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ORIGINAL ARTICLE • KNEE - ARTHROSCOPY

Clostridium difficile infection in the USA: incidence and associated factors in revision total knee arthroplasty patients

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Abstract

Introduction Revision total knee arthroplasty (TKA) procedures performed secondary to periprosthetic joint infection (PJI) are associated with significant morbidity and mortality. These poor outcomes may be further complicated by postoperative infection requiring antibiotics. However, antibiotic overuse may suppress patients' bacterial flora, leading to *Clostridium difficile* infection (CDI). Therefore, we aimed to study the: (1) incidence; (2) costs; and (3) risk factors associated with CDI in revision TKA patients.

Methods The National Inpatient Sample database was queried for individuals diagnosed with PJI who underwent revision TKA between 2009 and 2013 ($n = 83{,}806$). Patients who developed CDI during their inpatient stay were identified ($n = 799$). Logistic regression analysis was conducted to assess the association between hospital- and patient-specific characteristics and the development of CDI.

Results The incidence of CDI after revision TKA was 1.0%. These patients were older (mean age 69.05 vs. 65.52 years), had greater LOS (median 11 vs. 5 days) and greater costs ($30,612.93 vs. 18,873.75), and experienced higher in-hospital mortality (3.6 vs. 0.5%; $p < 0.001$ for all) compared to those without infection. Patients with CDI were more likely to be treated in urban, not-for-profit, medium/large hospitals in the Northeast or Midwest ($p < 0.05$ for all) and to have underlying depression (OR 4.267; $p = 0.007$) or fluid/electrolyte disorders (OR 3.48; $p = 0.001$).

Conclusion Although CDI is rare following revision TKA, it can have detrimental consequences. We demonstrate that CDI is associated with longer LOS, higher costs, and greater in-hospital mortality. With increased legislative pressure to lower healthcare expenditures, it is crucial to identify means of preventing costly complications.

Keywords *Clostridium difficile* · Periprosthetic joint infection · Total knee arthroplasty · Revision total knee arthroplasty · Joint infection

Introduction

Periprosthetic joint infection (PJI) is a devastating complication following total knee arthroplasty (TKA) and is currently the most common cause for revision TKA in the USA [1]. Given the projected increase in demand for TKA [2–5], the total number of PJIs is expected to grow substantially [6]. Surgical management consists of either a one- or two-stage revision procedure, which involves removal of the infected prosthesis, joint irrigation and debridement, antibiotic spacer implantation, and replacement with a long-term prosthesis. Intravenous or oral antibiotic therapy is used as an adjunct pre- and postoperatively to ensure infection eradication and prevent systemic dissemination [7–9].

However, the high antibiotic loads administered for treating PJI can have a bactericidal effect on normal gut flora and cause overgrowth of *Clostridium difficile* (CDI). CDI overgrowth is characterized by the overproduction of clostridium cytotoxins and endotoxins that can cause intestinal wall inflammation and destruction. In late-stage sequelae, this can lead to toxic megacolon, bowel perforation, and death;

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however, most patients will experience profuse/bloody diarrhea. The emergence of the virulent NAP1/B1/027 strain, coupled with increasing antibiotic resistance and a growing incidence of CDI, has catapulted CDI prevention to a high priority on a national level [10–12]. These efforts were underscored by the US government's decision to withhold Medicare reimbursement for hospitals with high incidences of *C. difficile* [13]. As such, there have been increasing efforts at institutional levels to reduce nosocomial acquired CDI with aims to improve patient outcome while reducing marginal costs. Currently, few studies explore CDI in revision TKA patients undergoing treatment for PJI. Thus, this study aimed to quantify the incidence of CDI in revision TKA patients with PJI, as well as its associated factors and effect on hospital costs. Specifically, we evaluated: (1) the incidence of CDI after revision TKA; (2) patient comorbidities and mortality associated with development of CDI; and (3) comparison of inpatient hospital costs between revision TKA with a primary diagnosis of PJI who did and did not develop CDI.

