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# Clostridioides difficile Infection in Chronic Kidney Disease/End-Stage Renal Disease

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# *Clostridioides difficile* Infection in Chronic Kidney Disease/End-Stage Renal Disease



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***Clostridioides difficile*** **infection (CDI) is a major health-care burden and increasingly seen in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Increased antibiotic use, alteration in host defenses, and gastric acid suppression are some of the etiologies for increased risk of CDI in these populations. Patients with CKD/ESRD have a higher risk of initial episode, recurrence, and development of severe CDI than those without CKD or ESRD. Diagnosis and management of CDI in patients with CKD/ESRD are similar to that in the general population. The mortality, length of stay, and health-care costs are higher in patients with CDI and CKD/ESRD. Antimicrobial stewardship with reduction in antibiotic use along with infection-control measures such as contact isolation and hand hygiene with soap and water is essential in the control and prevention of CDI in patients with CKD/ESRD.**



**Key Words:** *Clostridioides difficile* infection, End-stage renal disease, Fecal microbiota transplantation

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) represent major health-care problems with significant morbidity and cost. In patients with CKD/ESRD, infections are common, and consequently antibiotic exposure is increased.[1,2] *Clostridioides difficile* (previously *Clostridium difficile*) infection (CDI) is the most common cause of heath-care–associated diarrhea. CKD and ESRD are now recognized as risk factors for CDI.[3] CKD/ESRD also increases the risk for recurrent CDI and is associated with higher mortality.[4] CDI in patients with CKD/ESRD also adds to the duration of hospitalization and cost.[5] Reducing antibiotic use and enforcing stricter infection-control policies are essential to prevent CDI in this population.[6]

## OVERVIEW OF CDI

*Clostridioides difficile* is a gram-positive, anaerobic, spore-forming, toxin-producing bacterium and causes antibiotic-associated diarrhea and colitis. Typically, colonization of the intestine occurs via the fecal-oral route. Disruption of normal intestinal microbiota (dysbiosis), usually by antibiotics, can result in CDI.[7] Colonization of *C. difficile* is facilitated in patients with intestinal dysbiosis by pathogenic toxin production and altered host immune responses.[7] Well-established risk factors for CDI include advanced age (>65 years), health-care exposure, hospitalization, and antibiotic use[6] (Table 1). CDI can manifest as a spectrum of clinical manifestations from asymptomatic carriage to fulminant colitis.[6] Typically, it results in watery diarrhea (≥3 episodes of loose stools in 24 hours) with associated low-grade fever, lower abdominal pain, and leukocytosis. The diagnosis of CDI is ideally established by a stepwise algorithm of initial, positive stool testing for glutamate dehydrogenase and *C. difficile* toxins A and B by enzyme immunoassay (EIA) and reflexed to nucleic acid amplification (NAAT) testing for the toxin B gene in case of indeterminate EIA results.[6] Ordering and interpretation of stool testing for CDI should be based on pretest probability, which involves the presence of diarrhea and a change in characteristic of the stools from baseline. Management strategies include discontinuation of the inciting antibiotic followed by the administration of oral vancomycin or fidaxomicin.[6] Adherence to strict infection-control policies such as contact precautions and hand hygiene with soap and water is critical for prevention of nosocomial transmission.[6]

## RISK OF INFECTIONS IN CKD/ESRD

The appearance of immune dysfunction is common in advanced CKD and particularly during ESRD. Alterations in both the innate and adaptive immune systems occur in CKD/ESRD cases, with consequent increased risk of bacterial infections.[8]

Infections are common in patients with ESRD at a rate of 5.7 events per 1000 dialysis-days.[2] Urinary tract infections, pneumonia, and sepsis from central venous catheters are the most common infections in patients with ESRD.[1] Patients with ESRD are often hospitalized at least twice a year, with a 30-day readmission rate of 35%, an increased length of stay, and 2%-5% risk of nosocomial infections.[2,9] These factors result in excessive antibiotic use and consequently an increased risk of CDI. Patients with ESRD are also at risk of infection due to multidrug-resistant organisms, and antibiotic stewardship practices are required to curtail the overuse of broad-spectrum antibacterial agents.[10] The most likely risk factors for CDI in patients with CKD/ESRD include impaired immune function, increased antibiotic exposure, and gastric acid suppression.

