

Patient Transfers and Clostridioides Difficile Infections: A Case-Control Study

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Abstract

Background

Clostridioides difficile spores are present in the hospital environment. We hypothesized that patient transfers between rooms is an independent risk factor for *C. difficile* infections (CDI), as this increases the environmental exposition. We performed a retrospective case-control study at a public 400-bed hospital in western Sweden.

Methods

Hospital-acquired CDI cases at Södra Älvsborg Hospital, Sweden, during two different years (n = 65) were included in the case group. A random, unmatched selection of patients tested negative for CDI served as control group (n = 101). The number of rooms each patient occupied during hospitalization was the primary variable. Odds ratios (OR) for CDI were calculated by simple and multiple logistic regression.

Results

The number of rooms occupied was not an independent risk factor (OR per room 1.1, 95 % CI: 0.8–1.4) when data were adjusted for duration of hospitalization, which was the only statistically significant variable (OR per additional week of care: 1.7, 95 % CI: 1.2–2.3) in the multiple logistic regression model. The risk associated with the duration of hospitalization was larger among patients who stayed in four or more rooms (OR per additional week of care: 2.5, 95 % CI: 1.1–5.6) than among patients that stayed in one room only (OR per additional week of care: 1.3, 95 % CI: 0.7–2.4).

Conclusions

The risk for *C. difficile* infections increase with time of care, and patient transfers might amplify the risk, although we could not prove it to be an independent risk factor in this limited case-control study.

Background

Clostridioides difficile (previously known as *Clostridium difficile*¹) is a Gram-positive anaerobic bacterium, capable of sporulation.² It is part of the normal gut flora in the early life of humans³ and many other mammals,^{4–6} and then rarely causes disease.⁷ First described in 1935,⁸ its role in pseudomembranous colitis was made clear in the 1970's.⁹ In the 2000's, hypervirulent strains such as ribotype 027, characterized by high toxin production and extended antimicrobial resistance, have become more common in many countries.¹⁰ This could potentially be interpreted as an adaptation of the species to modern healthcare: instead of lying dormant in soil, waiting for an infant gut to temporarily colonize

without causing disease, these strains instead optimize for propagation in adult hosts who are subject to antibiotic treatment, and increased toxin production allows for effective transmission through diarrhea. Such a selection process might be further facilitated by a high frequency of patient transfers within hospitals, leading to more opportunities per time unit for spores to enter the digestive system of susceptible hosts as well as a wider dispersion of spores. Sweden has a high rate of *Clostridioides difficile* infections (CDI) by European standards, despite a prudent consumption of antibiotics and the absence of large CDI outbreaks.¹¹ Considering that the prevalence of multi-drug resistant organisms is low¹² with similar risk factors for transmission, the high CDI incidence seems paradoxical. The country also stands out regarding the number of hospital beds per person, which is among the lowest in the EU.¹³ The constant shortage of hospital beds may lead to a high turnover of patients and frequent patient transfers within and between wards, which has been linked to adverse outcomes¹⁴. We hypothesized that this situation could be facilitating the propagation of *C. difficile* and might be a possible explanation for the apparent paradox. To test the hypothesis, our aim was to determine whether intrahospital transfers between rooms were a risk factor for developing CDI.

Methods

Setting and design

We performed a case-control study at a public, secondary-care, 400-bed hospital in western Sweden, serving as primary referral center for a population of approximately 300,000 inhabitants. Two years were studied, 2012 and 2015.

Patients

Cases were defined as all patients 18 years or older that were tested positive for *C. difficile* toxin A or B upon clinical suspicion of CDI. Only hospital-acquired infections, as defined by McDonald et al¹⁵ were included: onset during hospital stay (> 48 h after admission) or after hospital stay (< 4 weeks after discharge). Recurrent infections, defined as the patient having tested positive for CDI during the previous 8 weeks, were excluded. The diagnostic method used at the hospital during the study period was a well-based enzyme immunoassay (Vidas® A&B, bioMérieux, Marcy-l'Étoile, France) as a standalone test. Among patients with inflammatory bowel disease or suspicion thereof, tests may have been ordered as a screening measure. Tests on solid stool were however not performed at the laboratory. Controls were drawn among patients tested negative for CDI, who, had the test been positive, would have been included in the case group. The selection was based on the Swedish personal identification number which includes a check digit. Patients whose check digit was 1 were included as controls.