Methods

Database

The National Inpatient Sample (NIS) database, conducted by the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality, is the largest publicly available all-payer inpatient healthcare database in the USA. Unweighted it contains data on over seven million hospital stays, and over 35 million hospital stays annually when weighted [14]. Each individual entry consists of demographic information, which includes age, sex, ethnicity, insurance and socioeconomic status, comorbidities, hospitalization outcome, length of stay (LOS), and the cost of hospitalization. The database contains one primary discharge diagnosis and up to 24 secondary discharge diagnoses during the period of hospitalization, and one primary procedure code and up to 14 secondary procedure codes. NIS does not contain patient-identifying information, and therefore this study did not require Institutional Review Board approval.

Patient selection

The National Inpatient Sample (NIS) database was queried for all individuals diagnosed with prosthetic joint infection using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) 996.66 and revision TKA (ICD 9-CM: 00.80 (all-component revision), 00.81 (tibial component revision), 00.82 (femoral component revision), 00.83 (patellar component revision), 00.84 (isolated tibial insert exchange), 80.06 (arthrotomy/removal of prosthesis), and 81.55 (revision TKA not otherwise specified) between the years 2009 and 2013. Patients who developed CDI during their inpatient hospital stay were identified using ICD-9-CM code 008.45. This yielded 83,806 (1.0% with CDI) patients with a mean age of 65 (standard deviation = 11.2).

Covariates

Patient demographics (age, gender, race and insurance status), hospital characteristics (rural, urban non-teaching, urban teaching; small bed size vs. large bed size, medium bed size vs. large bed size), hospital ownership [government, nonfederal (Public); Private, Not for Profit (Voluntary); Investor-Owned (Proprietary), Private] and patient comorbidities were utilized as covariates in the statistical models. Patient comorbidities were identified using HCUP comorbidity software, which utilizes select ICD-9 codes to isolate for 30 different comorbidities. Patient comorbidity severity level was calculated utilizing the Charlson–Deyo comorbidity score. Patient race was categorized as White, Black, Hispanic, Asian or Pacific Islander, Native American, or other.

Statistical analysis

An independent samples *T* test and a Chi-square analysis were conducted to assess continuous and categorical variables, respectively. A propensity score matching analysis was conducted to control for group differences in hospital demographics (Table 1). A subsequent stepwise conditional logistic regression analysis was conducted to assess the association between patient-specific characteristics and the development of CDI while limiting model over-fitting. A hierarchal model was utilized to account for residual hospital clustering not controlled for by propensity score matching and imbalance in racial demographics. Bonferroni correction was applied to control for the false discovery rate [15]. The model demonstrated good fit (Hosmer–Lemeshow p value = 0.122), with an area under the curve of 0.86 (95% CI 0.81–0.91; Fig. 1). Additionally, a multivariate regression analysis was conducted to assess costs in which multilevel categorical independent factors were transformed into dummy variables. Independence of predictor variables was evaluated through assessment of tolerance factors. Length of stay (LOS) and CDI were additionally imputed as an interaction term to evaluate the additive effect of CDI on costs for each increase in patient LOS. All continuous variables were imputed in regression models in their mean-centered form to improve interpretation [16, 17]. A two-tailed p value less than 0.05 was considered statistically significant. All data were analyzed using SPSS version 24 (Armonk, USA).

Table 1 Propensity score-matched demographics of revision TKA patients with PJI who developed CDI

	Clostridium difficile infection	No *C. difficile* infection	*p* value
Total number	799	786	
Age in years (SD)	66.97 (11.5)	69.05 (12.1)	< 0.001
Median LOS in days (IQR)*	11 (9)	5 (4)	< 0.001
Gender			
Male (%)	336 (42.1%)	405 (51.5%)	< 0.001
Female (%)	462 (57.9%)	381 (48.5%)	
Charlson–Deyo comorbidity score			
0	35 (4.4%)	56 (7.1%)	0.001
1	753 (94.2%)	730 (92.9%)	
2	6 (0.8%)	0 (0.0%)	
≥ 3	5 (0.6%)	5 (0.6%)	
Race			
White	556 (79.4%)	60,816 (81.4%)	< 0.001
Black	79 (11.3%)	7145 (9.6%)	
Hispanic	40 (5.7%)	3948 (5.3%)	
Asian/Pacific Islander	5(0.7%)	613 (0.8%)	
Native American	5 (0.7%)	533 (0.7%)	
Other	15(2.1%)	1615 (2.2%)	
Region			
Northeast	174 (21.8%)	245 (31.2%)	
Midwest	301(37.7%)	174 (22.1%)	
South	203 (25.4%)	120 (15.3%)	< 0.001
West	121 (15.1%)	247 (31.4%)	
Hospital bed size			
Small	25 (5.7%)	45 (5.7%)	< 0.001
Medium	205 (26.1%)	205 (26.1%)	
Large	535 (68.2%)	535 (68.2%)	
Hospital teaching status			
Rural/community	58 (7.4%)	37 (4.7%)	
Urban nonteaching	266 (33.9%)	298 (37.9%)	0.038
Urban teaching	461 (58.7%)	451 (57.4%)	
Control/ownership of hospital			
Government/public	40 (5.1%)	46 (5.9%)	
Private, not-for profit	686 (87.4%)	688 (87.5%)	0.65
Private, investor-owned	59 (7.5%)	52 (6.6%)	

