Community-associated *Clostridium difficile* infection in emergency department patients in Western Australia

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Abstract

Clostridium difficile infection (CDI) is primarily associated with hospitalised patients, however, community-associated CDI (CA-CDI) has increased in Australia. We aimed to investigate the epidemiology and outcomes of CA-CDI cases presenting to hospital emergency departments in Western Australia (WA). A retrospective case-control study of CA-CDI cases presenting at six emergency departments in WA from July 2013 to June 2014 was performed. Clinical signs, recent medication, hospitalisations and potential risk factors for CA-CDI were investigated for cases (n=34) and unmatched controls (n=62) who were infected with another gastrointestinal pathogen, including *Campylobacter* spp., *Salmonella* spp., *Aeromonas* spp., *Shigella sonnei* and *Escherichia coli* O157. Elevated white cell count (31.3% vs 8.2%, p<0.01), female gender (67.6% vs 41.9%, p<0.05), age ≥65 years (41.2% vs 21.0%, p<0.05) and antimicrobial use in the previous month (41.2% vs 11.3%, p<0.01) were significantly more frequent among cases compared to controls. After multivariable analysis, antibiotic use (odds ratio 8.49, 95% confidence interval 2.75-26.21) and age ≥65 years (3.03, 1.05-8.75) were significantly associated with CA-CDI. Ribotype (RT) 014/020 was most common (40.7%) among 27 *C. difficile* isolates followed by RTs 002 (14.8%), 001, 056 and 244 (all 7.4%).

CA-CDI was associated with advanced age and recent antibiotic use compared to those infected with other gastrointestinal pathogens. RT 014 has also recently been found at high prevalence in public lawn spaces, and previously RT 014 strains from humans and pigs in Australia were closely genetically related, suggesting CA-CDI may be linked with these community reservoirs.

Key words

Clostridium difficile; infection; epidemiology, emergency department; community-associated

Introduction

Over recent decades, major outbreaks of *Clostridium difficile* infection (CDI) have occurred in North America and Europe (1). *C. difficile* produces spores highly resistant to disinfection which, coupled with increasing rates of antibiotic usage worldwide, have contributed to it becoming one of the most common causes of nosocomial infection in developed countries (1), primarily in older patients with recent antimicrobial exposure. The most notable emergence of *C. difficile* to date was associated with a particular strain, ribotype (RT) 027. This fluoroquinolone-resistant, binary toxin (CDT)-producing strain has caused significant outbreaks in North America and Europe since the 2000s, and persisted ever since, particularly in the USA (2).

More recently, community-associated CDI (CA-CDI), where no hospitalisation has occurred in the previous 12 weeks (3), has been reported increasingly from many regions, representing proportions from 14% to 30% of all CDI in North America (4) and Europe (5). Patients with CA-CDI were younger and had fewer comorbidities than patients with healthcare facility-associated CDI (HA-CDI) (4).

The incidence of CDI in Australia increased recently, with 26% of cases thought to be CA-CDI (6). A strain of *C. difficile* with similarities to the epidemic RT 027 strain, RT 244, emerged in Australia in 2011 (7). RT 244 strains produced CDT but, unlike RT 027, were susceptible to fluoroquinolones (8). RT 244 has been associated with poor outcomes; a 30-day mortality of 42% was estimated in a case-control study in Melbourne (8) and increased mortality was reported in RT 244 cases in New Zealand (9). RT 244 infection was primarily seen in CA-CDI cases, and more broadly among CDI cases with onset of symptoms in the

community, suggesting a reservoir of infection outside hospitals. Whole genome sequencing of isolates from across Australia revealed close genetic relatedness between isolates despite geographic separation of many thousands of kilometres, further implying a clonal reservoir of infection across Australia and New Zealand (7).

The increase in CA-CDI incidence and emergence of strains causing severe disease among non-hospitalised patients highlighted the need for investigation of CDI within the community in Australia. The epidemiology of CA-CDI in Australia has not been studied extensively to date, but 50.8% of all CDI cases in Western Australia (WA) in July 2014 had onset of symptoms in the community, regardless of acquisition in the community or a healthcare facility (10). We aimed to describe the epidemiology of CA-CDI among patients at emergency departments in WA, and compare cases with emergency department patients presenting with diarrhoea due to other gastrointestinal pathogens, in order to assess the specific risk factors and outcomes associated with CDI in the community.