## EPIDEMIOLOGY OF CDI IN CKD/ESRD

A 14% prevalence of CKD in the United States has been reported over the past decade, with increasing diagnosis of ESRD.[9,11] Patients with CKD/ESRD are especially vulnerable to the development of CDI, attributable to

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frequent antibiotic exposure and other associated risk factors. CDI and recurrent CDI have long been reported in patients with CKD and ESRD. In a hospital environment, the incidence of CDI was higher in the nephrology department than in other departments as documented in an older, retrospective study.[12]

Based on the US National Hospital Discharge Survey (NHDS), 5% of 162 million patients discharged from 2005 to 2009 had CKD. CDI occurred at a rate of 1.49% compared with 0.70% in patients with and without CKD, respectively.[4] Patients with ESRD were twice as likely to develop CDI compared with non-CKD patients in this study ($P < 0.001$). In a study of all adult patients with a discharge diagnosis of ESRD or CDI from the US Nationwide Inpatient Sample 2009 database, CDI appeared in 2.8% of individuals with ESRD.[13] A meta-analysis of 20 case-control, cohort, and cross-sectional studies revealed pooled relative risks (RRs) of primary CDI of 1.95 (95% confidence interval [CI], 1.81 to 2.10) and 2.63 (95% CI, 2.04 to 3.38) in patients with CKD and ESRD, respectively.[14]

In a case-control study of 188 patients with CDI compared with age- and sex-matched controls without CDI, no significant difference occurred in prevalence of advanced CKD (odds ratio [OR], 1.38; 95% CI, 0.90 to 2.12; $P = 0.137$).[15] However, patients with ESRD undergoing dialysis had a significant association (OR, 2.60; 95% CI, 1.25 to 5.41; $P = 0.017$). Advanced CKD increased CDI risk was recorded in a South Korean study of CDI-positive patients ($n = 171$) and CDI-negative age- and sex-matched controls ($n = 342$). Patients with stages 4/5 CKD who were not undergoing renal replacement therapy by dialysis and patients with ESRD who were on dialysis had respective ORs of 2.9 and 4.9 for the risk of CDI.[16] This differential rate of CDI was also detected in another recent, retrospective analysis from Poland in which 67% of patients who tested positive for CDI had CKD stage 5 compared with 5.7% who had CKD stage 1.[17] The NHDS database revealed that CDI rates were greater with advancing CKD: 43.5% in CKD stage 5 on renal replacement therapy; 21.2% in CKD stages 3, 4, and 5; and only 2.46% in CKD stages 1 and 2.[4]

**CLINICAL SUMMARY**

- The epidemiology of *Clostridioides difficile* infection (CDI) identifies the greater disease burden in chronic kidney disease (CKD)/end-stage renal disease (ESRD).
- Diagnosis and management of CDI in patients with CKD/ESRD are similar to that in the general population.
- Patients with CKD/ESRD have greater risks of recurrent and severe CDI, and both are associated with greater mortality, length of hospitalization, and health-care costs.
- Infection-control and antimicrobial stewardship measures are essential for control of CDI in the CKD/ESRD population.

## CLINICAL MANIFESTATIONS, DIAGNOSIS, AND MANAGEMENT OF CDI IN CKD/ESRD

CDI may unfold a spectrum of clinical manifestations from asymptomatic carriage to mild diarrhea, severe disease with pseudomembranous colitis, or even fulminant colitis with death. The clinical manifestations of CDI in patients with CKD are similar to those experienced by the general population. However, patients with advanced CKD and ESRD are more likely to develop severe CDI. This concept was illustrated in uremic patients who developed severe CDI with systemic toxicity.[18] The various clinical manifestations of CDI are detailed in Table 2.

