Risk factors, course and outcome of Clostridium difficile infections

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Chapter 5

Time-interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics

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Abstract

Background: *Clostridium difficile* infections (CDIs) are common in developed countries and affect more than 250,000 hospitalized patients annually in the USA. The most important risk factor for the disease is antibiotic therapy.

Methods: To determine the period at risk for CDI after cessation of antibiotics, we performed a multicenter case-control study in the Netherlands between March 2006 and May 2009. Three hundred and thirty-seven hospitalized patients with diarrhoea and a positive toxin test were compared to 337 patients without diarrhoea. Additionally, a control group of patients with diarrhoea due to a cause other than CDI (n=227) was included.

Results: In the month prior to the date of inclusion, CDI patients more frequently used an antibiotic compared with non-diarrhoeal patients (77% versus 49%). During antibiotic therapy and the first month after cessation of the therapy, patients had a seven to ten-fold increased risk for CDI (OR 6.7-10.4). This risk declined in the period between one and three months after the antibiotic was stopped (OR 2.7). Similar results were observed when the second control group was used. All antibiotic classes, except first generation cephalosporins and macrolides, were associated with CDI. Second and third generation cephalosporins (OR 3.3 and 5.3, respectively) and carbapenems (OR 4.7) were the strongest risk factors for CDI. Patients with CDI used more antibiotic classes and more Defined Daily Doses, compared with non-diarrhoeal patients.

Conclusions: Antibiotic use increases the risk for CDI during therapy and in the period of three months after cessation of antibiotic therapy. The highest risk for CDI was found during and in the first month after antibiotic use. Our study will aid clinicians to identify high risk patients.

Introduction

Clostridium difficile infection (CDI) is an emerging disease in the western world and affects more than 25,000 people annually in England and over 250,000 hospitalized patients per year in the United States.[1, 2] Symptoms vary from mild diarrhoea to a severe pseudomembraneous colitis. Reported mortality due to CDI varies from 6% of the patients in endemic situations to 17% in outbreak settings in which the hypervirulent PCR ribotype 027 (NAP-1) is involved.[3, 4]

Known risk factors for CDI are previous hospitalization, advanced age (>65 years) and, most importantly, the use of antibiotics. Several antibiotic classes have been associated with the development of CDI, including clindamycin, cephalosporins and fluoroquinolones.[5, 6] Furthermore, the number of administered antibiotics, their dosage and the duration of therapy were previously identified as factors determining the risk for CDI.[7-9] An important question that remains unanswered concerns the time-interval of increased risk for CDI after exposure to antibiotics.

In recent studies, patients were defined as 'antibiotic users' when they used an antibiotic 'several days' up to '3 months' before CDI was diagnosed.[10-13] A study among a selected population of elderly patients who were admitted due to severe community-acquired CDI, however, suggested that the period of increased risk for CDI was at least thirty days.[14] Detailed knowledge about the risk of CDI after antibiotic exposure can aid clinicians to select high risk patients, improve antimicrobial stewardship and consequently decrease the incidence of CDI.[15] Furthermore, this knowledge can help future research to operate with a more appropriate definition of antibiotic use. Therefore, we evaluated risk factors for CDI in a multicenter case-control study with special interest for the precise time-interval of increased risk for CDI after exposure to antibiotics. Because diarrhoea (without CDI) is a common side effect of antibiotic use, we additionally evaluated the time-interval of increased risk for diarrhoea in general after exposure to antibiotics.

Methods

Patients and data collection

Between March 1st 2006 and May 1st 2009, a case-control study was conducted in nine Dutch hospitals, including Isala Klinieken (Zwolle), University Medical Center St. Radboud (Nijmegen), Leiden University Medical Center (LUMC; Leiden), VU University Medical Center (Amsterdam), St. Elisabeth Ziekenhuis (Tilburg), Amphia

Ziekenhuis (Breda), Kennemer Gasthuis (Haarlem), Academic Medical Center (Amsterdam) and University Medical Center Utrecht (Utrecht). During a minimum of six consecutive months (within the study period of more than three years), a participating hospital included all hospitalized CDI patients in the study. According to the proposed definitions, case patients were defined as patients with diarrhoea and a positive test for *C. difficile* toxin.[16] Diarrhoea was defined as three or more unformed stools (taking the shape of the container) per day. For each CDI patient, two control patients were selected: one patient with diarrhoea and a negative test for *C. difficile* (non-CDI diarrhoea) and one patient without diarrhoea (non-diarrhoeal). CDI and control patients were matched for hospital, ward and time of diagnosis, which implied selection of control patients that were hospitalized within 14 days of the day on which CDI was diagnosed in the case patient. When several potential control patients were eligible, the first patient on the alphabetical ward list was chosen. A non-CDI diarrhoeal patient was not always available at time of selection. Patients could participate in the study only once.

