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Original Article

Clostridioides difficile infection risk and contemporary antibiotic use: Evidence from a large real-world dataset highlighting the need for a comprehensive antibiotic stewardship in dentistry

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Abstract *Background/purpose:* In dental care, antibiotics are frequently used for infection control. While certain antibiotics are historically linked to the increased risk of *Clostridioides difficile* infection (CDI). Existing risk classifications may not reflect current prescribing practices or patient outcomes. This study seeks to investigate antibiotic exposure patterns in patients prior to CDI symptom emergence and diagnosis to better understand true risk associations.
Materials and methods: We performed a retrospective cohort analysis using the TriNetX healthcare database to examine prior antibiotic exposure in patients diagnosed with CDI. The study focused on adults with confirmed CDI cases. To isolate a distinct patient group, individuals who had received standard CDI treatments vancomycin, metronidazole, or fidaxomicin either before or after diagnosis were excluded. This approach aimed to assess antibiotic exposure without the influence of common CDI therapies.
Results: Out of 201,911 CDI patients analyzed, 33.9 % (68,535) had been exposed to antibiotics. Focusing on antibiotic use within the two weeks leading up to diagnosis. We identified distinct antibiotic classes, with the most used being extended-spectrum penicillin (18.6 %), third-generation cephalosporins (15.8 %), and amino penicillins (15.3 %).
Conclusion: This study sheds light on real-world antibiotic prescribing patterns among a broad

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clinical population. Notably, historically high-risk antibiotics like clindamycin and fluoroquinolones were not the most frequently used prior to CDI diagnosis. These insights underscore the importance of comprehensive antibiotic stewardship across all classes prescribed in dental care.

Introduction

Antibiotics are largely used across various clinical settings, including dentistry. Both narrow and broad-spectrum antibiotics agents are frequently used for prophylactic or therapeutic management of orofacial infections.[1] While these antibiotics are effective in eradicating bacteria, they are also capable of causing gut dysbiosis, which may lead to serious adverse effects such as *Clostridioides difficile* infection (CDI).[2]

CDI is a nosocomial infection, named among the top 5 antibiotics-related urgent public health threat in the United States.[3] It affects over 400,000 individuals and is associated with 29,000 deaths annually.[4] A 2014 multistate study identified CDI as the most common nosocomial infection, accounting for 12.1 % of all healthcare-associated infections, and noted that its incidence had been increasing over time.[5] More recent studies have also reported a rise in community-acquired CDI, highlighting its emergence as a growing public health concern.[6,7] Gut dysbiosis following exposure to antibiotics facilitates the growth of *C. difficile* spores to its vegetative forms, which is able to produce toxins and stimulate local inflammatory responses. Clinical manifestations of CDI range from asymptomatic colonization to mild or moderate diarrhea, and in severe cases, to fulminant colitis, which can lead to death. Although CDI primarily involves the colon, extra-intestinal complications—such as cellulitis, visceral abscesses, and septic arthritis—have also been reported.[8,9]

Antibiotic use remains the most significant modifiable risk factor for CDI, amongst other risk factors such as older age, multiple comorbidities, and inflammatory bowel disease.[10,11] Research has identified certain antibiotics as major contributors to gut microbiome disruption—an essential element in CDI pathogenesis. While many antibiotics are linked to increased CDI risk, clindamycin stands out as the most frequently associated with the infection.[12–16] In a meta-analysis of observational studies performed in outpatient population reported that clindamycin poses a significantly higher risk for *C. difficile* infection compared to other antibiotics.[15] Similarly, a recent retrospective cohort study found that among the 10 most frequently prescribed antibiotics in the outpatient setting, clindamycin was most strongly associated with CDI.[16] Findings from this study have contributed to antibiotics stewardship effort aimed at making changes to antibiotics prescription in the clinical and dental practice involving reduced use of some historically high-risk antibiotics and increased reliance on alternatives.

However, the continued rise in the number of CDI cases despite changes in the clinical protocol for prescription due to antibiotics stewardship effort suggest that our understanding of antibiotics-associated risk may be incomplete.[17] Hence, it is critical to re-evaluate the antibiotics commonly used, as those not traditionally labelled to be high-risk may even now play a more prominent role in CDI development due to changes in general medical and dental practices. This study aims to investigate the pattern of antibiotics exposure in patients prior to their CDI diagnosis confirmation, using a large real-world healthcare dataset, TriNetX. Our goal is to identify antibiotics more associated with CDI risk in both inpatient and outpatient population in contemporary clinical practice.

