Impact of coexisting pneumonia in the patients admitted with *Clostridium difficile* infection: a retrospective study from a national inpatient database

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ABSTRACT

Clostridium difficile is a gram-positive anaerobic spore forming bacillus that can cause infection in a setting of antibiotic use. Pneumonia is a major cause of morbidity and mortality in an inpatient setting and is frequently associated with significant antibiotic administration. This study aims to compare the outcomes of *C. difficile* infection (CDI) with and without pneumonia to determine the impact of pneumonia in hospitalized patients with CDI.

This population-based retrospective observational propensity matched analysis study uses data from the National Inpatient Sample database for the years 2016 and 2017. The primary outcomes were in-hospital mortality, total hospital charges, and mean length of stay. Secondary outcomes were the rates of sepsis, septic shock, non-ST elevation myocardial infarction (NSTEMI), acute renal failure, deep vein thrombosis, and pulmonary embolism.

In-hospital mortality was noted to be higher in patients with pneumonia than those without (6.5% vs 1.2%, adjusted OR (aOR) 3.85; 95% CI 2.90 to 5.11, p<0.001). The following outcomes were more prevalent in patients with pneumonia compared with those without pneumonia: sepsis (9.8% vs 1.8%, aOR 4.69, 95% CI 3.73 to 5.87, p<0.001), septic shock (4.0% vs 0.5%, aOR 6.32, 95% CI 4.43 to 9.03, p<0.001), NSTEMI (1.9% vs 0.5%, aOR 2.95, 95% CI 1.85 to 4.71, p<0.001), and acute renal failure (31.5% vs 23.1%, aOR 1.23, 95% CI 1.07 to 1.40, p=0.003). In conclusion, patients with pneumonia were associated with significantly higher rates of system-based complications and higher in-hospital mortality rates.

Significance of this study

What is already known about this subject?

- CDI has been reported to be the leading cause of hospital-acquired infection and gastroenteritis-associated mortality costing the USA upwards of $3 billion every year.
- Increasing age, chronic use of proton pump inhibitors, excessive antibiotic usage, end-stage renal disease, solid organ transplant recipient, and patients with inflammatory bowel disease are at increased risk for CDI.
- It has been established that pneumonia has the highest prevalence rates of CDI.
- Overdiagnosis of bacterial pneumonia may lead to inappropriate use of antibiotics, particularly broad-spectrum antibiotics, and has been associated with frequent CDI outbreaks.

What are the new findings?

- For inpatient admission with CDI, patients with coexisting pneumonia have higher rates of mortality, longer length of hospital stay, and higher mean total hospital charge as compared with those without pneumonia.
- Comorbidities such as diabetes mellitus, congestive heart failure, chronic kidney disease, chronic ischemic heart disease, prior cerebrovascular accident, chronic obstructive pulmonary disease, oxygen dependence, malignancy, and anemia were more prevalent in patients with pneumonia compared with those without pneumonia in all CDI hospitalizations.
- System-based complications such as sepsis, septic shock, non-ST elevation myocardial infarction, acute renal failure, deep vein thrombosis, and pulmonary embolism were found to be more prevalent in patients with pneumonia when compared with those without for CDI hospitalizations.

INTRODUCTION

Clostridium difficile is a gram-positive spore-forming anaerobic bacillus that colonizes the colon and can cause a spectrum of diseases ranging from diarrhea to pseudomembranous colitis, which can be fatal if left untreated.[1] *C. difficile* infection (CDI) has been on the rise in the USA, UK, and globally despite best efforts aimed at improving control.[1] CDI is strongly associated with broad-spectrum antibiotic usage

Significance of this study

How might these results change the focus of research or clinical practice?

