Title

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Clostridium Difficile Colitis in the United States: A Decade of Trends, Outcomes, Risk Factors for Colectomy, and Mortality after Colectomy

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BACKGROUND: Clostridium difficile colitis (CDC) is a major health concern in the United States (US), with earlier reports demonstrating a rising incidence. Studies analyzing predictors for total colectomy and mortality after colectomy are limited by small numbers.

STUDY DESIGN: The Nationwide Inpatient Sample (NIS) 2001 to 2010 was retrospectively reviewed for CDC trends, the associated colectomy and mortality rates. Patient and hospital variables were used in the LASSO algorithm for logistic regression with 10-fold cross validation to build a predictive model for colectomy requirement and mortality after colectomy. The association of colectomy

day with mortality was also examined on multivariable logistic regression analysis.
RESULTS: An estimated 2,773,521 discharges with a diagnosis of CDC were identified in the US over a decade. Colectomy was required in 19,374 cases (0.7%), with an associated mortality of 30.7%. Compared with the 2001 to 2005 period, the 2006 to 2010 period witnessed a 47% increase in the rate of CDC and a 32% increase in the rate of colectomies. The LASSO algorithm identified the following predictors for colectomy: coagulopathy (odds ratio [OR] 2.71), weight loss (OR 2.25), teaching hospitals (OR 1.37), fluid or electrolyte disorders (OR 1.31), and large hospitals (OR 1.18). The predictors of mortality after colectomy were: coagulopathy (OR 2.38), age greater than 60 years (OR 1.97), acute renal failure (OR 1.67), respiratory failure (OR 1.61), sepsis (OR 1.40), peripheral vascular disease (OR 1.39), and congestive heart failure (OR 1.25). Surgery more than 3 days after admission was associated with higher mortality rates (OR 1.09; 95% CI 1.05 to 1.14; $p < 0.05$).

CONCLUSIONS: Clostridium difficile colitis is increasing in the US, with an associated increase in total colectomies. Mortality rates after colectomy remain elevated. Progression to colectomy and mortality thereafter are associated with several patient and hospital factors. Knowledge of these risk factors may help in risk-stratification and counseling.

Clostridium difficile is a spore-forming gram-positive anaerobic bacterium thought to be responsible for 15% to 25% of antibiotic-associated diarrhea in the United States.[1] Several epidemiologic studies have reported rising numbers of both community and nosocomially acquired Clostridium difficile colitis (CDC) as well as an increased emergence of hypervirulent strains.[2-4] In some parts of the United States, CDC is now the most common cause of health care-associated infections.[5]

Abbreviations and Acronyms
CDC = Clostridium difficile colitis
NIS = Nationwide Inpatient Sample
OR = odds ratio

Although uncomplicated cases of CDC have been traditionally managed with metronidazole and oral vancomycin, recent reports suggest that hypervirulent strains of C. difficile are increasingly resistant to medical management. [6,7] Failure of medical management may lead to fulminant colitis and high mortality rates.[6,8] Surgical management in the form of total colectomy can become necessary and is thought to be required in 3% to 5% of fulminant CDC.[9-11] Unfortunately, colectomy for fulminant CDC is associated with high mortality rates ranging from 34% to 80 %.[11-18]

So it becomes important to identify patients with CDC who are likely to progress to fulminant colitis and subsequent colectomy, as well as patients at high risk for fatal outcomes after surgical management. Although these factors have been analyzed in small single-center series with significant disparities in the results, [9,11,19-23] there are currently no population-based studies analyzing these factors in different settings. Moreover, there are no recent population-based studies examining the trends of CDC and the associated colectomy rates in the United States. The purpose of this large retrospective review was to examine the most recent trends of CDC hospitalizations, the associated colectomy rates, and mortality after colectomy over a decade in the United States. The risk factors predictive of progression to total colectomy as well as the optimal timing of surgery are analyzed. Finally, the outcomes of colectomy for CDC and the predictors of mortality after surgery are presented. Knowledge of these risk factors may help in patient risk stratification and surgical decision-making.

METHODS

Study population

The Healthcare Cost and Utilization Project (HCUP)-Nationwide Inpatient Sample (NIS) database was retrospectively reviewed from January 1, 2001 to December 31, 2010 for all patients with a discharge diagnosis of CDC. The NIS is the largest all-payer inpatient care database in the United States containing information from nearly 8 million hospital stays each year across the country. The data set approximates a 20% stratified sample of American community hospitals, resulting in a sampling frame that comprises approximately 95% of all hospital discharges in the country. Data elements within the NIS are drawn from hospital discharge abstracts that allow determination of all diagnoses and procedures performed during a given hospitalization, length of hospital stay, charges, and outcomes. Approval for the use of the NIS patient-level data in this study was obtained from the institutional review board of the University of California Irvine and the NIS.

