Hospital Ward Antibiotic Prescribing and the Risks of \textit{Clostridium difficile} Infection

Kevin Brown, PhD; Kim Valenta, PhD; David Fisman, MD, MSc; Andrew Simor, MD; Nick Daneman, MD, MSc

\textbf{Importance} Only a portion of hospital-acquired \textit{Clostridium difficile} infections can be traced back to source patients identified as having symptomatic disease. Antibiotic exposure is the main risk factor for \textit{C difficile} infection for individual patients and is also associated with increased asymptomatic shedding. Contact with patients taking antibiotics within the same hospital ward may be a transmission risk factor for \textit{C difficile} infection, but this hypothesis has never been tested.

\textbf{Objectives} To obtain a complete portrait of inpatient risk that incorporates innate patient risk factors and transmission risk factors measured at the hospital ward level and to investigate ward-level rates of antibiotic use and \textit{C difficile} infection risk.

\textbf{Design, Setting, and Patients} A 46-month (June 1, 2010, through March 31, 2014) retrospective cohort study of inpatients 18 years or older in a large, acute care teaching hospital composed of 16 wards, including 5 intensive care units and 11 non-intensive care unit wards.

\textbf{Exposures} Patient-level risk factors (eg, age, comorbidities, hospitalization history, antibiotic exposure) and ward-level risk factors (eg, antibiotic therapy per 100 patient-days, hand hygiene adherence, mean patient age) were identified from hospital databases.

\textbf{Main Outcomes and Measures} Incidence of hospital-acquired \textit{C difficile} infection as identified prospectively by hospital infection prevention and control staff.

\textbf{Results} A total of 255 of 34,298 patients developed \textit{C difficile} (incidence rate, 5.95 per 10,000 patient-days; 95% CI, 5.26-6.73). Ward-level antibiotic exposure varied from 21.7 to 56.4 days of therapy per 100 patient-days. Each 10% increase in ward-level antibiotic exposure was associated with a 2.1 per 10,000 ($P < .001$) increase in \textit{C difficile} incidence. The association between \textit{C difficile} incidence and ward antibiotic exposure was the same among patients with and without recent antibiotic exposure, and \textit{C difficile} risk persisted after multilevel, multivariate adjustment for differences in patient-risk factors among wards (relative risk, 1.34 per 10% increase in days of therapy; 95% CI, 1.16-1.57).

\textbf{Conclusions and Relevance} Among hospital inpatients, ward-level antibiotic prescribing is associated with a statistically significant and clinically relevant increase in \textit{C difficile} risk that persists after adjustment for differences in patient-level antibiotic use and other patient- and ward-level risk factors. These data strongly support the use of antibiotic stewardship as a means of preventing \textit{C difficile} infection.

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Antibiotic exposure represents the principal risk factor for *Clostridium difficile* infection, and existing research estimates that inpatients taking antibiotics are, on average, 60% more likely to acquire the infection.\(^1\) Prolonged antibiotic exposure and exposure to larger antibiotic doses are associated with increased *C difficile* infection risk.\(^2\) and some antibiotics (clindamycin, cephalosporins, and fluoroquinolones) are associated with a greater risk relative to other antibiotic classes.\(^3\) Risk may increase over time with increased prescribing of certain antimicrobials.\(^5\)

Important gaps in knowledge remain with respect to the natural history of how *C difficile* bacteria are transmitted among hospitalized patients. Hospital environments are persistently contaminated with *C difficile* spores, and surfaces in rooms of infected patients are contaminated before, during, and after treatment for *C difficile* infection.\(^6\) Exposure to symptomatic patients with *C difficile* infection has been identified as an independent risk factor for transmission.\(^7\) However, exposure to spores from other symptomatic patients may not explain most new cases of *C difficile* infection acquired in hospitals.\(^8\) In a *C difficile* outbreak in a long-term care facility, almost half of the residents had asymptomatic colonization, and antibiotic exposure was the primary risk factor for asymptomatic colonization.\(^9\) Although asymptptomatically colonized individuals contribute less to environmental contamination at an individual level, asymptomatic carriers outnumber symptomatic patients by a ratio of 3:1 and as such could represent an important source of *C difficile* infection transmission.\(^10\)

In the absence of reliable measures of patient colonization and environmental contamination, transmission risks can potentially be estimated as a function of aggregated measures of patient risk factors for colonization, such as mean ward- or hospital-level antibiotic prescribing.\(^11\) Multilevel models can be used to tease apart the effect of individual-level risk factors that affect patient susceptibility (direct effects) from group-level effects that affect transmission risks that are independent of individual-level effects (indirect effects).\(^12\) We sought to establish the effect of ward antibiotic-prescribing rate on ward *C difficile* infection incidence and whether the effects observed extended beyond the direct antibiotic effects on patients’ infection risk.