- Patients with coexistent CDI and pneumonia were found to have higher rates of adverse outcomes such as mortality, longer hospital stays, higher hospital charges, and increased risk of system-based complications. Our study points out the disease burden on the US healthcare system and reflects the need for antibiotic stewardship to prevent adverse outcomes, decrease the disease burden and the system-based complications associated with CDI in a setting of pneumonia.

and is most often acquired at healthcare facilities, such as nursing homes, outpatient physician visits, and urgent care facilities.[1] CDI can occur secondary to use of numerous antibiotics and has been shown to be associated with clindamycin and third-generation cephalosporins among other antibiotic classes.[1]

Like CDI, pneumonia is a major cause of infection-related mortality and morbidity, and it is often an indication for initial broad-spectrum antibiotic administration in hospitals. Previous studies have aimed at assessing the incidence and risk factors associated with CDI in patients hospitalized with pneumonia. They report that a reduction in the overall antibiotic burden, length of antibiotic treatment, and in-hospital stay may reduce the incidence of CDI in patients hospitalized with pneumonia.[1]

While previous literature has focused on the impact of pneumonia and antibiotic usage on the development of CDI, this study focuses on the impact of concurrent pneumonia on CDI-related hospitalizations, mortality, and outcomes. Using the National Inpatient Sample (NIS), the main aim of this study is to examine the differences in patient characteristics, in-hospital mortality, and numerous complications for patients admitted with CDI with and without a secondary diagnosis of pneumonia in the same admission.

MATERIALS AND METHODS

Design and data source

This was a retrospective cohort study involving adult hospitalizations principally for CDI in the USA between January 1, 2016 and December 31, 2017. Data were sourced from the Nationwide Inpatient Sample (NIS). The NIS is a database of hospital inpatient stays derived from billing data submitted by hospitals to statewide data organizations across the US, covering more than 97% of the US population.[2] It approximates a 20% stratified sample of discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals. This dataset is weighted to obtain national estimates.[3] Both the 2016 and 2017 databases are coded using the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS). In the NIS, diagnoses are divided into two separate categories: principal diagnosis and secondary diagnoses. A principal diagnosis was the main ICD-10 code for the hospitalization. Secondary diagnoses were any ICD-10 code other than the principal diagnosis.

Study population

The NIS 2016 and 2017 database was searched for hospitalizations with a principal discharge diagnosis of CDI (A047). This group was divided into two based on the presence or absence of a secondary diagnosis of bacterial pneumonia (BP) (J13, J14, J15, and J18). Patients less than 18 years old were excluded.

Outcome measures

The primary outcome was comparing inpatient mortality in CDI between patients with and without BP. Secondary outcomes included development of sepsis, septic shock, acute kidney failure, non-ST elevation myocardial infarction (NSTEMI), deep vein thrombosis (DVT), pulmonary embolism (PE), as well as mean length of hospitalization (LOS) and mean total hospital charges (THCs).

Statistical analysis

Stata V.16 software (Stata, Texas, USA) was used for data analysis. All analyses were conducted using the weighting samples for national estimates in adjunct with Healthcare Cost and Utilization Project regulations for using the NIS database. Comorbidities were calculated as proportions of the cohort and χ^2 test was used to compare these characteristics between the subgroups. Propensity score matching was used for analysis of the outcome variables. An initial univariate screen with logistic regression analysis was done to identify confounders. Hospitalizations were matched for age, sex, race, household income, hospital region, hospital bed size, comorbid diabetes, hypertension, chronic kidney disease (CKD), heart failure, chronic obstructive pulmonary disease (COPD), anemia, and history of malignancy. The threshold for statistical significance was set as <0.05.

Ethical considerations

The NIS database lacks patient and hospital identifiers. This study was exempt from Institutional Review Board approval as it a retrospective database lacking protected healthcare information.

Data availability statement

The NIS is a large publicly available all-payer inpatient care database in the USA, containing data on more than seven million hospital stays yearly. Its large sample size is ideal for developing national and regional estimates and enables analyses of rare conditions, uncommon treatments, and special populations.

