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Risk factors for *Clostridium difficile* infection in hospitalized patients with community-acquired pneumonia

James D. Chalmers [a,*], Ahsan R. Akram [b], Aran Singanayagam [c], Mark H. Wilcox [d,e], Adam T. Hill [b,e]

[a] *Scottish Centre for Respiratory Research, University of Dundee, Dundee, DD1 9SY, UK*
[b] *Department of Respiratory Medicine, University of Edinburgh, New Royal Infirmary of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh, EH16 4SA, UK*
[c] *Airway Disease Infection Section, National Heart and Lung Institute, Imperial College, London, W2 1PG, UK*
[d] *Microbiology Department, Leeds Teaching Hospitals & University of Leeds, Old Medical School, Leeds General Infirmary, Leeds, LS1 3EX, UK*

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Summary *Objectives: Clostridium difficile* infection (CDI) is strongly associated with anti-biotic treatment, and community-acquired pneumonia (CAP) is the leading indication for anti-biotic prescription in hospitals. This study assessed the incidence of and risk factors for CDI in a cohort of patients hospitalized with CAP.
Methods: We analysed data from a prospective, observational cohort of patients with CAP in Edinburgh, UK. Patients with diarrhoea were systematically screened for CDI, and risk factors were determined through time-dependent survival analysis.
Results: Overall, 1883 patients with CAP were included, 365 developed diarrhoea and 61 had laboratory-confirmed CDI. The risk factors for CDI were: age (hazard ratio [HR], 1.06 per year; 95% confidence interval [CI], 1.03—1.08), total number of antibiotic classes received (HR, 3.01 per class; 95% CI, 2.32—3.91), duration of antibiotic therapy (HR, 1.09 per day; 95% CI, 1.00—1.19 and hospitalization status (HR, 13.1; 95% CI, 6.0—28.7). Antibiotic class was not an independent predictor of CDI when adjusted for these risk factors ($P > 0.05$ by interaction testing).

* Corresponding author. Tel.:+44 (0)1382 383642.
E-mail addresses: j.chalmers@dundee.ac.uk (J.D. Chalmers), ahsan.akram@ed.ac.uk (A.R. Akram), aransinga@gmail.com (A. Singanayagam), mark.wilcox@nhs.net (M.H. Wilcox), adam.hill318@nhs.net (A.T. Hill).
[e] Joint senior authors.

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Conclusions: These data suggest that reducing the overall antibiotic burden, duration of antibiotic treatment and duration of hospital stay may reduce the incidence of CDI in patients with CAP.

Introduction

Clostridium difficile is a Gram-positive, anaerobic, spore-forming bacillus that colonizes or infects the colon, and causes a spectrum of illnesses from relatively trivial diarrhoea to life-threatening pseudomembranous colitis. *C. difficile* infection (CDI) is most frequently acquired within healthcare facilities and is strongly associated with the use of broad-spectrum antibiotic therapy.[1] In recent years, there has been a dramatic rise in the incidence of CDI in many countries, including the UK, the USA and Australia.[2–5] Indeed, despite improved control of CDI in the UK, there were over 14,000 reported cases across all NHS Trusts in England between April 2014 and March 2015, with a corresponding CDI rate of 41.0 per 100,000 bed days.[6]

Community-acquired pneumonia (CAP) is a major cause of infectious morbidity and mortality in Western countries and is a frequent indication for antibiotic administration in hospitals.[7] Broad-spectrum antibiotic prescribing, particularly third-generation cephalosporin use, in CAP has been linked to a *C. difficile* epidemic.[8–10] With the current increase in the number of hospitalizations for CAP in Western countries, the risk of antibiotic-associated complications is also rising.[11]

Recently, guidelines have attempted to reduce the incidence of CDI as a consequence of CAP by promoting restricted use of cephalosporins, clindamycin and fluoroquinolones, considered to be major drivers of CDI.[1,12] Other risk factors for CDI include increasing age, use of gastric acid-suppressing medications, multiple comorbidities, and inflammatory bowel disease.[13] There is, however, a paucity of data in populations with CAP. The incidence of CDI specifically in patients with CAP is unknown, and the contribution of CDI to mortality in CAP has not been reported. A recent study of inpatient discharges from community hospitals, which included patients with CAP, found that CDI was associated with higher in-hospital mortality among patients discharged for pneumonia or urinary tract infection.[14]

The aim of this longitudinal study was to assess the incidence of and risk factors for CDI in a large cohort of patients hospitalized with CAP.

