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Clostridium difficile associated disease in hospitalized children in the United

States

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This work and its defense approved by:

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***Clostridium difficile* associated disease in hospitalized children in the United States**

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A thesis submitted to the

Graduate School of the University of Cincinnati

in partial fulfillment of the requirements for the degree of

Master of Science of Clinical and Translational Research

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of the College of Medicine by

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Abstract:

Background: *Clostridium difficile* associated disease (CDAD) can lead to prolonged hospital course, colectomy and death. In previous epidemiological studies there is evidence that the national rate and severity of CDAD are increasing. Little is known about the risks and impact of CDAD in children.

Objective: To evaluate epidemiology, and risk factors of CDAD in hospitalized children in the United States

Design: The Healthcare Cost and Utilization Project Kids' Inpatient Database (KID) was utilized to design a retrospective cohort study of hospitalized children in the United States over four time periods: 1997, 2000, 2003, and 2006.

Outcome measures: Trends in national cases of CDAD. Severity was measured by length of stay, hospital costs, colectomy rate and case fatality rate.

Results: The total discharges were 10,495,728 and those with CDAD were 21,274 over the four time periods. There was an increasing trend in CDAD ($p < .0001$). There was no trend in length of stay, colectomy rate or case fatality rate associated with CDAD over the four time periods. CDAD in children is associated with an increased risk of death, colectomy, longer length of stay and higher charges. Multivariate logistic regression results evaluating risk comorbid diagnoses associated with CDAD demonstrate a high risk in inflammatory bowel disease, odd ratio (95% CI) of 11.42 (10.16-12.83) and other comorbid diagnoses associated with immunosuppression, or with antibiotic administration.

Conclusion: There is an increasing trend of hospitalized children with CDAD. In contrast to adults, there is no increasing trend in the severity of CDAD in children. Children with certain

medical conditions including IBD, immunosuppression, or conditions requiring antibiotic administration are at high risk of CDAD.

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Figure 1.

Graph representing the trend in discharge cases of *Clostridium difficile* associated disease in hospitalized children

Table 1

Summary of demographic data for children with and without *Clostridium difficile* associated disease in hospitalized children across the years 1997, 2000, 2003 and 2006.

Table 2

Summary of the surrogate measures of severity for discharges with *Clostridium difficile* associated disease in hospitalized children, and without CDAD

Table 3

Show the odds ratios results from multivariate logistic regression models for the severity markers of *Clostridium difficile* associated disease in hospitalized children including mortality, colectomy, length of stay, and charges. These results include propensity scores values and all identified demographic and comorbid risk factors for CDAD.

Table 4

Results of both univariate and multivariate logistic regression models representing odds ratio of clinical comorbid and demographic risk factors for *Clostridium difficile* associated disease in hospitalized children.

Background:

Clostridium difficile is a gram-positive, spore forming anaerobic bacillus which infects the gastrointestinal tract and can lead to *Clostridium difficile* associated disease (CDAD). CDAD has a wide variation in severity of disease, ranging from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, bowel perforation and death. In recent years, the incidence, number of hospitalizations, associated deaths and severity of CDAD in adults has been on the rise.^{1, 2}

This increase in the rate and severity of CDAD has been observed in conjunction with the description of hypervirulent strains of *C. difficile* which have resistance to antibiotics such as fluoroquinolones and third generation cephalosporins, hypersecrete toxins A and B, and secrete an additional toxin known as binary toxin.^{3, 4} The hypervirulent strain is known as North American Pulsed Field type 1 (NAP1) and PCR ribotype 027 or NAP-1/027.^{5, 6} A new strain of hypervirulent strain NAP-1/078 has been reported.⁷ However, much of the increased frequency and severity of CDAD may be due to factors other than the emergence of these hypervirulent strains.

In previous nationwide studies of CDAD the rates have been highest in the elderly and in urban populations.^{1, 8} More recently there are reports of severe CDAD in previously young, healthy patients without hospital exposure, and in children.^{9, 10} There have been two large studies showing an increasing trend of CDAD in children over recent years.^{11, 12}

There are several known risk factors for the development of CDAD including medication administration i.e. antibiotics, acid suppression medication, and chemotherapy.¹³⁻¹⁶ In adults, conditions such as inflammatory bowel disease, and human stem cell transplantation, are associated with CDAD.^{17, 18} Children with solid tumors, organ transplantation, and inflammatory bowel disease are also at increased risk.¹⁹⁻²¹ While these studies have examined the relationship of CDAD in specific subgroups of patients there have been no broad investigations of clinical and demographic risk factors for CDAD in children. We sought to reevaluate the trend of CDAD in children, identify risk factors for CDAD in children, and evaluate the impact of CDAD in morbidity and costs utilizing a large national database.

