Supplemental Material

Annex A

Methods

Medical records of all 3 groups (HCFA-CDI, CA-CDI, and controls) were reviewed in order to study CDI occurrence, characteristics, and outcomes. Collected data included demographics (age, sex), date of diagnosis, hospitalization within 6 months, previous CDI, use of antibiotics within 6 months before admission, use of PPIs, use of nonsteroidal anti-inflammatory drugs (NSAIDs), other comorbid risk factors for CDI (immunosuppression, HIV status, transplantation, diabetes, chronic kidney disease, malignancy), isolation of BI/NAP1/027 strain, antibiotics used in the emergency room, antibiotics used during hospitalization, day of hospitalization at which CDI treatment started, length of stay till patient put under isolation, length of stay till CDI treatment started, CDI treatment used, positive imaging findings (megacolon, pancolitis, segmental colitis, ascites, free air, infarction), complications (need for hemodialysis, intubation, vasopressor use, intensive care unit transfer, surgical consults, and interventions), LOS, mortality, laboratory tests to assess the severity of CDI (WBC count, creatinine, albumin, and lactic acid levels at the day of diagnosis and during hospitalization).

Annex B

Results

Demographics and baseline characteristics

Cases vs. controls

59.6% of cases presented in the January to June period compared to 51.1% of controls whereas 40.4% of cases presented in the July to December period compared to 48.9% of controls, the difference was statistically significant (p = 0.038).

Compared to controls, CDI cases were significantly older (mean ± standard deviation: 71.8 ± 14.61 vs. 62.4 ± 18.54, respectively, p < 0.001), included more female patients (62.1% vs. 52.0%, respectively, p = 0.01), were more likely to have been hospitalized within the last 6 months (67.5% vs. 31.7%, respectively, p < 0.001), reported more previous CDIs (12.1% vs. 0.6%, respectively, p < 0.001), received more antibiotics within the last 6 months (64.0% vs. 18.9%, respectively, p < 0.001), received more PPIs (69.3% vs. 46.2%, respectively, p < 0.001), received more immunosuppressive drugs (7.6% vs. 1.8%, respectively, p = 0.001), received more corticosteroids (12.0% vs. 6.7%, respectively, p = 0.026), and were more likely to have a diagnosis of cancer (24.9% vs. 16.9%, respectively, p = 0.016) and chronic kidney disease (CKD 4) (9.2% vs. 2.1%, respectively, p = 0.001 and 7.3% vs. 1.8%, respectively, p = 0.002).

Cases received statistically significantly less NSAIDs than controls (34.8% vs. 45.7%, respectively, p = 0.007).

CA-CDI vs. HCFA-CDI

Compared to the HCFA-CDI group, patients in the CA-CDI group statistically significantly received less antibiotics within the last 6 months (48.9% vs. 72.2%, respectively, p < 0.001), less PPIs (55.3% vs. 77.1%, respectively, p < 0.001), and less NSAIDs (20.2% vs. 42.9%, respectively, p < 0.001) but had more female patients (72.3% vs. 56.5%, respectively, p = 0.011).

*Antibiotic use

Cases vs. controls

ER

Cases received statistically significantly more vancomycin, metronidazole, ciprofloxacin, and cefepime in the emergency room compared to controls (40.0% vs. 20.9%, p = 0.001; 31.3% vs. 12.4%, p = 0.001; 24.4% vs. 22.5%, p = 0.025; 23.8% vs. 17.1%, p = 0.002, respectively). ►Table 2 and ►Fig. 3 (annex) summarize the antibiotics received by the patients in the emergency room and in the in-hospital settings. (p < 0.05).

Among patients who received vancomycin in the emergency room, 75.0% of cases received intravenous vancomycin compared to 100% of controls, and 23.4% of cases received oral vancomycin compared to none of controls. The difference was statistically significant (p = 0.004) (►Table 2).

In-hospital

Cases received statistically significantly more in-hospital vancomycin, metronidazole, and carbapenems than controls (81.1% vs. 28.7%, respectively, p = 0.001; 62.5% vs. 21.7%, respectively, p = 0.001; 22.4% vs. 9.6%, respectively, p = 0.001, respectively).

