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Tobacco use as a screener for *Clostridium difficile* infection outcomes

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Abstract

We conducted a retrospective cohort study to evaluate the utility of self-reported tobacco use for developing a clinical prediction rule for poor outcomes of *Clostridium difficile* infection. We found that patients with any history of smoking were significantly less likely than never smokers to be cured of their infection within two weeks. Disease recurrence, readmission within thirty days, death before treatment completion, and the severity of *Clostridium difficile* infection were not associated with smoking status.

Introduction

Clostridium difficile (*C. difficile*) is the most common cause of hospital-acquired infections in the United States. *C. difficile* infections (CDIs) have a thirty-day attributable mortality rate of 6.9%, which increases to 16.7% mortality at one year [1]. Among all patients, approximately 30% will ultimately experience relapse.

These concerning trends necessitate the development of screening tools for predicting poor CDI outcomes. Characteristics such as the continued use of antibiotics, advanced age, renal failure, and infection with the NAP1/BI/027 strain are known risk factors for severe CDI, recurrent CDI, or death [2]. Cigarette smoking has been identified as a risk factor for developing an initial CDI [3]. Compared to never smokers, the odds of developing the infection are 80% higher for current smokers and 33% higher for former smokers [3].

Despite its known association with new infections, smoking has not been examined previously as a predictor of *C. difficile*-related outcomes among diagnosed CDI patients. Yet, tobacco use is a known risk factor for the increased severity of several other infectious diseases, including pneumonia, influenza, varicella, and tuberculosis [4]. It has also been shown to increase the virulence of another common healthcare-associated infection,

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methicillin-resistant *Staphylococcus aureus* [5]. Furthermore, tobacco use leads to the dysregulation of the gastrointestinal microbiota and immune system, two factors that are essential to the timely resolution of CDI [3,4,6].

Smoking status has the potential to be an easily implementable screener, as the measure is already incorporated into most electronic health records as part of routine history-taking. Given this expected ease of implementation and the association between smoking with poor health outcomes in the context of other diseases, we conducted a retrospective cohort study to evaluate the utility of self-reported tobacco use as a screener for predicting CDI health outcomes.

Methods

We conducted a retrospective chart review of adult patients in the University of Wisconsin Hospital and Clinics system from July 15, 2009 to April 22, 2014. Inclusion criteria included: age eighteen years or older, any diagnosis of CDI, as defined by the associated International Classification of Diseases (ICD)-9 code and irrespective of previous infection status, and the presence of recorded tobacco use data in the electronic medical record. Overall rates of hospital-acquired CDI range from 8 to 12 cases per 10,000 patient days at our facility.

Demographic and clinical information were extracted from our institution's data warehouse. The data warehouse contains electronic medical records and administrative data for all patients that receive care in the University of Wisconsin Hospital and Clinics system. Our choice of study period was dictated by data availability in the data warehouse. Clinical information included variables associated with the Hines Veteran Affairs CDI Severity Score, as well as human immunodeficiency virus, chronic kidney disease, and chronic liver disease status.

CDI outcome variables included fourteen-day cure, disease recurrence, readmission within thirty days, death before treatment completion, and CDI severity. Fourteen-day cure was defined as completion of treatment within fourteen days, without re-initiation of treatment within two weeks of the completion date. Disease recurrence was defined as a positive *C. difficile* laboratory test within eight weeks of the initial CDI cure date. Death before treatment completion was defined as dying while still receiving active CDI treatment. CDI severity was defined by the Hines Veterans Affairs CDI Severity Score, 48-hours after diagnosis.

Clinical prediction rules are useful tools to assist clinicians in their day-to-day decision making [7]. There are multiple approaches to developing prediction rules, each of which has its own strengths and weaknesses [7]. We chose to develop our prediction rule based on the results of univariate analysis. We estimated the effect of smoking on the odds of poor *C. difficile* outcomes across the entire study population and determined its merit as a screening tool. We did not seek to investigate the etiology or biological mechanisms underpinning associations between smoking and *C. difficile* outcomes in this study. Thus, we did not carry out multivariate regression.

Chi-squared tests and univariate logistic regression were performed using Stata software (version 14.0; StataCorp, College Station, TX). A p-value less than 0.05 was considered statistically significant.

Results

The study population included 953 patients who met inclusion criteria. Of these, 404 (42.4%) were never smokers, 413 (43.3%) were former smokers who stopped smoking prior to hospitalization, and 136 (14.3%) were current smokers. Demographic and clinical characteristics of each group are presented in Table 1. The baseline proportion of severe CDI cases at the time of diagnosis was similar across all three groups ($p=0.83$).

