughly evaluated. Thus, we used a US nationwide inpatient hospital database to determine whether CDI is associated with adverse outcomes in hospitalized patients with ESRD.

## MATERIALS AND METHODS

### Data Source

For this study, we used the Nationwide Inpatient Sample (NIS) database for the year 2009. The NIS is part of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. The NIS contains data from a 20% sample of US hospitals from 44 states (in 2009). Individual hospitalizations (ie, discharge level, not patient level information is collected) are de-identified and maintained in the NIS as a unique entry with 1 primary discharge diagnosis and up to 24 secondary diagnoses. Each entry also contains demographic details and hospitalization mortality, total charges, and length of stay (LOS). Discharge weights are provided in the NIS core file to generate national level estimates of the collected data.

### Variable Definition

The predictor variables in this study were the presence of ESRD or CDI. We used the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes to identify and evaluate cases with these diagnoses in the NIS database. We extracted all entries with a primary or secondary discharge diagnosis of ESRD (*ICD-9-CM* code 585.6) or CDI (008.45). These codes have been used in previous studies to identify cases of ESRD[10] and CDI.[11] Discharge entries with the diagnosis of ESRD were evaluated for associated hemodialysis (39.95) and peritoneal dialysis (54.98) procedure codes. The main outcome variables of in-hospital mortality, length of hospital stay, and hospitalization charges were collected. Age, sex, race, insurance status, and geographic location were obtained for the extracted cases. To evaluate the effect of comorbid conditions, we identified the presence of the most common infections in ESRD patients, pneumonia (480–487), urinary tract infection (UTI; 590.x), and blood stream infection (BSI; bacteremia, 790.7; dialysis catheter-related infections, 996.62).[12,13] In addition, as a global comorbid disease measure, we collected the diagnoses within the Charlson comorbidity index (Deyo modification).[14,15] This is a widely used

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Received September 22, 2011, and in revised form October 26, 2011.
Accepted for publication November 14, 2011.
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This paper was not supported by any grant.

ISSN: 1081-5589
DOI: 10.231/JIM.0b013e318242b313

index to measure comorbid disease burden.[4] The index includes 17 disease states not including pneumonia, UTI, or BSI. Higher scores indicate a greater burden of comorbidity. We modified the total comorbidity score to exclude kidney-related comorbid conditions.

## Statistical Analysis

The extracted cases were placed into 3 mutually exclusive groups: (1) patients with a primary or secondary discharge diagnosis of ESRD but not CDI (ESRD only), (2) patients with a primary or secondary discharge diagnosis of both ESRD and CDI (ESRD + CDI), and (3) patients with a primary or secondary discharge diagnosis of CDI but not ESRD (CDI only).

Statistical analyses were performed using SAS version 9.2 (SAS institute, Cary, NC). Our primary intent was to examine the effect of a concomitant diagnosis of *C. difficile* infection on hospitalization outcomes in ESRD. Discharge weights were used to generate national level estimates. $\chi^2$ tests and analysis of variance were used to compare categorical and continuous variables, respectively, among the 3 groups. Univariate regression was used to identify outcome predictors for mortality and analyze LOS and hospital charges. Outcome variables found to be significant at $P < 0.05$ were used in multiple regression analyses; a logistic regression model was used for the dichotomous variable of in-hospital mortality, and linear regression models were used for the continuous variables of LOS and hospitalization charges. Adjusted odds ratios (aORs) and adjusted regression coefficients were generated. The threshold for significance for these analyses was $P < 0.05$.

## RESULTS

We identified 184,139 cases with ESRD within the database of which 2.8% also had a discharge diagnosis of CDI. In addition, 59,793 cases of CDI without ESRD were identified. For the ESRD cases, 76.5% had associated hemodialysis and 2.6% peritoneal dialysis procedure codes. In the remaining cases (20.9%), the dialysis modality was not available as a discharge procedure code. The incidence of CDI was similar in the hemodialysis and peritoneal dialysis groups (3.0% vs 3.4%; $P = 0.076$). As shown in Table 1, there were significant differences in age, race, comorbid diseases, and, important to this study, outcomes between cases with both ERSD and CDI (ESRD + CDI) and those with ESRD alone (ESRD only). The proportion of in-hospital mortality in patients with ESRD + CDI was more than double that of the patients with ESRD only ($P < 0.001$). The LOS was more than twice as long in those with ESRD + CDI compared to those without CDI ($P < 0.001$). Similarly, hospital charges were approximately 2-fold greater in patients with ESRD + CDI ($P < 0.001$). In addition, for all three of these measures, ESRD + CDI had worse outcomes than those with CDI only ($P < 0.001$).

