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Major Article

Predictors of *Clostridium difficile* infection and predictive impact of probiotic use in a diverse hospital-wide cohort

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Key Words:
Clostridium difficile
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Background: Hospital-based predictive models for *Clostridium difficile* infection (CDI) may aid with surveillance efforts.

Methods: A retrospective cohort of adult hospitalized patients who were tested for CDI between May 1, 2011, and August 31, 2016, was formed. Proposed clinical and sociodemographic predictors of CDI were evaluated using multivariable predictive logistic regression modeling.

Results: In a cohort of 5,209 patients, including 1,092 CDI cases, emergency department location (adjusted odds ratio [aOR], 1.91; 95% confidence interval [CI], 1.51, 2.41; compared with an intensive care unit reference category, which had the lowest observed odds in the study) and prior exposure to a statin (aOR, 1.26, 95% CI, 1.06, 1.51), probiotic (aOR, 1.39; 95% CI, 1.08, 1.80), or high-risk antibiotic (aOR, 1.54; 95% CI, 1.29, 1.84), such as a cephalosporin, a quinolone, or clindamycin, were independent predictors of CDI. Probiotic use did not appear to attenuate the odds of CDI in patients exposed to high-risk antibiotics, but moderate-risk antibiotics appeared to significantly attenuate the odds of CDI in patients who received probiotics.

Conclusions: Emergency department location, high-risk antibiotics, probiotics, and statins were independently predictive of CDI. Further exploration of the relationship between probiotics and CDI, especially in diverse patient populations, is warranted.

Clostridium difficile (recently renamed *Clostridioides difficile*[1]) is the most common cause of health care–associated infection in the United States, affecting nearly half a million patients per year and requiring an estimated $4.8 billion in direct acute care costs.[2-4] Although mortality rates after *C difficile* infection (CDI) have improved,[5] recurrence after treatment occurs in as many as 20% of cases.[6] New antimicrobial therapies for CDI—as well as alternative methods to prevent or treat CDI, such as prebiotic and probiotic agents and fecal microbiota transplantation—have been developed.[7-12]

CDI prevention and treatment have become high priorities in the health care system. Hospital-level CDI data are compared with national benchmarks, and in January 2015, the Centers for Medicare and Medicaid Services began to withhold funding for hospitals in the lowest quartile. Hospital-onset CDI data are publicly reported on Medicare's Hospital Compare website.[13] Meanwhile, the association of CDI and antimicrobial exposure[14,15] has prompted increased support of antimicrobial stewardship programs in acute care hospitals.

Recently, we reviewed our hospital's experience with CDI over an approximately 5-year period at the University of New Mexico (UNM) Hospital, where CDI rates have been higher than expected compared with national benchmarks. We sought to identify CDI predictors that might be monitored or modified at the hospital level, with the long-term goal of reducing CDI rates at UNM.

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Table 1
Antibacterial risk strata used for logistic regression modeling, with corresponding unadjusted and adjusted odds ratios for *Clostridium difficile* infection for each stratum

High-risk antibacterial agents	Moderate-risk antibacterial agents	Low-risk antibacterial agents
Cefaclor	Amoxicillin	Amikacin
Cefadroxil	Amoxicillin-clavulanate	Azithromycin
Cefazolin	Ampicillin	Aztreonam
Cefdinir	Ampicillin-sulbactam	Clarithromycin
Cefepime	Avibactam-ceftazidime	Colistimethate
Cefixime	Dicloxacillin	Dapsone
Cefotaxime	Ertapenem	Daptomycin
Cefoxitin	Imipenem-cilastatin	Doxycycline
Cefpodoxime	Meropenem	Erythromycin
Cefprozil	Nafcillin	Fosfomycin
Ceftaroline	Oxacillin	Gentamicin
Ceftazidime	Penicillin G benzathine	Linezolid
Ceftriaxone	Penicillin G potassium	Minocycline
Cefuroxime	Penicillin G sodium	Nitrofurantoin
Cephalexin	Penicillin V potassium	Rifabutin
Ciprofloxacin	Piperacillin	Rifampin
Clindamycin	Piperacillin-tazobactam	Rifapentine
Levofloxacin	Vancomycin*	Rifaximin
Moxifloxacin		Streptomycin
Norfloxacin		Sulfadiazine
Ofloxacin		Sulfamethoxazole
		Sulfamethoxazole-trimethoprim
		Tetracycline
		Tigecycline
		Tobramycin
		Trimethoprim
Unadjusted OR = 1.46 (95% CI, 1.24, 1.72)	Unadjusted OR = 1.07 (95% CI, 0.93, 1.22)	Unadjusted OR = 0.96 (95% CI, 0.83, 1.11)
Adjusted OR = 1.60 (95% CI, 1.33, 1.92)†	Adjusted OR = 1.03 (95% CI, 0.89, 1.20)†	Adjusted OR = 0.83 (95% CI, 0.71, 0.98)†

