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SHORT REPORT
Epidemiology and factors associated with candidaemia following *Clostridium difficile* infection in adults within metropolitan Atlanta, 2009–2013

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SUMMARY

We assessed prevalence of and risk factors for candidaemia following *Clostridium difficile* infection (CDI) using longitudinal population-based surveillance. Of 13 615 adults with CDI, 113 (0·8%) developed candidaemia in the 120 days following CDI. In a matched case-control analysis, severe CDI and CDI treatment with vancomycin + metronidazole were associated with development of candidaemia following CDI.

Key words: Candidaemia, CDI treatment, *Clostridium difficile* infection, co-infection, severe CDI.

Clostridium difficile and *Candida* sp. are both important causes of healthcare-associated infections [1, 2]. Risk factors are similar for *Candida* infections and *C. difficile* infections (CDI), and include broad spectrum antibiotic (BSA) use and prolonged intensive-care unit (ICU) stays [3, 4]. CDI itself and CDI treatment with certain antibiotics may lead to disruption of the indigenous microbiota, predisposing patients to overgrowth of endogenous pathogens such as *Candida* sp. and dissemination into the blood through the compromised mucosal barrier present during CDI [5, 6]. The purpose of our study was to describe the prevalence and characteristics of adults developing candidaemia following CDI and evaluate the factors associated with developing candidaemia following CDI.

The CDCs Emerging Infections Program conducts population-based surveillance for CDI and candidaemia in the Atlanta area (population 3·8 million). The methods of CDI and candidaemia surveillance have been described previously [1, 7]; in brief, both surveillance systems rely on active laboratory-based case-fi nding in residents of the catchment area, followed by medical record abstraction for identified cases.

A CDI case was defined as a positive *C. difficile* toxin or molecular assay in a surveillance area resident aged ⩾18 years and a candidaemia case was defined as a *Candida* sp.-positive blood culture collected from a surveillance area resident aged ⩾18 years. Infection with CDI and candidaemia was defined as

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candidaemia occurring in the 120 days after CDI during 1 September 2009–31 December 2013. Cases with both infections were identified by merging the two surveillance databases by patient's name and date of birth.

To calculate the prevalence of candidaemia in adults with CDI, we divided the number with co-infection by the number with CDI in a given year. We used the Cochran–Armitage test for trend. We conducted a matched case-control study to identify factors associated with candidaemia following CDI. Controls were defined as CDI cases without candidaemia who had survived at least 120 days post-CDI episode. For each case with both candidaemia and CDI, we identified up to three controls matched by age group (18–44, 45–64, ⩾65 years) and location of CDI disease onset [healthcare facility onset (HCFO), community-onset healthcare-facility associated, community associated]. Not all cases had three controls available because only 10% of the HCFO CDI cases had a full medical record review based on surveillance methodology [1]. We used conditional logistic regression analysis to identify factors associated with candidaemia following CDI. In all analyses, the level of significance was set at $\alpha = 0{\cdot}05$.

Of 13 615 adults with CDI, we identified 113 (0·8%) patients who developed candidaemia in the 120 days after CDI. The prevalence of candidaemia following CDI declined from 1·4% in 2010 to 0·6% in 2013 ($P < 0{\cdot}001$), and varied by age group, with the highest prevalence in cases aged 45–64 years (1·1%) compared to the other two age groups (18–44 years: 0·8%; ⩾65 years: 0·7%; $P = 0{\cdot}036$).

Of the case-patients, median age was 62 years [interquartile range (IQR) 53–70 years], 54% were female, 54% were black, and 77% had CDI onset in a healthcare facility (Table 1). Diabetes (46·9%) was common. Vancomycin, β-lactam/β-lactamase inhibitors, and fluoroquinolones were the most common antibiotics administered to case-patients in the 12 weeks before CDI onset. Fifty (44·3%) case-patients experienced severe CDI. For CDI treatment, 40·7% of case-patients received metronidazole only, 10·6% received vancomycin only, and 39·8% received vancomycin + metronidazole; no case-patients received fidaxomicin.