Methods

Study setting and design

A case-control study was performed across six hospital emergency departments in WA; five in the Perth Metropolitan area and one regional hospital in the South West of the State. Faecal specimens were collected from patients ≥18 years of age presenting to emergency departments with diarrhoea (loose or watery stool, assuming its container's shape) from July 2013 to June 2014 and were processed routinely in local diagnostic laboratories, where an array of tests for bacterial pathogens was performed. Cases were defined as all patients presenting to an emergency department with diarrhoea, confirmed as having *C. difficile* by *tcdB* PCR using the BD MAX™ platform (BD Diagnostics, Franklin Lakes, NJ, USA), and fulfilling the definition of CA-CDI (see below), during the study period. A subset of controls,

who had diarrhoea and were diagnosed with a bacterial pathogen other than *C. difficile*, were selected randomly from a subset of patients presenting to five of the six emergency departments. Utilising controls who also presented to emergency department with diarrhoea and submitted a faecal sample reduces potential confounding due to differences in health care seeking behaviour.

Data collection

The emergency department medical record of cases and controls was reviewed to collect information on age, sex, medication use over the previous month and clinical findings during their presentation. If patients were admitted to the hospital for further treatment, information on treatments and outcomes was collected from their admitted patient records.

Microbiological analysis

C. difficile tcdB-positive faecal specimens were cultured on ChromID™ *C. difficile* agar (bioMerieux, Marcy l'Etoile, France) and isolates identified as previously described (10). DNA was extracted from pure cultures on blood agar plates and PCR detection of the toxin genes *tcdA*, *tcdB*, *cdtA* and *cdtB* and PCR ribotyping was performed as previously described (11), assigning internationally recognised RT numbers, or a local nomenclature prefixed by "QX".

Data analysis

Medical chart review information was collected in EpiInfo 7™ (CDC, Atlanta). SPSS® Statistics version 22.0 (IBM, Zurich) was used to merge patient laboratory results with corresponding chart review data, and for statistical analysis.

CA-CDI was defined as CDI in a patient with no history of hospital admission within the past 12 weeks. HA-CDI was defined as a CDI case who was hospitalised in the previous 4 weeks. Cases were defined as "indeterminate" where a case had been hospitalised in the previous 4-12 weeks (3). Recurrent CDI was defined as an episode of CDI occurring within 8 weeks after a previous, resolved episode. A history of CDI was defined as a resolved episode of CDI occurring > 8 weeks previous to the current episode.

Descriptive analyses of characteristics of patients were performed comparing proportions by χ^2 test between cases and controls. Medians were compared using the Mann Whitney U test. Risk factors for CA-CDI, comparing CA-CDI cases with controls, were determined by calculating univariable odds ratios (ORs) with 95% confidence intervals (CIs) and two-sided *p* values. A multivariable backwards stepwise logistic regression analysis was performed including variables where the univariable OR suggested an association ($p<0.2$), excluding variables where $n<5$.

Ethical approval

Ethical approval with a waiver of consent was granted by the Sir Charles Gairdner Group Human Research Ethics Committee (HREC) (#2012-185) with site approvals from the participating hospital HRECs and Research Governance units, as well as The University of Western Australia HREC (#RA/4/1/6130) and the Curtin University HREC (#HR 52/2013).

Results

During the 1 year study period, total 77 CDI cases presented across the six emergency departments, of which 34 (44.2%) were classified as CA-CDI and 38 (49.1%) were HA-CDI; another 2 cases (2.9%) were of indeterminate association while details of previous hospitalisations could not be obtained for 3 cases. Data were collected for all CA-CDI cases

and 62 controls with another gastrointestinal pathogen isolated, namely *Campylobacter* spp. (*n*=44), *Salmonella* spp. (*n*=11), *Aeromonas* spp. (*n*=4), *Shigella sonnei* (*n*=2) and *Escherichia coli* O157 (*n*=1).