CI, confidence interval; *OR*, odds ratio.
*Vancomycin administered by any systemic route (eg, intravenous infusion) was classified as a moderate risk antibacterial agent. Vancomycin administered by mouth, by feeding tube, or per rectum was classified as a possible *Clostridium difficile* treatment agent. Other treatment agents included metronidazole and fidaxomicin. Treatment agents were not included in the low-, moderate-, or high-risk strata.
†Adjusted ORs are from a multivariable model containing location type, age (≥65 vs <65 years), all 3 antibacterial risk strata, antifungal agents, probiotics, and statins.

METHODS

Hospital setting

The UNM Hospital is a >500-bed academic medical center in Albuquerque, New Mexico, which serves as a safety net hospital for a geographically expansive, "majority-minority" state and offers care for medically underserved populations throughout the state. It is also the only level 1 trauma center in New Mexico.

Data source

Data were retrospectively obtained from the UNM Clinical and Translational Science Center Clinical Data Warehouse, which extracts data from the UNM electronic medical records for research use. A unique study number was assigned to each patient in the cohort to permit linkage across analytic files, and original identifiers were removed before transmission of the data to the research team. The UNM institutional review board reviewed and exempted the study.

Cohort selection

All hospitalized adult patients (≥18 years of age) with ≥1 CDI assay recorded between May 1, 2011, and August 31, 2016, were eligible. A new CDI assay system was implemented at the UNM Hospital in April 2011, so data collection for our study began the month after this change. CDI tests using any assay (eg, enzyme immunoassay or nucleic acid amplification/polymerase chain reaction, which were in combined use during the study period) and any diagnostic result (eg, positive or negative) were included. In keeping with our hospital's laboratory protocol, only specimens conforming to the shape of the container were eligible.

Outcome definition

Patients with any positive CDI assay results at any time during the study period were classified as CDI cases. If ≥1 positive result was recorded for the patient, the first positive result during the study period was used as the index record. Patients with ≥1 CDI assay with no recorded positive result during the study period were classified as not having CDI, and the first negative result in the study period was used as the index record.

Sociodemographic predictors

Sex and race/ethnicity were based on the electronic medical record. Age was defined as the patient's age at the time of diagnosis and was analyzed as both a continuous and categorical variable (eg, ≥65 vs <65 years, based on findings elsewhere in the CDI literature[16]).

Spatiotemporal predictors

Season was defined using the month during which the CDI assay was performed (eg, December-February, March-May, June-August, and September-November). For modeling purposes, season was used instead of year of diagnosis. Seasonality may be associated with other important patterns (eg, other seasonal outbreaks and antimicrobial prescribing patterns)[17] and may be carried forward to future years as a meaningful temporal unit.

Table 2
Characteristics of patients with and without CDI (n = 5,209 unless otherwise specified)