Patients and methods

This is a secondary analysis of a prospective, observational cohort study of patients with CAP, conducted in two large teaching hospitals in Edinburgh, UK (2005–2010), serving a population of approximately 500,000 people.[15] The Lothian Research Ethics Committee approved the study.

Inclusion and exclusion criteria

Patients were included if they had a diagnosis of CAP on admission, defined as having a new radiographic infiltrate and three or more of the following symptoms or signs: cough, sputum production, haemoptysis, breathlessness, fever, pleuritic chest pain, or signs consistent with pneumonia on physical examination. Exclusion criteria were: hospital-acquired pneumonia, active thoracic malignancy and immunosuppression (defined as use of oral corticosteroids or other immunosuppressive drugs within 28 days before enrolment). Patients in whom active treatment was not considered appropriate (e.g. those receiving palliative care) were also excluded (Fig. 1).[16,17] Patients with suspected healthcare-associated pneumonia (HCAP; defined according to the 2005 guidelines of the Infectious Disease Society of America/American Thoracic Society [IDSA/ATS])[15,18] were not excluded, although risk factors for HCAP were recorded and patients were classified as having CAP or HCAP according to the IDSA/ATS guidelines.

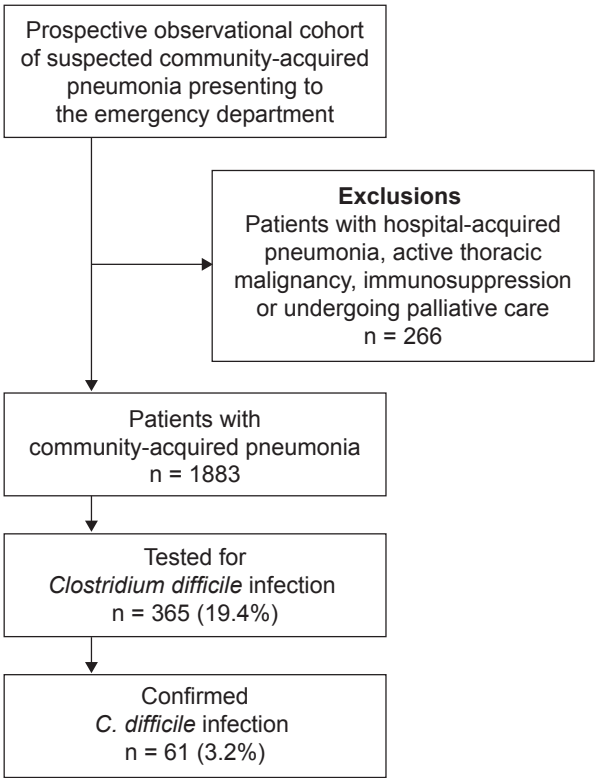

Figure 1 Flow chart illustrating the number of patients included and excluded in the study.

Antimicrobial therapy

Antimicrobial therapy was at the discretion of the attending physician, who was guided by a protocol based on clinical severity.[16] All antimicrobial treatment within 30 days of hospitalization with CAP, including antibiotic treatment during the 14 days preceding admission, was recorded. For the analysis, antibiotics were grouped by drug class (cephalosporins, amoxicillin/clavulanic acid, macrolides, fluoroquinolones, tetracyclines, carbapenems, piperacillin/tazobactam, narrow-spectrum penicillins). Duration of antibiotic therapy was recorded as the number of whole days of treatment with the same antibiotic within 30 days. This included antibiotics administered before admission to hospital and those administered in the 30 days after admission. Antibiotics used to treat CDI or received after CDI diagnosis were identified and excluded from analyses of antibiotic class and duration.