Characteristics of cases and controls at emergency departments are shown in Table 1. CDI cases were more commonly female (67.6% vs 41.9%, $p<0.05$) compared to controls. The age distribution of cases differed from controls; the majority of controls were aged <35 y (48.4%), while the majority of cases were aged ≥ 65 y (41.2%). Abdominal pain was more frequently seen among controls than cases (44.1% vs 77.4%, $p<0.01$). Fever (temperature ≥38°C) did not differ between groups (32.4% vs 38.7%). Elevated white cell count (WCC; ≥15,000 cells/µL, 31.3% vs 8.2%, $p<0.01$) and hypertension (11.8% vs 3.2%) on arrival were significantly more frequent among cases (Table 1).

The most common comorbidity among patients was hypertension, evenly distributed among 23.5% of cases and 22.6% of controls. GORD was less frequent among cases than controls (8.8% vs 16.1%), diabetes was more frequent among cases (11.8% vs 8.1%) and solid tumours were also more frequent among cases (8.8% vs 4.8%, Table 1); none of these differences was statistically significant.

The most commonly used medication in cases was antibiotics (41.2% cases vs 11.3% controls, $p<0.01$). Proton pump inhibitors (PPIs, 23.5% vs 25.8%) were used by a similar proportion of cases and controls. Where the class of antibiotic was recorded, cephalosporins (15.6% vs 3.3% in controls, $p<0.05$) were most frequently used, followed by amoxycillin (12.5% vs 0%, $p<0.01$) and fluoroquinolones (3.1% and 5.0%). Steroids were also more frequently used by cases (14.7% vs 3.2%, $p<0.05$, Table 1). No cases experienced complications such as toxic megacolon or pseudomembranous colitis, and no cases or controls were deceased after 30 days.

Comparing cases with controls by univariable analysis, antibiotic use was most significantly associated with CA-CDI (OR 5.50, 95% CI 1.94-15.59, $p<0.01$). Female gender and age ≥ 65 years were also associated with CA-CDI (ORs 2.90 [1.20-6.97] and 2.64 [1.06-6.60]) (Table 2). After multivariable analysis, only age ≥ 65 y (OR 3.03 [1.05-8.75] and antibiotic use (OR 8.49 [2.75-26.21]) were significantly associated with CA-CDI.

C. difficile isolates were recovered for 27 cases. RT 014/020 was the most common RT (*n*=11; 40.7%), followed by RT 002 (*n*=4; 14.8%), and RTs 001, 056 and 244 (all *n*=2; 7.4%). Three isolates were CDT-positive, two of which were RT 244, and one RT 078 (Table 3).

Discussion

CA-CDI continues to increase around the world (4, 5). In Australia, increases in CA-CDI have also been observed recently (6) prompting our study of emergency department presentations with diarrhoea at WA hospitals. We found a number of similarities with the results of studies elsewhere in the world. A substantial proportion of CDI cases (44.2%) presenting at WA emergency departments were CA-CDI, and CA-CDI cases were predominantly caused by RT 014/020 *C. difficile* (40.7%). CA-CDI cases were more likely than controls to be of advanced age and to have used antibiotics, both known primary risk factors for CDI (1). In the US, the greatest increase in rising CDI rates in emergency department patients occurred in patients aged 18-24 years, however the greatest proportion of cases overall was in the ≥65 year age group (12). Similarly, in our study the greatest proportion of all cases was aged ≥65 years (48.1%), however, a substantial proportion of CA-CDI cases were aged 18-35 years (35.3%). The proportion of CA-CDI found here (44.2%) mirrors a Canadian study where 44% of CDI cases in emergency departments were CA-CDI (13). A study in Taipei found that emergency department CDI cases more often occurred in

warm spring and summer seasons (14). In the present study, cases also peaked in the summer months (data not shown) although the significance of this finding or reasons for it is not apparent. Peaks in overall CDI rates in the summer months were also previously observed in 2011/2012 in WA, with a particular peak in cases caused by RT 244, discussed below (7).

It is interesting to note the predominance of RT 014/020 strains among CA-CDI cases in this study (40.7%, Table 3). RT 014/020 is consistently the most common strain isolated in CDI cases in Australia (11). This RT is also highly prevalent in Australian pigs (15). Genomic analysis of *C. difficile* RT 014 strains isolated from humans and pigs across Australia showed high clonality among some strains despite long-range geographic separation, suggesting either a common source of exposure or transmission of the strains between the two species (16). This finding suggests that *C. difficile* could potentially enter the human food chain via contamination of food, either meat or meat products or root vegetables, which are fertilised with manure from production animals. We have isolated *C. difficile* from root vegetables and gardening products in the Perth Metropolitan region (17, 18), and found an overall prevalence of *C. difficile* of 59% in 311 local public lawn space samples (19). RT 014/020 also predominated in lawns with 39% of isolates belonging to this RT, thus lawn spaces are likely a reservoir of CA-CDI in WA.