Methods:

Data Source

Data was obtained from the Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP-KID), sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP-KID is the first United States (U.S.) nationwide inpatient database devoted to children. The database used consists of a stratified random sample of a total of 5,754,377 inpatient discharges over four time periods 1997, 2000, 2003, 2006. Included are discharge data from 22-38 states (depending on the year) and for 2006 represents an estimated 88.8 % of the U.S. pediatric population. Each record in the database represents a primary hospital discharge and includes up to 14 other diagnostic related group (DRG) codes and up to 15 current procedural terminology (CPT) codes based on international statistical classification of diseases and related health

problems, ninth revision (ICD-9). Through the sampling technique HCUP generates weighted data which allows an accurate method of estimating national cases and trends. All children age <1 year were excluded. The exclusion of this age group is based on continued controversy over the true morbidity of *C. difficile* in infants. There is substantial evidence to support *C. difficile* as both normal commensal flora and non-pathogenic in infants less than a year of age²²⁻³⁰. The University of Cincinnati institutional review board was consulted and approval was obtained.

Variable Definition

The main predictor in this study is the presence or absence of a diagnosis of CDAD on an inpatient discharge record. Case selection was performed by searching the data base for the DRG code 008.45. This is the only code devoted to CDAD, has been previously validated as an accurate determinant of actual disease^{31,32}, and includes two descriptions: “Intestinal infection due to *Clostridium difficile*” and “Pseudomembranous colitis”. Demographic data includes race, sex, age, payer type, geographic region, and geographic location (urban vs. rural) of the hospital. HCUP-KID relies on individual states to provide race specific data; therefore, the categories of various races reported varies by state. To simplify the analysis race was grouped into white, black, Hispanic, and other. Payer type was grouped into Private insurance/HMO, Medicaid/Medicare, and other (no pay, self pay, and any other). The hospital region was designated Northeast, Midwest, South and West. A time variable was included to indicate the year the data was collected to test for trends over time.

The main outcomes studied were case fatality rate, colectomy rate, length of hospital stay (LOS) and inpatient stay charges. Case fatality rate was defined as the number of patients who died per number of discharges with the diagnostic code for CDAD. Colectomy was defined by the following ICD-9 CPT codes : 45.8 “Total intra-abdominal colectomy”, 45.7 “Partial excision of large intestine”, 45.71 “Multiple segmental resection of large intestine”, 45.72 “Cecectomy”, 45.73 “Right hemicolectomy”, 45.74 “Resection of transverse colon”, 45.75 “Left hemicolectomy”, 45.76 “Sigmoidectomy”, and 45.79 “Other partial excision of large intestine”. Charges were adjusted to 2009 dollars utilizing the consumer price index for inpatient hospital services ³³.

The most common 80 percent of comorbid diagnostic codes associated with the diagnosis of CDAD were examined which corresponded to any comorbid code which occurred at a frequency of 25 times or greater. It was felt that any diagnosis that occurred less likely not be a risk factor for disease. A total of 205 codes were then categorized into clinically similar groups and a logistic model was generated to establish the risk associated with other comorbid conditions. These categories include: bacterial infections, fungal infections, cystic fibrosis, neoplastic disease, hematologic disorders, solid organ transplant, hematopoietic stem cell transplantation, malnutrition, inflammatory bowel disease, appendicitis, renal disease, liver disease, HIV, cardiac disease, pancreatitis, gastrostomy tube status, lupus erythematosus, and gastroesophageal reflux.

Data Analysis

Categorical data was summarized as frequencies and percentages; continuous data was summarized as mean with standard error, and when data was not normally distributed, by median and quartiles. Comparisons between groups were conducted for appropriate variables utilizing Wilcoxon Rank Sum test, t-test, and chi-squared test. Analysis for trend across the four time periods was performed utilizing multivariate logistic regression. All reported results utilized the HCUP-KID provided weighted values for national estimates. SAS 9.1.3 (SAS Institute, Cary, NC) was utilized for all statistical analysis.