Results

The overall incidence of CDI after revision TKA was 1.0% between the years 2009 and 2013. There was an overall downward trend between 2009 (1.1%) and 2013 (0.7%) in the incidence of CDI (Fig. 2).

Patients that developed CDI were significantly older (mean age = 69.05 vs. 65.52 years; $p < 0.001$) and had a greater median length of hospital stay (11 vs. 5 days; $p < 0.001$) when compared to patients who did not develop CDI (Table 2). Univariate analysis revealed significantly higher rates of CDI in the Northeast (21.8 vs. 18.3%) and Midwest (37.7 vs. 26.0%; $p < 0.001$) regions, at institutions with medium (26.1 vs. 24.8%; $p < 0.001$) and large (68.2 vs. 60.6%; $p < 0.001$) hospital bed sizes, and at urban teaching hospitals (58.7 vs. 52.5%; $p < 0.002$) and private, not-for-profit hospitals (87.4 vs. 76.9%; $p < 0.001$).

After controlling for residual imbalances in hospital and racial characteristics, forward conditional logistic regression modeling demonstrated LOS (OR 1.249; $p < 0.001$), depression (OR 4.267; $p = 0.007$), and fluid and electrolyte disorders (OR 3.48; $p = 0.001$) as being associated with acquiring CDI (Table 3). Chi-square analysis demonstrated higher mortality rates in revision TKA patients with CDI when compared with revision TKA patients who did not develop CDI (3.6% vs. 0.5%; $p < 0.001$) (Table 4).

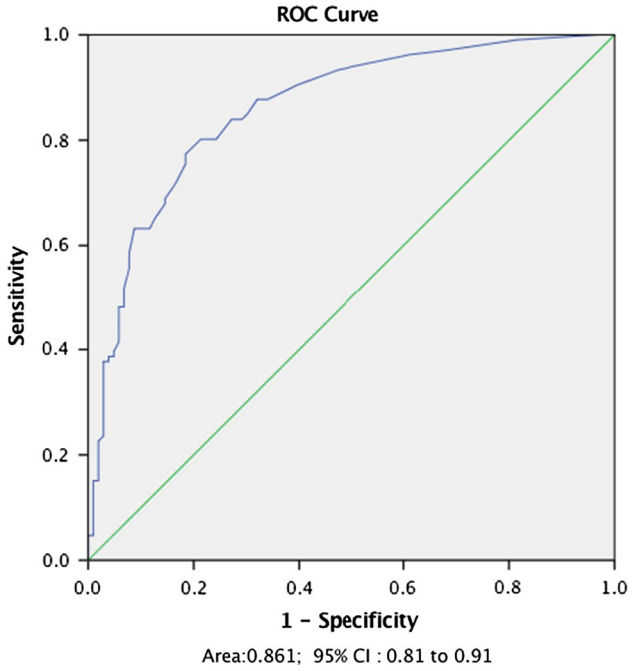

Fig. 1 Receiver under the operating curve for predictive analysis

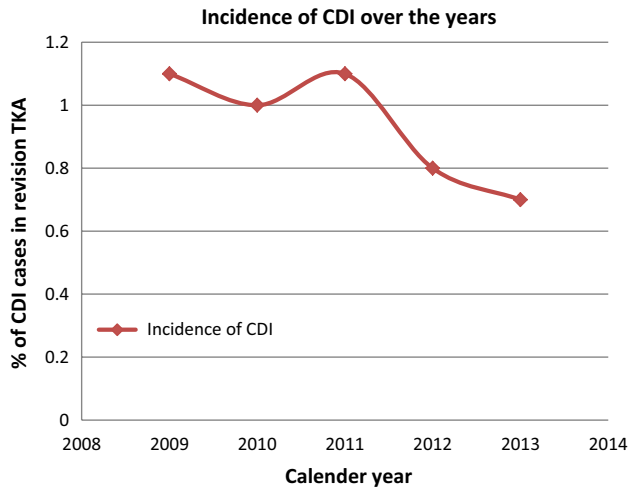

Fig. 2 Chart displaying the incidence of CDI over the years in patients who underwent revision TKA for PJI