RESULTS

Patient characteristics

The combined NIS database for 2016 and 2017 contained over 71 million weighted hospital discharges of which 196,945 satisfied the inclusion criteria for the study. These patients were adults with a principal discharge diagnosis of *C. difficile*. Of the total, 5990 (3.0) had coexisting BP.

The patients with BP were significantly older (71.1 vs 65.8 years, $p<0.001$), had a lower proportion of women (57.1% vs 64.9%, $p<0.001$), and were majorly insured through Medicaid. Patients with BP also had higher proportion of comorbid diabetes (32.5 vs 27.9%, $p<0.001$), congestive heart failure (CHF) (30.1% vs

Table 1 Patient and hospital characteristics of hospitalizations with *C. difficile* infection

Variable	With BP, %	Without BP, %	
n=196,945	n=5990 (3.0)	n=190,955 (97.0)	P value
Patient characteristics			
Age, mean years	71.1	65.8	<0.001
Women	57.1	64.9	<0.001
Racial distribution			0.731
White	76.8	75.4	
Black	10.0	10.4	
Hispanic	7.0	7.5	
Others	6.2	6.7	
Charlson Comorbidity Index score			<0.001
0	11.7	26.8	
1	18.0	20.8	
2	16.4	17.1	
≥3	53.9	35.3	
Insurance type			<0.001
Medicaid	79.2	66.1	
Medicare	8.5	11.3	
Private	11.0	20.2	
Uninsured	1.3	2.4	
Median annual income in patient's zip code, US$*			0.022
1–43,999	31.7	27.8	
44,000–55,999	26.2	27.3	
56,000–73,999	23.6	24.3	
≥74,000	18.5	20.6	
Comorbidities			
Diabetes	32.5	27.9	<0.001
Hypertension	37.7	40.9	0.023
Smoking history	35.1	35.8	0.633
CHF	30.1	15.7	<0.001
CKD	25.4	19.4	<0.001
Dyslipidemia	35.5	36.5	0.469
Obesity			
Chronic IHD	28.6	21.9	<0.001
Prior CVA	3.9	2.7	0.012
Liver disease	7.4	7.4	0.937
COPD	32.7	16.8	<0.001
Oxygen dependence	6.3	2.7	<0.001
History of malignancy	19.5	13.6	<0.001
History of anemia	46.5	35.3	<0.001
Hospital characteristics			0.178
Hospital region	16.9	18.7	
Northeast	24.4	24.2	
Midwest	42.1	39.5	
South	16.6	17.6	
West			
Hospital bed size			0.438
Small	22.5	21.0	
Medium	28.8	29.7	
Large	48.7	49.3	
Urban location	85.1	88.9	<0.001
Teaching hospital	54.2	60.8	<0.001

Continued

Table 1 Continued

Variable	With BP, %	Without BP, %	
n=196,945	n=5990 (3.0)	n=190,955 (97.0)	P value

*For 2017.

BP, bacterial pneumonia; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; IHD, ischemic heart disease.

15.7%, p<0.001), CKD (25.4% vs 19.4%, p<0.001), and COPD (32.7% vs 16.8%, p<0.001) compared with patients without BP. Patient and hospital characteristics are detailed in table 1.

Primary outcome: in-hospital mortality

Inpatient mortality for CDI was 1.3%. Patients with BP had higher odds of in-hospital mortality (adjusted OR (aOR): 3.85, 95% CI 2.90 to 5.11, p<0.001) when adjusted for comorbidities (age, sex, racial distribution, Charlson disease severity index, hospital location, hypertension, smoking history, CKD, CHF, dyslipidemia, diabetes, chronic ischemic heart disease (IHD), atherosclerosis, and liver disease) using multivariate logistic regression analysis.