Case selection

Patients with a primary or secondary diagnosis of CDC were identified using the ICD-9 CM diagnosis code 008.45. Patients who underwent total or subtotal colectomy for CDC were further identified using the associated ICD-9 CM procedure codes: 45.79, 45.8, 45.82, and 45.83. The choice of these procedure codes was based on previously published data.4 Patients with missing data for mortality were excluded from the analysis. To minimize the risk for coding errors, patients with concomitant ICD-9 diagnosis codes for ulcerative colitis, cancer, ischemic colitis, and lower gastrointestinal bleeding who had a diagnosis of CDC and underwent total or subtotal colectomy were also excluded from the analysis. Missing data on ethnicity, payer type, and hospital factors were excluded from the analysis as well. Case selection is illustrated in Figure 1.

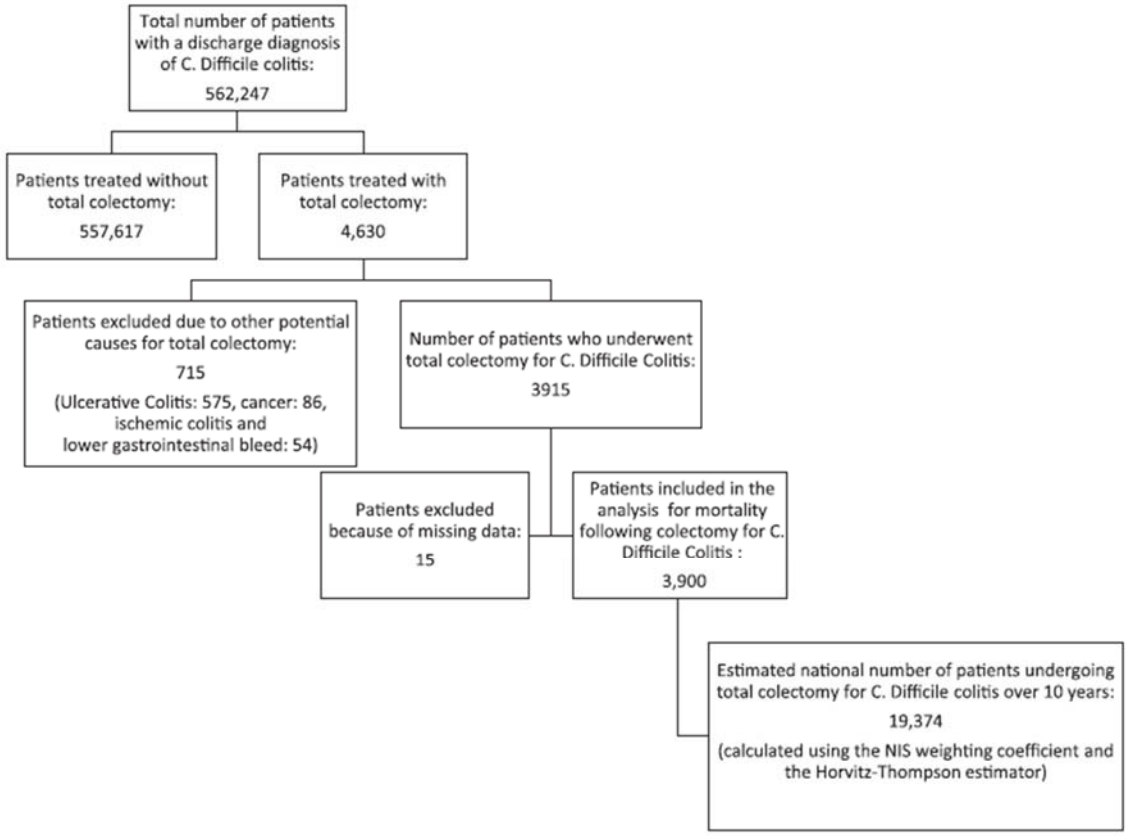


Figure 1. Case selection. Numbers provided are based on the 20% sample provided in the database. Last box in the diagram represent weighted numbers obtained using the Nationwide Inpatient Sample (NIS) weighting coefficient and the Horvitz-Thompson estimator.

