Clostridium difficile Colitis in Patients Undergoing Lower-extremity Arthroplasty

Rare Infection With Major Impact

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Abstract

Background The prevalence of *Clostridium difficile* colitis is reportedly increasing in surgical patients and can negatively impact their outcome. However, as yet there are no clear estimates of the *C difficile* infection colitis rate and its consequences among patients undergoing total joint arthroplasty (TJA).

Questions/purposes We asked: (1) What is the rate of *C difficile* colitis in TJA patients? (2) What are the risk factors of *C difficile* colitis in these patients? And (3) what is the effect of *C difficile* colitis on length of stay, in-hospital mortality, and estimated total charges?

Methods Using ICD-9-CM diagnosis and procedure codes, we queried the Nationwide Inpatient Sample database for patients undergoing TJA for the years 2002 to 2010. Demographic data, comorbidities, occurrence of *C difficile* colitis, length of hospital stay, mortality, and hospital charges were extracted. Logistic regression was performed to identify predictors of *C difficile* colitis and its impact on in-hospital mortality.

Results The incidence of *C difficile* remained less than 0.6% during the study period. Revision TJAs (odds ratio = 6.9 and 4.4 for hip and knee, respectively) and number of comorbidities (odds ratio = 1.5) increased risk of *C difficile* colitis. *C difficile* increased length of hospital stay by a week, hospital charges by USD 40,000, and in-hospital mortality to 4.66% from 0.24%.

Conclusions Using lower and fewer doses of antibiotics in revision TJAs and among patients with many comorbidities may diminish risk of *C difficile* colitis and its consequent mortality.

Level of Evidence Level II, prognostic study. See Instructions for Authors for a complete description of levels of evidence.

Introduction

Lower-extremity total joint arthroplasty (TJA) has become a routine surgical intervention with growing demand. The number of primary and revision THAs and TKAs performed annually is expected to reach 2.9 million by 2030 [20]. TJA relieves pain and restores patients' function [8, 25]. However, patients' outcomes may be compromised by development of postoperative infections [8, 18, 25].

One potential infection after TJA is *Clostridium difficile* colitis [19]. Varying rates of *C difficile* colitis have been reported in the orthopaedic population, ranging from 0.17% after primary THA and TKA [15] to 7.1% in open reduction and internal fixation of intertrochanteric femoral fractures [28]. Intestinal colonization with *C difficile*, a gram-positive, spore-forming bacterium, can range from asymptomatic carriage in 6.6% to 21% of patients [21] to pseudomembranous colitis and toxic megacolon in 3% to 8% of patients [14, 23]. The pathogenesis of *C difficile* colitis is thought to be

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Fig. 1A–C (A) The number of TJAs and (B) the number of *C difficile* diagnoses for all hospitalizations are climbing nationwide. (C) The rate of *C difficile* infection after TJA is holding steady. Pri = primary; rev = revision.

due to suppression of normal gut bacterial flora by routine antibiotics, creating an opportunity for subsequent infection and proliferation of *C difficile* and its associated cytotoxins and enterotoxins [3]. Colonization with *C difficile* often occurs in the hospital setting with administration of antibiotics [4] that disturb flora in the intestinal tract.

Two studies [16, 24] suggest incidence and associated mortality of *C difficile* colitis are increasing, most notably in patients undergoing surgical procedures [34]. In a study by Morris et al. [24], the incidence of *C difficile* colitis increased more than 30% compared to the previous 10 years. Similarly, the overall mortality rate increased to 15.3% from 3.5% [24]. In addition to the burden of increased mortality, *C difficile* has been associated with increased hospital stays and increased admission costs [31, 32]. A recent case-controlled study found a similar incidence of *C difficile* colitis after TJA of 0.16% and identified a greater risk for patients with higher American Society of Anesthesiologist (ASA) physical status scores or with a history of receiving multiple antibiotics [19]. The consensus of these studies is that *C difficile* colitis shows increasing rates and devastating consequences. However, these studies are limited by their relatively small sample sizes.

In the present study, using a large national database, we answered the following questions: (1) What is the rate of *C difficile* colitis in patients with TJA? (2) What are the risk factors of *C difficile* colitis in these patients? And (3) what is the effect of *C difficile* colitis on length of stay, in-hospital mortality, and estimated total charges?

