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A Tale of Two Healthcare-Associated Infections: *Clostridium difficile* Coinfection Among Patients with Candidemia

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Abstract

Candidemia and *Clostridium difficile* infection (CDI) are important healthcare-associated infections that share certain risk factors. We sought to describe candidemia-CDI coinfection using population-based surveillance data. We found that nearly one in ten patients with candidemia had CDI coinfection.

Keywords

Candidemia; Clostridium difficile; Infections; Hospital

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Candidemia and *Clostridium difficile* infection (CDI) are important healthcare-associated infections (HAIs). In a recent multistate point-prevalence survey of HAIs, CDI was the most commonly reported infection overall, and *Candida* species were the most common cause of healthcare-associated bloodstream infections [1]. There are an estimated 453,000 cases of CDI in the United States each year and 46,000 cases of candidemia, and each is associated with substantial morbidity and mortality (up to 9% for CDI and 30% for candidemia) [2–4]. Risk factors for the two infections overlap and include broad-spectrum antibiotic use and prolonged hospitalization [5,6]. They also share similar pathophysiology: when intestinal flora are disrupted (e.g., by use of antibiotics), overgrowth can occur and lead to infection [6,7]. Furthermore, candidemia has been linked to CDI, as CDI itself can cause damage to the gastrointestinal mucosa, and antibiotics used to treat CDI can lead to overgrowth of *Candidia* and translocation into the bloodstream [5]. Prior studies have identified factors associated with an increased risk of CDI-candidemia coinfection, including the type of antibiotic used to treat CDI (e.g., oral vancomycin, which has broad antimicrobial coverage and markedly suppresses anaerobic organisms), severity or recurrence of CDI, and a specific *C. difficile* strain (ribotype 027) [8–10].

We describe the prevalence and clinical characteristics of patients with candidemia and CDI coinfection and identify factors associated with coinfection.

Methods

CDC, in collaboration with state and local partners, conducts active, population-based surveillance for candidemia through its Emerging Infections Program (EIP). During 2014-2016, surveillance took place in 23 counties in five states (Georgia, Maryland, Oregon, and Tennessee; New York began surveillance in 2016), which included a population of ~9 million persons. Clinical, reference, and commercial laboratories that serve the population in the surveillance catchment areas were recruited to participate in the program and reported positive blood cultures for *Candida* to the local surveillance officer. A case of candidemia was defined as a blood culture positive for *Candida* species in a surveillance area resident. Any other blood cultures positive for *Candida* in the same patient within 30 days of the initial culture were considered part of the same case.

Once a case of candidemia was identified, surveillance officers gathered information on demographics, microbiology, underlying medical conditions, healthcare exposures, and patient outcome on a standardized case report form. Since 2014, information on occurrence of CDI in the 90 days before or after the incident candidemia specimen was collected by reviewing the medical chart for CDI diagnostic tests. In 2016, the question was modified to capture a shorter period of CDI occurrence: 90 days before to 30 days after incident candidemia. For this study, we included all candidemia cases in adults ≥18 years of age during 2014–2016 at the five surveillance sites. CDI coinfection was defined as CDI occurring within 90 days before or after candidemia (except in the 2016 cases where it was in the 90 days before and 30 days after candidemia). Statistical analysis was performed using SAS 9.4 (Cary, NC). Associations between variables and CDI status were analyzed using Chi-Square or Fisher's exact tests. Variables potentially associated with CDI coinfection were included as candidates for a multivariable regression model. From a string

of models resulting from forward selection using significance level to add variables, the final model was chosen based on lowest value for BIC, a penalized-likelihood fit criterion (similar to AIC) that attempts to minimize the risk of over-fitting a model.

Results

Among 2,026 candidemia cases, 189 (9%) had CDI coinfection. Of 173 with recorded dates of CDI diagnosis, 115 (66%) had CDI in the 90 days before or on the date of incident candidemia (median: 10 days; interquartile range (IQR): 40 days [4 – 38.5]), and 59 (34%) had CDI diagnosed ≤90 days after candidemia (median: 6 days; IQR: 26 days [2.5 – 27]). Median age of patients with coinfection was 62 years, and 99 (52%) were male. The most common underlying conditions were diabetes (81, 43%), liver disease (39, 21%), and solid organ malignancy (27, 14%). Eighty-six percent (162) received antibiotics in the 14 days before candidemia, 78% (148) had a central venous catheter (CVC) in place at the time of candidemia, 71% (134) had a prior separate hospital stay in the preceding 90 days, 60% (113) were admitted to the intensive care unit (ICU), 38% (71) underwent surgery in the prior 90 days, and 23% (43) received hemodialysis.