Testing for CDI infection

Testing for *C. difficile* was mandatory at the hospitals at the time of this study. The protocol required that all patients reporting more than two loose stools per day (or more stools than normal for them) provided a specimen for a *C. difficile* toxin test (Techlab *C. difficile* Tox A/B II kit; TechLab, Blackburg, VA, USA). CDI was defined as diarrhoea with a positive test for *C. difficile* toxin.

Outcomes

The primary outcome was the development of laboratory-confirmed CDI. Secondary outcomes were 30-day and 1-year mortality. Mortality was recorded for up to 1 year post-discharge using electronic medical records linked to the Scottish Register Office, which uses unique identifiers to accurately record all deaths in Scotland.

Statistical analysis

Data were analysed using SPSS v.13 (SPSS Inc., Chicago, IL, USA). To compare categorical data, the χ^2 test or Fisher's exact test (for comparisons involving fewer than 10 patients) was used. The Mann–Whitney *U* test was used to compare two groups of continuous data. To identify clinical factors independently associated with CDI, all potential risk factors that were considered to be clinically important, or that were statistically significantly associated with CDI in univariate analysis, were identified and entered into a Cox proportional hazard model. We used time-dependent Cox regression models to account for fluctuations in antibiotic exposure status during follow-up, and to account for duration of hospitalization prior to CDI diagnosis. Results are presented as estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs), with days of follow-up until diagnosis of CDI as a time variable, and hospitalization status and use of antibiotic treatments as time-dependent variables. Multivariable models were constructed based on modelling studies by Peduzzi et al., who suggest a maximum of one covariate per 10 events.[19] Two regression analyses were performed because combination antibiotic therapy was common, potentially leading to multicollinearity. In the first analysis, all predictors except antibiotic class were included to establish the patient- and treatment-related risk factors for CDI. In the second analysis, antibiotic classes (grouped as cephalosporins, amoxicillin/clavulanic acid, macrolides, fluoroquinolones, tetracyclines, carbapenems, piperacillin/tazobactam, narrow-spectrum penicillins) were individually included in the models to determine the independent contribution of antibiotic class to CDI risk. In sub-analyses, the additive effect of antibiotic combinations compared with monotherapy was assessed using separate survival models and estimates were compared using interaction testing.[20] The proportional hazards assumption was satisfied in each model. A *P* value of less than 0.05 was considered to be statistically significant.

Results

Study cohort

Overall, 1883 patients with CAP were included in these analyses (Fig. 1), and 30-day mortality was 9.0% ($n = 169$). Baseline demographic and clinical characteristics, and the most frequently used antibiotic regimens are shown in Table 1. The median age of patients was 68 years and 51% were male. The most frequently used empiric antibiotics were clarithromycin (58%), amoxicillin/clavulanic acid (47%) and amoxicillin (35%). Overall, 24% of patients had risk factors for HCAP.

C. difficile infection

Faecal samples from 365 patients (19.4%) were sent for testing, indicating a high frequency of diarrhoea symptoms in patients hospitalized with CAP. Overall, 61 patients (3.2%) had laboratory-confirmed CDI during the study period. Rates of CDI varied annually from 1.5% in 2005 to 4.2% in 2006 and 3.3% in 2007, peaking at a rate of 5.1% in 2008. In 2009 and 2010, rates of CDI fell to 2.9% and 2.2%, respectively.

Selected demographic, clinical and baseline characteristics of patients who developed CDI compared with those who did not develop CDI are shown in Table 2. There were significant differences in the characteristics of patients in these two groups; patients with CDI were older (median age, 79 years vs. 67 years; $P < 0.0001$), had more severe pneumonia (median pneumonia severity index [PSI] score, 4 vs. 3; $P < 0.0001$) and required longer periods of hospitalization (median, 30 days vs. 5 days; $P < 0.0001$). In those patients with CDI, the median duration of hospitalization prior to CDI diagnosis was 18 days and the median duration of admission after CDI diagnosis was 14 days.