To assess the various risk factors for CDAD among inpatient pediatric patients backwards logistic regression was performed. The main predictor variable is the diagnosis of CDAD and outcome variables include the demographic variables of age, sex, race, hospital region, urban vs. rural location of the hospital, and payer type, comorbid categories listed above and the year. To assess the effect of CDAD and the likelihood of colectomy, death, LOS, and charges backward logistic regression modeling was performed. LOS, and charges were dichotomized at their median values. The model was risk-adjusted for all variables included in the original CDAD model and included a propensity score established through modeling the risk of CDAD with all identified risk factors. Odds ratios are used to present the strength of the likelihood of colectomy, death, a LOS above the median value, charges above the median value, or to present the strength of the likelihood of CDAD for those with a diagnosis of CDAD compared to those without a diagnosis of CDAD.

Results:

Based on the sample included in the database, the total weighted discharges for the United States were 10,495,728 and those with CDAD were 21,274 (0.2 %). Demographic data by year is summarized in Table 1. The mean age ($\pm$ standard error of the mean) for those with CDAD was younger, 9.5 ($\pm$.06) vs. 12.0 ($\pm$.01) for all others ($p < .0001$). There were significant differences in the proportion of the CDAD group vs. all others in sex ($p < .0001$), race ($p < .0001$), region ($p < .02$), urban location ($p < .0001$), and payer type ($p < .0001$).

There was a large and significant increase in the national trend of cases of CDAD in hospitalized children (See Figure 1). The average annual percent increase with a discharge diagnosis of CDAD, 14.9 % ($p < .0001$). There was not, however, a significant trend in the four variables utilized as surrogates for disease severity (See Tables 2 and 3). The median length of stay remained steady for CDAD patients over the four time periods at 5 to 6 days without any trend ($p = 0.089$). The charges increased with an average annual percent increase of 4.4 % vs. 2.3 % for no CDAD. Despite the observed increase this trend was not found to be significant ($p = 0.063$). There was also no significant trend in either case fatality rate ($p = 0.17$) or colectomy rate ($p = 0.09$) among patients diagnosed with CDAD.

Comparing data from all years CDAD discharges vs. all other hospital discharges showed significant impact of disease (See Table 2). The median (interquartile range (IQR)) LOS for those with CDAD was 6 days (3-15) and 2 days (1-4) for all others. The median (IRQ) charge for those with CDAD was \$29,251 (\$11,247-\$90,801) and \$9,670 (\$5,715-\$17,918) for all others. The death rate without CDAD was 3.2 per 1000 discharges and the death rate in those with CDAD was 19.7 per 1000 ($p < .0001$). The colectomy rate without CDAD was 1.3 per

1000 discharges and for CDAD 9.0 per 1000 ($p < .0001$). In univariate logistic regression CDAD had an odds ratio for death 6.07(5.50-6.70) of and for colectomy 7.15(6.19-8.25). In multivariate logistic regression including all comorbidity risk factors of CDAD, demographic risk factors of CDAD and the propensity score, CDAD had an odds ratio for death of 1.54 (1.27-1.87) and for colectomy an odds ratio of 1.46 (1.09-1.96) (See Table 3). In evaluating LOS

Children with CDAD have a higher median number of diagnoses than those without 6(3-9) vs. 3(2-4), ($p < .0001$). In evaluating these comorbidities and other risk factors, there were nineteen comorbid categories, five demographic variables and time (year) included in the multivariate model. The highest comorbid diagnosis associated with CDAD was inflammatory bowel disease with an odds ratio (95% CI) of 11.42(10.17-12.83). The odds ratios were also high in several other comorbid conditions with primary or secondary immunodeficiency or likely exposure to antibiotics (See Table 4 for full list). The risk of CDAD was lower for blacks, Hispanics and other races when compared to whites. The risk of CDAD was highest in the West, lowest in the South and equal in the Midwest when compared to the Northeast. The risk was higher in urban hospitals vs. rural hospitals. The risk was lower in Medicaid/Medicare patients and other payer type (self pay, no pay) when compared to patients with private insurance/HMO.