Asymptomatic carriage is more common in patients with CKD. Patients without diarrhea admitted to 2 tertiary care hospitals in Australia had higher risk of colonization with toxigenic and nontoxigenic *C. difficile* when CKD was one of the clinical diagnoses.[19] Most patients with CKD or ESRD present with multiple episodes of watery diarrhea with mucus and/or foul odor. Associated clinical manifestations include lower abdominal pain/cramps, low-grade fever, volume depletion, electrolyte imbalance, and leukocytosis. Most individuals have an indolent course, whereas others may develop a severe disease that can progress to toxic megacolon and/or intestinal perforation and death.

The diagnosis of CDI should be suspected in patients with ≥3 episodes of loose stools in a 24-h period, with a change in the character of stool from baseline (usually loose stools with mucus and foul odor). Although stool testing for *C. difficile* toxin B gene by NAAT is highly sensitive, it is unable to differentiate between asymptomatic colonization and active infection. An ideal approach to stool testing for CDI (in patients experiencing diarrhea) may be a stepwise algorithm involving a combination of EIA for glutamate dehydrogenase/toxin testing with reflex NAAT testing in case of indeterminate EIA results.[6] The characteristics of general tests used for diagnosing CDI are displayed in Table 3. Currently, repeat stool testing for CDI is not recommended within 7 days of the same diarrheal episode.[6] Clinical cure is achieved with resolution of diarrhea. Stool-testing modalities should be avoided as demonstrative of "cure" because of high false-positive rates after an initial episode of CDI. Imaging modalities including computed tomography of the abdomen/pelvis and lower gastrointestinal endoscopy for recognition of mucosal pseudomembranes can be used in selected patients.

The primary management of CDI should include discontinuation of the inciting antibiotic where applicable. For an initial episode of CDI, oral vancomycin (125 mg every 6 hours) or fidaxomicin (200 mg every 12 hours) is preferred over oral metronidazole (500 mg every 8 hours).[6] The treatment duration for most patients with CDI is 10 days. For fulminant CDI, a high dose of oral vancomycin (500 mg every 6 hours) with intravenous metronidazole is recommended, although supporting data are limited.[6] In a *post hoc* analysis of 2 randomized, controlled phase 3 clinical trials of vancomycin vs fidaxomicin therapy as a treatment of CDI, the time to resolution of diarrhea was greater for CKD stages 3 or 4 than that for stage 2.[20] Also, patients with CKD stage 3 or higher with

**Table 1. Risk Factors for *Clostridioides difficile* Infection**

| Traditional | Additional |
|---|---|
| Age > 65 years | Contact with active carriers |
| Recent hospitalization | Consumption of contaminated food products such as processed meats |
| Increased hospital length of stay | Hypoalbuminemia |
| Long-term health-care facility residence | Use of proton-pump inhibitors |
| Antibiotic exposure | Gastrointestinal endoscopic procedures |
| Comorbidities such as malignancy, CKD/ESRD, inflammatory bowel disease, immunosuppression | Enteral tube feeding |

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease.
Data from McDonald et al.[6]

CDI had lower odds of cure and greater probability of recurrence. Cure rates were similar in both vancomycin and fidaxomicin groups. Notably, the vancomycin group had higher recurrence rates, independent of renal function. No dose adjustment is needed for oral vancomycin or fidaxomicin in patients with CKD/ESRD due to lack of absorption from gut lumen. Intravenous vancomycin has no role in the management of CDI.