Cases received statistically significantly less cephalosporins and fluoroquinolons than controls (46.7% vs. 56.7%, respectively, p = 0.001; 36.3% vs. 39.5%, respectively, p = 0.001) (►Table 2, ►Fig. 3 (annex)).

Among patients who received in-hospital vancomycin, cases received more oral vancomycin than controls (53.8% vs. 4.4%, respectively, p = 0.001) and more of both intravenous and oral vancomycin than controls (40.5% vs. 2.2%, respectively, p = 0.001) whereas cases received less intravenous vancomycin than controls (5.7% vs. 93.3%, respectively, p = 0.001). The difference was statistically significant in all groups (►Table 2).
CA-CDI vs. HCFA-CDI

ER

The CA-CDI group received statistically significantly more metronidazole and ciprofloxacin in the emergency room than HCFA-CDI group (47.1% vs. 18.9%, p = 0.001; 31.4% vs. 18.9%, p = 0.004, respectively). Both groups received other antibiotics at similar rates (▶ Table 2, ▶ Fig. 3 [annex]).

Among patients who received vancomycin in the emergency room, 63.6% of the CA-CDI group received intravenous vancomycin compared to 81.0% of the HCFA-CDI group; 36.4% of CA-CDI group received oral vancomycin compared to 16.7% of HCFA-CDI group. The difference was not statistically significant (p = 0.122) (▶ Table 2).

Annex C

*Outcomes

*Multivariate analysis of worse outcomes (mortality rate, ICU transfer, LOS > 4 days)

Cases vs. controls

In multivariate analysis, patients in the CD group had significantly higher odds of ICU transfer compared to controls after adjusting for NLR at the day of Max WBC and for in-hospital carbapenem use (OR [95% CI]: 3.52 [1.43–3.65], p = 0.006). CD group had also significantly higher likelihood of LOS >4 days compared to controls after adjusting for sex, age, in-hospital cefalosporin use, and diabetes mellitus (OR [95% CI]: 4.06 [1.83–9.02], p = 0.001). However, the mortality rate was not significantly different between the CD group and the control group.

▶ Table 3 shows the multivariate analysis of worse outcomes (mortality rate, ICU transfer, LOS >4 days) in the CD group and control group.

Annex D

NLR comparison between groups

Cases vs. controls

NLR was statistically significantly higher in cases compared to controls during all hospitalization (median [1IQ, 3IQ]: NLR 1: 7.77 [1.78–36.09] vs. 3.85 [1.12–21.63], respectively, p < 0.001; NLR 2–3: 5.98 [1.48–34.70] vs. 3.74 [1.18–17.26], respectively, p < 0.001; NLR 4–5: 5.48 [1.50–31.57] vs. 3.32 [1.10–15.49], respectively, p < 0.001; NLR day of Max WBC: 9.93 [2.21–44.06] vs. 4.38 [1.19–22.72], respectively, p < 0.001). ▶ Table 2 and ▶ Fig. 1 compare NLR between patients on days 1–3, 4–5, and day of Max WBC. (*p < 0.05)

In-hospital

Patients in the CA-CDI group received statistically significantly less cephalosporins, beta-lactams combination, and carbapenems than HCFA-CDI group (31.3% vs. 52.9%, respectively, p = 0.001; 3.1% vs. 9.9%, respectively, p = 0.044; 11.5% vs. 27.3%, respectively, p = 0.003). Both groups received other antibiotics at similar rates (▶ Table 2, ▶ Fig. 3 [annex]).

Among patients who received in-hospital vancomycin and compared to HCFA-CDI group, the CA-CDI group received statistically significantly more oral vancomycin (70.7% vs. 44.4%, respectively, p = 0.001) and less both intravenous and oral vancomycin (26.7% vs. 48.1%, respectively, p = 0.003) (▶ Table 2).