To more specifically evaluate the effect of CDI in hospitalized patients with ESRD, we analyzed the outcomes of the cohort of ESRD (ESRD only and ESRD + CDI) cases. On univariate analysis a coexisting diagnosis of *C. difficile* in those with ESRD was associated with significantly greater mortality (odds ratio [OR], 2.70; 95% confidence interval [CI], 2.60–2.80; $P < 0.001$). We next performed multiple logistic analyses using the variables found to have a significant association with

**TABLE 1.** Cases, Demographic Details, Comorbid Conditions, and Outcomes of Patients With ESRD and CDI

| | ESRD Only | ESRD + CDI | CDI Only | Comparison: ESRD Only, ESRD + CDI | Comparison: CDI Only, ESRD + CDI |
|---|---|---|---|---|---|
| Cases (Discharges), n | | | | | |
| Unweighted | 178,988 | 5151 | 59,793 | | |
| Weighted | 901,205 | 25,935 | 302,117 | | |
| Age, mean ± SD, yrs | 61 ± 16 | 66 ± 14 | 70 ± 17 | <0.001 | <0.001 |
| Sex, % | | | | | |
| Male | 52 | 51 | 42 | 0.01 | <0.001 |
| Female | 48 | 49 | 58 | 0.01 | <0.001 |
| Race, % | | | | | |
| White | 38.1 | 46.5 | 67.1 | <0.001 | <0.001 |
| African American | 28.6 | 23.6 | 8.8 | <0.001 | <0.001 |
| Hispanic | 13.7 | 12.1 | 6.4 | <0.001 | <0.001 |
| Other | 6.8 | 6.9 | 4.5 | 0.431 | <0.001 |
| Missing | 12.8 | 10.9 | 13.2 | | |
| Charlson Index, % | | | | | |
| 0 | 15.4 | 11.9 | 22.5 | <0.001 | <0.001 |
| 1 | 22.6 | 22.5 | 25.6 | 0.778 | <0.001 |
| 2 | 25.4 | 24.4 | 23.5 | <0.001 | 0.002 |
| ≥3 | 36.6 | 41.1 | 28.3 | <0.001 | <0.001 |
| Infection, % | | | | | |
| UTI | 9.3 | 21.6 | 27.8 | <0.001 | <0.001 |
| Pneumonia | 11.2 | 20.2 | 18.4 | <0.001 | <0.001 |
| BSI | 6.9 | 2.6 | 9.4 | <0.001 | <0.001 |
| Outcome | | | | | |
| Mortality, % | 5.3 | 13.2 | 8.9 | <0.001 | <0.001 |
| LOS, mean, d | 7.1 | 17.3 | 12.4 | <0.001 | <0.001 |
| Charges, mean, $ | 56,663 | 124,846 | 79,327 | <0.001 | <0.001 |

**TABLE 2.** Mortality in the ESRD Cohort (ESRD Only and ESRD + CDI) Using Multivariate Logistic Regression

| Variable | Reference Group | Odds Ratio | Confidence Interval (95%) | Significance (*P*) |
|---|---|---|---|---|
| Age, yrs | | | | |
| 36–50 | 18–35 | 1.51 | 1.40–1.63 | <0.001 |
| 51–65 | | 2.40 | 2.23–2.57 | <0.001 |
| ≥66 | | 4.35 | 4.06–4.67 | <0.001 |
| Male | Female | 1.1 | 1.08–1.13 | <0.001 |
| Charlson Index | | | | |
| 1 | 0 | 1.32 | 1.27–1.37 | <0.001 |
| 2 | | 1.31 | 1.26–1.36 | <0.001 |
| ≥3 | | 1.90 | 1.83–1.97 | <0.001 |
| UTI | Without UTI | 1.33 | 1.29–1.37 | <0.001 |
| Pneumonia | Without pneumonia | 2.68 | 2.62–2.74 | <0.001 |
| BSI | Without BSI | 1.15 | 1.11–1.19 | <0.001 |
| CDI | Without CDI | 2.15 | 2.07–2.24 | <0.001 |