Surgical management in the form of subtotal colectomy with preservation of the rectum is generally reserved for cases with fulminant CDI with acute abdomen, megacolon, perforation, or septic shock with organ dysfunction.[6] An alternative procedure of loop ileostomy with antegrade vancomycin lavage is a less morbid and colon-preserving procedure.[21] Probiotics have been helpful in prevention of antibiotic-associated diarrhea but are of minimal benefit in prevention of CDI.[6] Anion-binding resins are not recommended in the acute management of CDI.[6]

## RECURRENT CDI IN PATIENTS WITH CKD/ESRD

CDI is considered as recurrent when the infection occurs within 8 weeks of onset of the index infection.[6] Severe and recurrent CDIs have been reported in patients with CKD. After treatment of CDI, the risk of recurrence is at least 20%, with a possibly greater risk in patients with CKD/ESRD. In a meta-analysis of 20 case-control, cohort, and cross-sectional studies, the pooled RR of recurrent CDI in patients with CKD was 2.61 (95% CI, 1.53 to 4.44).[14] The risk of recurrence increases as episodes of CDI increase. The risk factors for recurrent CDI in patients with CKD/ESRD includes age over 65 years, repeat antibiotic exposure, and severe primary CDI (similar to patients without CKD/ESRD).

Treatment of the initial episode of recurrent CDI repeats the standard course of oral vancomycin or fidaxomicin.[6] Additional recurrences are generally treated with a tapered and pulsed course of oral vancomycin.[6] Oral vancomycin followed by a rifaximin "chaser" is an alternative strategy.[6] Fecal microbiota transplantation (FMT) is increasingly used as treatment for recurrent CDI for the prevention of recurrences in persons who have failed multiple courses of antibiotics.[6]

**Table 2. Clinical Manifestations of *Clostridioides difficile* Infection (CDI)**

| Asymptomatic Carriage | No Clinical Symptoms With Positive Stool Testing for CDI |
|---|---|
| Mild to moderate | Peripheral blood white blood cell count $< 15 \times 10^9$/L, serum creatinine level < 1.5 mg/dL |
| Severe | Peripheral blood white blood cell count $\geq 15 \times 10^9$/L, serum creatinine level > 1.5 mg/dL |
| Fulminant | Severe hypotension, shock, ileus, or megacolon |

Data from McDonald et al.[6]

## NOVEL THERAPIES FOR CDI IN PATIENTS WITH CKD/ESRD

Bezlotoxumab (Merck and Co.) is a monoclonal antibody directed against toxin B of *C. difficile*. This antibody was recently approved by the Food and Drug Administration for prevention of relapsing CDI.[22] Bezlotoxumab is administered as a single, intravenous dose (10 mg/kg) to provide passive immunity for at least 3 months' duration in patients with a history of CDI. It reduces the risk of an initial posttreatment CDI relapse by 40% compared with standard antibiotic treatment.[22] The global phase 3 clinical trials, MODIFY I and MODIFY II, determined the safety and efficacy of bezlotoxumab and included patients with CKD. However, the trials were not specifically designed to determine benefits in patients with CKD.[23] Bezlotoxumab is beneficial when given during the standard treatment of CDI and reduces the risk of recurrence in 1 of 6-10 patients compared with standard antibiotic therapy. The cost of this agent must be weighed against the expense for other *C. difficile* treatment modalities such as FMT.

FMT is currently recommended to prevent further relapse in patients with more than 2 episodes of CDI. FMT is considered safe, effective, and durable.[6] FMT repairs the intestinal dysbiosis of CDI via administration of microbiota from a healthy prescreened donor. Clinical trials reported a success rate of FMT ranging from 44% to 96% for the prevention of recurrent CDI, applying various formulations of FMT including fresh, frozen, and encapsulated organisms via inoculation by several delivery routes (oral, nasogastric/duodenal, enema, or colonoscopy).[24,25] Patients with CKD and ESRD have been included in multiple clinical trials and anecdotal case series of FMT for the management of CDI. The role of FMT to treat primary and refractory CDI or severe/complicated CDI remains anecdotal at present. Commercial microbiota products, including RBX2660 and SER 109/262, for the treatment of recurrent CDI are in clinical trial stages.[26,27]

Several new drugs such as ridinilazole are undergoing evaluation in clinical trials for treatment/prevention of relapse in CDI.[28] Vaccines containing formalin-inactivated toxins A and B and recombinant toxins against CDI are also being investigated in clinical trials.[29,30] Nontoxigenic *C. difficile* strains such as Nontoxigenic *C.*