	CDI (n = 1,092)	No CDI (n = 4,117)	*P* value*
Male sex	559 (51.2%)	2,105 (51.1%)	.97
Race/ethnicity (n = 5,073)			.61
White non-Hispanic	425 (39.9%)	1,551 (38.7%)	
Hispanic	379 (35.6%)	1,507 (37.6%)	
American Indian/Alaskan Native	189 (17.7%)	653 (16.3%)	
Black non-Hispanic	22 (2.1%)	85 (2.1%)	
Other	51 (4.8%)	211 (5.3%)	
Age			
Mean (median, SD) in years	56.6 (57.0, 17.1)	57.5 (59.0, 17.1)	.12
N (%) ≥65	365 (33.4%)	1,497 (36.4%)	.07
Season			.56
December-February	291 (26.7%)	1,066 (25.9%)	
March-May	273 (25.0%)	1,057 (25.7%)	
June-August	268 (24.5%)	1,076 (26.1%)	
September-November	260 (23.8%)	918 (22.3%)	
Location type (n = 4,599)			<.0001
General inpatient	519 (54.3%)	2,078 (57.0%)	
Emergency department	204 (21.3%)	538 (14.8%)	
Intensive care unit	195 (20.4%)	882 (24.2%)	
Other	38 (4.0%)	145 (4.0%)	
Proton pump inhibitor within preceding 180 days (n = 4,822)	477 (45.7%)	1,699 (45.0%)	.70
Immunosuppressant within preceding 180 days			
Any (n = 4,851)	453 (43.2%)	1,645 (43.3%)	.99
Steroid (n = 4,822)	365 (34.9%)	1,255 (33.2%)	.30
Statin within preceding 180 days (n = 4,822)	236 (22.6%)	720 (19.1%)	.01
Probiotic within preceding 180 days (n = 4,822)	117 (11.2%)	284 (7.5%)	.0002
Antibacterial agent within preceding 180 days (n = 4,822)			
High risk	817 (78.2%)	2,685 (71.1%)	<.0001
Moderate risk	508 (48.6%)	1,775 (47.0%)	.35
Low risk	349 (33.4%)	1,295 (34.3%)	.59
Antifungal agent within preceding 180 days (n = 4,822)	126 (12.1%)	482 (12.8%)	.54
Diabetes, ≥1 study criterion (n = 4,989)	384 (36.0%)	1,335 (34.1%)	.24

CDI, *Clostridium difficile* infection.
*All *P* values are from an unadjusted logistic regression model in which the modeled outcome is CDI and the variable listed in the table is the single predictor in the model. The *P* values shown in the table were used to determine eligibility for the multivariable selection procedure (eligible if $P < .10$).

Table 3
Multivariable predictive logistic regression model for *Clostridium difficile* infection (n = 4,278)

	Unadjusted OR (95% confidence interval)	Adjusted OR (95% confidence interval)*
Location type		
Emergency department	1.72 (1.37, 2.15)	1.91 (1.51, 2.41)
General inpatient unit	1.13 (0.94, 1.36)	1.11 (0.92, 1.34)
Other inpatient unit	1.19 (0.80, 1.75)	1.26 (0.84, 1.90)
Intensive care unit	1.00 (reference category)	1.00 (reference category)
High-risk antibacterial agent within preceding 180 days	1.46 (1.24, 1.72)	1.54 (1.29, 1.84)
Probiotics within preceding 180 days	1.55 (1.24, 1.95)	1.39 (1.08, 1.80)
Statin within preceding 180 days	1.24 (1.05, 1.46)	1.26 (1.06, 1.51)

OR, odds ratio.
*Adjusted ORs are from a model containing all of the variables shown in this table. The C-statistic for the adjusted model is 0.59.

Location was defined as the last recorded hospital unit prior to the CDI assay (eg, the presumed location of the patient at the time of diagnosis), and locations were classified into 4 broad categories—emergency department (ED); general inpatient units, including medical and surgical wards; intensive care units; and other inpatient units, including obstetrics/gynecology, rehabilitation, and preadmission units.

Clinical predictors

Antibacterial and antifungal agents, bacterial and fungal probiotics, steroids and other immunosuppressants, statins,[18,19] proton pump inhibitors (PPIs),[20] and antidiabetes medications[21] recorded within the 180-day window prior to the CDI diagnosis were included. Antibacterial agents were classified into low, moderate, and high CDI risk strata (Table 1).[14,15,22]

Diabetes was defined as having either a prescription for ≥1 antidiabetes medications (eg, metformin or insulin) within the 180-day window prior to the CDI assay or any hemoglobin A1c ≥6.5% during the study period, using the hemoglobin A1c value nearest to the date of the CDI assay.

Predictive modeling

Sociodemographic and clinical predictors of CDI were evaluated with predictive logistic regression modeling. Variables with $P < .10$ in an unadjusted model were eligible for inclusion in a multivariable

model. Variables with $P < .05$ in the multivariable model were retained. Manual forward and backward selection procedures were applied, and the resulting models were compared.

Although stringent P value cutoffs (as presented earlier) were applied to achieve a parsimonious model, a sensitivity analysis was performed with <.20 used for entry into the model and <.10 for retention. The classification of antibacterial agents into low-, moderate-, and high-risk strata was internally evaluated in our dataset by comparing the odds ratios (ORs) across strata. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC). P values <.05 were deemed statistically significant.