The Medical Review Ethics Committee of each participating hospital approved the study. No informed consent was required, because only data were used that were available as part of regular patient care. We extracted information on patients' age, sex, co-morbidity and ward of acquisition, previous use of antibiotics (name of drug, dosage, duration of therapy and dispensing dates), co-medication (gastric acid suppressors, non-steroidal anti-inflammatory drugs, immunosuppressive therapy and chemotherapy), admissions and invasive procedures. We used a time period of three months for previous use of medications, admissions and procedures. For CDI patients and for non-CDI diarrhoeal patients, this period was defined as the three months prior to the start of diarrhoea. For non-diarrhoeal patients, we used a three month period prior to a reference date, which was determined by adding the hospitalized period of the matched CDI patient (time between admission and start of diarrhoea) to the admission date of the non-diarrhoeal patient. Using a standardized questionnaire, the data were collected by consulting the physician in charge, using the electronic medical information system and individual patient records. Patients whose records regarding antibiotic use were missing (n=9) were excluded from the study.

Antibiotics were classified into eleven categories (depicted in table 2). The category 'Others' comprised tetracyclines, rifamycins, polymyxins and lipopeptides. We combined the duration and dosage of each prescribed antibiotic by calculation of the Defined Daily Dose (DDD), using a computer tool to calculate antibiotic consumption (ABC Calc 3.1b, available at www.escmid.org/esgap). Co-morbidity was

assessed by both the Charlson Comorbidity Index and the ICD-10 diagnosis, using the tenth revision of the International Classification of Diseases; mentioned in table 1.[17]

Microbiological analysis

Tests for CDI were performed upon request of the physician and on all unformed faecal samples from patients who had been admitted for two or more days, regardless the physicians' request. According to the standard of the local hospital, either one of the following *Clostridium difficile* tests were used: VIDAS *C. difficile* toxin A (bioMerieux), VIDAS *C. difficile* toxin A&B (bioMerieux), Premier *C. difficile* toxins A&B (Meridian), ImmunoCard *C. difficile* (Meridian) or cytotoxicity assay. Toxin positive faecal samples were cultured for the presence of *C. difficile* using a standardized protocol supplied by the Leiden University Medical Center (LUMC). Confirmation of *C. difficile* was performed at the LUMC by the detection of the *glu*D gene.[18] *C. difficile* isolates were further characterized by PCR-ribotyping as previously described.[19]

Statistical analysis

We compared cases to controls without diarrhoea. To determine the period of increased risk for diarrhoea after antibiotic therapy, we also compared cases to non-CDI diarrhoeal patients. We present both comparisons since the results of the first comparison slightly overestimate the effect of antibiotic therapy on the development of CDI and the comparison of cases to non-CDI controls will underestimate this effect, because diarrhoea is a frequent side effect of antibiotic therapy.

Binominal characteristics were compared using the Chi-square test. In all other analyses the individual matching was taken into account. The association between CDI and antibiotic use was analysed using conditional logistic regression, adjusting for age (in 3 categories), sex and Charlson Comorbitidy Index (in 4 categories). In the evaluation of a single antibiotic class this method is referred to as Method 1. Additional adjustments for the use of concomitant antibiotics of different classes were made in the evaluation of a single antibiotic class as a risk factor for CDI by entering all other antibiotic classes into one multivariable model (Method 2). Results are presented as odds ratios (ORs) with the accompanying 95% confidence interval (95% CI). Because we performed concurrent sampling for the selection of controls, the odds ratio is identical to the rate ratio.[20] Statistical significance was reached with a 2-sided p-value < 0.05. We analysed additive interaction between second and third generation cephalosporins and other antimicrobial classes by calculating

the synergy index.[21] We used PASW Statistics version 17.0 (SPSS Inc., Chicago, USA) and STATA software package 10.1 (StataCorp, College Station, USA) for our analyses.