Trends analysis

Using weighting coefficients provided by the NIS as well as the Horvitz-Thompson estimator,[24] we calculated the yearly numbers of hospitalizations in the United States for the following endpoints: Hospitalizations with a diagnosis of CDC; total or subtotal colectomy for CDC; and in-hospital mortality after colectomy for CDC. Furthermore, we provided the yearly rate of CDC per 1,000 discharges (calculated by dividing the yearly

numbers of CDC discharges by the yearly number of hospitalizations for all causes in the United States), the rate of colectomy for CDC per 1,000 discharges with a diagnosis of CDC, and the percent in-hospital mortality after colectomy for CDC.

Predictive models

Predictive models were built for the following endpoints: Progression to total colectomy in patients with CDC and mortality after colectomy for CDC. Secondary endpoint
In addition to the predictive models, we used multivariable logistic regression analysis to study the association of colectomy day with in-hospital mortality.

Study variables

The variables we used for the predictive models as well as the multivariable logistic regression analysis can be broadly divided into patient factors and hospital factors. Patient factors included age, sex, ethnicity (excluded from the prediction models), payer type, a list of 30 comorbidity variables provided by the NIS dataset and based on the Elixhauser model,[25] peritonitis, sepsis, and colonic perforation. Hospital factors as provided by the NIS dataset included type (teaching vs nonteaching), location (urban vs rural), and bed size (small vs medium vs large). The definition of hospital type, location, and bed size can be found on the Healthcare Cost and Utilization Project NIS website.[26]

Statistical analysis

Data extraction and statistical analyses were conducted using SAS, version 9.3 and the R Statistical Environment. Patient' demographics and comorbidities, hospital data, and outcomes are summarized using mean and interquartile range for continuous variables, and counts and percentages for categorical variables. Values of p are not reported for these data because information from these variables were unadjusted. In order to examine the association of colectomy day with mortality, we used multivariable logistic regression analysis after controlling for all confounding variables, namely, age, sex, comorbidities, and hospital factors. Statistical significance was declared for $p < 0.05$.

The LASSO algorithm for logistic regression[27] was used to identify predictive variables for colectomy and subsequent mortality in a complete case analysis (excluding ethnicity and missing data). Ten-fold cross-validation together with the 1-SE rule were used to determine the model size (number of variables) in order to control for overfitting.28 We use the LASSO for variable selection, and re-fit the model using a standard logistic regression model. If the coefficient is positive, it is predictive of the endpoint analyzed. Factors with a negative coefficient are protective and the degree of negativity is proportional to its "protectiveness." For a coefficient total of x, the risk is $ex/(1 + e^x)$. The receiver operating characteristic (ROC) curve and C-statistic were used to describe how well our models predicted endpoints.

RESULTS

From 2001 to 2010, there were an estimated 2,773,521 hospital discharges with a primary or secondary diagnosis of CDC. Total colectomy was performed in 19,374 patients (7 per 1,000 patients with a diagnosis of CDC). Mortality after colectomy was 30.7%.

Examining trends, we observed a yearly increase in the numbers of CDC discharges, total colectomy for CDC, and mortality after colectomy (Figs. 2 and 3). Compared with the 2001 to 2005 period, the second half of the decade (2006 to 2010) witnessed a 47% increase in the rate of CDC per 1,000 hospitalized patients, going from 5.73 in 1,000 to 8.45 in 1,000 ($p < 0.001$). An increase in the rate of total colectomies for CDC was also observed; there were 5.87 colectomies per 1,000 CDC cases in the 2001 to 2005 period compared with 7.72 in 1,000 in the second half of the decade (Fig. 4). Mortality rates after colectomy for CDC remained relatively stable showing a minor downward trend (average = -0.3% per year).