Secondary outcomes

The total length of hospitalization, and the THCs between the groups with and without BP were compared using multivariate linear regression model. Patients with BP had an increased mean length of hospitalization (aOR: 3.5, 95% CI 3.0 to 4.0, in days, p<0.001) and mean THC in US$ (aOR: $36,000, 95% CI $29,800 to $42,200, p<0.001) compared with patients without BP. Patients with BP were found to have higher aOR of having NSTEMI (aOR: 2.95, 95% CI 1.85 to 4.71, p<0.001), septic shock (aOR: 6.32, 95% CI 4.42 to 9.03, p<0.001), and acute PE (aOR: 2.05, 95% CI 1.09 to 3.04, p=0.025). Detailed outcomes are provided in table 2.

DISCUSSION

Clostridium difficile infection and pneumonia

C. difficile is known to colonize the colon and can cause a broad spectrum of illnesses, some of which can be life-threatening.[1] CDI has been reported to be a leading cause of gastroenteritis-associated mortality, and it remains a major cause of hospital-acquired infection.[4 5] CDI is the leading cause of healthcare facility-associated diarrhea with 70%–80% of CDIs associated with exposure at a healthcare facility, such as nursing homes, urgent cares, and outpatient physician visits, and has been estimated to cost the US more than $3 billion per year, once more underscoring the major healthcare burden of CDI.[6] Susceptibility to CDI is induced by disruption to the gut microflora, most often by antibiotics in healthcare facilities.[6] Certain patient populations are at higher risk for CDI, which may be secondary to frequent antibiotic use, host factors, or both.[5] Patients who are at higher risk include older adults, those using proton pump inhibitors or antibiotics, those with end-stage renal failure, recipients of solid organ transplants, and those with inflammatory

Table 2 Clinical outcomes of patients with *C. difficile*

Outcome	With BP, % n=5990 (3.0)	Without BP, % n=190,955 (97.0)	aOR (95% CI)	P value*
Primary outcome				
In-hospital mortality	6.5	1.2	3.85 (2.90 to 5.11)	<0.001*
Secondary outcomes				
Length of stay, mean	9.3	5.4	3.5† (3.0 to 4.0)	<0.001*
Total hospital charges, mean US$	75,700	36,900	36,000† (29,800 to 42,200)	<0.001*
Sepsis	9.8	1.8	4.69 (3.74 to 5.87)	<0.001*
Septic shock	4.0	0.5	6.32 (4.42 to 9.03)	<0.001*
NSTEMI	1.9	0.5	2.95 (1.85 to 4.71)	<0.001*
Acute renal failure	31.5	23.1	1.23 (1.07 to 1.40)	0.003*
Deep vein thrombosis	3.1	1.8	1.51 (1.05 to 2.15)	0.024*
Pulmonary embolism	0.9	0.4	2.05 (1.09 to 3.04)	0.025*

*Statistically significant.
†Adjusted mean difference.
aOR, adjusted OR; BP, bacterial pneumonia; NSTEMI, non-ST elevation myocardial infarction.

bowel disease.[5] Diagnosis of CDI may be done through enzyme immunoassays for *C. difficile* toxins, which has allowed for rapid diagnosis since their use as routine testing by many laboratories.[7]

Pneumonia is a respiratory illness that occurs when a host that is susceptible to a pathogen is exposed to a high-density inoculum of the pathogen, has compromised immunity (either systemic or secretory), or has an impaired clearance mechanism.[8] Patients typically have an initial colonization or infection of the upper respiratory tract with invasion of the lower tract occurring when normal defense mechanisms are impaired, such as in the case of viral infections, chronic malnutrition, chronic aspiration, postexposure to environmental pollutants, or impaired cough reflex.[8] BP may also occur through hematogenous spread.[8] Early stages of bacterial or lobar pneumonia may be characterized by the accumulation of protein-rich edema fluid that has multiple organisms, which can fill the alveoli and lead to capillary congestion. This leads to neutrophil exudation and intra-alveolar bleeding as well as decreased lung compliance, increased pulmonary resistance, small airway obstruction, changes in the ventilation-perfusion ratio, and air trapping. This ultimately leads to the clinical signs of respiratory distress in patients with pneumonia.[8]