CDI was also significantly associated with longer duration of antibiotic therapy (mean duration, 11.5 days for patients with CDI vs. 10.2 days for those without CDI; $P = 0.002$; Table 2) and a higher number of antibiotics received (mean, 2.6 for patients with CDI vs. 1.8 for those without CDI; $P < 0.0001$). The most frequently used antibiotic

Table 1 Baseline demographic and clinical characteristics.

Characteristic	Patients with CAP (n = 1883)
Demographics	
Male	961 (51.0)
Age (years), median (IQR)	68 (62–79)
Active smoker	650 (34.5)
Active alcohol abuser	189 (10.0)
Comorbidities	
COPD	496 (26.3)
Healthcare-associated pneumonia	451 (24.0)
Congestive cardiac failure	390 (20.7)
Diabetes mellitus	245 (13.0)
Cerebrovascular disease	191 (10.1)
Chronic renal failure	124 (6.6)
Liver disease	98 (5.2)
CAP severity on admission	
PSI risk class IV and V	667 (35.4)
Altered mental state	281 (14.9)
ICU admission	181 (9.6)
Physical findings on admission	
Temperature (°C), median (IQR)	37.5 (36.9–38.4)
Hypotension[a]	444 (23.6)
Heart rate (beats/minute), median (IQR)	104 (89–118)
Respiratory rate (breaths/minute), median (IQR)	25 (20–32)
SpO_2, median (IQR)	94 (91–95)
Laboratory values	
Arterial pH <7.35	247 (13.1)
White blood cells ($\times 10^9$ cells/mL), median (IQR)	14.2 (9.2–19.5)
Platelets ($\times 10^9$ cells/mL), median (IQR)	244 (192–322)
Glucose (mg/dL), median (IQR)	117 (101–142)
Sodium (mEq/L), median (IQR)	137 (134–140)
Chest radiograph findings	
Pleural effusion	385 (20.4)
Empiric antibiotic treatment	
Clarithromycin	1099 (58.4)
Amoxicillin/clavulanic acid	893 (47.4)
Amoxicillin	652 (34.6)
Cephalosporins	305 (16.2)
Piperacillin/tazobactam	56 (3.0)
Doxycycline	55 (2.9)
Clindamycin	12 (0.6)
Ciprofloxacin	31 (1.6)
Meropenem	9 (0.5)
Vancomycin	16 (0.8)
Co-trimoxazole	10 (0.5)
Others	122 (6.5)
Clinical outcomes	
Duration of hospitalization (days), median (IQR)	5 (3–11)
In-hospital mortality	169 (9.0)

Data are shown as n (%) unless otherwise stated.
CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CXR, chest radiograph; ICU, intensive care unit; IQR, interquartile range; PSI, pneumonia severity index; SpO_2, oxygen saturation.
[a] Defined as systolic blood pressure <90 mmHg and/or diastolic blood pressure <60 mmHg.

regimens that were associated with CDI were amoxicillin/clavulanic acid (63.9% of patients with CDI vs. 46.9% of those without CDI; $P < 0.009$), with or without macrolides, and regimens containing cephalosporins (27.9% of patients with CDI vs. 15.8% of those without CDI; $P = 0.01$). The majority of patients received multiple antibiotics (after excluding those used to treat CDI). The most common combination treatment was amoxicillin/clavulanic acid plus clarithromycin (508 patients, 27%).

Congestive cardiac failure ($P = 0.007$) and cerebrovascular disease ($P < 0.0001$) were significantly more common among patients with CDI than among those without CDI (Table 2). In addition, 57.4% of patients with CDI had risk factors for HCAP, compared with 22.8% of patients without CDI ($P < 0.0001$). Of the risk factors recorded for HCAP, 26 patients had a history of recent hospitalization, 6 were nursing home or care facility residents, 2 were receiving dialysis for chronic renal failure, and 1 received home infusion therapy.