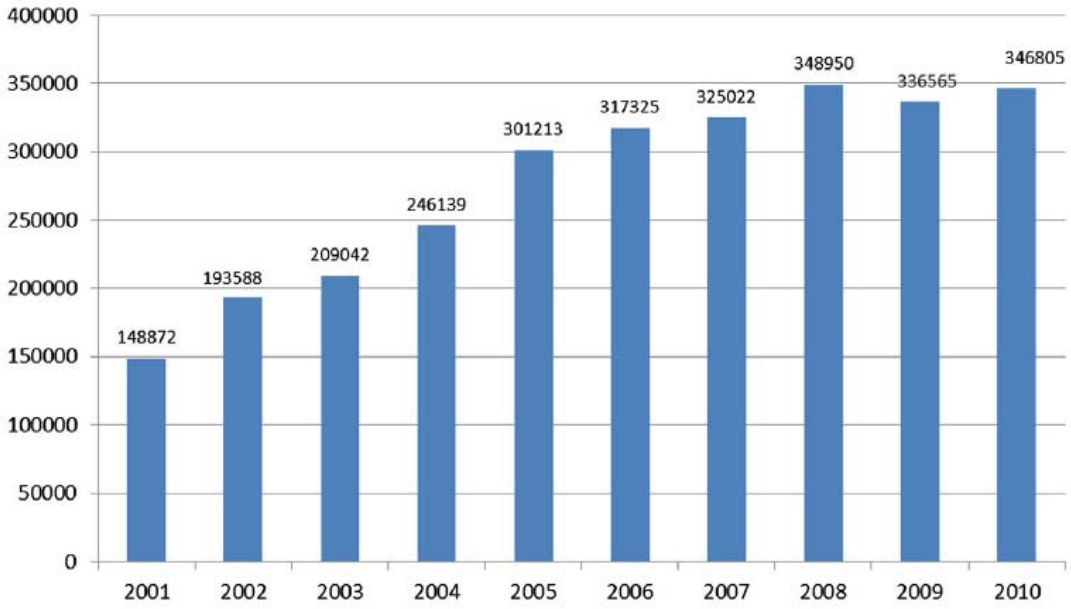


Figure 2. Yearly hospitalizations for Clostridium difficile colitis in the United States. Numbers represent patients with a primary or secondary diagnosis of Clostridium difficile.

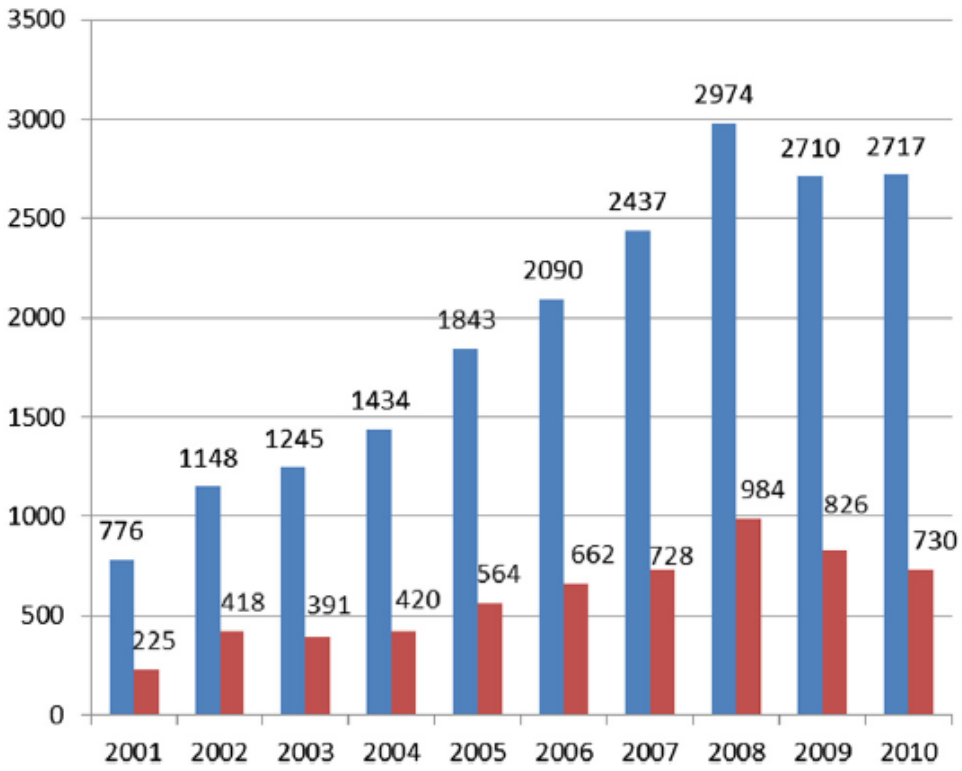


Figure 3. Yearly numbers of colectomy for Clostridium difficile colitis and mortality after colectomy. Blue bar, colectomy for Clostridium difficile; red bar, mortality after colectomy.

When the LASSO algorithm was applied to determine which patients with CDC progressed to severe colitis requiring total or subtotal colectomy, we found several predictive and protective factors, listed in Table 1. The presence of coagulopathy was the strongest factor that predicted requirement for surgery. Weight loss and fluid or electrolyte abnormalities (which included acid-base disturbances, hypo/hypernatremia, hypo/hyperkalemia, elevated blood urea nitrogen) were also found to be strongly associated with colectomy requirement. Hospital factors such as teaching and large hospitals were also found to be predictors of progression to colectomy. Conversely, we found that small hospitals, anemia, diabetes, and psychiatric and neurologic disorders had a negative association with progression to total colectomy. The area under the curve of the predictive model was 0.71.

