Major Article

Laxative use and testing for *Clostridium difficile* in hospitalized adults: An opportunity to improve diagnostic stewardship

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Background: It is recommended that that only unformed stool from patients with diarrhea be tested for *Clostridium difficile* infection. We determined the prevalence of and patient characteristics associated with antecedent laxative receipt among hospitalized adults undergoing *C difficile* testing.
Methods: In a case-control study of 5,452 *C difficile* tests from 5 hospitals in Southeast Michigan, patients who received laxatives (docusate, senna, polyethylene glycol 3350, bisacodyl, and magnesium hydroxide) in the 24 or 48 hours before testing were identified. Logistic regression was performed to identify patient characteristics associated with laxative receipt before testing.
Results: In 535 (9.8%) and 707 (13%) tests, patients received laxatives in the 24 and 48 hours before testing, respectively. The odds of antecedent laxative receipt were significantly greater for patients residing on a surgical service than a medical service (24 hours odds ratio [OR], 2.5; 95% confidence interval [CI], 2.1−3.1; 48 hours OR, 2.7; 95% CI, 2.3−3.2), patients residing in an intensive care unit (ICU) than a non-ICU (24 hours OR, 1.3; 95% CI, 1.0−1.6; 48 hours OR, 1.3; 95% CI, 1.1−1.6), and patients whose Elixhauser Comorbidity Score was 4 or higher (24 hours OR, 1.4; 95% CI, 1.1−1.7; 48 hours OR, 1.4; 95% CI, 1.2−1.7).
Conclusions: Among patients tested for *C difficile*, antecedent laxative use was common. Improving diagnostic stewardship around *C difficile* testing, particularly in surgical and ICU patients, is a significant opportunity and priority for quality improvement.
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BACKGROUND

Clostridium difficile is the most common cause of health care−associated infection in the United States, costing an estimated $3 billion annually, and is associated with as many as 30,000 deaths annually.[1-3] According to the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA), *C difficile* infection (CDI) is defined as both the presence of diarrhea (3 or more unformed stools in 24 or fewer consecutive hours) and a stool test positive for the presence of *C difficile* or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis.[3] Stool tests for *C difficile* cannot distinguish CDI from asymptomatic colonization with *C difficile*, which occurs in between 3%-51% of hospitalized adults.[3-7] Moreover, treatment of

asymptomatic colonization by *C difficile* can have several negative consequences, including inducing CDI[3,8]; increasing spore shedding, leading to greater environmental burden and transmission of *C difficile*[8,9]; decreasing quality of care and patient satisfaction because of placement in contact precautions[10]; contributing to the development of antibiotic resistance[11,12]; artificially increasing a hospital's rate of hospital-onset CDI, which may negatively impact reimbursement from the Centers for Medicare and Medicaid Services[13]; and promoting an inefficiency of hospital resources. To minimize the detection and treatment of asymptomatic *C difficile* colonization, only unexplained and new-onset unformed stools should be tested for *C difficile*.

The majority of hospital-onset diarrhea is noninfectious, with only 10%-20% caused by CDI.[14] Few studies have examined the association between laxative use and *C difficile* testing.[15-20] Our study examined the relationship between laxative use and *C difficile* testing across 5 hospitals in Southeast Michigan. Improving our understanding of the prevalence of antecedent laxative receipt among patients undergoing

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C difficile testing will help identify potential opportunities for quality improvement.