Smoking status was not associated with the rate of thirty-day hospital readmission, CDI recurrence, or death before treatment completion, or CDI severity at 48-hours after diagnosis (Table 2). Smoking status was associated with the failure of treatment to cure the infection within fourteen days ($p=0.038$). Ever smokers had a lower likelihood of cure within fourteen days compared with never smokers (odds ratio [OR]: 0.70, 95% confidence interval [CI]: 0.53–0.93; $p=0.014$). There was no difference in fourteen-day cure for current versus non-current smokers (OR: 0.96, 95% CI: 0.64–1.42; $p=0.82$). The screener's sensitivity for predicting failure to cure at fourteen-days based on never versus ever smoking status was 0.59 (95% CI: 0.54–0.63). The specificity was 0.50 (95% CI: 0.45–0.55).

Discussion

In a retrospective study of adult CDI patients, we found that ever smokers were significantly less likely than never smokers to be cured of their infection within fourteen days. Tobacco use data are already routinely collected at the time of hospital admission. Thus, implementation of a one-factor prediction rule for CDI treatment failure based on tobacco history would likely require minimal workflow changes and costs.

These results may have practical significance for *C. difficile* clinical management. Early identification of CDI patients who are particularly susceptible to treatment failure is essential to reducing poor CDI-related health outcomes. If a patient has a history of smoking, clinicians should be alerted that they are at an increased risk for treatment failure. Preemptive notifications may help providers to consider alternative strategies like vancomycin or fidaxomicin more quickly after failure to cure, resulting in better allocation of treatment resources. These antibiotics have higher clinical cure rates than metronidazole for severe CDIs and all infections, respectively [8]. Given the added cost of escalating CDI treatment, improved prediction of which patients require escalated therapy has the potential to be cost saving. The barriers and facilitators to implementation and economic impacts of a tobacco screening intervention for CDI treatment failure should be evaluated in future studies.

These results also have significant infection control implications. Given the higher risk of failure to cure among *C. difficile* infected ever-smokers, infection control practitioners should consider continuing contact isolation requirements for these patients throughout the entirety of their stay. This protocol change would preemptively help to protect against the

extended symptomatic periods of patients who fail treatment. Furthermore, antibiotic stewardship should be prioritized in smokers to remove all non-essential antibiotics, as concomitant antibiotic use puts patients at higher risk for treatment failure and extended symptom duration.

The biological mechanisms that underlie the association between smoking and *C. difficile* are poorly understood [3]. While differences between patient groups with regards to the prevalence of human immunodeficiency virus, chronic kidney disease, chronic liver disease, and other factors may have contributed to *C. difficile* outcomes, investigating the etiology of the association between *C. difficile* and smoking was not a goal of this research. Future studies that include a comprehensive evaluation of all relevant factors are critical to improving our understanding of the biological mechanism of this associations.

Nevertheless, there are two pathophysiological effects discussed in the smoking literature that may relate to *C. difficile* outcomes. One potential mechanism is via dysregulation of the immune system. Smoking disrupts immune function, including altered CD4⁺ and CD8⁺ lymphocyte counts, lower levels of circulating immunoglobulins and proinflammatory cytokines, and a decline in phagocytic activity [4]. It is well established that patients who are immunosuppressed because of organ transplantation, chemotherapy, or human immunodeficiency virus are at an increased risk for *C. difficile* complications. Thus, it is possible that tobacco use is related to failure to clear a CDI via a similar immune system mediated mechanism.

Another potential mechanism by which tobacco may affect CDI outcomes is via disruption of the gastrointestinal microbiome. An association between smoke exposure and phylum-level shifts in the microbiota has been shown in both mice and humans [6,9]. In general, smokers have lower levels of microbial diversity than non-smokers. Decreased diversity of the gastrointestinal microbiome is related to both an increased risk of developing an initial CDI and poorer subsequent disease outcomes. Thus, the microbial changes that occur in the gastrointestinal tract of smokers may predispose these patients to treatment failure. Given the somewhat transitory nature of the microbiome, we expect this mechanism to be of more importance among current smokers than former smokers.

There was no significant difference in the 14-day cure rate between current and non-current smokers. Thus, our prediction rule for failure to cure a CDI was based on ever versus never smoking status. However, a limitation of this study was the inability to comprehensively quantify tobacco use. The classifications of never, former, and current smoker do not provide adequate details regarding the quantity or duration of cigarette exposure during a patient's lifetime. It is therefore possible that former smokers, who had a median age eleven years older than current smokers, had a longer average duration of smoking history than current smokers. Given this lack of pack-history data, we were unable to evaluate a dose-response relationship between cumulative cigarette exposure and CDI outcomes. Future studies can overcome this by prospectively collecting a complete smoking history at the time of CDI diagnosis.