Power calculations

A multivariable model with ≤10 predictors was anticipated. Thus, a minimum of 100 cases was desired (eg, 10 CDI cases per predictor variable).[23] Hospital epidemiologic surveillance data available before this study suggested that an average of 200-300 cases of CDI occurred each year. Because this annual estimate can include recurrent cases, a conservative minimum of 100 cases per year was expected. To permit stratified analyses, >5 years of data were included.

Post hoc analyses

During the planned analysis, probiotics were identified as a positive predictor of CDI. Because probiotics are a proposed preventive therapy for CDI, their role as a surrogate marker of CDI risk (ie, as a clinical predictor but not necessarily a causal factor) was considered. A series of exploratory post hoc analyses was performed to better understand the context of probiotic use within the dataset, assess for potential evidence of bias, and generate future hypotheses.

First, to determine whether this finding reflected a diagnostic lag—that is, whether probiotics were ordered in the days or weeks before a CDI diagnosis in the setting of concurrent or unapparent CDI—probiotic orders recorded in the 0-60 days before the assay were compared with those recorded between 61 and 120 days and between 121 and 180 days.

Next, to determine whether the apparent relationship of probiotics and positive CDI assays was modified by any other variable in the model, antibacterial or antifungal use, or the type of assay used to diagnose CDI, interaction terms were tested for each of these variables in a multivariable model containing location type, age (≥65 vs <65 years), antibacterial use, and antifungal use.

Last, to evaluate whether the observed association was driven by a particular subtype of probiotics, probiotic orders were stratified into bacterial (including *Lactobacillus* or *Bifidobacterium* species) and fungal (including *Saccharomyces* species) subtypes. Adjusted ORs were compared for these subtypes.

RESULTS

Cohort characteristics

The cohort consisted of 5,209 patients who were tested for CDI during the study period, including 1,092 cases with ≥1 positive CDI assay during the study period. The characteristics of patients with and without CDI are summarized in Table 2. CDI cases were more likely to be <65 years of age ($P = .07$); to be located in the ED at the time of the diagnosis ($P < .0001$); and to receive a statin ($P = .01$), probiotic ($P = .0002$), or high-risk antibacterial agent ($P < .0001$) in the 180-day window before the CDI diagnosis. All of these variables were eligible for multivariable modeling.

There were no significant differences between groups with respect to sex, race/ethnicity, seasonality, diabetes, or other medication types (Table 2). The organization of antibacterial agents into high-, moderate-, and low-risk strata corresponded to an expected gradient in the ORs across the 3 strata (Table 1), although the low- and moderate-risk strata had similar odds and overlapping confidence intervals (CIs).

Multivariable model results

Inpatient location type, statins, probiotics, and high-risk antibacterial agents were significant independent predictors of CDI in the multivariable model (Table 3). Patients in the ED had the highest odds of a positive CDI assay (adjusted odds ratio [aOR], 1.91; 95% CI, 1.51, 2.41; compared with the intensive care unit reference category, which had the lowest odds). Receipt of high-risk antibacterial agents in the 180 days preceding CDI was associated with a >50% increase in the odds of a positive assay (aOR, 1.54; 95% CI, 1.29, 1.84).

The dichotomized age variable (≥65 vs <65 years) was not retained in the multivariable model ($P = .07$). In the sensitivity analysis, using $P < .20$ for entry into the model and $P < .10$ for retention, the dichotomized age variable was retained (aOR, 1.15; 95% CI, 0.98, 1.34; for age <65 vs ≥65 years). However, this model produced similar characteristics (Akaike information criterion and C-statistic) and similar beta estimates for the other variables in the model compared with the primary model. Similarly, forcing PPI or steroid use into the model shown in Table 3 revealed comparable beta estimates for all other variables.

Probiotics analysis

Probiotics recorded between 0 and 60 days and between 61 and 120 days were associated with significantly increased odds of CDI, with the highest odds observed between 61 and 120 days (Appendix Table A1). This pattern differed for another prescription-related predictor (ie, statins; Appendix Table A1), which was examined for comparison. Probiotics did not significantly interact with the type of diagnostic assay ($P = .40$) or the year of diagnosis ($P = .20$).