Data collection

Three sources were used for data collection. The database of the local microbiological laboratory, ADBakt (Autonik AB, Nyköping, Sweden), was used to find all patients tested for CDI. The electronic medical record system Melior (Cerner Corporation, North Kansas City, MO, USA) was used to determine eligibility

criteria and patient characteristics, and IBM Cognos (IBM, Armonk, NY, USA) was utilized to extract data on ward and room history from the local administration system database. Data on cases and controls were recorded in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Variables

The primary research variable was the number of different rooms that patients occupied during the hospitalization prior to their CDI test. For the room where the patient stayed longest, we collected additional data which might affect CDI risk: whether or not it was a single room, whether or not it was in a ward with a high CDI incidence (three wards with > 6 cases per year 2013–2014: gastroenterology, hematology and infectious diseases), and patient turnover (the number of other patients that had stayed in the room during the previous 30 days). Age and sex were determined from the Swedish personal identification number. Duration of hospitalization was defined as whole days between the date of admission and the date when the fecal specimen arrived at the laboratory. In other words, hospital stay after the CDI test was performed was not regarded, as this measure would be influenced by the extension of the hospital stay caused by the *C. difficile* infection. Comorbidities known for increasing the risk of CDI were recorded based on their presence in the admission records. When information on comorbidities was not clearly stated, they were recorded if the medical records of the last five years included the International Classification of Diseases 10th revision (ICD-10) codes K50-K51 (inflammatory bowel disease), C81-C96 (hematological malignancy), N18 (renal failure) or E11-E12 (diabetes mellitus). Antibiotic use was defined as at least one dose given during the hospitalization before the CDI test was taken. Outpatient antibiotics were not included due to lack of such data. Antibiotics were defined as any substance with the Anatomical Therapeutic Chemical (ATC) code J01; additionally, three drugs with other ATC codes were considered antibiotics: oral metronidazol, oral vancomycin, and rifampicin. Proton pump inhibitor (PPI) treatment was defined as treatment during the hospital stay, before the CDI test, with drugs with the ATC code A02BC in a daily dose corresponding to 20 mg omeprazol or more.

Statistical analyses

Patient characteristics, potential confounders, and the primary variable were compared between cases and controls. Continuous variables were presented as mean and standard deviation as well as median and range. Statistical significance was tested with Student's t-test for normally distributed variables, or Mann-Whitney U-test for variables with a skewed distribution. Categorical variables were presented as number of patients divided by the total number as well as percentage. Statistical significance of the difference between groups was tested with simple logistic regression. Variables that showed a statistically significant difference between cases and controls were included in a multiple logistic regression analysis after controlling that assumptions were met. A sensitivity analysis was performed where known risk factors (age, comorbidities) were included despite statistically non-significant differences in the study material. Potential interaction effects between the number of rooms and the number of days during the hospitalization were explored using a multiplicative variable in the logistic regression model as well as by stratification. IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA) was used for statistical analyses. A p value of < 0.05 was considered statistically significant.

Ethical aspects

The study was approved by the regional ethical review board in Gothenburg, Sweden (registration number 227 - 16).

Results

Patient characteristics and investigated variables for cases (N = 66) and controls (N = 101) are shown in Table 1. Among previously known risk factors, there were significant differences in treatment with antibiotics or PPI, and duration of hospitalization. No statistically significant differences were found regarding age and comorbidities.

Table 1
Patient characteristics and research variables in cases and controls.

	CDI, N = 66		Controls, N = 101		Odds Ratio	95 % Confidence Interval	P value
	Mean (SD) or n/N	Median (range) or percentage	Mean (SD) or n/N	Median or percentage			
Age (years)	77.1 (10.7)	76	74.9 (14.1)	78			0.52
Male	35/66	53.0%	51/101	50.5%	1.1	0.6–2.1	0.75
Body Mass Index (kg/m ²)	25.1 (5.2)	24.7	25.6 (5.9)	24.6			0.61
Hematological malignancy	5/66	7.6%	5/101	5.0%	1.6	0.4–5.7	0.49
Inflammatory Bowel Disease	3/66	4.5%	2/101	2.0%	2.4	0.4–14.5	0.38
Renal failure	14/66	21.2 %	18/101	17.8%	1.2	0.6–2.7	0.55
Diabetes	18/66	27.3%	18/101	17.8%	1.7	0.8–3.6	0.18
Use of Proton Pump Inhibitors	34/66	52.3%	34/101	33.6%	2.1	1.1–3.9	0.02
Use of Antibiotics	61/66	92.4%	80/101	79.2%	3.2	1.1-9.0	0.03
Rooms during hospitalization	2.7 (1.6)	2 (1–7)	2.0 (1.1)	2 (1–6)	1.5 per room	1.2–1.9	0.002
Duration of hospitalization (weeks)	2.4 (1.9)	1.9 (0.3-9.0)	1.3 (1.0)	1.0 (0.1–6.9)	1.8 per week	1.4–2.3	< 0.001
Patient turnover in room	16.9 (16.6)	12.5 (1–88)	17.7 (14.8)	14 (3–68)			0.52
Single room	27/66	40.9%	49/101	48.5%	0.7	0.4–1.4	0.33
High-incidence ward	24/66	36.4%	36/101	35.6%	1.0	0.5-2.0	0.92
30-day all-cause mortality	10/66	15.2%	17/101	16.8%	0.9	0.4–2.1	0.77