Results

Patient characteristics

A total of 337 CDI patients were included and matched to 337 non-diarrhoeal controls and 227 non-CDI diarrhoeal controls. Clinical and demographical data were complete for the majority of patients (2.7% missing data). Baseline characteristics of included patients are shown in table 1.

Table 1. Baseline characteristics of patients with CDI, control patients and patients with non-CDI diarrhoea.

Patient characteristics	CDI patients (N=337)		Non-diarrhoeal patients (N=337)		Non-CDI patients (N=227)	
Mean age, yr (±SD)	61.8	(±21.1)	59.5	(±21.3)	58.1	(±21.4)
Male sex, no. (%)	184	(54.6)	177	(52.5)	111	(48.9)
Hospital service, no. (%)						
Internal medicine	210	(62.3)	205	(60.8)	156	(68.7)
Surgery	71	(21.1)	78	(23.1)	43	(18.9)
Previous admission, no. (%)	176	(53.8)	97	(29.8)	73	(32.6)
Charlson co-morbidity index, no. (%)						
0	54	(16.2)	68	(20.2)	47	(20.7)
1-2	125	(37.4)	146	(43.3)	88	(38.8)
3-4	102	(30.5)	81	(24.0)	56	(24.7)
5+	53	(15.9)	42	(12.5)	36	(15.9)
Underlying diseases, no. (%) *						
Neoplasms	100	(29.9)	99	(29.5)	69	(30.4)
Respiratory system diseases	81	(24.2)	67	(19.9)	40	(17.6)
Digestive system diseases	91	(27.2)	58	(17.2)	66	(29.1)
Circulatory system diseases	185	(55.1)	170	(50.4)	109	(48.0)
Genitourinary system diseases	119	(35.4)	76	(22.6)	63	(27.8)
Musculoskeletal / connective tissue diseases	42	(12.5)	30	(8.9)	19	(8.4)
Antibiotic therapy, no. (%) **	283	(84.0)	195	(57.9)	132	(58.1)
Immunosuppressive agents, no. (%)	144	(43.4)	115	(34.2)	87	(38.5)
Cytostatic agents, no. (%)	55	(16.5)	39	(11.6)	33	(14.7)

* Underlying diseases were classified according to the tenth edition of the International Classification of Diseases (ICD-10).
** Antibiotic use was defined as the use of any antibiotic during the three-month period prior to the start of diarrhoea or the reference date.

CDI patients had a mean age of 61.8 years, compared to 59.5 and 58.1 years in non-diarrhoeal patients and non-CDI controls, respectively. The CDI patients more frequently had a previous admission to a healthcare facility and more frequently used antibiotics, immunosuppressive and cytostatic agents than non-diarrhoeal controls. All underlying diseases were more prevalent among CDI patients. The prevalence of diseases of the digestive and genitourinary system differed the most, and were present among 27.2% and 35.4% of the CDI patients, and among 17.2% and 22.6% of the non-diarrhoeal patients, respectively (both p<0.01). Non-CDI diarrhoeal patients more frequently had diseases of the digestive system compared to patients with CDI (29.1 versus 27.2 percent; p=0.62).

Table 2. Characteristics of antibiotic use in patients with CDI, control patients without diarrhoea and patients with non-CDI diarrhoea.

Use of antibacterial classes in the 3 months prior to CDI	**CDI patients**		**Non-diarrhoeal patients**		**Non-CDI patients**	
	N=337		*N=337*		*N=227*	
Antibiotic classes, no. patients (%)						
Cephalosporins	185	(56.2)	93	(28.1)	66	(29.3)
1st generation	28	(8.5)	35	(10.6)	12	(5.3)
2nd generation	62	(18.8)	24	(7.3)	26	(11.6)
3rd generation	128	(38.9)	43	(13.0)	41	(18.2)
Penicillins	158	(48.0)	100	(30.2)	78	(34.7)
Fluoroquinolones	89	(27.1)	60	(18.1)	48	(21.3)
Macrolides	17	(5.2)	12	(3.6)	8	(3.6)
Sulphonamides and/or trimethoprim	73	(22.2)	49	(14.8)	44	(19.6)
Aminoglycosides	49	(14.9)	29	(8.8)	31	(13.8)
Carbapenems	21	(6.4)	7	(2.1)	8	(3.6)
Glycopeptides (e.g. vancomycin)	44	(13.4)	24	(7.3)	22	(9.8)
Clindamycin	19	(5.8)	9	(2.7)	12	(5.3)
Metronidazole	53	(16.1)	23	(6.9)	16	(7.1)
Others	27	(8.2)	16	(4.8)	21	(9.3)
Determined within patients with antibiotic use	*N=283*		*N=195*		*N=132*	
No. of antibiotic classes used, mean *	2.68		2.24		2.74	
Time to reference date, geometric mean, days (95% CI) **	3.4	(2.9-3.9)	3.4	(2.8-4.2)	1.9	(1.5-2.4)