In a multivariable analysis, independent risk factors for CDI were identified as: age, total number of antibiotic classes received, total duration of antibiotic therapy, and the presence of one or more comorbidities (Table 3). The time-dependent variable hospitalization status was strongly associated with CDI diagnosis indicating patients were at significantly higher risk while they remained in hospital; this model did not include antibiotic class as a variable. When antibiotic class was subsequently included as an independent variable, there was a statistically significant association between macrolides (HR, 1.77; 95% CI, 1.03–3.03) and CDI, but no other statistically significant associations at the level of antibiotic class were identified (Table 3). Using interaction testing, there were no significant differences in risk estimates between amoxicillin/clavulanic acid and cephalosporins, macrolides or quinolones ($P > 0.05$ for all comparisons, Table 3), consistent with the view that these antibiotics confer similar risks of CDI. When repeating the analysis using the total duration of exposure to each antibiotic in a time-dependent analysis, similar results were observed (Table 4). Proton pump inhibitors were excluded from the models, as they were not significantly associated with CDI in any of the current analyses (odds ratio [OR], 0.81; 95% CI, 0.41–1.57; $P = 0.5$).

As combination therapy with macrolides is common in CAP, we investigated whether the addition of clarithromycin to any of the β-lactams (amoxicillin, amoxicillin/clavulanic acid or cephalosporins) resulted in an increase in CDI. Addition of clarithromycin to amoxicillin compared with amoxicillin treatment alone was associated with a non-significant increase in CDI (unadjusted HR, 1.31; 95% CI, 0.47–3.68; $P = 0.6$; adjusted HR, 1.19; 95% CI, 0.42–3.39; $P = 0.7$). Addition of clarithromycin to amoxicillin/clavulanic acid was associated with a significant increase in CDI risk compared with amoxicillin/clavulanic acid alone (unadjusted HR, 2.00; 95% CI, 1.00–4.02; $P = 0.04$; adjusted HR, 2.09; 95% CI, 1.04–4.21; $P = 0.04$). Fewer patients received cephalosporins, but the corresponding HRs for the addition of clarithromycin were 1.24 (95% CI, 0.47–3.31; $P = 0.6$; unadjusted) and 1.08 (95% CI, 0.39–3.03; $P = 0.9$; adjusted). There were no significant differences in the risk factors for CDI between

Table 2 Baseline demographic and clinical characteristics of patients with CDI and those without CDI.

Potential risk factor for CDI	Patients with CDI ($n = 61$)	Patients without CDI ($n = 1822$)	*P* value
Demographics, median (IQR)			
Age, years	79 (71–83)	67 (50–77)	<0.0001
Pneumonia severity index (PSI) score	4 (4–5)	3 (2–4)	<0.0001
Duration of hospitalization (days)	30 (12–46)	5 (2–10)	<0.0001
Antibiotic administration, mean (SD)			
Duration of antibiotic therapy (days)	11.5 (3.5)	10.2 (3.1)	0.002
Number of antibiotic classes	2.6 (1.2)	1.8 (0.6)	<0.0001
Antibiotic agents, *n* (%)			
Cephalosporins	17 (27.9)	288 (15.8)	0.01
Narrow-spectrum penicillins	15 (24.6)	637 (35.0)	0.09
Amoxicillin/clavulanic acid[a]	39 (63.9)	854 (46.9)	0.009
Macrolides	41 (67.2)	1058 (58.1)	0.1
Tetracyclines	2 (3.3)	53 (2.9)	0.9
Quinolones	5 (8.2)	26 (1.4)	<0.0001
Piperacillin/tazobactam	14 (22.9)	42 (2.3)	<0.0001
Comorbidities, *n* (%)			
COPD	21 (34.4)	475 (26.1)	0.1
Congestive cardiac failure	21 (34.4)	369 (20.3)	0.007
Diabetes mellitus	4 (6.6)	241 (13.2)	0.1
Cerebrovascular disease	18 (29.5)	173 (9.5)	<0.0001
Renal failure	7 (11.5)	117 (6.4)	0.1
Liver disease	5 (8.2)	93 (5.1)	0.3
Classification of disease, *n* (%)			
Risk factors for healthcare-associated pneumonia	35 (57.4)	416 (22.8)	<0.0001

CDI, *Clostridium difficile* infection; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PSI, pneumonia severity index; SD, standard deviation.
[a] With or without macrolides.

the subgroups of patients with risk factors for HCAP ($n = 35$) and those without such risk factors ($n = 26$; Table 4).