The median time between CDI and candidaemia diagnosis was 19 days (IQR 8–45 days). Eighty-eight percent of case-patients had a central venous catheter in place in the 2 days before candidaemia diagnosis. *Candida albicans* was the most frequent species recovered (37·2%). Thirty-three (29·2%) case-patients died within 30 days of candidaemia.

We identified 257 controls for 113 cases. Compared to controls, cases had higher odds of being black [matched odds ratio (mOR) 1·87, 95% confidence interval (CI) 1·16–3·05], having diabetes (mOR 1·66, 95% CI 1·01–2·77) or inflammatory bowel disease (mOR 5·07, 95% CI 1·29–23·67), and having a higher Charlson comorbidity index score (mOR 1·99, 95% CI 1·13–3·63) for score of ⩾2 *vs.* <2). In the 12 weeks before CDI, cases also had higher odds of having received proton pump inhibitors (mOR 2·10, 95% CI 1·28–3·53), or BSAs (see Table 1 for individual mOR). Cases were also more likely to have severe CDI (mOR 2·10, 95% CI 1·29–3·42), colectomy (mOR 13·26, 95% CI 1·54–114·08), ICU admission (mOR 2·31, 95% CI 1·00–5·39), and to receive CDI treatment with vancomycin + metronidazole compared to metronidazole alone (mOR 2·08, 95% CI 1·18–3·74).

Using data from two active population- and laboratory-based surveillance systems, we evaluated over 10 000 CDI patients for development of candidaemia and identified a total of 113 persons with both infections. We found that candidaemia following CDI was rare (<1%). The decline observed in the prevalence of CDI/candidaemia is similar to the decline in trends in overall candidaemia rates in the Atlanta area [7]. Distribution of *Candida* sp. causing infection in CDI patients was also similar to that reported in the general population [7]. Some factors, such as black race, diabetes, BSA use, and ICU admission, which have been reported in the past as risk factors for candidaemia [4, 8], continue to be important in patients with preceding CDI. However, this study also identified new potential risk factors for candidaemia in CDI patients, including severe CDI and CDI treatment with both vancomycin + metronidazole.

Treatment with vancomycin + metronidazole was associated with higher odds of developing candidaemia after CDI, compared to metronidazole alone. While treatment with both antibiotics could be a marker of severity of CDI illness [9], it may also be independently associated with development of candidaemia as more disruption of mucosal integrity and disruption of gut microbiota, including suppression of anaerobes and overgrowth of *Candida* has been reported with vancomycin treatment [5, 10]. Although we do not report on the relationship between daily dose of vancomycin used to treat CDI and risk of subsequent candidaemia in this study,

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Table 1. *Demographic and clinical characteristics of case-patients with candidaemia following* Clostridium difficile *infection (CDI) and controls (CDI infection only), Atlanta metropolitan area, 2009–2013*