Cost comparisons revealed higher median inpatient costs for revision TKA patients who developed CDI when compared to patients without ($30,612.93 vs. 18,873.75; $p < 0.001$) (Table 5). Model 1 of our multilevel regression analysis revealed increased costs for hospitals in the Northeast ($B = 0.081$; $p < 0.001$), South ($B = 0.026$; $p < 0.001$), and Western US census regions ($B = 0.132$; $p < 0.001$). Furthermore, Model 1 revealed increased costs for medium-bed-sized hospitals ($B = 0.032$; $p < 0.001$), government/nonfederal hospitals ($B = 0.039$; $p < 0.001$), rural ($B = 0.027$; $p < 0.001$), and urban teaching ($B = 0.071$; $p < 0.001$) hospitals. Model 2 significantly added to model prediction (adjusted R^2 change = 0.500). Results demonstrated a mean increase of $15,807.09 ($B = 0.697$; $p < 0.001$) for every additional day spent over the mean-centered LOS (7 days). There was a mean cost increase of $725.72 for each additional increase in Elixhauser comorbidity ($B = 0.032$; $p < 0.001$). The LOS * CDI interaction term revealed an increase of $816.43 for patients who developed CDI and stayed longer than the mean LOS (7 days) when compared to patients with a LOS > 7 days; however, CDI alone was not shown to be associated with a significant increase in costs ($B = -0.005$; $p = 0.221$).

Discussion

Antibiotic use is a vital treatment and prophylactic modality for patients undergoing revision TKA for PJI. Unfortunately, significant antibiotic exposure can precipitate CDI, which can lead to increased morbidity and mortality. This study utilized the NIS database to assess factors associated with the development of CDI in patients undergoing revision TKA for PJI. Our findings revealed higher rates of CDI in revision TKA patients with PJI in Northeast and Midwest regions, medium- and large-bed-sized hospital, and urban teaching, not-for-profit hospitals. Patient-specific factors associated with CDI included depression and fluid/electrolyte disorder. Additionally, patients with CDI had higher rates of mortality and higher inpatient hospital costs when compared to patients without CDI.

This study is not without its limitations. Our study utilizes a cross-sectional dataset that is highly dependent on the accuracy of administrative coding with the ICD-9-CM classification system. This system has since been updated in 2014 with ICD-10-CM, thus allowing for a more accurate and specific coding system. Despite this, the dataset provides an ample sample size to best analyze this particular cohort. Furthermore, the NIS database tracks patients from admission to discharge. Thus, patients who developed CDI after their inpatient stay were not included in our analysis. Additionally, the retrospective nature of this study rendered it difficult to establish cause and effect between predictor variable and the development of CDI. This limitation is characteristic of all retrospective studies [18]. Furthermore, limitations to the database rendered it impossible to identify type, dosage, duration, number, and route of antibiotic therapy used for revision TKA patients being treated for PJI. We acknowledge this to be a significant limitation of the present study and as such encourage future studies to explore these factors as causative or associated variables in the development of CDI. However, our study still provides significant value as it

Table 2 Incidence and demographics of revision TKA patients with PJI who developed CDI