A significant interaction was observed between probiotics and moderate-risk antibacterial agents ($P = .01$; Appendix Fig A1), in which coadministration of probiotics and moderate-risk antibacterial agents in the 180 days preceding the CDI diagnosis attenuated the odds associated with probiotics alone. A similar overall pattern was observed for both low- and high-risk antibacterial agents, although these interactions were not statistically significant ($P = .08$ for each test for interaction; Appendix Fig. A1). This pattern was not observed with antifungal agents ($P = .19$; Appendix Fig. A1).

Bacterial probiotics, including *Lactobacillus* and *Bifidobacterium* species, were associated with the highest independent odds of a positive CDI assay (aOR, 1.49; 95% CI, 1.11, 2.01; compared with no probiotics and adjusted for location type, age ≥65 vs <65 years, antibacterial and antifungal agents, and statins). Fungal probiotics, including *Saccharomyces* species, were associated with a weaker increase in the odds of CDI (aOR, 1.22; 95% CI, 0.75, 1.98; compared with no probiotics and adjusted as shown earlier).

DISCUSSION

In this diverse cohort of >5,200 hospitalized patients, including >1,000 CDI cases, several factors independently predicted the occurrence of CDI. Important contextual factors about our cohort should be noted. As a majority-minority state, New Mexico represents a unique study population with respect to race and ethnicity. Approximately one-third of the patients in our study identified as Hispanic, and >16% identified as American Indian/Alaskan Native.

A distinctive set of geographic and socioeconomic factors also influences health care in New Mexico. More than 40% of New Mexicans live in an area with a primary care health professional shortage, and about 20% of the state's population lives at or below the poverty line.[24] The UNM Hospital provides care for many medically underserved patients throughout the state.

Our model should be interpreted with 2 important methodological provisos in mind. First, it was constructed for the purposes of predicting CDI among those tested, not for demonstrating causal relationships between any 1 variable and the outcome of CDI. Second, patients with and without CDI were all tested for CDI and therefore may have shared more clinical factors compared with others in the hospital population. Thus, our results cannot be extrapolated directly to the risk of CDI resulting from the predictors that were significant—or not significant—in our model.

As an example, we did not observe significantly increased odds of CDI among patients who received PPIs or steroids. However, the cohort consisted of hospitalized patients in whom CDI was already suspected, with high overall rates of PPI (45.1%) and steroid (33.6%) use. Although PPIs and steroids did not predict CDI in our study, this does not exclude the possibility that either PPIs or steroids could increase CDI risk.

Similarly, we did not find age ≥65 years to be a significant predictor of CDI. In fact, older patients in our cohort were less likely to have CDI. This must also be interpreted in the context of the study population—adult hospitalized patients—for which our model predicts the odds of diagnosis and not necessarily the incidence of infection. Patients ≥65 years old may have been diagnosed at home, at nursing facilities, or at other hospitals where Medicare-eligible patients may be seen.

Variables that independently predicted CDI in our study (Table 3) were inpatient location type and use of high-risk antibacterial agents, statins, and probiotics. Patients were most likely to have a recorded location in the ED at or immediately preceding their CDI diagnosis. This finding could represent a number of underlying factors, such as a high frequency of ED visits, perhaps comprising a primary health care access point for many patients in the community; high frequencies of antibiotic prescribing or CDI testing in the ED; or potential delays in admission to other inpatient units owing to precautionary isolation practices. Similarly, statin use may constitute a measure of increased health care access in our study. The relationship of statin use and CDI remains a subject of interest in the literature,[18,19] although the nature and direction of this relationship is not yet clear.

The positive association of probiotic use with subsequent CDI was unexpected. Prior studies have suggested that probiotics may prevent CDI, although results have varied depending on the type, timing, and setting of CDI, as well as the type of probiotic.[8-12,25-27] To date, there is neither scientific consensus nor Food and Drug Administration approval for the uniform use of probiotics to prevent CDI.

As described above, this result should be interpreted with care. Probiotics independently *predicted* the odds of CDI in our cohort, but this does not demonstrate that probiotics caused or contributed to the causes of CDI. Even so, if probiotics had exerted a strong protective effect in the cohort, we might have expected probiotics to impose a negative (or perhaps a null) predictive impact. Recognizing that the direction of the association in our study was unexpected, we undertook a series of post hoc analyses to better understand the context of this result.

First, we anticipated that diagnostic lags between the onset of CDI symptoms (at which time probiotics might have been ordered) and CDI diagnoses may have created an inaccurate impression that probiotic use actually preceded the infection. As shown in the Appendix (Table A1), however, the odds of CDI after a probiotic prescription remain elevated for up to 4 months after recorded probiotic use; in fact, the highest odds were observed for probiotics recorded 2-4 months before the CDI diagnosis. Thus, it is not likely that short-term diagnostic lags can fully explain our observation.