* These characteristics were compared using an independent sample t-test.
** Time between the use of the last antibiotic and the start of diarrhoea / reference date; unknown for an additional 35 patients.

Table 3. Crude and adjusted odds ratios of eleven different antibiotic classes as a risk factor for CDI.

	Crude odds ratio (95% CI)	Method 1: Adjusted odds ratio (95% CI)	Method 2: Adjusted odds ratio (95% CI)
Any antibiotic	5.89 (3.57-9.71)	5.84 (3.51-9.70)	N.A.
Cephalosporins			
1st generation	0.77 (0.45-1.32)	0.75 (0.43-1.32)	1.05 (0.48-2.30)
2nd generation	3.47 (1.95-6.16)	3.28 (1.83-5.88)	3.37 (1.61-7.05)
3rd generation	5.53 (3.39-9.01)	5.32 (3.30-8.59)	4.87 (2.80-8.47)
Penicillins	2.41 (1.66-3.50)	2.30 (1.57-3.37)	2.28 (1.43-3.64)
Fluoroquinolones	1.91 (1.24-2.92)	1.82 (1.17-2.83)	0.94 (0.53-1.68)
Macrolides	1.45 (0.68-3.13)	1.31 (0.59-2.93)	0.67 (0.25-1.76)
Sulphonamides and/or trimethoprim	1.81 (1.16-2.83)	1.90 (1.20-3.03)	1.75 (0.98-3.12)
Aminoglycosides	1.86 (1.11-3.13)	1.74 (1.02-2.95)	0.83 (0.42-1.64)
Carbapenems	4.50 (1.52-13.3)	4.70 (1.57-14.1)	5.41 (1.38-21.2)
Glycopeptides (e.g. vancomycin)	2.13 (1.21-3.74)	2.11 (1.18-3.75)	1.05 (0.50-2.21)
Clindamycin	2.25 (0.98-5.17)	2.26 (0.97-5.31)	1.68 (0.58-4.85)
Metronidazole	3.31 (1.78-6.15)	3.35 (1.76-6.37)	2.39 (1.05-5.45)
Others	2.09 (1.02-4.29)	2.07 (0.99-4.32)	1.67 (0.66-4.21)

Each antibiotic class was separately analysed in two multivariable models, adjusting for the variables mentioned in method 1 or 2.
Method 1: corrected for Charlson's index, age and sex (graphically displayed in the online supplementary material).
Method 2: corrected for Charlson's index, age, sex and the use of other antibiotic classes (all classes displayed in the table were separately entered into the multivariable model).
N.A.: not applicable.

Antibiotic agents and the risk for CDI

Type of antibiotic agent – Cephalosporins (mainly cefuroxime and ceftriaxone, both 19%) and penicillins (mainly co-amoxiclav acid, 48%) were the most frequently used antibiotics (table 2). After adjustment for age, sex and Charlson Comorbitidy Index, all antibiotic classes, except 1st generation cephalosporins and macrolides, were associated with CDI (Table 3, 2nd column). Second and third generation cephalosporins and carbapenems had a strong association with CDI: odds ratios of 3.28 (95% CI: 1.83 to 5.88), 5.32 (95% CI: 3.30 to 8.59) and 4.70 (95% CI: 1.57 to 14.1), respectively. Combination therapy of several different antibiotic classes is common in hospitalized patients. We therefore also evaluated the association between antibiotic classes and CDI after adjustment for concomitant use of antibiotics. After these adjustments, confidence intervals overall widened, but second and third generation cephalosporins, penicillins, carbapenems and metronidazole remained significantly associated with CDI (table 3, 3rd column). Furthermore, we performed

an interaction analysis in which no synergistic effect of cephalosporins on any of the other antibiotic classes -or vice versa- was observed (data not shown).