Discussion:

There was an observed increase in the rate of pediatric CDAD over the four time periods. This increase in the rate of CDAD is consistent with previously published trends in adults and children.^{2, 11, 34} Zilberberg et al. utilizing a simplified version of the HCUP-KID data available

through internet access showed an increasing trend in CDAD in children. Our evaluation of trend while controlling for multiple factors confirms these finding through a more robust trend analysis.¹²

One of the primary risk factors for the development of CDAD is antibiotic administration. An upward outpatient trends in antibiotic could explain the inpatient upward trend in CDAD. There is evidence, however, of a downward trend in antibiotic administration in the United States during the same time period.³⁵ Another, more likely explanation is a more widespread dissemination of a more virulent stain of *Clostridium difficile* such as the restriction endonuclease analysis group BI, North American pulsed filed gel electrophoresis type 1, chain reaction ribotype 027 (BI/NAP1/027). It is this strain which has been attributed to the rise in the number of cases and the severity in adult patients.^{36, 37} It could also be possible that there is an increasing awareness among health care providers leading to increase testing in symptomatic patients.

There was no significant trend in the severity of CDAD in children as measured by length of stay, charges, case fatality rate, colectomy rate and death. The lack of increase in both colectomy and death associated with CDAD agrees with a previous report in children and contrasts the results in to adult studies.^{2, 11} This is the first time trends of charges or length of stay related to CDAD have been reported in children. It is likely that children have not been affected to the degree that adults have in recent years or that in 2006 we have yet to see the upward trend of CDAD severity in children. We did observe an increase in the CPI adjusted charges over the time periods, however the trend was not significant ($p=.063$). Possible explanations of this may

be shifts in the treatment of CDAD with more expensive antibiotics such as oral Vancomycin or decreasing reimbursement to charge ratios.

There is a significant impact of disease when comparing LOS, charges, case fatality rate and colectomy rate in discharges with diagnosis of CDAD vs. all others. The increase risk of colectomy is expected as this is the treatment for severe CDAD. However, the rate of colectomy per discharge with CDAD is 10 times less than reports in adult patients, while the death rate in those with in our study with CDAD is the same as in an adult study of CDAD.² The increase in LOS and charges associated with CDAD in children mirrors previous reports in adults.^{38, 39} These observed differences in the markers of severity of disease may not be entirely attributable to the effects of CDAD as we cannot determine temporality of a CDAD diagnosis during a hospitalization from our dataset. Comorbidity is also known risk factor for CDAD in adults and we have shown this in children.⁴⁰

We identified inflammatory bowel disease as the single highest associated comorbid diagnosis with CDAD with an odds ratio of 11.42. This supports previous reports in both adults and children.^{18, 41, 42} The additional diagnostic groups identified with an increased risk of CDAD were similar for known risk factors such as hematopoietic stem cell transplantation, solid organ transplantation, and solid tumors previously reported.^{17, 19, 20, 43} These diagnostic categories in addition to the others reported in our study reinforce the known risk of immune suppression or antibiotic exposure.⁴⁴⁻⁴⁶

Proportionately there were more males than females with CDAD. The finding that CDAD is more common in males agrees with previous reports in pediatrics however this gender discrepancy is reversed in adult hospitalized patients.^{2, 11} Patients with CDAD were significantly younger than those without. This could possibly be explained by increased antibiotic pressure in the younger children, bias to test for CDAD in the younger patients, or a true susceptibility to disease at a younger age. In adults, it is the elderly who are at the greatest risk of disease thus CDAD may be a disease affecting the extremes of age with adolescents and younger adults being relatively spared. It is also interesting in the overall multivariate analysis there was a decreased risk of CDAD associated with Medicaid or other pay types (self pay/no pay). This may represent a true decreased risk of disease in these patients because of a lower exposure to antibiotics for routine infections (acute otitis media etc.) compared to those with private insurance.

The HCUP-KID provides an excellent national representative sample of pediatric hospitalizations and can be applied to extrapolate nationwide estimates and trends. The size of the HCUP-KID provides us with the largest and broadest study of CDAD in children. HCUP-KID does, however, have several weaknesses. Our definition of CDAD is entirely based on ICD coding. As in all studies utilizing diagnostic codes there is concern for accuracy in the coding process and a paucity of clinical information. We had no method to verify laboratory results, the strain of *C. difficile* or the diagnosis of CDAD. We are unable to evaluate medical treatments. An additional limitation to the HCUP-KID database is that it reports hospital discharges not individual patients. It is possible to capture patients readmitted to the hospital for the same

diagnosis. We also cannot determine whether the CDAD was acquired as an outpatient or as a nosocomial infection.