METHODS

A case-control study was conducted at 5 hospitals comprising a regional health system in Southeast Michigan. The study was approved by the St. Joseph Mercy Health System Institutional Review Board. Hospital size ranged from 133 to 537 beds, and all hospitals were designated as community teaching hospitals. The study included all instances of *C difficile* tests performed for patients 18 years of age or older at each hospital during the 2016 calendar year. Hospitals 1-3 used a 2-step *C difficile* testing algorithm. The first step consisted of an enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH) and an EIA for detection of toxins A and B (*C. diff* Quik Check Complete; Alere, Waltham, MA). If the GDH test result was positive and the EIA for toxins A and B was negative, the second step consisted of a confirmatory commercial polymerase chain reaction (PCR) assay (Xpert *C. difficile*; Cepheid, Sunnyvale, CA). Using the definitions for laboratory surveillance and reporting to National Health Safety Network,[21] CDI was diagnosed with either GDH positivity and toxin positivity, or GDH positivity and PCR positivity. Hospitals 4 and 5 used the 1-step PCR-based test. CDI was diagnosed with PCR positivity using the National Health Safety Network definitions.[21] None of the hospitals had protocols allowing nurses to send stool for *C difficile* testing without a physician order.

Cases were defined as patients who received laxatives in the 24 and 48 hours before *C difficile* testing, whereas control subjects included patients who received testing without antecedent laxative use in the prior 24 and 48 hours. Laxatives considered in this study were those included in the electronic medical record (EMR) laxative order set for the hospitals: docusate, senna, polyethylene glycol 3350, bisacodyl, and magnesium hydroxide. Magnesium citrate and lactulose were initially considered for inclusion, but manual chart review revealed that, in the vast majority of instances, magnesium citrate had been used to treat magnesium deficiency and lactulose to treat hepatic encephalopathy. Chart review also revealed that the laxatives included in the EMR order set accounted for well over 90% of all laxative use in the dataset. For each patient, the following variables were abstracted from administrative databases via the EMR: laxative receipt in the 24 and 48 hours before and after *C difficile* testing, age, sex, *C difficile* test result, Elixhauser Comorbidity Score (ECS),[22] type of unit (surgical or medical) at the time of testing, intensive care unit (ICU) stay at the time of testing, and whether the patient had undergone an operative procedure in the 30 days before testing. Data were validated for 10% of observations from each hospital.

All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC). For all analyses, $P < .05$ was considered significant. Kruskal-Wallis nonparametric 1-way analysis of variance was used to compare non-normally distributed continuous variables, and χ^2 testing was used to compare binary and categorical variables. Individual effects on laxative receipt before *C difficile* testing were assessed using univariate logistic regression for the following patient characteristics: age ≥ 40, sex, residence on surgical service at the time of testing, residence in an ICU at the time of testing, and ECS ≥ 4. Patient age was dichotomized into <40 and ≥ 40 to capture an increase in odds of laxative receipt before testing that occurred at 40 years of age. For the analysis, we had initially considered modeling age by decades. This comparison showed the odds of antecedent laxative receipt were similar for the decades of the 20s and 30s, increased from the 30s to 40s, and then remained stable for the 40s and older decades. ECS was dichotomized into <4 and ≥ 4 because 4 was the median ECS of the dataset.

Collinearity between patient characteristics showing significant individual effects was assessed using the variance inflation factor (VIF). A cutoff of VIF > 10 was used to identify patient characteristics that were linearly predicted by other patient characteristics, and those with VIF > 10 were not included in the multivariate model. The patient characteristics remaining after collinearity analysis were used in multivariate logistic regression to identify those that were independently associated with antecedent laxative use in the 24 and 48 hours before *C difficile* testing.

RESULTS

A total of 5,452 *C difficile* tests performed at 5 hospitals were included in this study (Table 1). The median age of the study population was 69 years (interquartile range, 57-80 years). Of the study population, 58.9% were female (range, 57%-67.5%); 22% resided on a surgical service at the time of testing (range, 6.7%-27.4%); 14.3% resided in an ICU (range, 6.8%-21.1%); and 6.7% had undergone an operative procedure in the 30 days prior (range: 2.6%-8.2%).