The presence of CDT-positive RT 244 was also notable, having caused widespread outbreaks across Australia in the summer of 2011/2012 with an apparent common, as yet unidentified, source (7). The two cases with RT 244 infection in this study presented two months apart at two different hospitals. Given that patients here presented at emergency departments with RT 244 infection in 2013/14, a reservoir in the community may still exist. Otherwise, a single RT 078 strain, also CDT-positive, was also isolated. Since RT 078 is rarely identified in

Australia (11), it may possibly have been acquired during overseas travel. We were unable to obtain any travel history for the case. However, RT 078 is highly prevalent in production animals in the Northern Hemisphere (20, 21), has been shown to contaminate food (23, 24), and is a common cause of human infection (5). Thus RT 078 may have entered Australia on imported food, the most likely culprit being pork.

This study has some limitations. We had limited access to emergency department patient information so we were unable to calculate the prevalence or incidence rates of CA-CDI among emergency department patients. Thus cases were compared with unmatched controls randomly selected from available information from a subset of hospitals, which may have biased our results. Another limitation was the requirement for a stool sample from emergency department patients. All patients presenting to emergency departments with diarrhoea were asked to provide a stool sample during the study period, however, many patients may not have provided one during their emergency department visit. Those experiencing more severe symptoms may have been more likely to produce a sample, which could have introduced a bias in our results regarding severity. However, this would not differ between cases and controls. Also, patients who were recently hospitalised may have been more likely to seek further hospital care.

Despite limitations the study highlighted that patients in the community are exposed to and infected with *C. difficile* strains which are known to cause severe CDI. The sources of these strains need to be investigated in further detail, as well as identifying risk factors for CA-CDI specifically. Further studies should employ highly discriminatory techniques including whole genome sequencing to compare CA-CDI strains with environmental, animal and food strains to determine how transmission is occurring within the community.

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Table 1. Characteristics of diarrhoeal patients with CA-CDI (cases) or infection with another gastrointestinal bacterial pathogen (controls) on emergency department presentation.

Characteristic	**Cases (*n*=34)**	**Controls (*n*=62)**	**Total (N=96)**
Female	23 (67.6)	26 (41.9)*	49 (51.0)
Age group			
18-34 y	12 (35.3)	30 (48.4)	42 (43.8)
35 - 49 y	4 (11.8)	9 (14.5)	13 (13.5)
50 - 64 y	4 (11.8)	10 (16.1)	14 (14.6)
≥ 65 y	14 (41.2)	13 (21.0)*	27 (28.1)
emergency department presentation			
History of CDI	5 (14.7)	2 (3.2)*	7 (7.3)
Abdominal pain	15 (44.1)	48 (77.4)**	63 (65.6)
Hypertension	4 (11.8)	2 (3.2)	6 (6.3)
Hypotension	1 (2.9)	1 (1.6)	2 (2.1)
Fever (≥38°C)	11 (32.4)	24 (38.7)	35 (36.5)
Elevated white cell count	10 (31.3)	5 (8.2)**	15 (16.1)
Comorbidities			
Inflammatory bowel disease	2 (5.9)	1 (1.6)	3 (3.1)
Hypertension	8 (23.5)	14 (22.6)	22 (22.9)
Diabetes	4 (11.8)	5 (8.1)	9 (9.4)
Solid tumour	3 (8.8)	3 (4.8)	6 (6.3)
Leukaemia	1 (2.9)	1 (1.6)	2 (2.1)
GORD	3 (8.8)	10 (16.1)	13 (13.5)
Myocardial infarction	1 (2.9)	1 (1.6)	2 (2.1)
Peptic ulcer	1 (2.9)	4 (6.5)	5 (5.2)
COPD	1 (2.9)	1 (1.6)	2 (2.1)
Liver disease	3 (8.8)	1 (1.6)	4 (4.2)
Renal disease	3 (8.8)	1 (1.6)	4 (4.2)
Cerebrovascular disease	1 (2.9)	0	1 (1.0)
Congestive heart failure	1 (2.9)	0	1 (1.0)
Connective tissue disease	1 (2.9)	1 (1.6)	2 (2.1)
Peripheral vascular disease	2 (5.9)	0	2 (2.1)
Previous medication			
Steroid	5 (14.7)	2 (3.2)*	7 (7.3)
PPI	8 (23.5)	16 (25.8)	24 (25.0)
H_2RA	0	2 (3.2)	2 (2.1)
Probiotic	0	2 (3.2)	2 (2.1)
Chemotherapy	3 (8.8)	2 (3.2)	5 (5.2)
Antibiotic	14 (41.2)	7 (11.3)**	21 (21.9)
Cephalosporin	5 (15.6)	2 (3.3)*	7 (7.6)
Amoxycillin/amoxycillin clavulanate	4 (12.5)	0**	4 (4.3)
Metronidazole	1 (3.1)	0	1 (1.1)
Trimethoprim/sulfamethoxazole	2 (6.3)	0	2 (2.2)
Fluoroquinolone	1 (3.1)	3 (5.0)	4 (4.3)
Laxative	3 (8.8)	2 (3.2)	5 (5.2)
Admitted	19 (55.9)	27 (43.5)	46 (47.9)