Our population-based data in our study provide additional evidence that CDAD cases are increasing among hospitalized children. We found no evidence of an increasing trend in severity of CDAD in children. To our knowledge this is the largest population-based data analysis of CDAD in children in the United States and the first to systematically evaluate risk factors involved in the development of CDAD in hospitalized children. Our results provide a background for understanding changing trends and risk factors of CDAD in children. Increasing awareness of these risk factors and an upward trend in hospitalized children with CDAD is the first step in controlling this important infection.

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Figure 1. Trend in CDAD in hospitalized children

	1997		2000		2003		2006	
CDAD Status	CDAD	No CDAD	CDAD	No CDAD	CDAD	No CDAD	CDAD	No CDAD
Number	3,565	2,205,678	4,356	2,740,560	5,574	2,775,426	7,779	2,752,790
Mean Age $\pm$ SE (Years)	7.8 $\pm$ 0.2	10.1 $\pm$ 0.1	9.8 $\pm$ 0.2	12.6 $\pm$ 0.1	9.7 $\pm$ 0.1	12.3 $\pm$ 0.1	9.9 $\pm$ 0.1	12.5 $\pm$ 0.1
Female	46.9%	55.0%	46.2%	61.7%	48.8%	60.5%	49.2%	61.1%
Race								
White	70.2%	58.1%	67.8%	56.3%	62.2%	51.9%	59.1%	51.8%
Black	11.5%	22.4%	12.5%	19.1%	11.8%	19.1%	13.1%	18.8%
Hispanic	14.2%	15.8%	15.6%	19.8%	20.0%	23.2%	22.2%	23.8%
Other	4.1%	3.7%	4.1%	4.8%	6.0%	5.8%	5.6%	5.6%
Geographic Region								
Northeast	27.9%	21.0%	23.3%	18.9%	16.8%	17.3%	16.6%	17.7%
Midwest	21.6%	22.9%	20.6%	20.8%	25.3%	23.0%	23.1%	22.5%
South	22.5%	34.8%	30.5%	38.0%	35.2%	38.6%	32.4%	39.0%
West	28.0%	21.3%	25.6%	22.3%	22.7%	21.1%	27.9%	20.8%
Urban	91.1%	84.3%	91.2%	85.0%	91.0%	85.6%	93.5%	88.0%
Payer type								
Private/HMO	61.1%	50.5%	60.7%	48.1%	54.7%	44.3%	51.4%	41.1%
Medicaid/Medicare	31.8%	39.0%	33.1%	41.7%	37.6%	45.6%	39.3%	48.4%
Other	7.1%	10.5%	6.2%	10.2%	7.7%	10.1%	9.3%	10.5%

Table 1 Demographic data for children with and without CDAD.

	1997		2000		2003		2006	
CDAD Status	CDAD	No CDAD	CDAD	No CDAD	CDAD	No CDAD	CDAD	No CDAD
Length of Stay (days)								
25 th percentile	3	1	3	1	3	1	3	1
Median	5*	2*	6*	2*	6*	2*	6*	2*
75 th percentile	14	3	15	3	14	3	15	3
Charges								
25 th percentile	9,542	5,175	10,232	5,404	11,765	5,938	12,263	6,414
Median	23,036*	8,667*	30,317*	9,014*	28,724*	10,015*	31,957*	10,893*
75 th percentile	78,633	15,840	88,199	16,551	87,635	18,538	99,488	20,217
Death Rate per 1000	23.6*	3.7*	19.4*	3.4*	16.8*	3.1*	19.2*	2.9*
Colectomy Rate per 1000 CDAD cases	10.0*	1.1*	8.6*	1.2*	8.0*	1.3*	9.5*	1.4*

Table 2 Summary of measures of severity for discharges with CDAD, and without CDAD; Charges are in 2009 consumer price index inflation adjusted dollars for hospital inpatient services; * p<.0001 CDAD vs no CDAD by year, Wilcoxon Rank Sum test (Charges, LOS) and Chi-squared test (Death and Colectomy).