The use of eleven different antibiotic classes of patients with CDI was compared to non-diarrhoeal patients to calculate the strength of the risk of antibiotic use on the development of CDI. This risk was expressed in Odds ratios with a 95% confidence interval. Due to the wide distribution of the effect of cephalosporins, we display three subgroups of cephalosporins separately.

Number of antimicrobials – CDI patients used more different antibiotic classes than non-diarrhoeal controls; a mean of 2.7 versus 2.2 different classes, respectively ($p<0.01$).

Duration and dosage – Figure 1 depicts the effect of dosage and duration (combined in the DDD calculation) of antibiotic therapy on the risk for CDI. This risk increased along with an increasing number of DDDs. The use of ≥14 DDDs of antibiotic in the three months prior to the index date, had the strongest association with CDI (OR 8.50; 95% CI: 4.56 to 15.9).

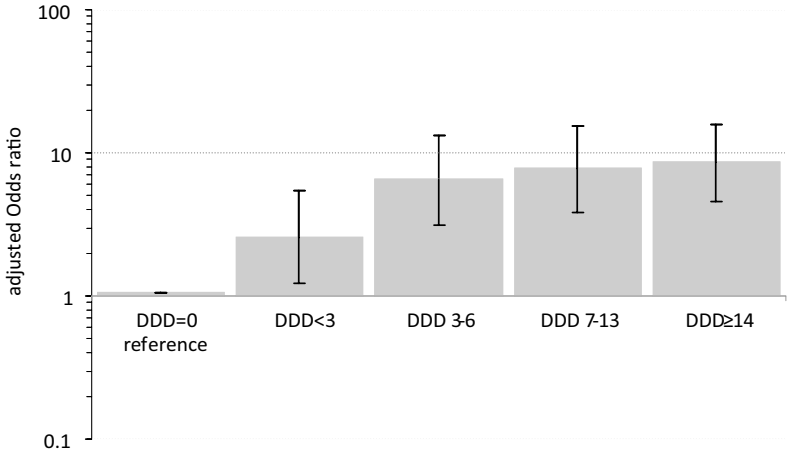


Figure 1. Dose-response relation of antibiotic therapy on the development of CDI. Dose and duration of antibiotic therapy were combined in the calculation of the Defined Daily Dose (DDD). Antibiotic use of CDI cases was compared to that of non-diarrhoeal patients. No use of an antibiotic was used as reference category. Odds ratios were adjusted for Charlson index, sex and age.

Period of increased risk – To determine the time-interval of increased risk for CDI after exposure to antibiotics, we divided the three months prior to the reference date into six intervals (figure 2). In the month prior to the reference date, 242 CDI patients used an antibiotic (76.8%), compared to 157 non-diarrhoeal patients (48.9%)

(p<0.01). Of these, 110 CDI patients (35%) and 80 non-diarrhoeal patients (25%) used an antibiotic at time of diagnosis (p=0.01). Multivariate analysis showed a more than six fold increased risk for CDI during antibiotic use and in the first month after cessation of the antibiotic therapy (OR between 6.67 and 10.37). This risk declined during the period between one and three months after the antibiotic was stopped (OR 2.72; 95% CI: 1.20 to 6.15). Additionally, we displayed the comparison of CDI patients versus non-CDI diarrhoeal patients in figure 2. This comparison also showed an increased risk for CDI in the first month after cessation of antibiotic therapy (OR between 5.24 and 9.35). When an antibiotic was used at the start of diarrhoea, the risk for CDI was lower (OR 2.41; 95% CI 1.30 to 4.46), which can be explained by the occurrence of antibiotic associated diarrhoea in non-CDI diarrhoeal patients.