greater mortality on univariate analysis including age, sex, race, insurance status, geographic location, pneumonia, UTI, BSI, and Charlson comorbidity index. After adjusting for the indicated variables in a multiple logistic regression model, CDI remained independently associated with in-hospital mortality (aOR, 2.15; 95% CI, 2.07–2.24; $P < 0.001$; Table 2). Other independent variables significantly associated with in-hospital mortality included advanced age, a greater comorbid burden, and the presence of UTI, BSI, and pneumonia (Table 2). Sex and insurance status did not remain significantly associated with mortality in the final regression model. Among racial groups, Hispanic patients had the lowest mortality (aOR, 0.82; 95% CI, 0.80–0.85; $P < 0.001$; reference group, whites). Patients from the Midwest region had a lower mortality than patients from the Northeast (aOR, 0.80; 95% CI, 0.78–0.83; $P < 0.001$).

Additionally, multiple linear regression modeling revealed that compared to patients with only ESRD, patients with ESRD + CDI experienced significantly longer hospitalizations (mean difference, 9.4 days, 95% CI, 9.2–9.5; $P < 0.001$) and greater hospital charges (mean difference, $62,824; 95% CI, 61,615–64,033; $P < 0.001$).

To help address whether our logistic multiple regression model accounted for all variables significantly associated with mortality, we performed a secondary analysis including LOS, one of our outcome variables, in the model. This was based on the postulate that a situation leading to a prolonged hospital stay might be associated with increased mortality, whereas the longer hospitalization itself increased the risk of CDI. To this end, we found that LOS was associated with a slight increase in mortality (aOR, 1.02; 95% CI, 1.02–1.02; $P < 0.001$). However, CDI remained significantly associated with mortality (aOR, 1.71; 95% CI, 1.64–1.78; $P$ <0 .001) when LOS was adjusted for in the logistic multiple regression model for mortality.

## DISCUSSION

In this study, our goal was to evaluate the effect of CDI on the hospital outcomes of patients with ESRD. Therefore, we interrogated a database containing information from approximately 8 million hospital stays from 1000 hospitals for all cases of ESRD and CDI and extracted information regarding outcomes and potential confounding variables. The database used in this study (NIS) has been used in a similar manner by other investigators.[4,10] Major strengths of this database include a large number of entered cases, the unbiased manner in which the data are collected (eg, all payers, no a priori plan for data analysis), the inclusion of cases from hospitals throughout the United States including public hospitals and academic medical centers, and the ability to adjust the data to achieve national level estimates.

Multiple regression analyses of the extracted data demonstrates that CDI is associated with approximately 2 times greater in-hospital mortality, 9.5 days longer hospital stay, and $63,000 in additional charges in patients with ESRD. We feel these results are robust in that we evaluated a large number of cases and controlled for variables that might affect patient outcomes such as age, sex, geographic location, insurance status, race, common infections, and comorbid disease burden. We did not perform secondary analyses to evaluate the association of adverse outcomes with dialysis modality owing to the large amount of missing data. In this regard, the calculated incidence of CDI in the cases with hemodialysis and peritoneal dialysis procedure codes must be interpreted with caution. We used the Charlson comorbidity index as a means to measure overall disease burden; however, this index might be insufficient to account for all the comorbidities in the patient cohort[4,15] and is a limitation of this study. To partially address this limitation, we performed a secondary analysis including LOS as a predictor variable. On this analysis, CDI continued to be significantly associated with mortality. The association of CDI with worse outcomes for a specific disease is not unique to ESRD, as a similar association has been described for cirrhosis.[4] As expected, advanced age, other infections (pneumonia, UTI, and BSI), and the presence of a greater comorbid disease burden were independent risk factors for mortality. These conditions have been reported to be associated with poor outcomes in patients with ESRD.[16,17] The reasons for the observed adverse effect of CDI on the outcomes are not clear. We can speculate that patients with ESRD might be more vulnerable to diarrhea-induced perturbations in fluid and electrolyte or the systemic inflammatory response associated with severe cases of CDI than the general hospitalized patient population.[18]

In summary, this is the first study using multi-institutional data to evaluate the effect of CDI on the outcomes of patients with ESRD. Our results strongly implicate CDI as a complicating factor that results in significantly worse outcomes in hospitalized patients with ESRD. Consideration of this finding with previous reports that patients with ESRD are predisposed to CDI indicates that there should be ongoing efforts to reduce the risk of acquiring this infection and enhanced awareness for its diagnosis and prompt treatment.

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