Patients and Methods

We used the Nationwide Inpatient Sample (NIS) database, the largest all-payer database of hospital discharges in the

United States (Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality), to estimate the rate of *C difficile* colitis in patients undergoing primary or revision lower-extremity arthroplasty over the period 2002 to 2010. This study was exempt from review by the institutional review board because the NIS database has been sufficiently deidentified.

Patients were identified by ICD-9-CM procedure codes of 81.51 (THA), 81.53 (revision of THA), 81.54 (TKA), and 81.55 (revision of TKA). Patients with *C difficile* were flagged based on ICD-9-CM diagnosis code 008.45. For all patients with TJA, we also queried for patient demographics (age, sex, and race), insurance type, hospital type (urban academic, urban private, or rural), hospital size (large, medium, or small), region (Northeast, Midwest, South, and West), the 29 Elixhauser comorbidities [1] tracked by the NIS, length of stay, total hospital charges, and in-hospital mortality. The Elixhauser comorbidities index [12] has been used frequently in previous studies using NIS data [11, 17, 29]. Based on recent studies, the Elixhauser comorbidity index performs well in predicting outcome of patients [5, 9, 22] and based on the recent systematic review performed by Sharabiani et al. [27], the Elixhauser comorbidity index seems to be one of the best comorbidity indexes for predicting outcome of patients in administrative databases. Therefore, we decided to use this comorbidity index in our analyses.

Total hospital charges in various years were adjusted to 2010 USD using government estimates of inflation posted on the Bureau of Labor Statistics website [6]. We assessed the impact of *C difficile* colitis on total charges and length of stay, both left-skewed distributions, using a Wilcoxon test. Multivariate logistic regressions were used to identify predictors of *C difficile* colitis and in-hospital mortality. In these regressions, a full model was created using all

Fig. 2 The IQR of length of stay is longer and associated with wider variation in stay when *C difficile* is present.

possible factors and the model was simplified to remove all parameters not affecting the predictive power of the model. These models did not include interaction terms and treated all variables as independent. An interaction term for age by sex was added ad hoc to the model based on an implication in the plotted data that younger males were susceptible to *C difficile* colitis. Similarly, a year by *C difficile* infection term was used to explore whether *C difficile* posed an increasing threat to patient mortality over the period of the study. All analyses were performed using R 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria) using the 'rms' package to perform the logistic regression.

Results

The number of *C difficile* colitis cases nationwide (all procedures, not just TJA) and the number of TJAs performed increased annually, while the incidence of *C difficile* colitis after lower-extremity arthroplasty remained stable through the study period 2002 to 2010 (Fig. 1). The rate of *C difficile* colitis was higher ($p < 0.001$) after revision than primary arthroplasty (0.40% versus 0.07%). Rates were also higher ($p < 0.001$) after THA at 0.16% compared to TKA at 0.08%. Length of hospital stay was longer ($p < 0.001$) in patients with *C difficile* colitis at a median of 10 days (interquartile range [IQR]: 7–17 days) versus those without infection at 3 days (IQR: 3–4 days). This trend was not associated with the number of comorbidities (Fig. 2). Hospitalization charges were also higher ($p < 0.001$) in patients with *C difficile* colitis at a median of USD 77,782 (IQR: USD 48,110–130,889) compared to USD 38,470 (IQR: USD 28,929–53,110).

Revision of hip arthroplasty (odds ratio [OR] = 6.93; 95% CI: 6.06–7.93; $p < 0.001$) or knee arthroplasty (OR = 4.46; 95% CI: 3.81–5.21; $p < 0.001$) were both associated with greater infection (Table 1). The Elixhauser comorbidity index was associated with greater risk of infection (OR = 1.50 per comorbidity; 95% CI: 1.45–1.54; $p < 0.001$). Patients at medium and large hospitals had greater rates of *C difficile* than smaller hospitals. Females had a lower ($p < 0.001$) risk of *C difficile* colitis (OR = 0.83; 95% CI: 0.75–0.92). By adding age and sex to the model, we found a nonsignificant trend for younger males to also have a higher risk of *C difficile* colitis (Fig. 3).