**Methods**

**Ethics Statement**

Study approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre. The board waived the need for patient consent because there was no contact with patients and patient anonymity was assured.

**Study Design and Participants**

A retrospective cohort study design was used to assess the association of individual- and ward-level risk factors with the incidence of *C difficile* infection among patients admitted to Sunnybrook Hospital, a large, acute care teaching hospital located in Toronto, Ontario, Canada. The source cohort consisted of all patients older than 18 years without a previous *C difficile* infection diagnosis who were hospitalized in an acute care ward at Sunnybrook Hospital from June 1, 2010, through March 31, 2014. We excluded patients in the hospital’s psychiatry, obstetrics, neonatal, and long-term care wards given a low expected event rate of *C difficile* infection.

**Case Definition**

Patients infected with *C difficile* were identified by the Infection Prevention and Control Department via active surveillance during the study period. A *C difficile* infection case was defined as any hospitalized patient with laboratory confirmation of a positive toxin assay result together with diarrhea or visualization of pseudomembranes on sigmoidoscopy, colonscopy, or histopathologic analysis.\(^13\) For the purposes of case identification, *diarrhea* was defined as 3 or more loose or watery bowel movements in a 24-hour period, which was unusual or different for the patient, and with no other recognized cause. When a patient developed a *C difficile* infection, the remaining hospitalized days were excluded from the at-risk patient-days. Toxin assays at the hospital have been performed by polymerase chain reaction (BD GeneOhm Cdiff; Becton, Dickinson and Company) since September 2009, which includes the entire study period.

For *C difficile* infection case admissions, event time was the number of days from hospital admission to symptom onset or positive toxin assay result for rare cases (<1%) in which symptom onset was missing. For noncase admissions, censoring time was the number of days from hospital entry until discharge, study termination, or death. In addition to excluding hospitalized days after *C difficile* infection, the first 2 days of each hospital admission were also excluded because patients are not at risk of nosocomial infection at the beginning of a hospital stay.

**Antimicrobial Exposure Assessment**

Patient antibiotic exposures were drawn from pharmacy dispensing records. We examined records for receipt of any antibiotic in the prior 10 days but excluded exposure to metronidazole, oral vancomycin hydrochloride, or fidaxomicin because these may be treatments for *C difficile* infection.\(^15\) Antibiotic receipt was classified according to the Anatomical Therapeutic Chemical (ATC) Classification System, 17th edition.\(^16\) As per previous work,\(^4\) we classified individual patients according to whether they had received a *high-risk antibiotic* (defined as receipt of cephalosporins or carbapenems, fluoroquinolones, or clindamycin and other lincosamides; ATC codes: J01D, J01M, and J01FF), had received a *medium-risk antibiotic* but not a high-risk antibiotic (defined as penicillins, sulfonamides and trimethoprim, macrolides and streptogramins, or aminoglycosides; ATC codes: J01C, J01E, J01FA, J01FG, and J01G), or had received no antibiotics or a *low-risk antibiotic only* (defined as receipt of tetracyclines; ATC code: J01A).

**Patient Risk Factors**

Patient age, sex, admission unit (classified as medical, surgical, or oncologic), and number of previous admissions were retrieved from hospital administrative records. Any patient receiving insulin or an antidiabetic medication (ATC code: A10)
at any point during any hospitalization was considered diabetic. We also examined the use of antacids (ATC code: A02), chemotherapeutic agents (ATC code: L01), and feeding tubes (gastric, nasogastric, or jejunostomy). To account for the time delay between transient pharmaceutical exposures and C. difficile infection risk, we measured receipt in any of the previous 10 days rather than receipt on a given day.