Characteristic	Cases ($N = 113$) *n* (%)	Controls† ($N = 257$) *n* (%)	Matched OR (95% CI)	*P* value
Age group, years				
18–44	19 (16·8)	37 (14·4)	Not applicable	
45–64	50 (44·2)	88 (34·2)	matched by this	
⩾65	44 (38·9)	132 (51·3)	criteria	
Female sex	61 (54·0)	154 (59·9)	1·22 (0·74–2·00)	0·479
Black race	61 (54·0)	95 (37·0)	1·87 (1·16–3·05)	0·009*
Location of CDI disease onset				
Community acquired	12 (10·6)	36 (14·3)	Not applicable	
Community-onset healthcare-associated	14 (12·4)	42 (16·3)	matched by this	
Healthcare facility onset (HCFO)	87 (77·0)	179 (69·7)	criteria	
Underlying medical conditions				
Diabetes	53 (46·9)	92 (35·8)	1·66 (1·01–2·77)	0·046*
Renal disease	39 (34·5)	69 (26·9)	1·38 (0·82–2·33)	0·244
Heart failure	28 (24·8)	55 (21·4)	1·26 (0·71–2·24)	0·471
Obstructive pulmonary disease	21 (18·6)	55 (21·4)	0·85 (0·45–1·57)	0·704
Liver disease	5 (4·4)	10 (3·9)	0·95 (0·24–3·17)	1·0
Inflammatory bowel disease	7 (6·2)	4 (1·6)	5·07 (1·29–23·67)	0·018*
Peptic ulcer disease	4 (3·5)	6 (2·3)	1·40 (0·28–6·12)	0·834
Solid organ malignancy	8 (7·1)	30 (11·7)	0·66 (0·25–1·53)	0·415
Haematologic malignancy	5 (4·4)	9 (3·5)	1·18 (0·24–3·86)	1·0
Solid organ transplant	4 (3·5)	2 (0·8)	4·06 (0·55– 46·89)	0·214
Bone marrow transplant	4 (3·5)	0	9·09 (1·48–∞)	0·042*
HIV/AIDS	7 (6·2)	15 (5·8)	0·81 (0·18–3·0)	0·983
Dementia	14 (12·4)	30 (11·7)	1·34 (0·61–2·84)	0·528
Cerebrovascular accident	12 (10·6)	37 (14·4)	0·71 (0·30–1·58)	0·488
None	10 (8·99)	36 (14·0)	0·66 (0·27–1·48)	0·373
Charlson comorbidity index				
<2	91 (35·4)	24 (21·2)	Ref.	0·015*
⩾2	166 (64·6)	89 (78·7)	1·99 (1·13–3·63)	
Prior healthcare exposure				
Chronic haemodialysis	16 (14·2)	31 (12·1)	1·02 (0·48–2·14)	1·000
Surgical procedure in the last 12 weeks‡	46 (40·7)	77 (30·0)	1·63 (0·98–2·72)	0·061
Long-term care facility in last 12 weeks‡	29 (25·7)	44 (17·1)	2·10 (1·09–4·09)	0·025*
Emergency room in last 12 weeks‡	28 (24·8)	79 (30·7)	0·78 (0·45–1·33)	0·405
Hospitalized at the time of or within 7 days after stool collection				
Yes	100 (88·5)	190 (73·9)	2·67 (1·32–6·00)	0·005*
Medications received in the 12 weeks before CDI episode				
Proton pump inhibitors	76 (67·3)	123 (47·9)	2·10 (1·28–3·53)	0·002*
H2 blockers	25 (22·1)	39 (15·2)	1·40 (0·77–2·52)	0·289
Steroids	31 (27·4)	47 (18·3)	1·56 (0·87–2·78)	0·141
Chemotherapy	5 (4·4)	20 (7·8)	0·44 (0·13–1·25)	0·148
Antibiotic exposure in the 12 weeks before CDI episode				
Aminoglycoside	8 (7·1)	4 (1·6)	3·76 (0·98–17·57)	0·055*
β-lactamase inhibitors	51 (45·1)	60 (23·4)	2·49 (1·48–4·26)	<0·001*
Carbapenems	24 (21·2)	10 (3·9)	8·94 (3·25–30·60)	<0·001*
1st- and 2nd-generation cephalosporins	12 (10·6)	22 (8·6)	1·26 (0·55–2·76)	0·663
3rd- and 4th-generation cephalosporins	25 (22·1)	31 (12·1)	2·07 (1·05–4·13)	0·035*
Clindamycin	4 (3·5)	13 (5·1)	0·68 (0·15–2·38)	0·728
Fluoroquinolones	46 (40·7)	75 (29·2)	1·68 (1·01–2·82)	0·044*
Vancomycin	52 (46·0)	53 (20·6)	3·12 (1·85–5·39)	<0·001*
Macrolides	15 (13·3)	12 (4·7)	2·92 (1·22–7·20)	0·015*

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Table 1 (*cont.*)