*p<0.05; **p<0.01

GORD, gastro-oesophageal reflux disease; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; H_2RA, H_2 receptor agonist

Table 2. Risk factor analysis for CA-CDI cases compared with controls.

Characteristic	**Univariable OR (95% CI)**	***p***	**Multivariable OR (95% CI)**	***p***
Female	2.90 (1.20-6.97)	0.02		
Age group				
18-34 y	0.58 (0.25-1.38)	0.22		
35 - 49 y	0.79 (0.22-2.77)	0.70		
50 - 64 y	0.69 (0.20-2.40)	0.56		
≥ 65 y	2.64 (1.06-6.60)	0.04	3.03 (1.05-8.75)	0.04
History of CDI	5.17 (0.05-28.28)	0.06		
Comorbidities				
Inflammatory bowel disease	3.81 (0.33-43.67)	0.28		
Hypertension	1.06 (0.39-2.84)	0.92		
Diabetes	1.52 (0.38-6.09)	0.55		
Solid tumour	1.90 (0.36-9.99)	0.45		
Leukaemia	1.85 (0.11-30.52)	0.67		
GORD	0.50 (0.13-1.97)	0.32		
Myocardial infarction	1.85 (0.11-30.52)	0.67		
Peptic ulcer	0.44 (0.05-4.10)	0.47		
COPD	1.85 (0.11-30.52)	0.67		
Liver disease	5.90 (0.59-59.12)	0.13		
Renal disease	5.90 (0.59-59.12)	0.13		
Connective tissue disease	1.85 (0.11-30.52)	0.67		
Previous medication				
Steroid	5.17 (0.95-28.28)	0.06	6.01 (0.99-36.68)	0.05
PPI	0.89 (0.33-2.35)	0.81		
Chemotherapy	2.90 (0.46-18.30)	0.26		
Antibiotic	5.50 (1.94-15.59)	0.001	8.49 (2.75-26.21)	<0.001
Laxative	2.90 (0.46-18.30)	0.26		

OR: Odds ratio; CI: Confidence interval

Table 3. Molecular characteristics of *C. difficile* isolates from emergency department presentations with CA-CDI.

RT	Toxin profile	CA-CDI
014/020	A+B+CDT-	11 (40.7)
002	A+B+CDT-	4 (14.8)
001	A+B+CDT-	2 (7.4)
056	A+B+CDT-	2 (7.4)
244	A+B+CDT+	2 (7.4)
005	A+B+CDT-	1 (3.7)
015	A+B+CDT-	1 (3.7)
081	A+B+CDT-	1 (3.7)
QX 013	A+B+CDT-	1 (3.7)
010*	A-B-CDT-	1 (3.7)
078	A+B+CDT+	1 (3.7)
Total		27 (100.0)

*non-toxigenic strain likely to be carried with toxigenic strain not isolated by culture.