Table 1
Characteristics of *Clostridium difficile* testing and laxative administration by hospital

Hospital characteristic	Combined	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	P value*
No. *C difficile* tests (%)	5452	2234 (50)	1502 (27.6)	1399 (25.7)	194 (3.6)	123 (2.3)	—
Bed size	—	537	304	443	136	133	—
Tests per 10,000 patient days	—	159.7	201.8	149.1	236.1	70.1	—
No. positive tests (%)	898 (16.5)	355 (15.9)	262 (17.4)	218 (15.6)	40 (20.6)	23 (18.7)	.26
No. laxative receipt in 24 hours before test (%)	535 (9.8)	275 (12.3)	101 (6.7)	144 (10.3)	14 (7.2)	1 (.8)	<.001
No. positive tests when laxatives received in 24 hours prior (%)	81 (15.1)	41 (14.9)	15 (14.9)	22 (15.3)	3 (21.4)	0 (0)	—
No. laxative receipt in 48 hours before test (%)	707 (13.0)	365 (16.3)	127 (8.6)	194 (13.9)	17 (8.8)	4 (3.3)	<.001
No. positive tests when laxatives received in 48 hours prior (%)	106 (15.0)	54 (14.8)	18 (14.2)	27 (13.9)	5 (29.4)	2 (50.0)	—
Median age (IQR)	69 (57-80)	67 (56-77)	73 (58-83)	67 (55-79)	70.5 (61-84)	73 (60-81)	<.001
No. female (%)	3211 (58.9)	1274 (57.0)	929 (61.9)	812 (58.0)	113 (58.3)	83 (67.5)	.01
No. residing on medical service (%)	4252 (78.0)	1621 (72.6)	1236 (82.3)	1101 (78.7)	181 (93.3)	113 (91.9)	<.001
No. residing on surgical service (%)	1200 (22.0)	613 (27.4)	266 (17.7)	298 (21.3)	13 (6.7)	10 (8.1)	<.001
No. with operation in prior 30 days (%)	336 (6.7)	148 (6.6)	89 (5.9)	114 (8.2)	5 (2.6)	10 (8.1)	.02
No. residing in an ICU (%)	777 (14.3)	356 (15.9)	102 (6.8)	260 (18.6)	33 (17.0)	26 (21.1)	<.001
Median ECS (IQR)	4 (2.5-6)	4 (2-5)	4 (3-6)	5 (3-6)	4 (2-5)	4 (2-6)	<.001

ECS, Elixhauser comorbidity score; *ICU*, intensive care unit; *IQR*, interquartile range; *SD*, standard deviation.
*Kruskal-Wallis nonparametric one-way analysis of variance was used to test for differences between non-normally distributed continuous variables including age and Elixhauser Comorbidity Score. The χ^2 test was used to test for differences between hospitals for binary variables including laxative receipt in the 24 hours prior to *C difficile* testing, laxative receipt in the 48 hours before testing, sex, residence on a surgical service, an operative procedure in the 30 days before testing, residence in an ICU, and positive test result. $P < .05$ was considered significant for all statistical tests.

The median ECS of the study population was 4 (interquartile range, 2.5-6). Of the 5,452 *C difficile* tests, 898 (16.5%) were positive (range, 15.6%-20.6%). The percent of *C difficile* test results that were positive was not significantly different among the 5 hospitals.

Five hundred thirty-five *C difficile* tests (9.8%) were preceded by laxative administration in the 24 hours before testing (range, 0.8%-12.3%), and this prevalence was significantly different among hospitals (*P* < .001). Laxatives were continued for at least 24 hours after testing in 236 of these 535 orders (44.1%), and 81 of these 535 tests (15.1%) yielded a positive result (range, 0%-21.4%). Seven hundred seven *C difficile* tests (13%) were preceded by laxative administration in the 48 hours before testing (range, 3.3%-16.3%), and this prevalence was significantly different among hospitals (*P* < .001). Laxatives were continued for at least 48 hours after testing in 354 of these 707 orders (50.1%), and 106 of these 707 tests (15%) yielded a positive result (range, 13.9%-50%) (Table 1, Fig. 1). Of the 898 positive *C difficile* test results, laxatives were given for 24 and 48 hours after testing in 68 (7.6%) and 99 (11%) cases, respectively.