Materials and methods

This study utilized data from the TriNetX Research Network, comprising 102 healthcare organizations across 11 countries. The analysis covered a five-year period ending one day prior to July 8, 2025. Adult CDI cases (≥18 years) were identified based on a positive *C. difficile* test—via PCR or enzyme immunoassay—and/or ICD-10 diagnosis codes A04.7 (enterocolitis due to *C. difficile*) or A04.72 (not specified as recurrent). To isolate untreated cases, patients administered vancomycin (RxNorm: 11124), fidaxomicin (RxNorm: 1111103), or metronidazole (RxNorm: 6922) before diagnosis were excluded. A two-week lookback window prior to CDI symptom onset was used to examine antimicrobial exposure. In total, 201,911 patients met all criteria. A parallel analysis focused on older adults (≥65 years) using the same diagnostic parameters, yielding 79,491 qualifying cases. Key variables recorded included age, sex, and prior antibiotic use. Data from TriNetX were de-identified, and the A.T. Still University IRB classified the study as exempt from human subjects' research requirements.

Results

Table 1 summarized the demographics and patterns of antibiotic use in *Clostridioides difficile* infections among adults aged 18 and older. Among patients aged 18 and older, 201,911 patients met the inclusion and exclusion criteria, with a mean age of approximately 55 years. Females were more represented at 56 % of the cohort. Within two weeks before CDI diagnosis, 68,535 patients (33.9 %) had documented antibiotic use. Of the 15 identified

Table 1 Demographics and patterns of antibiotic use in Clostridioides difficile infections among adults aged 18 and older.

	Number of patients	% of cohort
Age at index in years (Mean ± SD)	54 ± 23.1	
Gender		
Female	113,708	56
Male	84,045	42
Unspecified	4158	2
Patients on antibiotics	68,535	
Antibiotic class		
Extended-spectrum penicillin	12,742	18.59
Cephalosporins — 3rd gen	10,799	15.76
Amino penicillins & combos	10,475	15.28
Macrolides	5387	7.86
Cephalosporins — 1st gen	5725	8.35
Quinolones	5195	7.58
Methenamine salts	4561	6.65
Sulfonamides & related	3366	4.91
Cephalosporins — 4th gen	2317	3.38
Tetracyclines	2698	3.94
Beta-lactams — other	1407	2.05
Aminoglycosides	1200	1.75
Lincomycins (clindamycin)	1044	1.52
Nitrofurans	959	1.40
Cephalosporins — 2nd gen	660	0.96

SD — standard deviation, gen — generation.

Table 2 Demographics and patterns of antibiotic use in Clostridioides difficile infections among adults aged 65 and older.

	Number of patients	% of cohort
Age at index in years (Mean ± SD)	74.7 ± 6.4	
Gender		
Female	49,986	59
Male	30,772	49
Unspecified	1733	2
Patients on antibiotics	49,700	
Antibiotic class		
Cephalosporins — 3rd gen	9233	18.58
Beta-lactams inhibitors	7875	15.85
Extended-spectrum penicillin	4938	9.94
Cephalosporins — 1st gen	3888	7.82
Quinolones	3810	7.67
Macrolides	3772	7.59
Amino penicillins & combos	3579	7.20
Sulfonamides & related	3053	6.14
Cephalosporins — 4th gen	2098	4.22
Tetracyclines	1944	3.91
Carbapenems	1114	2.24
Polypeptide antibiotic	871	1.75
Oxazolidinone	824	1.66
Nitrofurantoin	785	1.58
Aminoglycosides	633	1.27
Cephalosporins — 2nd gen	537	1.08
Lincomycins (clindamycin)	475	0.96

SD — standard deviation, gen — generation.

antibiotic classes, extended-spectrum penicillin (Piperacillin) were most common (18.6 %), followed by third-generation cephalosporins (Ceftriaxone, Cefdinir, Cefpodoxime, Ceftazidime, and Cefixime) (15.8 %) and amino penicillin combinations (Amoxicillin and Ampicillin) (15.3 %).