	Mortality Odds Ratio (CI)	Colectomy Odds Ratio (CI)	Length of Stay Odds Ratio (CI)	Charges Odds Ratio (CI)
<i>Clostridium difficile</i> Associated Disease	1.54 (1.27-1.87)	1.46 (1.09-1.96)	4.73 (4.28-5.23)	2.46 (2.30-2.62)
Inflammatory Bowel Disease	0.25 (0.17-0.37)	99.19 (90.00-109.33)	1.43 (1.35-1.52)	1.68 (1.60-1.76)
Solid Organ Transplant	1.00 (0.82-1.23)	1.11 (0.75-1.65)	1.04 (0.99-1.09)	1.80 (1.72-1.89)
HIV	2.50 (2.03-3.09)	0.10 (0.01-0.67)	1.07 (0.99-1.16)	1.88 (1.75-2.01)
Hematopoietic stem cell transplantation	3.60 (3.14-4.13)	0.72 (0.37-1.39)	0.98 (0.90-1.06)	1.65 (1.52-1.78)
Neoplastic Disease	2.16 (2.03-2.31)	1.11 (0.92-1.34)	1.79 (1.75-1.82)	2.66 (2.62-2.70)
Fungal Infection	2.42 (2.13-2.76)	2.28 (1.72-3.01)	2.55 (2.37-2.75)	2.33 (2.22-2.45)
Cystic Fibrosis	2.04 (1.73-2.41)	0.78 (0.51-1.19)	3.20 (3.00-3.41)	6.50 (6.16-6.86)
Pancreatitis	1.52 (1.28-1.80)	0.98 (0.70-1.37)	2.73 (2.59-2.88)	2.33 (2.22-2.45)
Hematologic disorders	1.08 (1.02-1.16)	1.04 (0.93-1.16)	1.88 (1.85-1.90)	1.46 (1.44-1.48)
Gastrostomy	5.54 (4.84-6.34)	1.55 (1.09-2.21)	1.50 (1.41-1.60)	2.60 (2.45-2.76)
Liver Disease	4.66 (4.27-5.08)	1.79 (1.44-2.23)	1.61 (1.55-1.67)	2.43 (2.35-2.52)
Malnutrition	1.65 (1.46-1.86)	2.11 (1.75-2.54)	2.74 (2.61-2.87)	2.39 (2.31-2.48)
Renal disease	4.18 (3.93-4.46)	1.81 (1.54-2.14)	1.11 (1.08-1.13)	1.97 (1.93-2.00)
Systemic lupus erythematosus	1.07 (0.87-1.31)	0.53 (0.26-1.11)	0.71 (0.67-0.75)	1.20 (1.14-1.27)
Gastroesophageal reflux	0.80 (0.70-0.93)	1.07 (0.86-1.32)	1.39 (1.36-1.43)	1.85 (1.81-1.88)
Bacterial Infection	1.70 (1.63-1.78)	1.63 (1.49-1.77)	2.02 (2.00-2.04)	1.23 (1.22-1.23)
Cardiac disease	5.28 (4.96-5.62)	1.23 (1.02-1.49)	1.22 (1.20-1.25)	3.11 (3.05-3.17)
Appendicitis	0.10 (0.07-0.14)	4.24 (3.85-4.67)	0.99 (0.98-1.00)	6.40 (6.30-6.52)
Asthma	0.35 (0.32-0.38)	0.43 (0.37-0.50)	1.08 (1.07-1.08)	0.89 (0.88-0.90)
Demographic Variables				
Female	0.47 (0.45-0.49)	0.47 (0.44-0.51)	1.20 (1.19-1.20)	0.72 (0.71-0.72)
Black vs. white	1.11 (1.05-1.17)	0.99 (0.90-1.08)	1.23 (1.22-1.23)	1.19 (1.19-1.20)
Hispanic vs. white	0.94 (0.89-0.99)	0.84 (0.77-0.92)	1.19 (1.18-1.20)	1.25 (1.25-1.26)
Other race vs white	1.29 (1.19-1.40)	1.22 (1.13-1.33)	1.12 (1.12-1.14)	1.16 (1.15-1.17)
Midwest vs Northeast	1.30 (1.21-1.40)	1.37 (1.24-1.52)	1.04 (1.03-1.05)	0.66 (0.65-0.66)
South vs Northeast	1.26 (1.20-1.33)	1.08 (1.03-1.17)	1.11 (1.10-1.12)	0.83 (0.83-0.84)
West vs Northeast	1.42 (1.35-1.49)	1.22 (1.13-1.33)	0.74 (0.74-0.75)	1.57 (1.56-1.58)
Urban vs rural	4.01 (3.53-4.57)	2.08 (1.80-2.39)	1.28 (1.27-1.29)	3.19 (3.16-3.22)
Medicaid/Medicare vs. Private insurance/HMO	0.91 (0.88-0.96)	0.77 (0.71-0.83)	1.34 (1.33-1.35)	0.89 (0.89-0.90)
Other payer type (self pay, No pay) vs private insurance/HMO	1.70 (1.61-1.80)	0.96 (0.87-1.06)	0.91 (0.91-0.92)	0.91 (0.90-0.92)
Year				
2000 vs. 1997	0.90 (0.85-0.96)	0.96 (0.87-1.07)	0.99 (0.99-1.00)	1.02 (1.01-1.02)
2003 vs. 1997	0.81 (0.76-0.85)	0.97 (0.88-1.07)	1.02 (1.01-1.02)	0.96 (0.96-0.97)
2006 vs. 1997	0.71 (0.67-0.75)	1.04 (0.95-1.15)	1.01 (0.99-1.01)	0.90 (0.89-0.90)

