Medication risk factors associated with healthcare-associated Clostridium difficile infection: a multilevel model case–control study among 64 US academic medical centres

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Objectives: The main objective of this study was to determine patient- and hospital-level medication risk factors associated with Clostridium difficile infection (CDI) occurrence among patients clustered within hospitals using a multilevel model.

Methods: Patients with healthcare-associated (HA)-CDI were identified from among 64 academic medical centres in 2009. A frequency match was conducted; for each case, up to two controls were selected, matched on similar pre-infection length of stay and clinical service line. Patient- and hospital-level medication use, including antibacterial and gastric acid-suppressant agents, was assessed using a two-level logistic regression model.

Results: A total of 5967 CDI cases and 8167 controls were included in the analysis. The odds of acquiring HA-CDI increased with the following medications [OR (95% CI)]: anti-methicillin-resistant Staphylococcus aureus agents [1.38 (1.22–1.56)]; third- or fourth-generation cephalosporins [1.75 (1.62–1.89)]; carbapenems [1.60 (1.44–1.79)]; β-lactam/β-lactamase inhibitor combinations [1.49 (1.36–1.64)]; vancomycin [1.73 (1.57–1.89)]; and proton pump inhibitors [0.74 (0.63–0.87)]. The odds of acquiring HA-CDI decreased with the following medications: clindamycin [0.74 (0.63–0.87)]; and macrolides [0.88 (0.77–0.99)]. Controlling for patient-level covariates, no hospital-level medication covariates that we analysed had statistically significant effects on HA-CDI. The odds of acquiring HA-CDI increased with the hospital proportion of patients aged ≥65 years [1.01 (1.00–1.02)].

Conclusions: We found several medications that were associated with the risk of patients developing HA-CDI, including β-lactam/β-lactamase inhibitor combinations, third- or fourth-generation cephalosporins, carbapenems, vancomycin, proton pump inhibitors and anti-methicillin-resistant S. aureus agents. There were no medication effects significant at the hospital level.

Keywords: proton pump inhibitors, antibacterial risk factors, healthcare-associated infections

Introduction

Clostridium difficile is an important cause of healthcare-associated (HA) infections and is the leading cause of infectious diarrhoea. Since the early 2000s, outbreaks of C. difficile infection (CDI) have been reported in hospitals across North America and Europe due to an emerging epidemic strain of C. difficile. Non-modifiable risk factors for CDI include advanced patient age and length of hospitalization;3 modifiable risk factors include antibacterials and gastric acid-suppressant (GAS) medication use. A few studies have examined risk factors aggregated at the hospital level (ecological studies). A study conducted among hospitals in Canada reported that a larger number of hospital beds, a longer length of hospital stay, a greater proportion of elderly patients, a greater number of comorbidities and certain geographical regions were associated with an increased CDI incidence. Among Dutch hospitals, second-generation cephalosporins and total antibacterial use were associated with CDI caused by the epidemic CDI strain.

Ecological studies may be prone to erroneous conclusions as they do not account for patients clustered within hospitals. To our knowledge, no study has examined the extent to which CDI occurrence can be attributed to hospital-level factors while considering patient-level factors. Therefore, the aim of this study was to use multilevel modelling techniques to assess the extent to
which patient- and hospital-level factors, specifically medication use, are associated with incidence of CDI.

Methods

Study design and population

The contributions of hospital- and patient-level factors to HA-CDI development were determined from a sample of patients at least 18 years of age discharged from US academic medical centres of the University HealthSystem Consortium (UHC) during the 2009 calendar year. A subset of UHC hospitals (n = 64 in 2009) participated in the Clinical Resource Management (CRM) database programme, which provides data concerning diagnoses, procedures and inpatient medication use. Details of the CRM database have been previously described.10 The Virginia Commonwealth University Human Subjects Review Board approved this study as the category ‘Exempt’. This study was designed as a case–control study, whereby patient risk factors among those who developed HA-CDI were compared with those who did not. Multi-level logistic regression models were used to simultaneously consider both hospital- and patient-level factors.

A case of HA-CDI was defined as a discharged patient with any ICD-9-CM code for CDI (008.45) who had also received drug treatment for CDI (e.g. metronidazole or oral vancomycin) for at least 3 days starting on or after day 3 of hospitalization, with a hospital stay ≤ 90 days. The index date was defined as the date of initiation of drug therapy for CDI. If a patient met these criteria more than once, only the earliest hospital admission was included.