**Hospital Ward Risk Factors**

Using hospital bed assignment information, we identified the ward occupants for each inpatient day; when a patient was located in multiple wards on a given day, we considered that patient to be an occupant of the ward on which he or she was located at noon. We calculated ward-level risk factors that represented mean characteristics of the ward patient population during the 46-month study period. The following 5 ward-level measures were retrieved from the hospital information system: age (mean age), antibiotic use in days of therapy (DOTs) per 100 patient-days, antacid use (DOTs per 100 patient-days), chemotherapeutic agent use (DOTs per 100 patient-days), and feeding tube use (tube in situ per 100 patient-days). Within each ward, observer nurses measured hand hygiene adherence at specific hand hygiene moments (before entering patient room, after leaving patient room, before aseptic procedure, and after body fluid contact) on a quarterly basis through the study period, as per provincial guidelines. Adherence was pooled across periods and hand hygiene moments and was reported as a percentage of total hand hygiene opportunities.

**Statistical Analysis**

**Patient Risk Factors**

To estimate the effect of individual risk factors on C. difficile infection risk, we developed a Poisson regression model that aimed to predict the time elapsed from hospital admission to the occurrence of a first C. difficile infection. Our data were structured in counting process format with one record for each patient-day. The crude incidence rate ratio was assessed in a Poisson regression for each of the 12 individual-level risk factors.

**Hospital Ward Risk Factors**

Using the ward-level risk factors above in addition to ward-level C. difficile infection incidence, we developed 5 bivariate inverse-variance-weighted linear mixed-effects regression models to estimate the effect of each ward-level factor on C. difficile infection incidence, which were fitted using the Hartung-Knapp-Sidik-Jonkman method. We also considered the best-fitting, 2-covariate, ward-level model by comparing model Akaike Information Criterion for all 15 two-covariate models. As a sensitivity analysis, we examined the association between ward-level antibiotic use and C. difficile infection incidence among the 11 non-intensive care unit (ICU) wards separately, excluding the 5 ICU wards.

To clearly distinguish patient-level and ward-level antibiotic effects, we measured the association between ward-level antibiotic prescribing and C. difficile risk separately in patients with and without direct recent antibiotic exposure. We tested whether there was a difference in association of ward-level antibiotic use and C. difficile risk between the 2 groups using the Δ method.

**Multilevel Model**

To assess the independent effect of individual exposures and aggregate ward-level antibiotic exposure, we developed a multilevel Poisson regression model with random intercepts corresponding to wards. The multilevel model included 8 individual-level risk factors: time since admission (modeled as a spline with a knot at 5 days for first admission and readmission separately), patient age (per 10-year increase), sex, diabetes mellitus, and individual exposure to antibiotics, gastric acid inhibitors, chemotherapeutic agents, and presence of a feeding tube. The number of adjustment factors was restricted to ensure at least 10 events per covariate, and the selection of covariates was based on established associations with C. difficile infection risk.

Analyses were conducted using R statistical software, version 3.0.2 (R Foundation for Statistical Computing); the glm, rma, and glmer functions were used for the unadjusted, bivariate mixed-effects and the multivariate mixed-effects statistical models, respectively.

**Results**

**Inpatient Cohort**

We identified 34 298 patients who had an acute care hospital stay that exceeded 2 days at Sunnybrook Hospital from June 1, 2010, through March 31, 2014. These patients spent 428 588 patient-days in the 16 study wards during the 46-month study period. The median age of the cohort was 68.4 years (interquartile range, 54.3-81.0 years), whereas 9718 (28.3%) of the 34 298 patients had additional admissions. Patients received antibiotics in 21 239 (45.5%) of 46 661 admissions and had feeding tubes in 4765 (10.2%) of 46 661 admissions.

**Patients Developing C. difficile Infection**

We identified 255 patients developing a new-onset C. difficile infection during the 46-month study period (incidence rate, 5.95 per 10 000 patient-days; 95% CI, 5.26-6.73). Cases were distributed across 3 types of admitting services, with 111 among patients admitted via surgery services, 110 admitted via medicine services, and 34 admitted via oncology services.

**Individual Patient Characteristics and the Risk of Infection**

The incidence rates for patients with and without individual-level risk factors are given in Table 1. The individual-level risk factors associated with C. difficile infection were age, readmission, direct exposure to antibiotics, and use of a feeding tube. Each 10-year increase in age was associated with a 1.07-fold increase in C. difficile infection risk (95% CI, 1.00-1.17). Having a previous admission was associated with a 1.42-fold increase in risk (95% CI, 1.10-1.82).