Contribution of CDI to clinical outcomes in CAP

Mortality in patients with CAP who developed CDI during hospitalization was 21.3%, compared with 8.6% in patients without CDI ($P < 0.0001$), rising to 42.6% after 1 year (compared with 1-year mortality of 20.5% in those without CDI [$P < 0.0001$] and 21.3% for all patients with CAP [$P = 0.0001$]). However, when adjusted for age, comorbidities, and CAP severity using PSI scores, CDI was no longer an independent predictor of 30-day mortality (HR, 1.68; 95% CI, 0.78–3.63; $P = 0.2$). Variables independently associated with 30-day mortality were: age (HR, 1.02 per year;

Table 3 Time-dependent Cox Proportional Hazards regression analysis of independent risk factors for CDI in a population of patients with CAP.

Risk factor	Multivariate hazard ratio (95% CI)	*P* value
Baseline model		
Age (per year)	1.06 (1.03–1.08)	<0.0001
Comorbidities (per additional comorbidity)	1.21 (0.91–1.60)	0.2
PSI class (per additional class)	0.86 (0.65–1.12)	0.3
Duration of antibiotic therapy (per day)	1.09 (1.00–1.19)	0.04
Number of antibiotic classes (per additional class)	3.01 (2.32–3.91)	<0.0001
Hospitalization status	13.1 (6.0–28.7)	<0.0001
Antibiotic classes (any exposure model)		
Cephalosporins	1.48 (0.83–2.63)	0.2
Amoxicillin/clavulanic acid	1.66 (0.98–2.83)	0.06
Macrolides	1.77 (1.03–3.03)	0.04
Quinolones	1.35 (0.53–3.41)	0.5
Amoxicillin	0.94 (0.52–1.72)	0.6

CAP, community-acquired pneumonia; CDI, *Clostridium difficile* infection; CI, confidence interval.

Table 4 Time-dependent Cox Proportional Hazard regression analysis of duration of antibiotic exposure and risk of CDI in a population of patients with CAP, and risk of CDI over time.

Risk factor	Multivariate hazard ratio (95% CI)	*P* value
Duration model (per day)		
Cephalosporins	1.02 (0.91–1.14)	0.8
Amoxicillin/clavulanic acid	1.10 (1.05–1.15)	<0.0001
Macrolides	1.13 (1.07–1.20)	<0.0001
Quinolones	1.01 (0.93–1.10)	0.8
Amoxicillin	1.05 (0.99–1.12)	0.1
Sensitivity analysis excluding HCAP		
Age (per year)	1.09 (1.04–1.14)	<0.0001
Comorbidities (per additional comorbidity)	1.18 (0.76–1.84)	0.5
PSI class (per additional class)	0.74 (0.46–1.18)	0.2
Duration of antibiotic therapy (per day)	1.06 (0.93–1.21)	0.4
Number of antibiotic classes (per additional class)	3.07 (1.85–5.09)	<0.0001
Hospitalization status	7.79 (2.57–23.6)	<0.0001
Sensitivity analysis – HCAP only		
Age (per year)	1.05 (1.02–1.08)	0.002
Comorbidities (per additional comorbidity)	1.33 (0.91–1.95)	0.2
PSI class (per additional class)	0.94 (0.67–1.32)	0.7
Duration of antibiotic therapy (per day)	1.08 (0.96–1.22)	0.2
Number of antibiotic classes (per additional class)	2.54 (1.84–3.51)	<0.0001
Hospitalization status	17.7 (5.67–55.0)	<0.0001

CAP, community-acquired pneumonia; CDI, *Clostridium difficile* infection; CI, confidence interval; HCAP, healthcare-associated pneumonia.