Table 1. Analysis of Predictive and Protective Factors Associated with Colectomy Requirement for Clostridium difficile Colitis

Factor	Coefficient*	LASSO odds ratio
Intercept	−5.47	0.00
Factors that predict progression to colectomy		
Coagulopathy	1.00	2.71
Weight loss	0.81	2.25
Teaching hospitals	0.32	1.37
Fluid and electrolyte abnormalities	0.27	1.31
Large hospitals	0.16	1.18
Chronic lung disease	0.09	1.09
Factors that protect against progression to colectomy		
Hypothyroidism	−0.03	0.97
Depression	−0.04	0.96
Diabetes-uncomplicated	−0.08	0.92
Chronic liver disease	−0.09	0.91
Hypertension	−0.11	0.90
African-American race	−0.13	0.88
Small hospitals	−0.15	0.86
Diabetes-complicated	−0.19	0.83
Deficiency anemia	−0.21	0.81
Neurologic disorder	−0.33	0.72

*Coefficients can be added together along with the intercept coefficient to calculate the likelihood of progression to colectomy for each individual. For a coefficient total of x, the risk of requiring colectomy is ex / (1 + e^x).

Demographics and comorbidities of patients undergoing total colectomy for CDC are listed in Table 2. These are divided into 2 groups based on in-hospital mortality (survivors and nonsurvivors). Hospital characteristics in survivors and nonsurvivors are listed in Table 3.

Table 2. Demographics, Comorbidities, and Conditions Present at Admission in Patients Who Underwent Total Colectomy for Clostridium difficile

Characteristic	Survivors	Nonsurvivors
n	13,425	5,949
Age, y (range)	65 (56–78)	73 (66–82)
Sex		
Male	43.7	45.6
Female	56.3	54.4
Ethnicity		
White	64.9	65.1
African-American	7.2	6.5
Hispanic	5.8	5.0
Other	4.1	3.7
Missing	18.0	19.7
Payer Type		
Medicare	61.8	78.3
Medicaid	8.7	5.7
Private	25.4	13.6
Other	3.9	2.3
Missing	0.2	0
Comorbidities		
Deficiency anemia	21.2	16.4
Blood loss anemia	4.2	1.9
Hypertension	37.3	40.1
Diabetes-uncomplicated	14.0	12.4
Diabetes-complicated	3.4	3.0
Obesity	4.8	3.3
Weight loss	34.6	25.4
Hypothyroidism	7.9	6.2
Congestive heart failure	18.2	28.4
Chronic lung disease	25.4	33.4
Chronic liver disease	2.3	3.4
Chronic kidney disease	14.2	21.2
Peripheral vascular disease	6.6	12.4
Neurologic disorder	6.5	5.6
Depression	8.0	4.5
Drug abuse	1.5	0.3
Conditions present at admission or during hospitalization		
Electrolyte abnormalities	61.4	71.5
Sepsis/septic shock	40.9	64.3
Coagulopathy	15.6	32.9
Peritonitis	10.3	8.1
Colonic perforation	6.5	6.1

Groups are divided based on in-hospital mortality. Continuous variables are reported as mean and interquartile range, and categorical variables are reported as percentages of the total number for each group (listed in the second row). For sex, ethnicity, and payer type, percentages in each group add up to a sum of 100.0% or 99.9% due to rounding effect.

Table 3. Hospital Characteristics in Patients Who Underwent Colectomy for Clostridium difficile Colitis

Characteristic	Survivors	Nonsurvivors
n	13,425	5,949
Hospital type		
Nonteaching	40.8	43.4
Teaching	58.8	56.3
Missing	0.4	0.3
Hospital location		
Urban	92.8	92.8
Rural	6.9	6.9
Missing	0.4	0.3
Hospital bed size		
Small	8.6	8.6
Medium	19.8	20.0
Large	71.2	71.1
Missing	0.4	0.3

Groups are divided based on in-hospital mortality. Numbers represent percentages. Total numbers for each group are provided in the second row. Percentages in each group add up to a sum of 100.0% or 100.1% due to rounding effect.

Analyzing the association of colectomy day with mortality, we used patients who underwent colectomy on the day of admission (day 0) to day 2 as the reference group. After controlling for all confounding variables including whether CDC was the admitting diagnosis or a secondary diagnosis, we found that patients who underwent total colectomy on hospital day 3 to 8 were at a higher risk for mortality (odds ratio [OR] 1.04; 95% CI 1.01 to 1.08). Patients who underwent operations more than 8 days after admission had the highest risk of mortality (OR 1.09, 95% CI 1.05 to 1.14).

The outcomes of patients undergoing total colectomy for CDC are listed in Table 4. Here we noted high hospital charges, long lengths of stay, and a high incidence of postoperative complications.