The number of rooms during hospitalization was significantly higher among cases than controls. Patient turnover or care in a single room had no apparent effect on the CDI risk. Only the duration of hospitalization before the CDI test turned out as an independent risk factor for CDI (OR per additional week: 1.7, 95 % confidence interval: 1.2–2.3, p = 0.002) in the multiple logistic regression analysis, where

antibiotics, PPI, rooms occupied, and duration of hospitalization were included as covariates. A sensitivity analysis where known risk factors (age and comorbidities) were included did not change the results.

The duration of hospitalization and the number of rooms were moderately correlated ($R^2 = 0.38$). We stratified the data by the number of rooms, which showed that the odds ratio for the duration of hospitalization increased with the number of rooms a patient stayed in (Fig. 1). We explored a possible interaction effect between the two variables by adding a multiplicative joint variable to the multiple regression model; this variable did however not show a statistically significant effect on the outcome when adjusted for the other two.

Discussion

In this study, we investigated whether intrahospital room transfers were an independent risk factor for developing hospital-acquired CDI, in a setting with a low number of hospital beds with a high turn-over of patients, and low antibiotic prescriptions rates. Our results suggest that time spent hospitalized is the most important risk factor for healthcare facility-associated CDI, which is supported by previous studies.^{16–18} The reasons for this, however, are not clear. Being admitted to, and staying at, a hospital is correlated with risk factors such as age, antibiotics, and comorbidities, but also possibly to a higher risk of encountering *C. difficile* spores. Indeed, Pai et al¹⁹ found that in-hospital CDI cases showed clear spatiotemporal clustering while aspiration pneumonia did not. A recently published case-control study found a statistically significant connection between intrahospital transfers and healthcare-onset CDI risk.²⁰ Furthermore, a recent retrospective cohort study with network analysis found that inpatient mobility, along with other factors, could predict CDI risk at the unit level.²¹ Although we did not find a statistically significant effect modification of intrahospital transfers on the risk of hospital stay duration, this hypothesis might be worthwhile to test in larger patient materials and with more sensitive diagnostic methods.

Given the known importance of age as a risk factor for CDI,²² the lack of a statistically significant difference regarding this variable was somewhat unexpected. The 30-day mortality rate was also similar and high in both groups, reflecting that patients tested for CDI quite often are near the end of their lives. The results for CDI patients are in line with a 2012 review on 30-day all-cause mortality which found a range of 9–38% in 24 studies.²³ The similarities between cases and controls in our study may suggest a representative control group drawn from a restricted population of hospitalized patients with suspected CDI, but could also reflect the diagnostic method – well-based enzyme immunoassay toxin tests have a sensitivity around 60–70 %²⁴ and are usually not recommended as standalone tests for CDI. Thus, the control group may include a significant number of false negatives, who would have been included in the case group had a more sensitive method been used. Incorrectly classifying true cases as controls is a measurement error that may dilute true differences between cases and controls.

The main strengths of this study are that all CDI cases during two years were accounted for, with little information loss, and all data were individually extracted from primary sources. Characteristics of the

rooms which patients occupied add new insight to the factors contributing to hospitalization being an important risk factor for CDI. Limitations of the study include the limited number of cases and controls which restricts the power. This is the likely explanation for the absence of statistically significant differences in this analysis for the established risk factors antibiotic treatment and PPI use, where confidence intervals were wide. The diagnostic method used, likely leading to misclassification of some cases as controls as mentioned above, is another limitation.