The in-hospital mortality rate was higher ($p < 0.001$) in patients with *C difficile* colitis at 4.66% versus those without *C difficile* at 0.16%. The diagnosis of *C difficile* colitis increased the odds of death by a factor of 7.75. The rate of in-hospital mortality due to *C difficile* outstripped the rates expected from greater age or more comorbidities (Fig. 4). Factors associated with in-hospital mortality after *C difficile* colitis are summarized (Table 2). We added an

Table 1. Multivariate analysis results for identifying risk factors of *Clostridium difficile* colitis

Factor	Odds ratio	Lower 95% CI	Higher 95% CI	p value
Patient age (per year)	1.04	1.03	1.04	< 0.001
Elixhauser Comorbidity Index	1.50	1.46	1.55	< 0.001
Female	0.83	0.75	0.92	< 0.001
Versus small hospital				
Medium	1.42	1.19	1.71	< 0.001
Large	1.59	1.35	1.88	< 0.001
Versus urban academic hospital				
Rural	0.68	0.59	0.78	< 0.001
Urban private	0.62	0.54	0.71	< 0.001
Versus Northeast region				
Midwest	0.62	0.53	0.72	< 0.001
South	0.73	0.60	0.88	< 0.001
West	1.18	1.06	1.31	< 0.001
Versus Medicare primary payer				
Medicaid	1.48	1.09	2.00	0.01
Private	0.91	0.79	1.06	0.22
Self-pay	1.45	0.75	2.81	0.27
No charge	2.11	0.52	8.53	0.29
Other	0.73	0.48	1.11	0.14
Primary THA	1.86	1.64	2.10	< 0.001
Revision THA	6.94	6.07	7.93	< 0.001
Revision TKA	4.46	3.82	5.21	< 0.001
Calendar year	0.94	0.92	0.96	< 0.001

interaction term (year by *C difficile* infection) to the model to examine whether the disease was becoming deadlier over time, but again this term was not statistically significant.

Discussion

Previous studies indicate increasing rates of *C difficile* colitis in hospitalized patients [16, 24]. The emergence of a hypervirulent, fluoroquinolone-resistant *C difficile* strain corresponded with a rise in the incidence of *C difficile* colitis between 2003 and 2005 [7]. *C difficile* colitis is associated with increased mortality, hospitalization cost, and prolonged length of hospital stay [10, 31, 32]. Most previous studies are limited by their relatively small sizes. In the present study, using a large national database, we answered the following questions: (1) What are rates of *C difficile* colitis in patients with TJA? (2) What are the risk factors of *C difficile* colitis in these patients? And (3) what is the effect of *C difficile* colitis on length of stay, in-hospital mortality, and estimated total charges?

Fig. 3A–B (A) A histogram shows the age distribution of *C difficile* cases in TJA. (B) A graph shows possible sex-related differences in age versus rate of *C difficile*, although this is not supported in statistical analysis (see text).

This study has some limitations that need to be highlighted. First, the NIS only tracks patients from admission to discharge. Patients diagnosed with *C difficile* after discharge would not be detected, nor would patients who died post-discharge. Second, it is impossible to parse preexisting comorbidities from those resulting from *C difficile* infections within this database. Similarly, we do not know whether longer length of stay was due to infection or was a risk factor for infection. However, Forster et al. [13] similarly found *C difficile* infection increased length of stay independent of baseline risk of death. Third, coding reliability is always an issue with administrative databases and may affect results of studies using these databases. There is no information in the NIS database about how *C difficile* colitis was diagnosed in study patients. Finally, no medication information is available in the NIS database, which prevents any assessment of the association between excessive antibiotic use and *C difficile* colitis.

Although we found the national incidence of *C difficile* colitis after TJA during the study period was stable, other reports indicate the overall incidence of *C difficile* colitis is increasing [26, 31]. A single-center study comparing the incidence of *C difficile* colitis from the period 1984–1994 with the period 1994–2000 found a 30% increase; however, most cases occurred in immunocompromised patients while only 9.5% of cases occurred in patients with perioperative antibiotics as a sole risk factor [7]. This suggests the increasing overall incidence of *C difficile* colitis is due to a rise in primary cases, rather than complications of perioperative antibiotics. The other point that may explain the difference in the trends of *C difficile* in our study compared to previous studies that mainly focused on nonorthopaedic patients is the type of antibiotic prophylaxis [7]. Carignan et al. [7] specifically examined the risk of *C difficile* colitis after perioperative antibiotic

Fig. 4A–B The effect of *C difficile* on mortality outstrips effects associated with (A) increasing age or (B) number of comorbidities. No Cdiff = no *C difficile* present; Cdiff = *C difficile* present.

prophylaxis in patients undergoing various types of surgeries and found patients receiving monotherapy with cephazolin, the primary antibiotic therapy used in THAs, were at lesser risk than patients receiving other antibiotic prophylaxis regimens.