Table 4. Outcomes of Patients Undergoing Total Colectomy for Clostridium difficile Colitis

Outcome	Survivors	Nonsurvivors
n	13,425	5,949
Total charge, $	189,771 (77,753–233,623)	186,110 (68,967–225,172)
Length of stay, d	27 (14–32)	19 (6–25)
Postoperative complications		
Cerebrovascular accident	0.3	0.7
Pulmonary complications	51.4	74.9
Cardiac complications	2.6	4.2
Acute renal failure	39.8	66.0
Postoperative bleeding	4.2	4.3
Urinary tract infection	21.5	21.1

Groups are divided based on in-hospital mortality. Continuous variables are reported as mean and interquartile range, and categorical variables are reported as percentages of the total number for each group (listed in the second row).

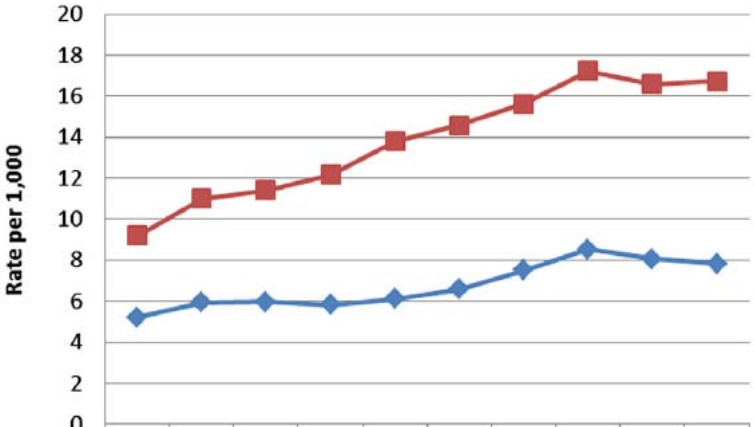
The predictors of mortality after colectomy are presented in Table 5. The strongest predictor for mortality was coagulopathy followed by age greater than 60 years, acute renal failure, respiratory failure requiring intubation and mechanical ventilation, and sepsis. Conversely, factors that were found to be protective of mortality included anemia and weight loss. The area under the curve of the predictive model was 0.72.

Table 5. Predictive and Protective Factors for Mortality after Colectomy for Clostridium difficile Colitis

Factor	Coefficient*	LASSO odds ratio
Intercept	−1.62	0.20
Predictors of mortality		
Coagulopathy	0.87	2.38
Age >60	0.68	1.97
Acute renal failure	0.51	1.67
Respiratory failure	0.47	1.61
Sepsis/septic shock	0.34	1.40
Peripheral vascular disease	0.33	1.39
Congestive heart failure	0.22	1.25
Fluid and electrolyte abnormalities	0.21	1.23
Chronic kidney disease	0.12	1.13
Chronic lung disease	0.06	1.06
Chronic liver disease	0.02	1.02
Protective factors		
Obesity	−0.01	0.99
Hypothyroidism	−0.13	0.88
Depression	−0.14	0.87
Deficiency anemia	−0.18	0.83
Drug abuse	−0.28	0.76
Weight loss	−0.32	0.73
Blood loss anemia	−0.50	0.61

*Coefficients can be added together along with the intercept coefficient to calculate the predicted mortality following colectomy for Clostridium difficile colitis. For a coefficient total of x, the risk of mortality after colectomy is $ex / (1 + e^{x})$.

After total colectomy, only a small minority of patients who survived the operation were sent home on a routine basis without ancillary care (14.1%). The majority of survivors were discharged to a skilled nursing facility (51.3%), home health (18.4%), and hospice (2.8%). A small minority died after discharge (0.2%). Discharge information was missing for 13.3% of patients.



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Rate of Colectomy per 1,000 C Diff patients	3.98	5.08	5.46	6.34	7.68	8.01	8.12	8.7	8.53	8.89
Rate of C. Diff per 1,000 hospitalized patients	5.21	5.93	5.96	5.82	6.12	6.58	7.5	8.52	8.05	7.83

Figure 4. Yearly rates of for Clostridium difficile per 1,000 hospitalized patients, and yearly rates of colectomy per 1,000 patients with for Clostridium difficile.