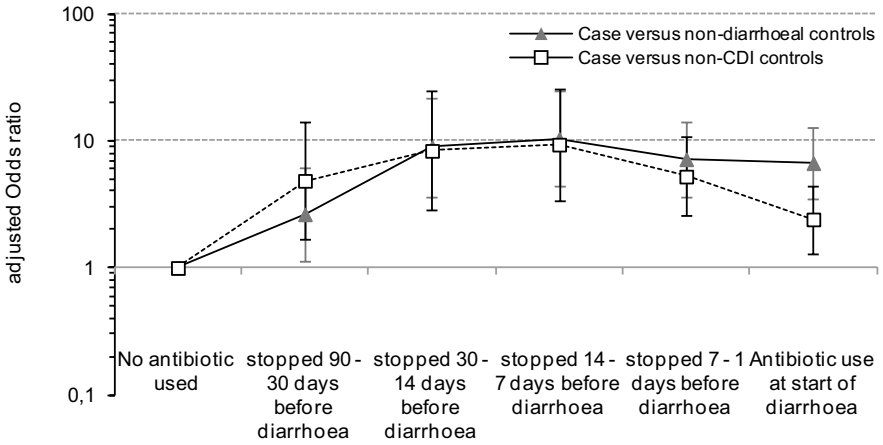


Figure 2. The period at risk for CDI after cessation of antibiotic therapy. The use of antibiotics of patients with CDI compared to non-diarrhoeal patients and patients with non-CDI diarrhoea, stratified in six time intervals. This was done to calculate the risk for CDI after cessation of antibiotic therapy. The Odds ratio was adjusted for age, sex and Charlson index.

Microbiological characteristics

Isolates from 211 (58%) CDI patients were available for further characterization. In 192 (91%) of these, we were able to perform PCR ribotyping. Type 014 was the most frequently found type (n=34; 18%), followed by type 078 (n=24; 13%), type 001 (n=17; 9%) and 027 (n=16; 8%).

Discussion

In this multicenter case-control study, we analysed the period of increased risk for CDI after antibiotic therapy. We found a seven to ten fold increased risk for CDI during antibiotic therapy and the first month after cessation of antibiotics. Another important finding of our study was that antibiotic use one to three months before development of diarrhoea could still be associated with CDI. Second and third generation cephalosporins and carbapenems were the most potent risk factors. The risk for CDI increased when a larger amount of antibiotics and more antibiotic classes were used.

Our findings regarding the time-interval of increased risk are in accordance with the results of a previous study that investigated a specific patient population of elderly patients, who were admitted due to severe community-acquired CDI.[14] The generalizability of this Canadian study was however limited, because it comprised only a small fraction of the patient population that was included in our study. The period of increased risk also coincided with changes in the gut microbiota that occur within days after the start of antibiotic therapy and can persist for weeks or even years after cessation of the antibiotic.[22, 23] Because the intact commensal bowel flora protects against intestinal colonization and infection by *C. difficile*, disruption of the flora during and after antibiotic therapy can result in outgrowth and toxin production of *C. difficile*.[24]

The duration of therapy and dosage of antibiotics, expressed as DDD, showed a positive correlation with the risk of CDI, which is in line with previous reports, as well our finding that virtually all antibiotic classes were associated with CDI.[8, 25, 7] In the literature, fluoroquinolones have mainly been associated with CDI due to PCR ribotype 027.[25] Because we encountered this type in only 8% of our patients, this antibiotic class was not among the most potent risk factors in our study. First generation cephalosporins, which are regularly used as a perioperative prophylaxis, were not associated with CDI in our analyses. This is in line with previous studies, where this antibiotic class was associated with a relatively small risk, or even a decreased risk, on the development of CDI. [8, 25, 26] The latter was suggested to be a result of not severely ill patients with short admissions who received small amounts of first generation cephalosporins. Because cases and controls in our study were selected from the same department and patients receiving a first generation cephalosporin did not represent a specific population (same age and Charlson comorbidity index as patients not receiving this cephalosporin), we assume that

first generation cephalosporins affect the gut microbiota to a lesser extent and do not increase the risk for development of CDI. Administration of metronidazole or vancomycin has infrequently been associated with an increased risk for CDI.[8, 25] In the present study, most patients received intravenous metronidazole or vancomycin for systemic treatment of infections other than CDI, but 6.5% of the patients were treated orally. After excluding these patients, metronidazole and vancomycin remained associated with CDI but the association became weaker (adjusted ORs 3.08 and 1.68 for metronidazole and vancomycin, respectively, according to method 1).