By bivariable analysis, odds of CDI coinfection, compared with candidemia alone, were significantly greater for patients of black race (51% vs 42%; OR 1.45), with diabetes (43% vs 32%; OR 1.56), or solid organ transplant (6% vs 2%; OR 4.08), those who had received antibiotics in the prior 14 days (86% vs 75%; OR 2.05), those undergoing hemodialysis (23% vs 12%; OR 2.15), those who had a prior hospital stay in the past 90 days (71% vs 58%; OR 1.78) and those who had a CVC at the time of candidemia (78% vs 69%; OR 1.65) (Table 1). There were no significant differences in 30-day mortality (26% in both groups) or in *Candida* species; however, *C. parapsilosis* was less common in the coinfection group compared with candidemia alone (11% vs 16%).

By multivariable analysis, solid organ transplant (aOR 2.95, 95% CI 1.45-6.00), antibiotics in the prior 14 days (aOR 1.84, 95% CI 1.20-2.81), hemodialysis (aOR 1.86, 95% CI 1.28-2.72), and prior hospitalization (aOR 1.61, 95% CI 1.16-2.25) were significantly associated with coinfection. We examined factors associated with coinfection specifically for cases in which CDI occurred before candidemia (n = 115) and the findings were not substantially different from those reported above for all cases of CDI coinfection (data not shown).

Discussion

Nearly one in ten patients with candidemia also had CDI coinfection in this study. This prevalence is high and likely underappreciated by clinicians and public health personnel. The true prevalence of coinfection may in fact be higher than 9%. We primarily captured CDI diagnoses that occurred during the same hospitalization as candidemia, but given that less than half of CDI episodes that are healthcare-associated occur during a hospitalization, we may have missed some cases of coinfection [2].

In a previous study of candidemia among 13,000 patients with hospital- or community-onset CDI, approximately 1% had candidemia in the 120 days following CDI [11]. The lower

prevalence of candidemia in the CDI group is expected given that there is a larger pool of patients with CDI (i.e., CDI is nearly ten times more prevalent than candidemia), and a substantial proportion of CDI is community-associated whereas candidemia is primarily a nosocomial infection. Another study of 400 patients hospitalized with CDI found that 18% developed nosocomial bloodstream infections (BSI), for which the most common causative pathogens were *Candida* species (47%) [12]. This estimate is similar to the 9% coinfection we saw in our study.

The definition for CDI-candidemia coinfection in this study included a broad window of 90 days before or after incident candidemia. Even so, most CDI cases occurred within one week before or after incident candidemia, supporting the idea that the risk factors and pathophysiology for the two infections are intertwined. Although there was no statistical difference in the proportion of *Candida parapsilosis* among coinfection cases and those with candidemia alone, there is biological plausibility that would suggest a difference in risk: *C. parapsilosis* most commonly colonizes skin, whereas *Candida albicans, Candida glabrata*, and other *Candida* species are more commonly found in the gastrointestinal tract [13,14]. This finding may lend credence to the idea that disruption from antibiotics, CDI, or the treatment for CDI enables translocation of *Candida* that live in the gastrointestinal tract. There are likely complex interactions within the gut microbiome that facilitate this coinfection and have not yet been elucidated. As our understanding of the microbiome improves, we may better understand how the two infections occur together.

Although antibiotic use is already known to be an independent risk factor for both candidemia and CDI, it was not surprising that receipt of antibiotics during the 14 days before candidemia was also a risk factor for CDI coinfection. Antibiotic stewardship has been shown to decrease CDI rates and may also help prevent candidemia and CDI-candidemia coinfection [15]. Antimicrobials prescribed to patients at risk for both infections, as in all patients, should be carefully assessed for appropriateness. Reinforcing prevention efforts for each of the infections individually might also help reduce the burden of coinfection; for example, infection control measures for CDI and best care practices for central venous catheters to prevent candidemia.