**Ward Characteristics and C. difficile Infection Incidence**

The 16 study wards included 2 level II ICUs (patients requiring detailed observation) and 3 level III ICUs (patients requir-
ing advanced respiratory support), 2 cardiology wards, 4 internal medicine wards, 4 surgery wards, and 1 oncology ward. Ward-level characteristics are given in Table 2. The rate of antibiotic use in wards varied from 21.7 DOTs per 100 patient-days in ward 6 to 56.4 DOTs per 100 patient-days in ICU 3 (median, 30.6 DOTs per 100 patient-days; interquartile range, 26.6-36.9 DOTs). Mean antibiotic use in the 5 ICUs was 47.2 DOTs per 100 patient-days compared with 30.9 DOTs per 100 patient-days in non-ICU wards (P < .001).

At the ward level, antibiotic use was the strongest predictor of C difficile infection incidence (Figure 1). Each 10% increase in ward-level antibiotic use was associated with an increased incidence of C difficile infection of 2.1 per 10,000 patient-days (slope = 2.1, P < .001, R² = 0.50). The largest negative outlier in the association was ICU 5, which was the hospital burn ICU. Rate of ward-level feeding tube exposure was marginally associated with C difficile infection (slope = 0.59, P = .10, R² = 0.11). Other ward-level factors, including hand hygiene adherence, mean inpatient age, and rates of antacid use and chemotherapeutic agent use, were not significantly associated with C difficile infection incidence. The addition of any of the other 4 ward-level factors to the model with ward-level antibiotic use did not alter the association between ward-level antibiotic use and C difficile infection incidence (data not shown). When we examined the association between ward-level antibiotic use and C difficile infection incidence among the 11 non-ICU wards, the association remained statistically significant (slope = 4.1, P = .03, R² = 0.41).

We separately measured the association between C difficile infection incidence and ward antibiotic exposure rate among patients recently exposed and those not recently exposed to antibiotics (Figure 2). Each 10% increase in ward-level antibiotic

Table 1. Individual-Level Risk Factors and Clostridium difficile Infection Incidence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. of Cases</th>
<th>No. of Patient-days</th>
<th>Incidence per 10 000 Patient-days (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>35</td>
<td>66 530</td>
<td>5.3 (3.8-7.3)</td>
<td>1.07 (1.00-1.17)**</td>
</tr>
<tr>
<td>50-59</td>
<td>24</td>
<td>55 321</td>
<td>4.3 (2.9-6.5)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>43</td>
<td>80 493</td>
<td>5.3 (4.0-7.2)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>63</td>
<td>93 691</td>
<td>6.7 (5.3-8.6)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>90</td>
<td>132 553</td>
<td>6.8 (5.5-8.3)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>140</td>
<td>235 784</td>
<td>5.9 (5.0-7.0)</td>
<td>1.00 (0.78-1.27)</td>
</tr>
<tr>
<td>Female</td>
<td>115</td>
<td>192 804</td>
<td>6.0 (5.0-7.2)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First hospitalization</td>
<td>150</td>
<td>286 846</td>
<td>5.2 (4.5-6.1)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Additional admission(s)</td>
<td>105</td>
<td>141 742</td>
<td>7.4 (6.1-9.0)</td>
<td>1.42 (1.10-1.82)</td>
</tr>
<tr>
<td>Admission service</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>110</td>
<td>188 869</td>
<td>5.8 (4.8-7.0)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Oncology</td>
<td>34</td>
<td>48 953</td>
<td>6.9 (5.0-9.7)</td>
<td>1.19 (0.81-1.88)</td>
</tr>
<tr>
<td>Surgery</td>
<td>111</td>
<td>190 766</td>
<td>5.8 (4.8-7.0)</td>
<td>1.00 (0.77-1.34)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>176</td>
<td>297 798</td>
<td>5.9 (5.1-6.8)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>79</td>
<td>130 610</td>
<td>6.0 (4.9-7.5)</td>
<td>1.02 (0.79-1.34)</td>
</tr>
<tr>
<td>Any antibiotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>63</td>
<td>191 604</td>
<td>3.3 (2.6-4.2)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>192</td>
<td>236 984</td>
<td>8.1 (7.0-9.3)</td>
<td>2.46 (1.85-3.28)</td>
</tr>
<tr>
<td>Antibiotic risk index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or low</td>
<td>65</td>
<td>196 073</td>
<td>3.3 (2.6-4.2)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Medium</td>
<td>23</td>
<td>47 663</td>
<td>4.8 (3.2-7.3)</td>
<td>1.46 (0.90-2.34)</td>
</tr>
<tr>
<td>High</td>
<td>167</td>
<td>184 852</td>
<td>9.0 (7.8-10.5)</td>
<td>2.73 (2.05-3.63)</td>
</tr>
<tr>
<td>Antacid exposure in previous 10 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65</td>
<td>115 764</td>
<td>5.6 (4.4-7.2)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>190</td>
<td>312 824</td>
<td>6.1 (5.3-7.0)</td>
<td>1.08 (0.82-1.43)</td>
</tr>
<tr>
<td>Chemotherapeutic agent exposure in previous 10 d</td>
<td>214</td>
<td>375 439</td>
<td>5.7 (5.0-6.5)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>53 149</td>
<td>7.7 (5.7-10.5)</td>
<td>1.35 (0.97-1.89)</td>
</tr>
<tr>
<td>Feeding tube in situ in previous 10 d</td>
<td>176</td>
<td>330 733</td>
<td>5.3 (4.6-6.2)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>79</td>
<td>97 855</td>
<td>8.1 (6.5-10.1)</td>
<td>1.52 (1.16-1.98)</td>
</tr>
</tbody>
</table>