DISCUSSION

Consistent with studies from the 1990s and the first half of the 2000s, which reported a rising incidence of CDC in the United States,[4,29-31] the results of our study demonstrate that the incidence of CDC continues to increase among hospitalized patients. This appears to be a worldwide health concern, as reports from Japan,[32] Europe,[33-36] and Canada[37] are also documenting rising trends of CDC cases. The more concerning facts are the rising numbers of colectomies performed for CDC, which appear again as a continuation of a previously observed trend that started in the mid 1990s.[4] This could be a marker of a more severe disease associated with the emergence of hypervirulent strains such as the PCR ribotype 001 and 010,38 106,39 BI/NAP1/027,[6,35,40,41] and strains carrying the binary toxin gene.[42] All these strains have been shown to be associated with failure of medical management, multidrug resistance, and increased recurrence rates.[43] These strains, which are more likely to be present in tertiary care centers as demonstrated in previously published data,[20,41,44] may explain why large and teaching hospitals appeared in the predictive model for colectomy requirement. Conversely, smaller hospitals appear to have a lower rate of progression to colectomy. Other factors such as an aging population, rising numbers of immunosuppressed patients,[45,46] the widespread use of fluoroquinolones,[35,36,40] and proton-pump inhibitors,[47] and better detection rates,48 have been implicated in the rising incidence of CDC. This rising incidence of CDC and the associated colectomy rates call for preventive measures aiming at reducing the spread of this disease. Several measures have been shown to lower the incidence of CDC.[49-52] These include hand hygiene promotion, infection control measures with the use of special detergents,[51,52] and policies to limit antimicrobial usage.[49,50]

Although preventive methods are effective, when infection with Clostridium difficile occurs, most cases are managed medically with the use of metronidazole and vancomycin. More recently, fidaxomicin53 and stool transplant[54] have shown some success in refractory cases of CDC. Only a very small subset of patients as shown in our results (0.7% of all CDC cases) required total or subtotal colectomy and end ileostomy, which is the most common surgical technique used in the management of CDC. Despite offering a survival advantage when compared with medical management in fulminant CDC,[11,18,44] this procedure remains associated with a high mortality rate of 31.7% without major improvements over the past decade. These results are probably the best estimate we have so far of mortality rates after total colectomy because previous data were limited by small sample sizes and have shown wide discrepancy in mortality rates ranging from 34% to 80%.[11-18] The mortality rate observed in our study was lower than that found in a recent meta-analysis of 31 studies evaluating the outcomes of emergency surgery for CDC.[55] In fact, this meta-analysis found a mortality rate of 41.3% after total colectomy, but mortality information was available for only 387 of 1,433 patients included in the analysis.[55] In an effort to reduce mortality rates of fulminant CDC, a technique involving creation of a diverting loop ileostomy with colonic lavage has been recently shown to reduce mortality from 50% to 19% when compared with total colectomy.[56] Unfortunately, the results of this study were compared with historical controls, and long-term data on recurrence rates in treated subjects are unavailable. As such, total colectomy still remains the most commonly used surgical method to manage fulminant CDC.[55]

Because early surgery may be associated with lower mortality rates, which is in line with previous reports,[14,18,57,58] knowledge of the risk factors that predict requirement for total colectomy becomes essential. Our validated model revealed that when all the factors listed in Table 1 are absent, the risk of progressing to fulminant CDC and colectomy is 0.4%. When all risk factors are present without any of the protective factors, the risk of requiring colectomy rises 14-fold, to 5.6%. It has to be mentioned that many of these factors include several components. For example, weight loss includes ICD-9 codes for protein malnutrition and hypoalbuminemia, which have been shown to be independently associated with fulminant colitis requiring olectomy.[59,60] Coagulopathy and fluid or electrolyte abnormalities usually occur in the setting of severe sepsis. The latter is well known to occur with fulminant colitis.[18,57]

Operating early before the onset of sepsis and organ dysfunction, such as respiratory and renal failure, may also reduce mortality rates. If we apply the formula that predicts mortality after colectomy, we find that patients without any of the risk factors listed in Table 5 have a mortality rate of 16.5%. The risk increases to 24.8% with acute renal failure. If we add sepsis to the equation, the mortality rate increases to 31.6%. Furthermore, if respiratory failure develops in addition to the previous factors, mortality rises to 42.6%. To our knowledge, this represents the first cross-validated model for mortality after colectomy with an acceptable predictive power. So again timing is of the essence in the management of fulminant CDC. This model also tells us that surgery may not be beneficial in patients with multiple risk factors. In the presence of all predictive factors, the risk of mortality is 85%. The risk factors we found correlate well with previously published data. Advanced age,[11,12,21,44,55,60] acute or chronic kidney

disease,[12,21,22,55,60] chronic lung disease,[22,60] heart disease, and acute respiratory failure[11,12,22,55,61] have all been shown to predict mortality after colectomy for CDC. As for coagulopathy and fluid or electrolyte disorders, these go hand in hand with severe sepsis, which has been demonstrated to increase mortality as well.[10,14,18,21,44,55,57] The strength of these findings is that factors are independent of each other and can be added together to calculated the predicted mortality risk.