Our study had several limitations. Minimal information about CDI was available, only date of diagnosis, so risk factors related to CDI severity or treatment could not be assessed. Type of test used to make the diagnosis of CDI was not collected; recent studies have suggested that molecular tests may result in overdiagnosis of CDI through identification of asymptomatic carriers [16]. In addition, we have likely underestimated mortality, given that we only captured deaths during that hospitalization, and it is possible that some patients died after discharge from the hospital.

Nonetheless, these findings highlight that clinicians should be vigilant in looking for CDI in the context of candidemia, given that nearly 1 in 10 patients with candidemia had CDI coinfection. When one of these infections is present in patients with certain underlying conditions, including solid organ transplant, recent antibiotics, hemodialysis, or recent hospitalization, testing for the other pathogen should be considered. Clinicians should also review patients' prescriptions and discontinue unnecessary antimicrobial medications. Even

though we did not see evidence of increased mortality among those with coinfection compared with candidemia alone in our study, having both infections adds to the complexity of illness and healthcare costs. Ongoing research into the intestinal microbiome will undoubtedly contribute to better understanding of these infections in the future, and importantly, how to prevent them.

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Table 1:

Demographic and clinical characteristics of patients with candidemia and *Clostridium difficile* infection (CDI) at 5 U.S. Emerging Infections Program surveillance sites, 2014-2016.

	Candidemia & CDI (*N* = 189)	Candidemia alone (*N* = 1837)	Bivariable analysis	Multivariable model[b]
Characteristic	***n* (%)**	***n* (%)**	**OR (95% CI)**	**aOR (95% CI)**
Age group, years				
18-44y	43 (22)	453 (23)	0.94 (0.66-1.34)	
45-64y	72 (37)	704 (36)	1.04 (0.77-1.41)	
>65y	74 (38)	680 (35)	1.15 (0.85-1.56)	
Male sex[a]	99 (52)	967 (53)	0.99 (0.73-1.34)	
Black race[a]	96 (51)	765 (42)	**1.45 (1.07-1.95)**	
Underlying conditions				
Diabetes	81 (43)	596 (32)	**1.56 (1.15-2.12)**	
Liver disease	39 (21)	330 (18)	1.19 (0.82-1.72)	
Solid organ malignancy	27 (14)	366 (20)	0.67 (0.44-1.02)	
Solid organ transplant	12 (6)	30 (2)	**4.08 (2.05-8.12)**	**2.95 (1.45-6.00)**
Pancreatitis	12 (6)	66 (4)	1.82 (0.96-3.43)	
Hematologic malignancy or SCT	9 (5)	95 (5)	0.92 (0.46-1.85)	
Inflammatory bowel disease	6 (3)	34 (2)	1.74 (0.72-4.20)	
HIV infection	6 (3)	38 (2)	1.55 (0.65-3.72)	
Healthcare exposure				
Antibiotics in prior 14 days	162 (86)	1370 (75)	**2.05 (1.34-3.12)**	**1.84 (1.20-2.81)**
CVC in place at time of candidemia	148 (78)	1261 (69)	**1.65 (1.15-2.36)**	
Prior hospital stay prior 90 days	134 (71)	1061 (58)	**1.78 (1.28-2.47)**	**1.61 (1.16-2.25)**
ICU stay	113 (60)	975 (53)	1.31 (0.97-1.78)	
Surgery in prior 90 days	71 (38)	598 (33)	1.25 (0.91-1.70)	
Hemodialysis	43 (23)	221 (12)	**2.15 (1.49-3.11)**	**1.86 (1.28-2.72)**
Antifungals in prior 14 days	28 (15)	221 (12)	1.27 (0.83-1.95)	
Candida species				
C. albicans	77 (41)	693 (39)	1.11 (0.82-1.51)	
C. glabrata	50 (27)	507 (28)	0.93 (0.66-1.30)	

Characteristic	Candidemia & CDI (*N* = 189) *n* (%)	Candidemia alone (*N* = 1837) *n* (%)	Bivariable analysis OR (95% CI)	Multivariable model[b] aOR (95% CI)
C. parapsilosis	21 (11)	281 (16)	0.68 (0.43-1.09)	
30-day mortality	49 (26)	483 (26)	0.98 (0.70-1.38)	

Abbreviations: SCT=stem cell transplant; CVC=central venous catheter; ICU=intensive care unit

[a] There were missing values for sex (n=15) and race (n=157).

[b] Only the variables in the selected model are shown.