** Per 10-year increase in age.
Table 2. Variation in Ward-Level Characteristics and *Clostridium difficile* Infection Incidence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Care Unit</th>
<th>Non-Intensive Care Unit Ward</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Patient-days, in thousands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand hygiene, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication receipt, DOTs per 100 patient-days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding tube, tube-days per 100 patient-days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C difficile</em> infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence per 10 000 patient-days</td>
<td>6.4</td>
<td>19.7</td>
</tr>
</tbody>
</table>

Abbreviation: DOTs, days of therapy.

* Burn intensive care unit.

Figure 1. Association of Ward-Level Exposures With Ward *Clostridium difficile* Infection (CDI) Incidence

A, Antibiotic use; B, hand hygiene; C, antacid use; and D, feeding tube use. Each symbol represents a hospital ward. The size of the symbols is proportional to the amount of follow-up time on each ward. DOTs indicates days of therapy.
use was associated with a 1.8 per 10,000 increase (slope = 1.8, \( P = .005, R^2 = .50 \)) in the incidence of \( C. difficile \) infection among patients without direct recent exposure and a 1.6 per 10,000 increase (slope = 1.6, \( P = .05, R^2 = .14 \)) among patients with direct recent exposure to antibiotics. The effect of ward-level antibiotic exposure on \( C. difficile \) infection incidence did not differ significantly between patients directly using or not directly using antibiotics (\( P = .16 \)).

**Ward-Level Antibiotic Use and \( C. difficile \) Infection Incidence: Multilevel Model**

After adjustment for patient characteristics, the ward-level antibiotic exposure remained associated with \( C. difficile \) infection risk (Table 3). Each 10% increase in ward antibiotic exposure rate was associated with a 1.34-fold increase in \( C. difficile \) infection risk (95% CI, 1.16-1.57).

**Discussion**

In this 46-month cohort study of \( C. difficile \) infection risk, we found that ward-level antibiotic exposure is the main risk factor for infection. The effect of antibiotic prescribing reaches beyond individual-level antibiotic use, such that all patients, irrespective of whether they receive antibiotics directly, are at higher risk of \( C. difficile \) infection in high antibiotic-prescribing wards. Ward-level \( C. difficile \) infection risk was not confounded by other ward-level aggregate patient characteristics, including antacid use, chemotherapy, feeding tube presence, age, or crowding, or by individual-level patient comorbidities or antibiotic exposures.