Table 3. Odds ratios results from multivariate logistic regression models including propensity scores values and all identified demographic and cormorbid risk factors for CDAD (See table 3) for each of the four surrogate variable of severity: mortality, colectomy, length of stay , and charges. Charges inflation adjusted to June 2009 dollars utilizing the consumer price index for hospital inpatient services. Length of stay and charges modeled as dichotomous values at the median value. Confidence Interval (CI)

Comorbid Disease Category	Univariate Odds Ratio	95% CI	Multivariate Odds Ratio	95 % CI
Inflammatory Bowel Disease	12.81	11.75-13.97	11.42	10.16-12.83
Solid Organ Transplant	7.76	6.91-8.71	4.53	3.92-5.24
HIV	6.16	4.94-7.69	4.09	3.16-5.30
Hematopoietic stem cell transplantation	19.38	17.54-21.42	3.31	2.87-3.82
Neoplastic Disease	6.84	6.53-7.16	3.10	2.89-3.31
Fungal Infection	13.28	12.13-14.53	2.71	2.39-3.07
Cystic Fibrosis	4.00	3.47-4.61	2.65	2.22-3.17
Pancreatitis	5.06	4.44-5.77	2.86	2.41-3.39
Hematologic disorders	5.16	4.94-5.39	2.50	2.34-2.66
Gastrostomy	6.81	5.90-7.84	2.00	1.67-2.39
Liver Disease	6.74	6.11-7.42	2.04	1.80-2.32
Malnutrition	8.50	7.85-9.22	2.39	2.14-2.67
Renal disease	6.81	6.45-7.20	2.09	1.99-2.19
Systemic lupus erythematosus	2.95	2.36-3.70	2.06	1.58-2.68
Gastroesophageal reflux	3.32	3.04-3.63	1.97	1.76-2.20
Bacterial Infection	2.57	2.47-2.68	1.84	1.74-1.94
Cardiac disease	2.06	1.86-2.26	1.38	1.23-1.56
Appendicitis	0.92	0.82-1.02	1.46	1.28-1.66
Asthma	0.53	0.49-0.57	0.54	0.49-0.59
Demographic Variables				
Female	0.62	0.60-0.65	0.83	0.79-0.96
Black vs. white	0.54	0.50-0.58	0.63	0.58-0.68
Hispanic vs. white	0.78	0.73-0.82	0.78	0.74-0.83
Other race vs white	0.86	0.78-0.95	0.85	0.77-0.94
Midwest vs Northeast	0.96	0.90-1.02	0.94	0.86-1.02
South vs Northeast	0.77	0.73-0.81	0.80	0.76-0.85
West vs Northeast	1.14	1.08-1.20	1.08	1.02-1.15
Urban vs rural	1.90	1.76-2.05	1.42	1.29-1.59
Medicaid/Medicare vs. Private insurance/HMO	0.68	0.65-0.71	0.80	0.76-0.85
Other payer type (self pay, No pay) vs private insurance/HMO	0.63	0.58-0.68	0.80	0.73-0.88
Year				
2000 vs. 1997	0.98	0.91-1.06	1.07	0.98-1.16
2003 vs. 1997	1.24	1.17-1.33	1.35	1.25-1.46
2006 vs. 1997	1.75	1.65-1.86	1.87	1.74-2.01

Table 4. Odds ratio of CDAD by logistic regression analysis, both univariate and multivariate models; Confidence Interval (CI).