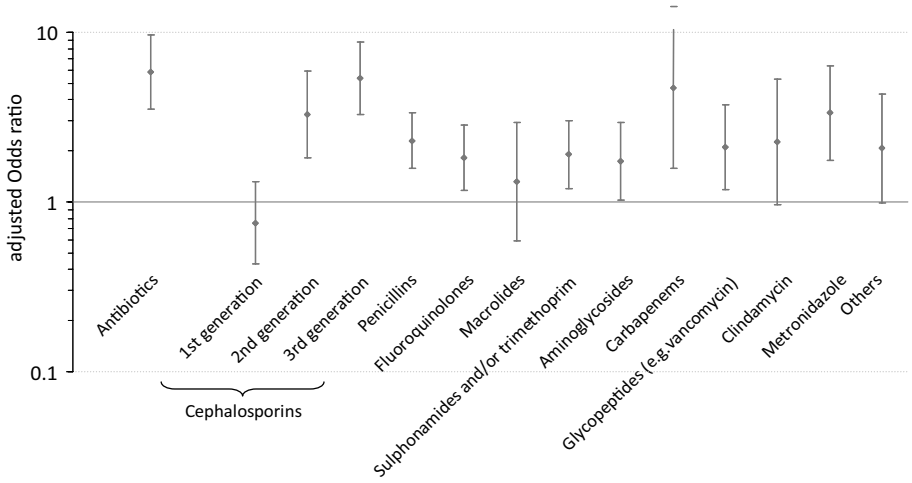
One approach to analyse the risk for CDI associated with a certain antibiotic class, is to restrict the analysis to cases and controls not using other antibiotics. Since only a minority of our CDI patients used antibiotic monotherapy (n=36; 11%), this approach was not feasible. We therefore analysed the effect of a single class of antibiotics by including all cases and controls and adjusting in a logistic model for the use of concomitant antibiotic classes. The advantage is an increased power of the analyses because all cases and controls are included. The estimated Odds ratios will be valid provided that confounding will be adequately adjusted for, a condition that cannot be proven empirically.[27] Confounding was, however, minimised by adjusting for all antibiotic classes.

The most important strength of this study is the robustness of the dataset that was generated by combining data from electronic medical systems, patient records and direct consultation of the physician. Furthermore, we reduced ascertainment bias by testing all unformed stool samples, irrespective of the physician's request. Matching CDI patients and their controls on ward and time of admission ensured us that these patients originated from a setting with a comparable CDI pressure, which has been described as an important risk factor for CDI.[28] Finally, our results are applicable to non-outbreak situations, since the study was performed in a setting in which multiple PCR ribotypes caused CDI (39 different types).

A limitation of our study is the use of various enzyme immuno assays to diagnose CDI. The reported sensitivity of these tests varies between 60% and 85%.[29, 30] Therefore, patients in our study could have been missed as patients with CDI. Consequently, the time of increased risk of non-CDI diarrhoea after antibiotic use might have been overestimated. A second limitation of our study is the use of two control groups. About ten percent of the patients admitted to a (university) hospital experience diarrhoea during their admission. Therefore, a control group that would have been selected without considering the presence of diarrhoea would have been more representative.[31, 32] Analysis of our data after combining the control groups

of patients with non-CDI diarrhoea and non-diarrhoeal patients did however not influence our conclusions (data not shown).

In conclusion, the interval of increased risk for CDI after antibiotic therapy comprises the time from the actual antibiotic use until three months thereafter. The highest risk for CDI is found during and in the first month after antibiotic use. Clinicians should be aware that antibiotic use can increase the risk for CDI a tenfold, even if the antibiotic use preceded the symptoms by one month. Additionally, the results of our study could help future researchers to more accurately define the period of increased risk for CDI after antibiotic exposure.



Supplementary figure. The Odds ratios of eleven different antibiotic classes as a risk factor for CDI. The use of eleven different antibiotic classes of patients with CDI was compared to non-diarrhoeal patients to calculate the strength of the risk of antibiotic use on the development of CDI. This risk was expressed in Odds ratios, using a confined correction method, correcting for Charlson index, age and sex. Odds ratios are displayed with a 95% confidence interval. Due to the wide distribution of the effect of cephalosporins, we display three subgroups of cephalosporins separately. Absolute numbers are displayed in Table 3, 2nd column.

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