Empirical evidence has noted the concurrence of pneumonia with CDI in the USA, attributing the correlation to the use of antimicrobial treatment.[5] Misdiagnosis of pneumonia and improper use of antimicrobials have been associated with a CDI outbreak.[5] CDI is also a severe but frequent complication of antibiotic treatment in elderly patients hospitalized with pneumonia.[8] Pneumonia leads to increased intrahospital antibiotic treatment and often is treated with broad-spectrum antibiotics empirically, which may lead to CDI by inducing dysbiosis of the intestinal flora.[9 10] Increased broad-spectrum antibiotic use has been linked to the increased number of hospitalizations with pneumonia and underscores the potential for increased CDI.[10]

Previous research has examined the impact of CDI on patients with pneumonia and found that CDI is very prevalent in patients with pneumonia.[5] Additionally, an NIS database analysis from 2009 to 2011 data collection showed that CDI was associated with increased in-hospital mortality, LOS, and THC compared with those without CDI.[5] Despite the known connection, there is a lack of objective data comparing the differences in hospitalization outcomes in patients with known CDI with and without pneumonia, data which may be valuable in guiding clinical management of patients with CDI.

Age and gender

A higher average age was found in the group with pneumonia than the group without pneumonia (table 1). Risk of CDI is known to be greater with increased age, which is reflected in the overall average age of both groups.[5] Specifically, previous studies report that individuals aged 65 years and older are at increased risk of CDI.[10] Older age is a known risk factor for pneumonia, especially in patients over the age of 65.[11] Older adults who are frail are reported to be at risk of pneumonia because of the presence of underlying illnesses and functional differences in ability compared with non-frail, younger counterparts, which increases the risk of acquiring infectious diseases, including pneumonia.[12] One large population-based US study found that the annual attack rate of community-acquired pneumonia increased from 1.8% in people aged 65–69 years to 5% in adults aged over 85 years.[13] This study affirms previous findings associating age and pneumonia.

Women were more prevalent than men in both groups, but the group without pneumonia had more women than the group with pneumonia (table 1). Previous research examining differences in postinjury pneumonia between genders found no difference in mortality that was gender-specific, but men were found to have a higher incidence of postinjury pneumonia.[14] On the other hand, previous research has also established that women have a lower incidence of ventilator-associated pneumonia but increased mortality and increased rates of severe features.[15] Previous research has also reported that both sexes were equally