	Clostridium difficile infection	No *C. difficile* infection	*p* value
Mean age in years (SD)	69.05 (12.09)	65.52 (11.22)	< 0.001
Median length of stay (IQR)	11 (9)	5 (4)	< 0.001
Gender			
Male (%)	336 (42.1%)	41,685 (50.2%)	< 0.001
Female (%)	462 (57.9%)	41,313 (49.8%)	
Charlson–Deyo comorbidity score			
0	35 (4.4%)	7041 (8.5%)	< 0.001
1	753 (94.2%)	75,697 (91.2%)	
2	6 (0.8%)	171 (0.2%)	
≥ 3	5 (0.6%)	98 (0.1%)	
Race			
White	556 (79.4%)	60,816 (81.4%)	0.728
Black	79 (11.3%)	7145 (9.6%)	
Hispanic	40 (5.7%)	3948(5.3%)	
Asian/Pacific Islander	5(0.7%)	613 (0.8%)	
Native American	5 (0.7%)	533(0.7%)	
Other	15(2.1%)	1615 (2.2%)	
Region			
Northeast	174 (21.8%)	15,200 (18.3%)	
Midwest	301(37.7%)	21,587 (26.0%)	
South	203 (25.4%)	31,294(37.7%)	< 0.001
West	121 (15.1%)	14,926 (18.0%)	
Hospital bed size			
Small	25 (5.7%)	11,975 (14.6%)	< 0.001
Medium	205 (26.1%)	20,396 (24.8%)	
Large	535 (68.2%)	49,892 (60.6%)	
Hospital teaching status			
Rural/community	58 (7.4%)	7103 (8.6%)	
Urban nonteaching	266 (33.9%)	31,994 (38.9%)	0.002
Urban teaching	461 (58.7%)	43,166 (52.5%)	
Control/ownership of hospital			
Government/public	40 (5.1%)	7811 (9.5%)	
Private, not-for profit	686 (87.4%)	63,223 (76.9%)	< 0.001
Private, investor-owned	59 (7.5%)	11,229 (13.7%)	

Table 3 Forward conditional regression modeling demonstrating factors associated with CDI

	Odds ratio	*p* value	95% Confidence interval
Length of stay[a]	1.249	< 0.001	1.114–1.363
Alcohol abuse	0.000	1.000	0.000
Depression	4.267	0.007	1.482–12.287
Liver disease	7.968	0.076	0.806–78.770
Fluid and electrolyte disorder	3.48	0.001	1.642–7.376

[a]Mean-centered length of stay

Table 4 Comparison of in-hospital mortality rates and costs in revision TKA patients with a primary diagnosis of PJI that developed CDI

	CDI	No CDI	*p* value
In-hospital mortality	3.60%	0.50%	< 0.001
Median total hospital costs (IQR)	$30,612.93 ($22,830.20)	$18,873.75 ($13,557.44)	< 0.001

identifies regional differences in incidence as well as differences in costs and resource utilization between patients who acquire and do not acquire CDI. Furthermore, our model was able to identify patient-level comorbidities that were associated with the development of CDI during the

Table 5 Multivariate regression analysis demonstrating the effect of independent factors (patient comorbidities, LOS, and CDI) on total acute care hospital costs (B_0 = $22,678.75)

	Model 1		Model 2	
	B	*p* value	*B*	*p* value
Constant		< 0.001		< 0.001
Hospital region				
Northeast	0.081	< 0.001	0.013	0.001
South	0.026	< 0.001	− 0.008	0.045
West	0.132	< 0.001	0.130	< 0.001
Hospital bed size				
Small	0	0.933	0.033	< 0.001
Medium	0.032	< 0.001	0.060	< 0.001
Hospital control				
Government, nonfederal	0.039	< 0.001	0.036	
Private, investor-owned	− 0.026	< 0.001	− 0.039	
Hospital location/teaching status				
Rural	0.027	< 0.001	0.030	< 0.001
Urban teaching	0.071	< 0.001	0.006	0.106
Patient-specific factors				
Length of stay			0.697	< 0.001
Elixhauser comorbidities			0.032	< 0.001
LOS * CDI			0.036	< 0.001
CDI			− 0.005	0.221
Model sensitivity				
Adjusted R-squared	0.025		0.525	
Adjusted R-squared change	0.025		0.500	
F-change	121	< 0. 001	11.232	< 0. 001

inpatient period, which may lay the foundation for future work among researchers looking to improve care quality.