Similarly, if the observed impact of probiotics differed significantly over time—that is, if this was concentrated early in the study period—we might have concluded that probiotics were markers of existing CDI and that most of the cases driving the association were preexisting or recurrent infections. However, the relationship of probiotics and CDI diagnosis did not change significantly over time, as evidenced by the absence of a significant statistical interaction between probiotics and the year of diagnosis.

Next, we considered the possibility that patients were more likely to be treated with probiotics during periods of increased exposure to the health care environment. The observed temporal patterns in the Appendix Table A1 do not support this. The highest odds of probiotic use occurred in a time window distinct from that in which the CDI diagnosis was made, and this pattern differed from the association of CDI and statin prescriptions—another possible surrogate for health care exposures.

Finally, we anticipated that probiotics might be a surrogate marker for another correlated variable or set of variables. To obtain preliminary, hypothesis-generating information, we assessed whether the predictive impact of probiotics differed according to other clinical factors, including antimicrobial therapies. This analysis revealed several further, unexpected findings (Appendix Fig. A1).

Coadministration of probiotics with high-risk antibacterial agents in the 180 days preceding the CDI diagnosis did not significantly attenuate the odds of CDI associated with high-risk antibacterial therapies (Appendix Fig A1C). Instead, coadministration of moderate-risk antibacterial agents with probiotics in the 180 days preceding the CDI diagnosis actually appeared to attenuate the odds of CDI associated with probiotics (Appendix Fig A1B). This general pattern was observed for all antibacterial strata but not for antifungal agents (Appendix Fig A1). Meanwhile, bacterial probiotics were also stronger predictors of CDI than fungal probiotics.

Prior evidence suggests that race, ethnicity, and socioeconomic position may all impact CDI risk[28] and microbiomic composition at various anatomic sites.[29,30] If so, specific probiotic therapies for CDI may only be useful insofar as we understand the underlying microbiomic environments across which these are applied. Further attention may need to be directed to understanding the CDI epidemic and its microbiomic drivers in diverse and medically underserved populations to distinguish between the causes of CDI on a population level—a worldwide problem and one clearly still observed in our hospital—and not just the causes of individual cases.[31,32]

In this diverse cohort, patients with CDI were most commonly diagnosed while in the ED and were likely to have prior exposures to high-risk antibacterial agents, probiotics, and statins. Our study is limited by the retrospective and observational nature of data collection. Specific information about clinical impressions, adherence with prescribed therapies, and exposure to therapies other than those recorded in the electronic medical record was not available for this study. Future prospective CDI research should consider potential differences in microbiomic composition, CDI prevention, and CDI treatment in diverse and medically underserved populations.

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APPENDIX

This document contains 2 supplemental exhibits from the post hoc analysis of probiotic use and *Clostridium difficile* infection as described in the main article text.