Table 2 summarized the demographics and patterns of antibiotic use in *Clostridioides difficile* infections among adults aged 65 and older. In the subgroup of patients aged 65 and older, 82,491 individuals qualified for the study, averaging around 75 years old. Females were more represented at 59 % of this group. Within this cohort, 60.2 % (49,700 patients) had recorded antibiotic use in the two weeks preceding diagnosis. The most frequently used antibiotic classes were third-generation cephalosporins (Ceftriaxone, Cefdinir, Cefpodoxime, Ceftazidime, and Cefixime) (18.6 %), beta-lactams inhibitors (Tazobactam, Clavulanate, Sulbactam, Avibactam, Ceftolozane, and Vaborbactam) (15.9 %), and extended-spectrum penicillin (Piperacillin) (9.9 %).

Discussion

Using a large contemporary real-world dataset from 102 healthcare organizations, we found that clindamycin did not rank among the top 10 antibiotics associated with CDI in adults aged 18 and older, nor in the subgroup aged 65 and older. In both age groups, the antibiotics most commonly linked to CDI were extended-spectrum penicillins (e.g., piperacillin) and third-generation cephalosporins (such as ceftriaxone, cefdinir, cefpodoxime, ceftazidime, and cefixime).

These findings are consistent with prior research.[18,19] A systematic review and meta-analysis by Slimings and Riley, covering literature from January 2013 to December 2020, identified carbapenems and third- and fourth-generation cephalosporins as being strongly associated with healthcare facility-onset CDI (HF-CDI), with affected individuals more than twice as likely to have had recent exposure to these antibiotics.[18] Similarly, a study by Webb et al. analyzing antibiotic exposure across 21 hospitals (2006—2012) reported the highest CDI odds were associated with second- and third-generation cephalosporins, especially oral cefuroxime and cefdinir, as well as IV ceftriaxone and cefoxitin.[19] Additionally, research by Yun et al. examined the impact of antibiotic stewardship on CDI incidence. Despite reductions in fluoroquinolone and clindamycin use, HF-CDI rates increased during the study period, correlating with greater usage of β-lactam/β-lactamase inhibitors—highlighting that targeted reductions in specific antibiotics alone may not suffice to lower HF-CDI rates.[20]

In dental practice, both narrow- and broad-spectrum antibiotics are commonly employed for infection management. However, clindamycin is no longer recommended for

prophylaxis or initial treatment of dental infections due to its elevated risk of inducing CDI.[21] This aligns with the 2021 American Heart Association guidance, which advises against clindamycin for infective endocarditis IE prevention in patients allergic to amoxicillin or ampicillin.[22] Huynh et al. conducted a study analyzing antibiotic prescribing trends among general dentists between 2018 and 2022, revealing that they accounted for 9.8 %–12.1 % of all outpatient oral antibiotic prescriptions in the United States.[23]

The β-lactam class—including penicillins, cephalosporins, carbapenems, and β-lactamase inhibitors—remains the most frequently prescribed group for prophylaxis and initial treatment in dentistry.[24] Huynh et al. reported that amoxicillin was the predominant antibiotic prescribed by general dentists in the United States, comprising 64.0 %–68.1 % of all prescriptions between 2018 and 2022.[23] In this study, amino penicillin combinations was the third most common antibiotic associated with CDI. While clindamycin has been traditionally viewed as a key contributor to CDI risk, our findings and those from other studies indicate that β-lactam antibiotics also play a significant role in CDI pathogenesis.

This study presents several important limitations. Although the TriNetX database offers access to a large and diverse patient population, its aggregated and de-identified nature restricts the depth of data analysis. Consequently, variables such as CDI severity and demographic nuances within affected subgroups could not be thoroughly evaluated. A more comprehensive approach—such as direct chart reviews by clinicians—would have enhanced the robustness of the findings. Furthermore, CDI diagnoses were based on ICD coding and laboratory confirmation via PCR or enzyme immunoassay. While these methods are widely accepted, they remain susceptible to inconsistencies in coding practices and interpretation across clinical settings.

In summary, this study sheds light on real-world antibiotic prescribing patterns among a broad clinical population. Notably, historically high-risk antibiotics like clindamycin and fluoroquinolones were not the most frequently used prior to CDI diagnosis in this cohort. These insights underscore the importance of comprehensive antibiotic stewardship across all classes prescribed in dental care.

Declaration of competing interest

The authors declare no conflict of interest. This research received no external funding.

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