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Major article

Recurrent *Clostridium difficile* infection in intensive care unit patients

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Background: The purpose of this study was to assess the 12-week cumulative incidence of recurrent *Clostridium difficile* infection (rCDI) and identify risk factors for rCDI in patients that acquired index *C difficile* infection (CDI) while in the intensive care unit (ICU).

Methods: This retrospective single-center cohort study reviewed adult patients from 6 different ICUs who developed a CDI between February 2010 and September 2013.

Results: Out of 162 included ICU patients, 34 experienced rCDI. Risk of rCDI was higher in the ICU versus non-ICU group (21% vs 17%, $P = .03$). The incidence of rCDI was highest in the surgical intensive care unit (SICU) at 43.8%. A multivariable logistic regression model was constructed and identified 5 significant risk factors for rCDI: previous CDI (odds ratio [OR], 8.03; 95% confidence interval [CI], 1.90-34.02; $P = .005$), log10 ICU length of stay in days (OR, 3.67; 95% CI, 1.13-11.85; $P = .03$), acquisition of CDI in the medical intensive care unit (MICU) (OR, 5.35; 95% CI, 1.60-17.85; $P = .006$) or SICU (OR, 15.30; 95% CI, 4.09-57.23; $P < .001$), and chronic obstructive pulmonary disease (COPD) (OR, 3.55; 95% CI, 1.41-8.94; $P = .007$).

Conclusion: ICU adults had a significantly higher 12-week incidence of rCDI than non-ICU patients. Risk factors for rCDI after acquisition of infection in an ICU include MICU and SICU patients, previous CDI, COPD, and length of stay.

Clostridium difficile infection (CDI) is a significant cause of morbidity and mortality[1,2] and is the most common nosocomial infection in the United States.[3] The estimated attributable costs of CDI range from $3,197-$11,868 per case, with associated annual costs of $1-$3.6 billion.[4] A significant proportion of costs are attributed to the treatment of recurrent disease because approximately 25% of patients will have recurrence after initial cure.[5] Risk factors for recurrent *C difficile* infection (rCDI) are common among intensive care unit (ICU) patients and include antibiotic exposure, gastric acid suppression, increased contact with the health care system, advanced age, and impaired immune response.[5] There are limited data defining the incidence of rCDI in ICU patients and associated risk factors.[6] Identifying patients at high risk for recurrence could lead to targeted interventional strategies to minimize rCDI and rehospitalization.

MATERIALS AND METHODS

Study location and patient population

This single-center retrospective cohort study was conducted at the University of Michigan Hospitals and Health System and received investigational review board approval. Adult patients diagnosed with CDI during their ICU stay from February 2010-September 2013 were eligible for inclusion. Patients from 6 adult ICUs were included: medical, surgical, trauma-burn, neurology, cardiac, and cardiothoracic surgery. Patients were excluded if CDI

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was diagnosed before ICU admission. Patients who died during their ICU stay were excluded from the risk factor analysis for rCDI.

Microbiologic data

Diarrheal stool testing was performed using a 3-step algorithm, previously shown to have excellent performance characteristics, including a negative predictive value of 99%.[7] The first 2 steps were performed concurrently using the C. DIFF QUIK CHEK COMPLETE test (TECHLAB, Blacksburg, VA) for *C difficile* glutamate dehydrogenase antigen and toxins A or B by enzyme immunoassay. If discordant (glutamate dehydrogenase positive and toxin negative), stools were then subjected to analysis by the third step, detection of the *tcdB* gene by real-time polymerase chain reaction (BD GeneOhm Cdiff Assay; BD, Franklin Lakes, NJ).

Definitions

CDI was defined as diarrhea plus positive testing for *C difficile* in stool, for the index CDI case and rCDI case. Recurrence was defined as a repeat positive CDI diagnosis within 12 weeks after completion of antibiotic therapy for the index CDI episode. Severe CDI was defined as white blood cell count $\geq$15,000 cells/μL or serum creatinine $\geq$1.5 times the premorbid level. Complicated CDI was defined by the presence of septic shock-hypotension (need for vasopressor supportive therapy [norepinephrine, epinephrine, phenylephrine, dopamine, or vasopressin]), ileus, or toxic megacolon. History of CDI was defined as having a CDI episode within the last year prior to the index CDI episode in the ICU. Immunosuppressive disease was defined as documentation of any of the following conditions in the patient's medical record: solid organ transplant, HIV, acquired immune deficiency syndrome, or any active cancer.