**Table 3. Common Clinical Testing for *Clostridioides difficile* Infection**

| Test | Detected Substance | Sensitivity | Specificity |
|---|---|---|---|
| Toxin A and B enzyme immunoassays (EIAs) | Free toxins | Low | Moderate |
| Glutamate dehydrogenase (usually combined with EIAs for toxins) | *Clostridioides difficile* common antigen | High | Low |
| Nucleic acid amplification test | *Clostridioides difficile* gene for toxin | High | Low |

Modified and reprinted from McDonald et al.[6]

*difficile*–M3 spores have been successful in preventing recurrent CDI in a phase 2 clinical trial.[30]

## OUTCOMES AND COST OF CDI IN PATIENTS WITH CKD/ESRD

CDI is associated with significant morbidity/mortality, hospital length of stay, and health-care–related costs. An analysis of the US NHDS database disclosed that CKD patients with CDI compared with uninfected CKD patients had longer hospitalizations, higher colectomy rates (adjusted OR [aOR], 2.30; 95% CI, 2.14 to 2.47), discharges to a health-care facility (aOR, 2.22; 95% CI, 2.19 to 2.25), and increased in-hospital mortality (aOR, 1.55; 95% CI, 1.52 to 1.59; all $P < 0.001$).[4] In a meta-analysis of 4 cohort studies with more than 8 million participants, the pooled RR of mortality attributed to CDI was 1.73 (95% CI, 1.39 to 2.15) in patients with CKD.[31] In the same analysis, patients with ESRD had a pooled RR of mortality of 2.15 (95% CI, 2.07 to 2.23). In a retrospective, case-control study, patients with advanced CKD (estimated glomerular filtration rate $< 30$ mL/min per 1.73 $m^2$) experienced greater in-hospital mortality.[16] In the US Nationwide Inpatient Sample database, all-cause, unadjusted in-hospital mortality was significantly greater for CDI patients with ESRD than for those without CDI (11.6% vs 7.7%; $P < 0.001$).[13] ESRD patients with CDI had longer hospitalization by 2 days and greater hospitalization costs than the non-ESRD group ($35,588 USD vs $23,505 USD, indexed to the value of the 2013 dollar; $P < 0.001$).[5] In an analysis of hospital episode data from 4 European countries, patients with comorbidities including CKD, chronic obstructive pulmonary disease, heart failure, and diabetes had increased length of stay attributable to the diagnosis of CDI.[32]

## INFECTION CONTROL MEASURES FOR CDI IN PATIENTS WITH CKD/ESRD

Patients with suspected CDI should be immediately placed in contact isolation requiring gloves/gowns, with pending stool test results.[6] Hand hygiene should be performed with soap and water during the care of patients with CDI. Soap and water handwashing is more effective in eliminating *C. difficile* spores than alcohol-based hand sanitizers.[6] Contact isolation may be discontinued after 48 hours after the disappearance of diarrhea.[6] CDI incidence rates decreased significantly (by 33% to >90%) after implementation of an antimicrobial stewardship program involving the reduction of antibiotic use. This observation was concluded from the results of 15 quasiexperimental studies published between 1994 and 2013.[6] Antimicrobial stewardship that stringently minimizes high-risk antibiotic use will facilitate the reduction of CDI in all patients, including those with CKD/ESRD.

## CONCLUSION

CDI is more common in patients with CKD/ESRD and is associated with more severe disease and increased mortality. Length of hospitalization and health-care costs escalate after the development of CDI in patients with CKD/ESRD. Management of CDI is similar in patients with or without CKD/ESRD. Oral vancomycin or fidaxomicin is favored over oral metronidazole in the initial management as per the current CDI guidelines.[6] Stricter adherence to infection-control measures and antimicrobial stewardship practices will reduce the burden of CDI in the CKD/ESRD population.

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