Conclusions

The risk for *C. difficile* infections increase with time of care. Patient transfers might amplify the risk associated with hospital care, although we could not prove it to be an independent risk factor in this limited case-control study. Future studies investigating the role of hospitalization on CDI risk could investigate patient transfers as a potential effect modifier.

Declarations

Ethics approval and consent to participate

The study was approved by the regional ethical review board in Gothenburg, Sweden. Consent was waived (registration number 227-16).

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JEW designed the study under supervision of MW and SS. JEW collected and analyzed the data. All authors contributed to the interpretation of data and the writing of the final manuscript.

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Figures

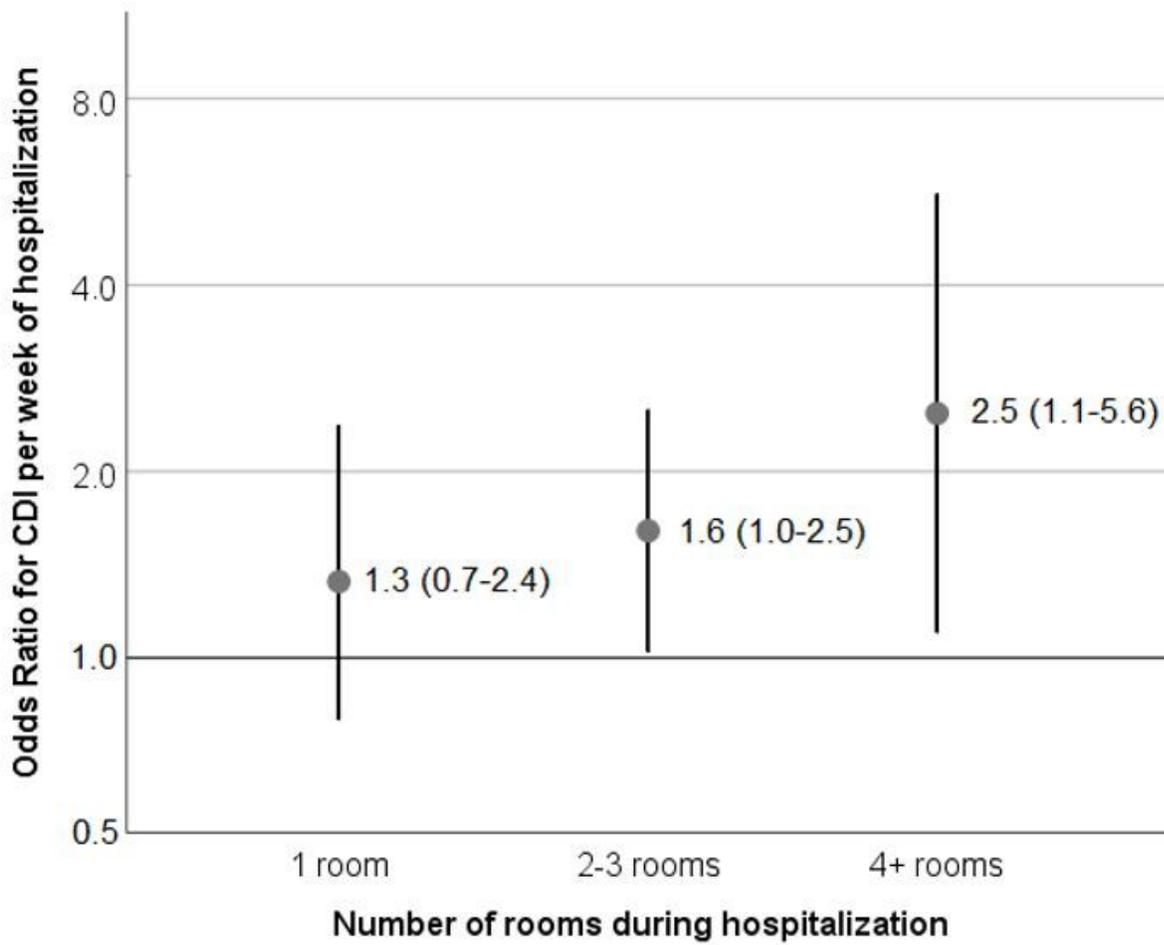


Figure 1

Stratification of the OR of the duration of hospitalization by the number of rooms. Whiskers show 95 % confidence intervals of the Odds Ratio (dots).