Exposure to antibiotics, corticosteroids, acid-suppressive therapy, or vasopressors was defined as administration within 3 days prior until 14 days after the positive CDI assay. Acid-suppressive therapies included proton-pump inhibitors and histamine-2 receptor antagonists. Steroid use was categorized into low dose, treatment, and chronic. A prednisone dose of <20 mg/d (or steroid equivalent) defined the low-dose steroid group, whereas prednisone $\geq$20 mg/d (or steroid equivalent) defined the treatment steroid group. Chronic steroid use was defined as administration of any steroid for at least 4 weeks.

Study design and data collection

In this single-center retrospective cohort study, the primary objective was to evaluate the 12-week cumulative incidence of rCDI and risk factors for recurrence in ICU patients. The ICU population was divided into 2 groups: nonrecurrent *C difficile* infection (nrCDI) versus rCDI. Patients did not have to be in the ICU for their rCDI but must have had their initial case in the ICU. Data collection included patient demographics, course and treatment of CDI, and traditional and potential ICU-specific risk factors. Potential ICU-specific risk factors assessed included length of ICU stay; exposure to vasopressors, mechanical ventilation, tube feeds, or extracorporeal membrane oxygenation; and renal replacement therapy (RRT). RRT included hemodialysis, peritoneal dialysis, or continuous RRT.

Statistical analysis

All analyses were done in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Data were first checked for consistency and out-of-range values and were explored with descriptive statistics, including measures of central tendency spread for continuous variables and proportions for categorical variables. Different variable constructions and transformations were also explored and incorporated if thought to better fit the data. Simple logistic regression was used to model the primary outcome, rCDI, with individual covariates.

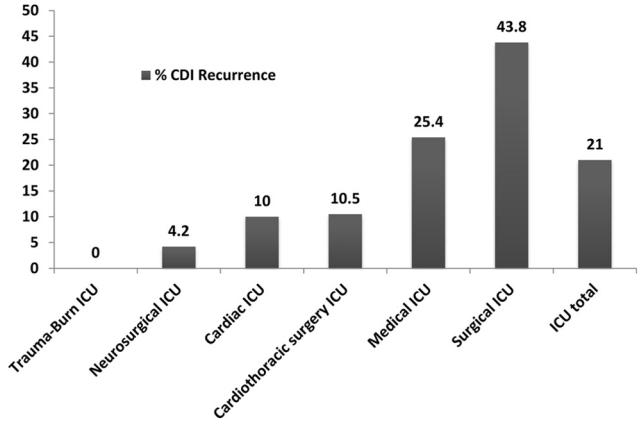

Fig 1. Cumulative incidence of CDI recurrence: overall 12-week incidence of recurrence stratified by patients located in non-ICU versus ICU units and further divided by specific ICU unit. Risk of developing recurrent CDI was significantly greater in the ICU versus non-ICU population ($P = .031$). *CDI*, *Clostridium difficile* infection; *ICU*, intensive care unit.

A multivariable predictive model was constructed via backward elimination using a χ^2 test on the likelihood ratios and an α of <0.1. Candidate variables included all of those tested in univariate analysis, with the exception of those with null values or a $P > .90$. Additional covariates with a priori study or clinical significance were added to the resulting model if not already present and considered for inclusion based on the results. Tests for collinearity included examination of variance inflation factors and effects on other terms during stepwise model construction. Interactions between all terms in the final model were also tested.

Model fit was assessed using the Hosmer-Lemeshow test. Receiver operator characteristic curves were constructed and the area under the curve was calculated along with bootstrapped confidence intervals (10,000 replicates) for specificity using the R package pROC. To better assess the precision of our estimates, the confidence intervals for the odds ratios in the final model were bootstrapped with 10,000 replicates using the R package boot and a bias-corrected accelerated bootstrapping method.

RESULTS

There were 2,931 CDI cases in our health system (inpatient and outpatient) between February 2010 and September 2013, including 162 patients in the ICU that met inclusion criteria. A total of 86 patients with CDI expired during the ICU stay and were excluded. Cumulative incidence of rCDI was higher in ICU patients than non-ICU patients (20.8% vs 17%, $P = .031$). Of the cases in the ICU, approximately 50% of patients experienced rCDI within 4 weeks after finishing CDI therapy. Patients in the surgical intensive care unit (SICU) experienced the highest incidence of rCDI (43.8%) followed by medical intensive care unit (MICU) patients (25.4%) (Fig. 1). The rCDI risk in the cardiothoracic-surgical, cardiovascular, trauma-burn, and neurology ICUs was <11%. Median ICU length of stay for the rCDI cohort was greater than the nrCDI group (25.5 vs 18.5 days, $P = .08$). Demographics between ICU patients categorized into the rCDI and nrCDI groups were generally similar (Table 1). No differences were noted in age, sex, ethnicity, antibiotic exposure, underlying immunosuppression, CDI disease severity, CDI