Despite the morbidity associated with CDI in revision TKA patients, its incidence remains low. In a retrospective study utilizing the NIS database between 2002 and 2010, Maltenfort et al. reported a 0.6% incidence of CDI in patients who underwent lower-extremity joint arthroplasty [19]. Likewise, Kurd et al. [20] reported a 0.16% incidence of CDI in a retrospective review of 9880 total joint arthroplasty patients. Our results demonstrate a slightly higher incidence (1.0%) of CDI among patients undergoing all revision TKA secondary to PJI. This observation may be due to larger antibiotic administration frequently employed for longer durations in patients with PJI undergoing revision TKA [21]. Stevens et al. [22] illustrated this association in their retrospective cohort study entailing 10,154 hospitalizations. There, the authors reported increased hazard ratios for the development of CDI among patients who received 2, 3–4, or 5 antibiotic regimens when compared to patients receiving only one antibiotic regimen [2.5 (95% confidence interval [CI] 1.6–4.0), 3.3 (CI 2.2–5.2), and 9.6 (CI 6.1–15.1), respectively].

Previous studies have also reported an association between patient LOS and CDI. In a retrospective review utilizing the NIS database (years 2009–2011), Miller et al. [23] reported a 1% hospital-associated increase in CDI with each additional day of inpatient hospital stay when compared to the mean ($p < 0.001$). Similarly, in a retrospective matched cohort study of 1260 adult patients who were admitted to an acute care facility (630 cases vs. 630 controls), Song et al. [24] reported a longer mean LOS (+ 4 days; $p < 0.001$) for patients with CDI when compared to patients without CDI after matching for confounding variables.

Our study revealed an association between depression and the development of CDI, which was similarly reported by Rogers et al. [25]. In their two-part study (Study 1: longitudinal investigation of 16,781 patients; Study 2: retrospective study of 4067 patients with CDI), the authors demonstrated greater odds for CDI in persons with major depression (OR 1.36; 95% CI 1.06–1.74) and depressive disorder (OR 1.35; 95% CI 1.05–1.73). However, the association between fluid/electrolyte disorder and CDI, made evident in our study, may be a function reverse causality. This can be elucidated when considering the pathomechanism of CDI, which involves impaired gut absorption, fluid loss, and electrolyte imbalances such as a nonanion gap acidosis.

The present study revealed higher mortality rates among PJI patients that developed CDI. Similarly, Maltenfort et al. [19] reported higher mortality rates among lower-extremity arthroplasty recipients who developed CDI (4.66% vs. 0.16%; $p < 0.001$). A subsequent log regression analysis from the same authors revealed 775% increased odds of death in the same patient group when compared to lower-extremity recipients without CDI ($p < 0.001$). In the same study, the authors reported higher mean costs of care for lower-extremity arthroplasty recipients who developed CDI ($77,782 vs. $38,470; $p < 0.001$). However, the study authors failed to isolate causes for increased costs. Conversely, our study revealed that the variability in cost of care was most explained by an increased LOS among revision TKA patients with a primary diagnosis of PJI, in which patients with CDI experienced steeper cost increases (+ 3.6%; $p < 0.001$) with each additional day over the mean. As per our model, this represented an additional $816 in costs for each additional day over 7 days in patients with CDI versus patients without CDI.

Although this study demonstrated significantly increased lengths of stay, mortality rates, and costs of inpatient care between revision TKA patients with and without CDI, we did note that the overall incidence of CDI in this patient population decreased between 2009 (1.1%) and 2013 (0.7%). However, despite this downward trend, judicious use of antibiotics and attenuation of CDI risk factors are still of paramount importance. As long-term prophylactic antibiotics are becoming a standard adjunct to revision TKA in many

institutions, it is expected that the incidence of CDI will considerably increase if cautions are not taken [26]. In addition to directly increasing inpatient hospital costs—primarily via longer LOS—higher rates of CDI would negatively impact hospital reimbursements. With current hospital payment models emphasizing quality of care over volume of care, Medicare reimbursements for hospitals due to CDI are now being withheld [27]. As such, increased collaboration between arthroplasty surgeons, internal medicine specialists, and other hospital staff is crucial in optimizing both patient and provider outcomes.

Conclusion

CDI can be devastating in patients undergoing revision TKA for PJI. The present study revealed higher mortality rates, increased LOS, and higher costs of care for revision TKA patients with a primary diagnosis of PJI who subsequently developed CDI. Additionally, depression and fluid/electrolyte disorder were associated with CDI. With increasing pressures to reduce the incidence of hospital-acquired CDI, recognizing associated factors may prove beneficial in optimizing care and reducing costs. Long-term prospective studies are needed in order to capture incidences of CDI that may occur in the post-acute care setting.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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