CA-CDI vs. HCFA-CDI

Compared to HCFA-CDI group, patients in the CA-CDI group statistically significantly had more diarrhea 3 days after CDI diagnosis (66.7% vs. 29.4%, respectively, p < 0.001), more segmental colitis (21.3% vs. 7.1%, respectively, p < 0.001), and more ascites (17.0% vs. 8.9%, respectively, p = 0.05).

In multivariate analysis, patients in the CA-CDI group had significantly lower likelihood of LOS >4 days compared to HCFA-CDI group after adjusting for in-hospital cephalosporin use (OR [95% CI]: 0.06 [0.01–0.37], p = 0.002). In addition, the odds of ICU transfer and the mortality rate were not significantly different between the CA-CDI group and HCFA-CDI group.

▶ Table 3 shows the multivariate analysis of worse outcomes (mortality rate, ICU transfer, LOS >4 days) in the CA-CDI group and HCFA-CDI group.

CA-CDI vs. HCFA-CDI

NLR was statistically similar during all hospitalization in CA-CDI group compared to HCFA-CDI group (median [1IQ, 3IQ]: NLR 1: 8.17 [1.92–38.78] vs. 7.36 [1.78–32.09], respectively, p = 0.178; NLR 2–3: 6.16 [1.27–28.29] vs. 5.89 [1.67–34.94], respectively, p = 0.952); NLR 4–5: 5.23 [1.43–20.53] vs. 5.72 [1.58–35.22], respectively, p = 0.221; NLR day of Max WBC: 10.75 [3.75–40.69] vs. 9.23 [1.98–45.60], respectively, p = 0.916) (▶ Table 2, ▶ Fig. 1).
Annex E

*CDI treatment

Cases

Regarding CDI treatment, patients received oral vancomycin in 79.6% of cases and metronidazole in 54.0% of cases. Table 2 and Fig. 2 show the CDI treatment received by cases. (*p < 0.05)

Annex F

Discussion

Demographics and baseline characteristics

Cases vs. controls

A recent retrospective study of the U.S. National Hospital Discharge Survey noted a higher CDI incidence in the spring followed by winter, summer, and fall, respectively, with the highest CDI incidence in the northeast [6]. Regional variation could not be assessed in our single-center study. CDI incidence was found to increase 1–2 months after seasonal peaks in other infections, namely influenza, pneumonia, and respiratory syncytial virus [6]. The major role that antibiotics play in occurrence of CDI underscores the importance of their adequate utilization. One study indicated that a 30% decrease in antibiotic use in hospitalized patients would result in a 26% decrease in CDI and suggested the urgent need for an antibiotic stewardship program to limit the unnecessary and erroneous use of antibiotics [6]. Other proposed reasons for the increase in CDI in winter months include more severe illnesses during winter months, hospital overcrowding, inter-hospital transfer, change in infection control practices, and reduced hospital staffing [6].

In our study, CDI occurred more frequently in patients with previous CDI, older age, female sex, use of PPIs prior to diagnosis, immunosuppressive drug use, corticosteroids use, and cancer but not with chemotherapy or diabetes mellitus. Patients in the C Diff group had more CKD IV and V, suggesting that immunosuppression including advanced stages of CKD might predispose to CDI. The increased risk of CDI associated with PPIs is controversial, with recent studies disputing their contribution [7]. This study, however, found PPI use to be significantly associated with CDI.

Curiously NSAIDs use was not associated with CDI in our study. This result counters the results of a recent meta-analysis of 8 observational studies that concluded to an association between NSAIDs use and CDI [8]. However, that meta-analysis was limited by the low number of studies, their observational nature, and the vast heterogeneity among them [8].

CA-CDI vs. HCFA-CDI

HCFA and CA-CDI groups had similar history of prior CDI, had similar rates of diarrhea upon diagnosis, and were equally positive for CDI PCR and for NAP1 strain. Patients in both groups used immunosuppressive drugs, chemotherapy, and steroids at similar rates and both groups demonstrated similar proportions of diabetic and cancer patients. Previous studies suggested that functional disability, presence of nasogastric tube, use of antibiotics, chemotherapy, extended-spectrum β-lactamases infection, and mean albumin values are independent factors associated with HCFA-CDI whereas being in close contact with a family member who was hospitalized in the previous 6 months, inflammatory bowel disease, and home density index are independent factors associated with CA-CDI [10].