This is the first study, to our knowledge, to consider ward-level antibiotic exposure as a risk factor for \( C. difficile \) infection. In a previous multilevel study considering individual- and hospital-level risk factors, Pakyz et al. found that hospital-level antibiotic exposure rates were not a significant predictor of hospital-level \( C. difficile \) infection incidence. This finding suggests that hospital-level antimicrobial use may not differ meaningfully across centers or that factors that were not considered, such as infection control practices or \( C. difficile \) diagnostic testing rate, may have confounded an underlying association.

We hypothesize that the marked effects of ward-level antibiotic exposure rate are likely explained by an increase in the number of patients colonized with, and shedding, \( C. difficile \) in wards with high rates of antibiotic use. This high prevalence of antibiotic use would increase environmental contamination and the incidence of \( C. difficile \) infection. This mechanism is supported by research indicating that antibiotic exposure is the principal risk factor for \( C. difficile \) colonization and that approximately half of \( C. difficile \) strains among \( C. difficile \) infection cases in hospitals cannot be genetically linked to previously identified symptomatic patients. The hospital burn center was the only outlier, with lower-than-expected \( C. difficile \) infection incidence given its high ward-level antibiotic use. The burn center is unique in that it had a low nurse-patient staffing ratio, single-bed rooms, and a younger patient population, which is consistent with findings from a prior study. Our multilevel statistical model revealed that younger age and patient pharmaceutical exposures did not completely account for the lower-than-expected incidence in the burn ICU, suggesting that other patient or ward characteristics may have been at play.

The independent association of ward antibiotic exposure with \( C. difficile \) infection risk most likely reflects the nonindependence of communicable disease cases. Communicable diseases differ from other classes of disease because a case is also a risk factor. In the context of \( C. difficile \) infection, this statement means that an increase in disease-related force of infection could occur via antibiotic exposure in individuals who never themselves become symptomatic cases. Such indirect effects are well recognized with communicable disease control interventions, and indeed this effect may be conceptualized as an inverse of herd immunity seen with vaccines.
Clostridium difficile infection

Analogously, beneficial herd effects would logically be seen in wards with reduced antibiotic prescribing, as was observed in our study. A previous meta-analysis\(^6\) of antimicrobial stewardship interventions lends credibility to this explanation because these interventions have produced substantial reductions in \textit{C difficile} infection incidence with only small reductions in antibiotic prescribing.

As such, the principal clinical implication of this study is that aggregate ward-level antibiotic use should be subject to surveillance by infection control and stewardship personnel. Hospital antimicrobial stewardship programs consistently achieve substantial reductions (22\%-36\%) in overall antibiotic use,\(^7\) and such interventions reduce \textit{C difficile} infection incidence by 50\%.\(^8\) Because almost all antibiotics are associated with increased \textit{C difficile} infection risk,\(^4\) antimicrobial stewardship initiatives aiming to reduce infection incidence should aim to reduce overall antimicrobial exposure in addition to reducing use of specific high-risk agents. Furthermore, our results suggest that hand hygiene with soap and water should be considered before and after caring for patients using antibiotics, especially in ICU wards with high levels of antibiotic use.

Like any observational study, ours was subject to a number of limitations, including confounding by unmeasured patient characteristics, such as comorbidities, and outcome ascertainment bias related to potential systematic differences in physicians’ vigilance for detecting milder cases of infection. This was a single-hospital study, and the overall number of wards at our study hospital was small (n = 16). Furthermore, our study was subject to limitations because of incomplete follow-up information on patients after hospital discharge. We considered patients who were discharged as censored, but patient censoring may not have been independent of the study outcome.\(^28\)

**Conclusions**

Our 46-month study of inpatient \textit{C difficile} infection risk across 16 wards of a large tertiary care hospital found a strong association between ward antibiotic prescribing and \textit{C difficile} infection incidence that affected patients with and without recent antibiotic exposure. Future studies of \textit{C difficile} infection etiology should seek to quantify patient, ward, and airborne contamination with \textit{C difficile} spores to more clearly describe the mechanisms that link ward-level antimicrobial use and infection incidence. These findings strongly support the further funding and development of hospital antibiotic stewardship programs.

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Study concept and design: Brown, Valenta, Fisman, Daneman.

Acquisition, analysis, or interpretation of the data: Brown, Simor, Daneman.

Drafting of the manuscript: Brown.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Brown.

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Study supervision: Fisman, Daneman.

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**REFERENCES**