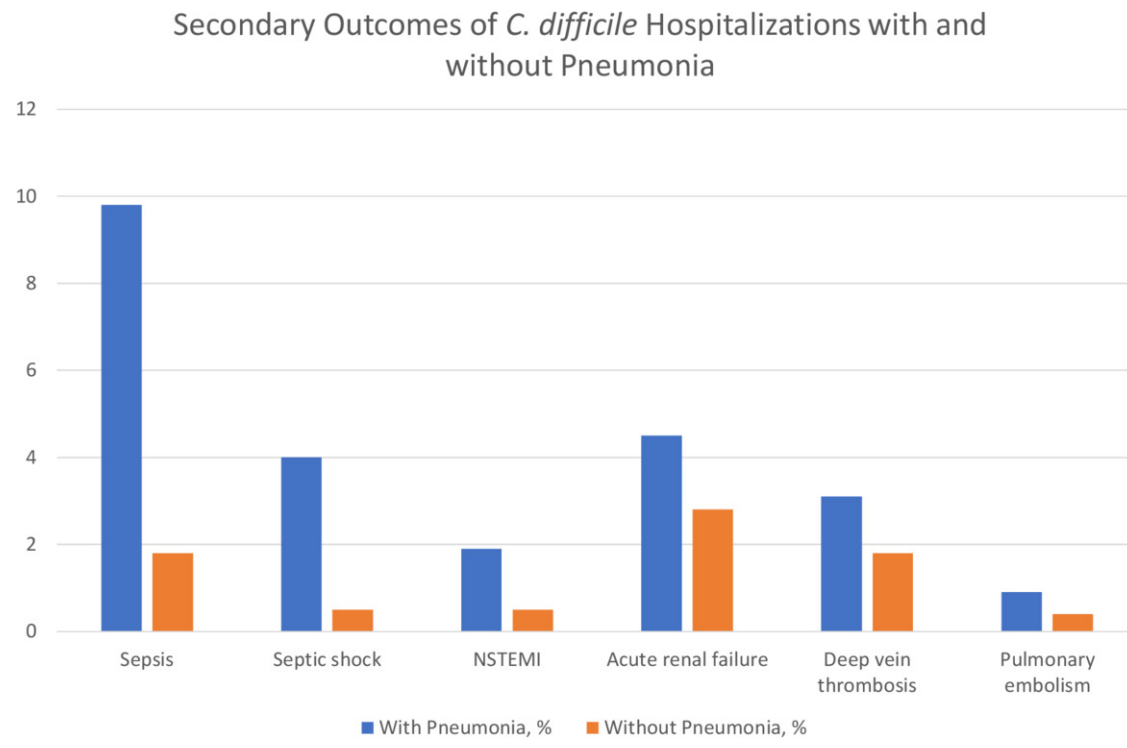

Figure 1 Secondary outcomes of *Clostridium difficile* hospitalizations with and without pneumonia. Blue indicates the per cent of patients with pneumonia and orange indicates the per cent of patients without pneumonia. NSTEMI, non-ST elevation myocardial infarction.

likely to contract pneumonia.[16] The findings of this study may simply be secondary to hospitalizations recorded or may point to potential gender-related differences in pneumonia development in patients with CDI, but there is a need for more information with future studies before a true consensus or hypothesis can be established.

Charlson Comorbidity Index and comorbidities

The Charlson Comorbidity Index (CCI) was developed as a tool to predict 1-year mortalities in over 600 patients.[17] It is based on comorbidity data that is gathered from hospital chart review that is weighted based on the potential effect on patient mortality.[17] The CCI has been modified as a tool for increased applicability to help in the prediction of outcomes and risks of mortality with numerous comorbid conditions.[18] CCIs of 3 and greater were more prevalent in the group with pneumonia, while CCIs of 0–2 were more prevalent in the group without pneumonia (table 1). Additionally, the following comorbidities were more prevalent in the group with pneumonia: diabetes, CHF, CKD, chronic IHD, prior cerebrovascular accident, COPD, oxygen dependence, history of malignancy, and history of anemia (table 1). The higher prevalences of numerous comorbidities may be secondary to increased age, as with increasing age, the frequency of numerous comorbidities rises.[19] Comorbidities that have been associated with increased risk of community-acquired pneumonia include COPD, CHF, chronic liver disease, chronic renal disease, diabetes mellitus, malignancy, and cerebrovascular accident.[19] The findings of our study reflect this, as CHF, CKD, prior cerebrovascular accident, malignancy, and COPD (among other comorbidities) were more prevalent in patients with pneumonia than those without pneumonia.

In-hospital complications

Rates of the following in-hospital complications were higher in the group with pneumonia than without pneumonia: sepsis, septic shock, NSTEMI, acute renal failure, DVT, and PE (table 2, figure 1). Previous research has looked at the sequelae of pneumonia, including sepsis. The PROWESS trial is a large phase III trial that examined severe community-acquired pneumonia as a cause of severe sepsis.[20] The PROWESS trial found that community-acquired pneumonia was present in a large percentage of patients with severe sepsis, with markedly abnormal biomarkers of inflammation and coagulation being found in the community-acquired pneumonia subgroup.[20] The circulating cytokine response to pneumonia has been shown to continue over a week after presentation and many patients may seek hospital care when the classic cytokine cascade is already fully activated.[21] Additionally, patients with pneumonia with high circulating levels of anti-inflammatory cytokines and proinflammatory cytokines had markedly increased severe sepsis risk and risk of death.[21] The link between pneumonia and sepsis (and potentially subsequent septic shock) is known, and the findings of this study reinforce the known correlation between the two. Regarding DVT and PE, several common respiratory disorders, including pneumonia, are considered to be hypercoagulable states, which results in increased risk for venous thromboembolism.[22]