Additional limitations include the possibility that the association between smoking history and CDI fourteen-day cure is a false positive association due to type I error and our use of the ICD-9 code to define a CDI diagnosis. The sensitivity and specificity of the ICD-9 code for *C. difficile* are 71% and 99% respectively [10].

Conclusions

Our study supports the utility of smoking history as an easily implementable screening tool to predict CDI treatment failure. Unlike hematology or radiology tests, self-reported smoking history requires no additional costs to collect and is already routinely recorded. Enhanced vigilance of *C. difficile* infected past and current smokers can help provider decision making improve CDI outcomes.

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Conflict of interest: All authors report no conflicts of interest relevant to this article.

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Table 1

Characteristics of 953 patients with CDI according to smoking status, 2009 – 2014

Characteristic	All patients n = 953 n (%)	Never smoker n = 404 n (%)	Former smoker n = 413 n (%)	Current smoker n = 136 n (%)	p-value
Sex, female	478 (50.2)	222 (55.0)	191 (46.3)	65 (47.8)	0.038
Median age in years (IQR)	60 (49–69)	58 (46–68)	64 (54–72)	53 (40.5–63)	<0.001
Race (n = 948)					0.27
White	855 (90.2)	356 (88.8)	378 (92.0)	121 (89.0)	
Nonwhite	93 (9.8)	45 (11.1)	33 (8.0)	15 (11.0)	
Chronic kidney disease	276 (29.0)	103 (25.5)	142 (34.4)	31 (22.8)	0.005
Chronic liver disease	85 (8.9)	28 (6.9)	38 (9.2)	19 (22.4)	0.043
HIV positive	5 (0.5)	2 (0.5)	0 (0.0)	3 (2.2)	0.008
Severe CDI at diagnosis ^a (n = 752)	96 (12.8)	44 (13.5)	38 (11.9)	14 (13.1)	0.83
Components of the Hines VA CDI Severity Score ^a					
Fever (38.0 °C; n = 802)	76 (9.5)	37 (10.4)	31 (9.3)	8 (7.1)	0.57
Ileus on x-ray ^b	114 (12.0)	58 (14.4)	40 (9.7)	16 (12.8)	0.12
Systolic blood pressure < 100 mmHg	324 (34.0)	108 (26.7)	163 (39.5)	53 (39.0)	<0.001
Leukocytosis score ^c (n = 769)					0.849
0	598 (77.8)	271 (79.5)	246 (76.6)	81 (75.7)	
1	153 (19.9)	62 (18.2)	67 (43.8)	24 (22.4)	
2	18 (2.3)	8 (2.3)	8 (2.5)	2 (1.9)	
Number of findings on CT ^d					0.523
0	790 (82.9)	338 (83.7)	341 (82.6)	111 (81.6)	
1	116 (12.2)	44 (10.9)	56 (13.6)	16 (11.8)	
2	47 (4.9)	22 (5.5)	16 (3.9)	9 (6.6)	

Abbreviations: CDI, *Clostridium difficile* infection; CT, computed tomography; HIV, human immunodeficiency virus; IQR, inter-quartile range;

^aDefined by the Hines VA CDI Severity Scale, with a score of three or more considered severe CDI;

^b patients for whom no x-ray was conducted were classified as negative;

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$WBC < 15,000/mm^3 = 0$; $WBC \geq 15,000/mm^3 < 30,000/mm^3 = 1$; $WBC \geq 30,000/mm^3 = 2$;
possible findings include a thickened colonic wall, colonic dilatation, and ascites: one point for each finding, up to a maximum of two points

Table 2

CDI outcomes among 953 patients with CDI according to smoking status, 2009 – 2014

Outcome	All patients n (%)	Never smoker n (%)	Former smoker n (%)	Current smoker n (%)	p-value
Cure within fourteen days (n = 796)	338 (42.5)	169 (47.2)	120 (37.5)	49 (41.5)	0.038
Never vs. ever smoker		169 (47.2)	169 (38.6)		0.014
Not-current vs current smoker		289 (42.6)		49 (41.5)	0.82
Readmission within thirty days (n = 953)	212 (22.3)	84 (20.8)	94 (22.8)	34 (25.0)	0.56
Recurrence within eight-weeks (n = 835)	74 (8.9)	30 (8.2)	32 (9.2)	12 (10.2)	0.77
Death before completion of therapy (n = 838)	33 (3.9)	10 (2.7)	18 (5.2)	5 (4.1)	0.22
Severe CDI 48-hours after diagnosis ^a (n = 585)	74 (12.7)	30 (11.6)	33 (18.4)	11 (13.9)	0.78

Abbreviations: CDI, *Clostridium difficile* infection;

^aDefined by the Hines Veterans Affairs CDI Severity Scale, with a score of three or more considered severe CDI