95% CI, 1.01–1.04; $P = 0.006$) and PSI (HR, 1.03; 95% CI, 1.02–1.04; $P < 0.0001$).

Discussion

Although *C. difficile* has been linked with antibiotic treatment for respiratory tract infections for more than a decade, there have been no previous studies describing the risk factors for CDI in a CAP population.[8–10] This is surprising, as management practices for lower respiratory tract infections have changed substantially in response to the rising incidence of CDI, particularly in the UK.[21–23] These changes are specifically mentioned in the 2004 and 2009 updates of the British Thoracic Society guidelines for CAP as a driver for reducing broad-spectrum antibiotic consumption.[24,25]

Our results suggest that at least some CDI risk factors are modifiable, and that some cases of CDI are therefore preventable. Among the major risk factors identified in our time-dependent regression models were duration of antibiotic therapy and the number of antibiotic classes used, both of which are modifiable to some degree. Not surprisingly, given that CDI is most frequently a nosocomial infection, patients were at much higher risk of acquiring CDI during hospitalization than after hospital discharge. Duration of hospital admission for CDI is also modifiable and our analysis suggests that initiatives to reduce the length of hospital stay for CAP may also impact on CDI risk. Strikingly, however, we did not identify a strong relationship between antibiotic class and CDI. Our data suggest that all of the broad-spectrum antibiotics commonly used in CAP, including amoxicillin/clavulanic acid, cephalosporins and quinolones, carry a similar level of risk. This is in contrast to previous studies, which found a strong association between an increased frequency of CDI and the use of cephalosporins and clindamycin in particular.[1,9] This may reflect the dominance of only a few antibiotic classes in CAP, with the majority of patients receiving β-lactams or cephalosporins, with or without macrolides.[22,23] Moreover, a recent analysis of antibiotic prescribing policies and CDI rates in NHS Trusts in England suggested that policies recommending the empiric use of broad-spectrum antibiotics in patients with CAP may be associated with higher rates of CDI.[26] Importantly, however, the study focussed on the hospital policies and did not demonstrate a causal relationship between antibiotic use and CDI, and did not assess factors such as treatment duration or whether the use of broad-spectrum antibiotics in patients with CAP was appropriate.

Interestingly, amoxicillin/clavulanic acid and macrolides were the antibiotics most often associated with CDI in the present cohort. National UK guidelines recommended replacing cephalosporins with amoxicillin/clavulanic acid in part because of concerns about the risk of CDI.[24,25] However, our data suggest that this change did not substantially reduce the frequency of CDI during 2005–2010; indeed, the incidence of CDI substantially increased during the period in which amoxicillin/clavulanic acid was replacing cephalosporins as first-line therapy.[27] CDI rates have subsequently declined in the UK, following concerted efforts to improve antimicrobial-prescribing practices and initiatives to prevent transmission in hospitals.[6,28] In contrast, rates of CDI remain high in North America.[2,29] A recent, 46-month, retrospective cohort study of 34,298 inpatients from a large, acute care hospital in Canada reported an incidence of CDI of 5.95 per 10,000 patient-days. Moreover,

the study demonstrated that ward-level antibiotic prescribing was significantly associated with an increased risk of CDI, with each 10% increase in antibiotic exposure associated with an increase in the incidence of CDI of 2.1 per 10,000 patient-days.[29] These data are consistent with the findings from our study, and highlight the need for broad antimicrobial stewardship focussing on a reduction in total antibiotic exposure.