We found 171 patients with HCFA-CDI (64.04% of cases) and 96 patients with CA-CDI (35.96% of cases). That proportion was comparable to the reported national and international rates [9]. Both CA and HCFA-CDI groups were equally admitted in the January to June and July to December periods compared to controls.

The HCFA received more NSAIDs prior to diagnosis than the CA-CDI group; however, more studies are needed to clarify the role of anti-inflammatory medications in CDI occurrence especially in the hospital setting.

The high use of PPIs and antibiotics in the HCFA-CDI group was consistent with previous reports [12]. Patients in the HCFA-CDI group had more CKD I and II. CKD is well recognized risk factor for CDI [13]. Previous studies evaluated the role of acute kidney injury in CDI; however, the assessment of CDI, its severity, and clinical outcomes in patients with baseline renal dysfunction is not well studied [13]. A lower female-to-male ratio was seen in the HCFA-CDI group compared to CA-CDI group [11]. In our study, female sex was a risk factor for CDI especially for CA-CDI. The female gender predominance in CA-CDI was previously reported. Possible explanations included a different symptom interpretation, a higher healthcare-seeking behavior, and specialist referral in females [11].

Outcomes

Cases vs. controls

Previous studies noted that the main cost drivers were costs related to direct health care and to increased length of stay [14, 15]. There is a 40% increase in hospital costs, as much as $7200 per admission, as well as a 77% readmission rate in patients diagnosed with CDI [14, 15]. Length of stay has been reported to be 55% longer per admission [14, 15].
A recent study noted that CDI was responsible for nearly half a million infections in the United States and almost 29,000 deaths in 2011 [16]. The study suggested that previous demographic and epidemiological reports underestimated the actual burden of CD occurrence [16]. In addition, despite a higher number of CDI occurring outside the hospital settings, the majority of these patients confirmed having an inpatient or outpatient healthcare exposure before the disease onset [16]. An additional concern is the recurrence of CDI, which poses further challenges in terms of treatment and ongoing risk of transmission [16]. The 30-day case-fatality rate of CDI was 9.9% in previous studies. However, the attributable mortality of CDI was 8.03% in studies published since year 2000 compared to 3.64% in those published before year 2000, which indicates the expanding harm caused by CDI [17].

CA-CDI vs. HCFA-CDI

Despite that CA-CDI is traditionally considered a milder clinical entity than HCFA-CDI [9], patients with CA and HCFA-CDI had similar mortality rate and time from diagnosis to death in our study. Moreover, patients with CA-CDI had more segmental colitis, ascites, and diarrhea 3 days after diagnosis. The comparable and even higher severity in clinical outcomes of CA-CDI is consistent with observations seen in recent studies [15]. Suggested explanations include earlier diagnosis in HCFA-CDI patients and more severe disease in CA-CDI possibly related to the emergence of new CD hyper virulent ribotypes [9], similarly to the toxigenic strain BI/NAP1/O27 strain that resulted in an international epidemic between 2002 and 2006 [18].

CDI treatment

Cases vs. controls

Oral vancomycin use should be limited to mild cases where there is lack of improvement after 5–7 days, severe CDI, complicated CDI, or CDI in pregnant or breastfeeding patients [17]. Failure to follow these guidelines may lead to emergence of vancomycin-resistant microorganisms and unnecessary healthcare costs are raised [17]. Therefore, the implementation of an antibiotic stewardship program seems unanimously required [17]. Only 1.2% of cases received vancomycin enema and fidaxomicin. Vancomycin enemas are only recommended for use when oral antibiotics cannot reach a segment of the colon [17]. The use of fidaxomicin in the guidelines is somewhat nondefinitive [18]. There is generally no advantage in clinical cure compared to the less expensive vancomycin ($3000 vs. $1000 per course); however, there may be an advantage in subgroups in decreasing recurrence rates from 25% to 15% [18].