Of special interest are protective factors that appeared in our 2 predictive models. Although it may be intuitive to think that diabetic patients are more likely to progress to fulminant colitis and surgery, this was not the case. Moreover, the presence of diabetes did not appear to be associated with mortality after colectomy. It may be the case that aggressive medical management is instituted early on in diabetic patients, preventing them from progressing to fulminant colitis, colectomy, and death. The other protective factor that merits special attention is anemia, which was found to be protective against colectomy and mortality after colectomy. A possible explanation for this finding is that low iron levels, as found in iron-deficiency anemia, blood loss anemia, and the anemia of critically ill patients, is an important strategy of the innate human antimicrobial defense system based on depriving pathogens of this essential nutrient.[62] Furthermore, decreased iron stores may downregulate the expression of interleukin-6, tumor necrosis factor a, and nitric oxide, which are key factors in severe inflammation. [62,63] This also may explain why chronic liver disease, which causes altered iron metabolism, appeared to be protective against progression to colectomy and had only a weak effect on mortality after colectomy. These findings, however, warrant further evaluation.

Colectomy for CDC is not only associated with a high mortality, but also with high morbidity, as seen in the relatively high incidence of pulmonary and renal complications. The length of hospital stay in survivors was, on average, 27 days, which appeared to be independent of other complications, as previously demonstrated.[64] The high hospital charges ($189,771) are not only related to the prolonged length of stay but also the cost of care of these patients. Wang and Stewart[65] showed a 2-fold increase in hospital charges associated with CDC, a fact confirmed by 2 large economic evaluations demonstrating that CDC is associated with significantly higher mean cost and longer length of stay compared with matched controls.[66-68] Clinicians should be aware of the financial impact of CDC, and the application of appropriate infection control measures is recommended to reduce spread.

Patients who survive surgery are debilitated and require ancillary services after discharge, as seen in our results. Total colectomy for CDC has a slow recovery phase, which along with the physical deconditioning of prolonged hospital stay, serves to explain why only a minority of patients were discharged on a routine basis. Of note is that patients who survive colectomy for CDC fare poorly, as demonstrated in a study by Miller and associates[13] showing a 5-year survival of only 38%.

We acknowledge that our study may have some limitations related to its retrospective nature and its inherent biases. The results of toxin assays and other tests used to diagnose CDC are unavailable in the NIS dataset; therefore, we relied on the ICD-9 coding system to identify patients. This is an acceptable method as demonstrated in multiple studies that found a good correlation between ICD-9 codes and toxin assay results.[69,70] Administrative databases may be prone to coding errors, so in an attempt to limit these errors we excluded other surgical methods used to treat fulminant CDC.

Among these methods are limited colon resections, which are rarely used because they have been shown to be associated with unacceptably high mortality and recurrence rates.[23,71,72] Details such as leukocytosis and requirement for vasopressors were found in multiple studies to be associated with mortality.[11,15,18,21,22,61] These variables, unfortunately, are not available in the NIS dataset. However, they are surrogates of sepsis and septic shock, which we included in our study. Leukocytosis, despite having been shown to predict mortality in several small studies, did not appear to have a measurable effect on mortality in the large meta-analysis by Bhangu and coworkers.[55] Immunosuppression, which has been also shown to correlate with mortality,[22,44,59] is also not available in the NIS dataset. Mortality rates in this study may be slightly underestimated because the NIS provides information related to 1 hospital stay, so 30-day mortality is unknown. This limitation is unlikely to change the results in a significant manner because the mean length of stay in survivors was long (27 days) and only a small percentage died after discharge. Nevertheless, this is the largest and the most up-to-date study evaluating the trends of CDC at the national level. Moreover, this is the only study with validated models for disease progression to colectomy and mortality after colectomy.

CONCLUSIONS

During the past decade, the overall numbers of CDC cases and the associated colectomy rates have increased in the United States without an appreciable improvement in mortality. Although only a small subset of patients with CDC require colectomy, this progression can be predicted by patient and hospitals factors. Early colectomy may reduce mortality. The latter can also be predicted using the validated model presented in this article. Knowledge of these predictors will help in better patient and family counseling, decision making, and risk stratification.

Author Contributions

Study conception and design: Halabi, Mills
Acquisition of data: Nguyen
Analysis and interpretation of data: Halabi, Nguyen, Carmichael, Mills
Drafting of manuscript: Halabi, Carmichael, Pigazzi, Mills
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