Most of the previous reports of CDI associated with CAP, and indeed with specific antibiotics, have been in the context of epidemics or outbreaks, and so have inherent limitations and biases.[30] Thus, the longitudinal nature of this cohort is a particular strength. Although there have been no previous longitudinal studies of CDI in CAP, Bruns and colleagues described a prospective study of 107 patients with CAP with consecutive stool and skin cultures; *C. difficile* was carried asymptomatically by 9.4% of patients on admission to hospital and was acquired by a further 11.2% of patients while in hospital, although no cases of active CDI were identified.[31] The results of the analysis by Bruns et al. and the present study agree, in that while there was not a strong relationship between choice of empiric antibiotic and acquisition of *C. difficile*, prolonged antibiotic therapy and prior hospitalization were the leading risk factors.[31]

The antibiotic classes most strongly associated with the development of CDI include clindamycin and third-generation cephalosporins; more recently, quinolones, carbapenems and aminopenicillins have also been implicated.[32,33] Macrolides are widely used in CAP and can also induce CDI because of their activity against gut anaerobes.[34] Macrolides are rarely used as monotherapy, and therefore, estimating their individual effect independent of the cephalosporins or aminopenicillins is challenging. Although interaction testing suggested no significant difference in risk between the individual antibiotics evaluated in the present study, macrolides and amoxicillin/clavulanic acid had the highest HR, and our data suggest that addition of macrolides to β-lactam therapy was associated with an increased risk of CDI. However the relationship was only statistically significant for the addition of clarithromycin to amoxicillin/clavulanic acid, and it should be noted that study power to detect independent effects of macrolides was limited. If macrolide use is associated with CDI this would be particularly interesting in light of recent data suggesting that, outside the intensive care unit, the addition of macrolides to β-lactams for CAP may not improve outcomes. A cluster-randomized trial in the Netherlands demonstrated no advantage for mortality of adding of macrolides compared with β-lactam monotherapy.[35]

The present study identified duration of antibiotic therapy as a key risk factor for CDI. Antibiotic regimens as short as 3 days may be as effective as longer courses in the majority of patients with mild-to-moderate CAP.[36,37] Despite this evidence, a recent international audit reported the mean duration of antibiotic treatment for hospitalized patients to be 10—11 days.[38] One of the most striking findings of the audit was a lack of association between pneumonia severity and the duration of antibiotic therapy, indicating that treatment duration is often a matter of practice and convention rather than being based on objective measures of treatment response.[38] Shortening antibiotic treatment duration can have multiple benefits, including reduced side effects, reduced hospital costs, shortened length of stay, and reduced likelihood of developing antimicrobial resistance. The effects of a multidisciplinary programme to reduce antibiotic duration were demonstrated in a recent prospective before-and-after intervention study in 502 patients with lower respiratory tract infections. The programme, which incorporated antibiotic treatment duration based on the CURB65 score, automatic stop dates, and pharmacist feedback to prescribers, significantly reduced the duration of antibiotic treatment by 18% ($P < 0.001$) and the incidence of treatment-related adverse events by 39% ($P = 0.03$), with no increase in mortality or length of stay.[39]

Well-established clinical stability criteria and a reduction in C-reactive protein levels can identify patients who have responded to treatment and are thus at low risk of complications.[40] Once stability has been reached, discontinuing antibiotic therapy early appears to have a good safety profile, while efficacy is not diminished compared with longer treatment durations.[40] This is clearly an area for further investigation, as reducing length of antibiotic therapy may reduce CDI risk.

Notably, this study used the Techlab *C. difficile* Tox A/B II EIA to define CDI cases, which has been demonstrated to be the most sensitive toxin EIA available.[5,41] Thus, while some CDI cases may have been missed, we believe that within the confines of real-world testing, the conclusions we have drawn are valid.

Our study demonstrates that CDI is a relatively uncommon complication of CAP, occurring predominantly in elderly patients with comorbidities. The development of CDI in patients with CAP is associated with increased 30-day and 1-year mortality. Moreover, because CAP is the most common community-acquired infection requiring hospitalization in developed countries, its contribution to the current global CDI epidemic is considerable. CDI is potentially preventable, and our study suggests that reducing total antibiotic exposure, limiting treatment duration and reducing the length of hospital stay may be at least as important as changing antibiotic class in reducing disease incidence.

Conflicts of interest

A. R. A., A. S. and A. H. declare that they have no conflicts of interest in relation to the present manuscript. J. D. C. reports consultancy for Basilea Pharmaceutica International Ltd. M. H. W. reports consultancy for Basilea Pharmaceutica International Ltd.

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