Controls selected from the study population comprised patients discharged without an ICD-9-CM code for CDI, with a hospital stay ≤ 90 days. A frequency match was conducted; each case was matched to up to two controls with a minimum length of stay (LOS) similar to the case pre-infection LOS (defined as the number of days from admission to the index date) and a similar UHC Clinical Service Line (CSL). The UHC derives a total of 35 CSLs that are based upon similar Medicare Severity Diagnosis Related Groups. These 35 CSLs were further collapsed into 14 categories: behavioural health; bone marrow transplant; cardiovascular; ear/nose/throat; general medicine; general surgery; gastroenterology/urology; neuroscience; obstetrics/gynaecology; oncology; orthopaedics/spine; solid organ transplant; trauma; and ungroupable.

Data analysis

Patient-level variables

Individual patient use of antibacterials was expressed as a binary variable to indicate administration. For case patients, use was only captured for the time period before the index data. Antibacterials were grouped into 15 classes: aminoglycosides; β-lactam/β-lactamase inhibitor combinations (of which 80% was due to piperacillin/tazobactam use); β-lactamase-labile penicillins; antistaphylococcal penicillins; carbapenems; first-generation cephalosporins; second-generation cephalosporins; third- or fourth-generation cephalosporins; fluoroquinolones; vancomycin; clindamycin; macrolides; oxazolidinones/lipopeptides; glycylcyclines [anti-methicillin-resistant Staphylococcus aureus (MRSA) agents]; sulphonamides; and tetracyclines. Metronidazole and oral vancomycin use were not evaluated given their inclusion in the definition of CDI cases. The GAS agents received before the index date for cases, including proton pump inhibitors (PPIs) and histamine-2 receptor antagonist agents, were also considered. We also assessed the demographic variables age, race and gender. In addition to matching by CSL and pre-infection LOS as described, we included CSL and the Charlson comorbidity index, a measure of the burden of coexistent comorbidities, as model covariates.11

Hospital-level variables

The main independent variables included at the hospital level included aggregated measures of GAS agents and antibacterials, per the categories expressed earlier, plus metronidazole, as hospital-level use of metronidazole is not limited to CDI treatment. Use was expressed as the total number of days that charges existed for each particular medication (days of therapy (DOT) per 1000 patient days (PDs)) for the 2009 calendar year. Other hospital factors included were: geographical location, as previous reports have shown hospitals in the north-east region are more likely to have higher rates of CDI;12 bed size;7 overall hospital case-mix index;13 the proportion of patients aged ≥ 65 years;7 and the average LOS.7

Statistical analysis

First, descriptive analyses were reported for patient and hospital characteristics. Univariate regression analyses were then conducted to determine associations between patient-level variables and HA-CDI. Then, multilevel logistic regression was performed to assess the individual and joint effects of patient- and hospital-level variables. Patient- and hospital-level factors were added one at a time to the final multilevel model in a forward stepwise fashion based on their significance level in a multilevel model fitted with all potential model variables, retaining those that made improvements in fit as assessed by the deviance information criterion (defined as minus twice the natural logarithm of the likelihood). χ² statistical tests were used by hierarchical linear and non-linear modelling software to test differences between deviance results, which are generated using Laplace approximation.14

The deviance test was also used to compare differences between three separate models: an ‘empty’ model containing a random intercept only; a model with only patient-level variables; and the multilevel model. Associations for the fixed effects were reported as ORs and 95% CIs. Robust standard errors were calculated in the analyses; an α-level of 0.05 was considered significant.