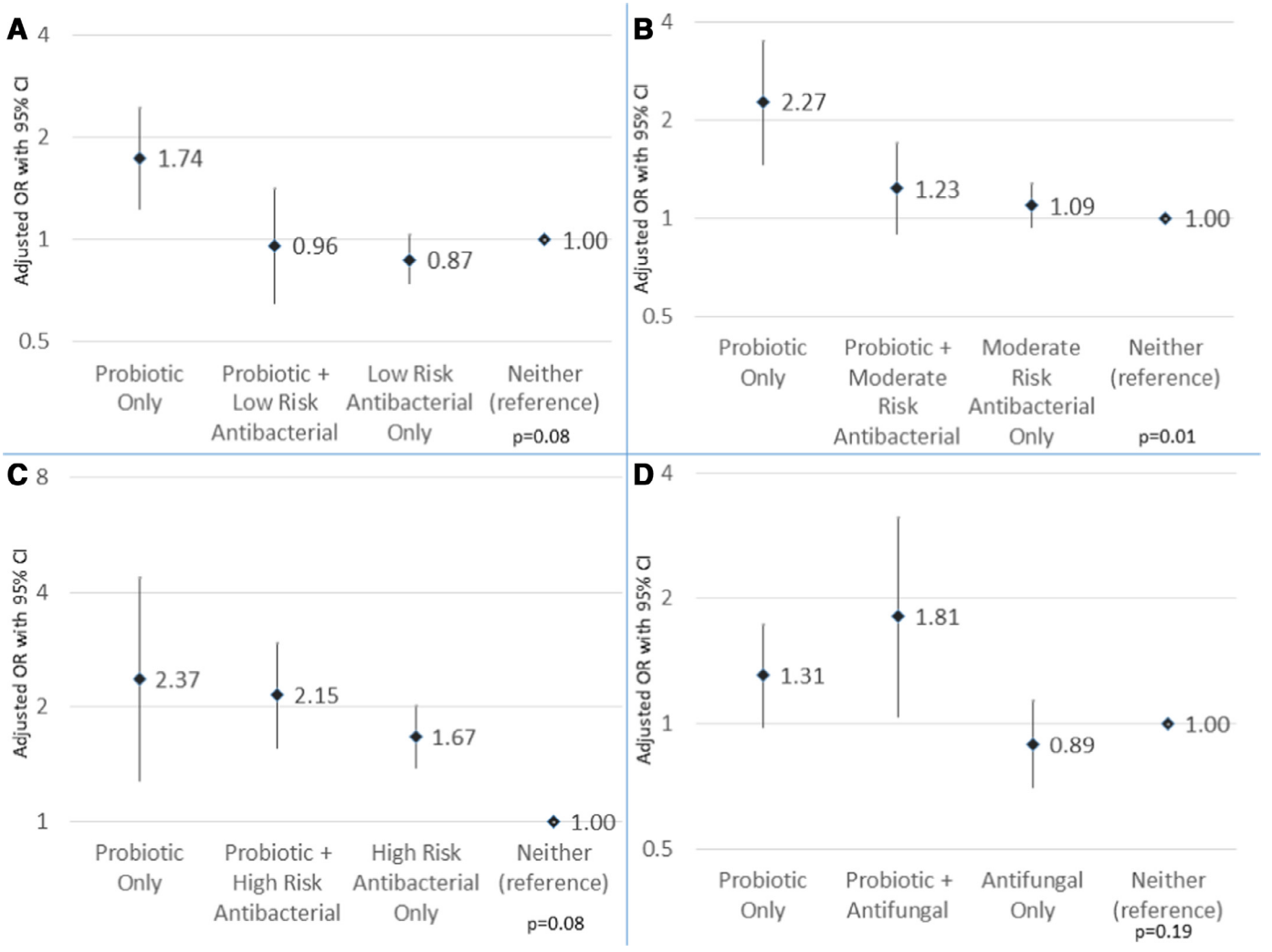

Fig. A1. Association of probiotics and *Clostridium difficile* infection stratified by coexposure to low-risk antibacterial agents (A), moderate-risk antibacterial agents (B), high-risk antibacterial agents (C), or antifungal agents (D) (n = 4,278). A statistically significant interaction was observed between probiotics and moderate-risk antibacterial agents ($P = .01$). Adjusted ORs and 95% CIs are shown for patients who received probiotics with or without an antimicrobial agent in the same 180-day period. Each panel (A-D) represents a separate model. ORs are adjusted for location type, age (≥65 vs <65 years), statins, and all other antibacterial and antifungal strata not already included in the interaction term. For instance, the moderate-risk panel (B) shows the ORs for a hybrid variable combining moderate-risk antibacterial agents with or without probiotics, and the ORs in that figure are adjusted for low- and high-risk antibacterial agents, antifungal agents, statins, age, and location. *CI*, confidence interval; *OR*, odds ratio.

Table A1
Comparative odds of *Clostridium difficile* infection for patients exposed to probiotics or statins in different time windows within the 180-day period before diagnosis

Time window	Probiotics OR (95% confidence interval)*	Statins OR (95% confidence interval)*
0-60 days (n = 4,209)	1.32 (0.99, 1.77)	1.24 (1.03, 1.51)
61-120 days (n = 1,199)	1.84 (1.02, 3.32)	0.84 (0.58, 1.20)
121-180 days (n = 948)	0.95 (0.41, 2.18)	1.31 (0.90, 1.91)

OR, odds ratio.
*ORs correspond to a multivariable model containing probiotics, statins, location type, age (≥65 vs <65 years), all 3 antibacterial risk strata, and antifungal agents. ORs represent the odds of *C difficile* infection for patients exposed to the medication vs those not exposed (eg, probiotic vs no probiotic, statin vs no statin).