We found patients undergoing revision TJA had a higher risk of *C difficile* colitis. Given the complex nature of revision cases, the ensuing hospitalizations are lengthier and revision cases may have increased exposure to antibiotics that can predispose them to hospital-acquired *C difficile* infection. The balance between antibiotic prophylaxis and risk for *C difficile* colitis remains controversial. Kurd et al. [19] demonstrated use of multiple antibiotics, and not duration of regimen, was associated with *C difficile*

colitis [19]. Single-dose versus extended-dose prophylaxis remains controversial, although a systematic review found no difference in infection prevention for internal fixation of fractures [30]. There remains an argument for reducing exposure to perioperative antibiotics, particularly in patients at risk for *C difficile* colitis [15, 33]. Aside from limiting antibiotic exposure, targeted prophylaxis regimens using single-dose gentamicin and flucloxacillin or teicoplanin have demonstrated efficacy in reducing the incidence of *C difficile* colitis [2]. Consistent with previous research, males and patients with an underlying comorbidity were at a higher risk for *C difficile* colitis [7]. Interestingly, increased age was not a risk factor for *C difficile* colitis in this analysis. In nonorthopaedic patient populations,

Table 2. Multivariate analysis results for identifying risk factors of in-hospital mortality

Factor	Estimated odds ratio	Lower 95% CI	Higher 95% CI	p value
Patient age (per year)	1.08	1.08	1.09	0.00
Elixhauser Comorbidity Index	1.50	1.46	1.54	0.00
Female	0.60	0.55	0.66	0.00
Versus Northeast region				
Midwest	0.86	0.75	1.00	0.04
South	1.12	1.00	1.26	0.05
West	0.78	0.68	0.91	0.00
Versus white				
Black	1.51	1.28	1.79	0.00
Hispanic	1.10	0.87	1.39	0.41
Asian	1.23	0.79	1.92	0.36
Native American	0.89	0.37	2.16	0.80
Other	1.70	1.31	2.21	0.00
Versus Medicare primary payer				
Medicaid	1.95	1.44	2.64	0.00
Private	0.95	0.82	1.10	0.52
Self-pay	2.09	1.18	3.71	0.01
No charge	1.62	0.40	6.59	0.50
Other	1.12	0.78	1.62	0.54
Primary THA	3.90	2.56	5.94	0.00
Primary TKA	2.03	1.32	3.11	0.00
Revision THA	7.86	5.18	11.92	0.00
Revision TKA	3.54	2.28	5.50	0.00
Calendar year	0.89	0.87	0.90	0.00
<i>Clostridium difficile</i>	7.76	5.80	10.37	0.00

increased age has been associated with *C difficile* infection [26, 31]. It has been suggested that increased age serves as a marker of increased comorbidities and exposure encounters in the hospital setting [4]. It is possible, due to the advanced age of patients presenting for lower-extremity arthroplasty, there may be a selection bias favoring an older population without substantial variation in age between patients with or without *C difficile* colitis.

Our findings suggest hospital type and location influence the incidence and outcome of *C difficile* colitis after TJA. As mentioned earlier, coding reliability is one of the limitations of administrative databases and this finding may reflect better detection and reporting, rather than more infections, among different hospital types or geographic regions. Previous studies showed mixed results in this regard. One NIS-based study [34] reported large, north-eastern US, urban teaching hospitals have a higher rate of *C difficile* colitis after general surgery procedures. However, another [31] suggested self-pay patients in smaller hospitals have a higher risk of death from *C difficile* colitis,

but this may reflect better reporting rather than greater infection rates. However, similar to our study, in both an NIS study [31] and a Pennsylvania state database [32], *C difficile* colitis was associated with increased hospital costs, regardless of hospital type or size. Our multivariate model indicated *C difficile* colitis increased the odds of in-hospital mortality. Increased mortality of *C difficile* colitis may result from hypervirulent strains with increased antibiotic resistance [7]. The question is confounded by comorbidities: sicker patients are expected to be at greater risk for mortality and for *C difficile* colitis, but in this database, we could not rule out comorbidities arising from the *C difficile* infection.

In conclusion, we can state *C difficile* infection is currently a rare event in TJA but a damaging one. *C difficile* is associated with longer hospital stay, higher hospital charges, and in-hospital mortality after TJA. More cautious administration of antibiotics in patients with revision TJAs and more comorbidities may diminish risk of *C difficile* colitis and its consequent mortality.

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