Results

A total of 5967 unique HA-CDI cases and 8167 controls were included in the analysis. The number of HA-CDI cases in any one hospital ranged from 19 to 364. The most common CSLs included general medicine (20%), general surgery (16%), gastroenterology/urology (14%) and cardiovascular (13%). Table 1 displays the characteristics of cases and controls. Approximately 44% of cases were aged ≥ 65 years compared with ~56% of controls. For both cases and controls, the most common medication was the PPIs, which were used by 76.3% of cases and 66.5% of controls. The most commonly used antibacterial among the study population was intravenous vancomycin, which was received by 69.1% of cases and 45.4% of controls. Univariate analyses of patient-level variables showed that the following were significant and positively associated with HA-CDI: anti-MRSA agents; fluoroquinolones; vancomycin; macrolides; PPIs; histamine-2 receptor antagonists; aminoglycosides; β-lactam/β-lactamase inhibitor combinations; carbapenems; β-lactamase-labile penicillins/antistaphylococcal penicillins; sulphonamides; and tetracyclines. Hospital characteristics are displayed in Table 2. The mean number of beds was 668 and the average LOS was 5.6 days. The most commonly used medications, expressed as the mean total DOT/1000 PDs, were: PPIs (469.6); histamine-2 receptor antagonists (190.3); intravenous vancomycin (140.8); and fluoroquinolones (115.1).
Table 3 displays the patient- and hospital-level variables that were included in the final multilevel model, and the results of the analysis. Most of the patient-level medication-use variables were statistically significantly associated with increased odds of developing HA-CDI, except for clindamycin, macrolides and age, which were associated with a statistically significant decrease in odds. The sulphonamides and aminoglycosides did not have an increased or decreased risk of HA-CDI. Regarding the hospital-level factors, the variable proportion of patients aged \( \geq 65 \) years had a significantly positive effect. None of the hospital-level medication-use variables was significantly associated with HA-CDI. The deviance values for the empty, patient-level and multilevel model were 45226, 43429 and 43395, respectively; the deviance values were significantly different between the models, suggesting that the multilevel model had the best fit and that multilevel techniques were appropriate.

**Discussion**

We conducted a large case–control study to ascertain the risks of medication use, such as antibacterials, on the risk of acquiring HA-CDI, while accounting for individual patients clustered within hospitals. Similar to other patient-level studies, we found that the use of \( \beta \)-lactam/\( \beta \)-lactamase inhibitor combinations, \(^3,5\) third- or fourth-generation cephalosporins, \(^5\) carbapenems \(^5\) and vancomycin \(^5,15\) were associated with an increased risk of developing HA-CDI. Previous studies have found an association between clindamycin and HA-CDI, and CDI epidemics have been attributed to a clindamycin-resistant strain. \(^3,16,17\) We found that clindamycin use was associated with a reduced risk of acquiring HA-CDI; another recent investigation has also shown the use of clindamycin not to be risk-promoting for CDI. \(^5\) Our findings also corroborate other investigations regarding the increased risk of HA-CDI with the use of PPIs. \(^3,4,6\)
We also found the anti-MRSA agent category, comprising linezolid, daptomycin and tigecycline, to be associated with an increased risk of developing HA-CDI. The anti-MRSA agent linezolid has been evaluated as a potential agent to prevent the development of HA-CDI, and it has been shown to have good in vitro activity against CDI isolates in a gut model of CDI. Further, tigecycline has been used as a treatment option for refractory CDI. This finding warrants further investigation to elucidate the relationship between each individual agent’s usage and acquisition of HA-CDI.

**Limitations of the study**

One limitation to the study stems from using administrative data. In an attempt to overcome the potential limitations associated with using ICD-9-CM codes alone to detect HA-CDI, drug treatment information was incorporated into the case definition. Combining ICD-9-CM code data with drug data improves the positive predictive value for identifying HA infections; however, there is still the possibility that CDI case misclassification occurred. There is a chance, too, that our definition of HA-CDI may have over- or underestimated the actual time of HA-CDI occurrence, as surveillance accuracy depends on the availability of clinical data. In addition, we used a binary variable to represent antibacterial use at the patient level and DOT at the hospital level; representing use in different ways, such as defined daily dose and at the CSL level, may lead to different conclusions. Further, as antibacterial use for the entire hospitalization was considered for control patients, it is possible that the results are biased by the fact that controls had longer antibacterial exposure than cases. Though we accounted for comorbidities and the CSL, residual confounding remains possible. Further, it is possible that the effect of competing risks may have introduced bias in the analysis and influenced the patient-level coefficient directions, such as the patient-level variable age. That is, the outcome—HA-CDI occurrence—is subject to competing risks such as discharge or death without HA-CDI development. Also, regarding variable measurement, we aggregated hospital antibacterial use by year, and there exists possible seasonality in antibacterial use that was not accounted for in the analyses.

Further, data were not available concerning the infection prevention measures that hospitals employed. Data suggest that the acquisition of CDI in hospitals stems from many sources such as discharge or death without HA-CDI development. Also, regarding variable measurement, we aggregated hospital antibacterial use by year, and there exists possible seasonality in antibacterial use that was not accounted for in the analyses.

Conclusions

In conclusion, this study evaluated factors related to the risk of HA-CDI acquisition among hospitalized patients while accounting for the clustering of patients in hospitals. The use of several medications was found to be associated with an increased risk of
HA-CDI. These data can aid in informing hospitals of potential areas of improvement through hospital-wide policies regarding the use of high-risk medications for HA-CDI.

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