Length of stay, total hospital charges, and in-hospital mortality

In-hospital mortality, LOS, and THC were greater in the group of patients with pneumonia compared with the group without pneumonia (table 2). Previous studies have confirmed that in patients with pneumonia, CDI increases LOS, THC, and in-hospital mortality rates.[5] The differences in LOS and THC may be secondary to the need for additional consultants based on the presence of more comorbidities (table 1) and greater rates of in-hospital complications (table 2) in patients with pneumonia and CDI than those with CDI alone. The greater in-hospital mortality rate finding reflects that those hospitalized with CDI who develop subsequent pneumonia are at increased risk of serious complications, greater financial burden, and longer hospital stays and of death. The presence of comorbidities has been reported as a risk factor for mortality in patients with community-acquired pneumonia; therefore, the higher prevalence of numerous comorbidities may impact the overall in-hospital mortality.[19] Moreover, previous research has commented on the relationship between age and mortality in patients with pneumonia, finding that mortality rose at ages 80 and older independent of the number of comorbidities present.[19] Our study found an older age in the group with pneumonia, which may explain the higher overall mortality of patients in the group with pneumonia. A recent retrospective database study found that the overwhelming majority of patients who died of pneumonia had one or more severe chronic conditions, and researchers attributed the mortality difference to the presence of chronic conditions.[23]

Strengths and limitations

This study has several strengths, one of which is the study population. The population used for analysis is drawn from what is thought to be a large, multiethnic hospital-based registry of the USA. Moreover, the study includes and examines numerous outcome-oriented facets and demographics of CDI hospitalizations, allowing for a thorough and comprehensive overview of CDI admissions with pneumonia as a secondary diagnosis.

As with any study, this study also has limitations. NIS is an administrative database that uses ICD-10 codes to gather hospitalization information and clinical outcomes; thus, there is a possibility of coding errors. The NIS database does not contain information about the time of diagnosis or severity of disease for any diagnosis. The data gathered from the NIS was not on individual patients but on CDI hospitalizations. As a result, people admitted numerous times for CDI would be included several times in the data set. Additionally, this study is subject to biases present in retrospective studies.

Despite the limitations, this study's large sample size, scientific questions, and analysis technique contribute to a better understanding of hospitalizations for CDI with concurrent pneumonia and aims to stimulate and encourage future larger controlled multicenter prospective studies on the subject.

CONCLUSION

CDI is a common but potentially deadly infection in hospitalized patients. Pneumonia is a common but potentially deadly infection. Previous research has examined the relationship between these two infectious processes by examining whether antibiotic prescription for pneumonia has impacted or led to the development of infection with *C. difficile*. However, there is a lack of objective data examining the differences in outcomes of patients hospitalized with CDI with and without a secondary diagnosis of pneumonia. Our study found that those who had CDI and pneumonia had higher THCs, longer lengths of stay at the hospital, greater rates of numerous complications, and overall greater in-hospital mortality than those without pneumonia. Additionally, the data showed higher prevalence of comorbid conditions and a higher prevalence of Charlson Comorbidity Index scores of 3 or greater in patients with pneumonia and CDI than those with CDI alone. In conclusion, we strongly believe that patients who are hospitalized with CDI who also have pneumonia may bet at higher risk of serious complications, including death. Thus, aggressive yet appropriate monitoring for complications is recommended in these hospitalized patients.

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