Characteristic	Cases ($N = 113$) *n* (%)	Controls† ($N = 257$) *n* (%)	Matched OR (95% CI)	*P* value
Severe CDI§	50 (44·3)	69 (26·9)	2·10 (1·29–3·42)	0·003*
Ileus	10 (8·9)	3 (1·2)		
Toxic megacolon	3 (2·7)	1 (0·40)		
Pseudomembranous colitis	4 (3·9)	2 (0·8)		
High white blood cell count (>15 000/μl)	41 (36·3)	65 (25·3)		
Colectomy	5 (4·4)	1 (0·4)	13·26 (1·54–114·08)	0·019*
Intensive-care unit admission (within 7 days after CDI diagnosis)	15 (13·2)	15 (5·8)	2·31 (1·00–5·39)	0·049*
Prior CDI episode	25 (22·1)	38 (15·1)	1·76 (0·94–3·25)	0·078
Other gastrointestinal pathogen present	2 (1·8)	7 (2·7)	0·58 (0·06–3·20)	0·793
CDI treatment				
Metronidazole only	46 (40·7)	120 (46·7)	Ref.	
Vancomycin only	12 (10·6)	31 (12·1)	0·94 (0·40–2·10)	1·00
Vancomycin + metronidazole	45 (39·8)	60 (19·1)	2·08 (1·18–3·74)	0·010*
Fidaxomicin only	0	1 (0·4)	3·75 (0–71·30)	1·00
Other	10 (8·9)	42 (16·5)	0·70 (0·28–1·60)	0·480
Type of *Candida* sp.				
albicans	42 (37·2)	Not applicable		
glabrata	28 (24·8)			
parapsilosis	21 (18·5)			
tropicalis	13 (11·5)			
Other	5 (4·4)			
Multiple	2 (1·8)			
Previously known candidaemia risk factors				
Received systemic antibiotics in the 14 days prior to candidaemia	101 (89·4)	Not applicable		
Had a central venous catheter in the 2 days prior to candidaemia	100 (88·0)			
Received total parenteral nutrition in the 14 days prior to candidaemia	43 (38·1)			
Previous candidaemia episode	10 (8·9)			

OR, Odds ratio; CI, confidence interval.

† Controls were matched on age group (18–44, 45–64, $\geqslant$65 years) and location at the time of CDI onset. Note that not all cases had 1:3 matching; HCFO cases in age groups 18–44 and 45–64 years had only one or two controls each because of lack of availability of controls in these groups.

‡ Refers to 12 weeks before CDI onset.

§ Severe CDI = having one or more of the following: ileus, toxic megacolon, pseudomembranous colitis (within 5 days before or after initial *C. difficile* + stool, or a white blood cell count >15 000 cells/μl within 1 day before or after initial *C. difficile* + stool.

* Significant *P* value.

previous research has shown that higher daily doses of vancomycin ($\geqslant$500 mg/day) was an important risk factor for development of bloodstream infections, including candidaemia, following CDI [11]. Poor outcomes, including recurrent CDI and worse histopathology have also been noted in mice treated with vancomycin compared to untreated mice [12]. There is the potential for even greater disruption of the normal microbiome with exposure to two CDI antibiotics. Severe CDI may contribute to an increased risk of candidaemia due to severe mucosal damage, which may facilitate translocation of *Candida*, particularly in the setting of *Candida* overgrowth occurring during CDI treatment. Severe CDI may also be a marker for patients who require ICU admission, surgical intervention, or placement of a central line, all of which are known to be risk factors for candidaemia. Our findings are consistent with a recent smaller study from Italy in which severe CDI was also found to be associated with candidaemia [13].

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This study has several limitations. Although we were not able to conduct a multivariable analysis because data on antibiotic use after CDI diagnosis, other than those used for CDI treatment, and presence of a central line, both important risk factors for candidaemia [4], were not available for all CDI patients, we were able to find some associations that will be important for evaluation and confirmation in future studies. We were unable to identify three controls per case due to surveillance methodology, which may have limited our ability to find significant associations. The effect of fidaxomicin use on development of candidaemia could not be evaluated since no cases received fidaxomicin.

The prevalence of candidaemia in patients with recent CDI is low. However, clinicians should be vigilant for candidaemia in CDI patients who have previously recognized risk factors for candidaemia, and those with severe CDI or CDI treatment with certain two-drug regimens. Further research is needed to evaluate independent risk factors for candidaemia following CDI.

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CONFLICT OF INTEREST

None.

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