Individual effects of patient characteristics on odds of laxative receipt before *C difficile* testing comparing cases with control subjects are summarized in Table 2. Antecedent laxative use was significantly associated with patient age ≥40 years, residence on a surgical service at the time of testing, residence in an ICU at the time of testing, and ECS ≥4. An operative procedure in the 30 days before testing was not significantly associated with antecedent laxative receipt, likely given the elective nature of many of these procedures and a lower acuity of illness compared with residence on a surgical service. Female sex was associated with significantly decreased odds of antecedent laxative receipt. In collinearity analysis, all patient characteristics had a VIF <1.2, and the following characteristics were selected for use in multivariate logistic regression: residence on a surgical service at the time of testing, residence in an ICU at the time of testing, ECS ≥4, age ≥ 40 years, and female sex.

The results of multivariate logistic regression are summarized in Table 3. Residence on a surgical service was associated with a significant 2.5-fold increase in odds of laxative receipt in the 24 hours before *C difficile* testing (95% CI, 2.1-3.1; *P* < .001) and a significant 2.7-fold increase in the 48 hours prior (95% CI, 2.3-3.2; *P* < .001). ECS ≥4 was associated with a significant 1.4-fold increase in odds of laxative receipt in the 24 hours (95% CI, 1.1-1.7; *P* = .002) and 48 hours (95% CI, 1.2-1.7; *P* < .001) before testing. Residence in an ICU was associated with a significant 1.3-fold increase in odds of laxative receipt in the 24 hours (95% CI, 1.0-1.6; *P* = .04) and 48 hours (95% CI, 1.1-1.6; *P* = .009) before testing. Female sex was associated with a 20% decrease in odds of laxative receipt that was not significant in the 24 hours before testing (OR,

0.8; 95% CI, 0.7-1.0; *P* = .07) but was significant in the 48 hours before (95% CI, 0.7-0.99, *P* = .04). Age was not significantly associated with laxative administration before *C difficile* testing.

DISCUSSION

CDI is among the most common health care−associated infections and results in significant morbidity and mortality.[1-3] Guidelines from the IDSA and the SHEA recommend that only unexplained and new-onset unformed stool from patients with diarrhea (3 or more stools in 24 or fewer consecutive hours) be tested for *C difficile* to reduce the detection and treatment of asymptomatic *C difficile* colonization.[3,4] An update in the recently released guidelines recommends that patients who have received laxatives in the prior 48 hours not be tested for *C difficile*.[3] This reflects the growing concern surrounding this testing practice,[13,14,18,19,23] but there is only "very low quality of evidence" and this is a "weak recommendation."[3] Further investigation is needed to generate sufficient evidence to improve the strength of this recommendation. Future studies should be large-scale multicenter studies given that this testing practice is heterogeneous between hospitals (Table 1), and only investigating a single hospital may introduce bias.

Given the high rates of asymptomatic *C difficile* colonization in hospitalized adults,[3-7] the negative consequences of treating asymptomatic *C difficile* colonization,[3,8-13] and that only 10%-20% of all hospital-onset diarrhea is caused by *C difficile* whereas the majority of hospital-onset diarrhea has a noninfectious cause,[14] appropriate diagnostic stewardship should recommend that *C difficile* testing likely not be performed if a patient is receiving or has recently received laxatives. The few studies that have examined this practice report that between 14%-50% of patients tested for *C difficile* received laxatives in the 48 hours before stool collection.[15-20]

Among 5,452 *C difficile* tests from 5 hospitals in Southeast Michigan, 535 (9.8%) and 707 (13%) tests were preceded by laxative administration in the 24 and 48 hours before testing, respectively. The

Table 2
Univariate analysis of patient characteristics on odds of laxative receipt prior to *Clostridium difficile* testing

Patient characteristic	24 hours			48 hours		
	OR	95% CI	P	OR	95% CI	P
Residence on a surgical service	2.8	2.4-3.4	<.001	3.1	2.6-3.6	<.001
Residence in an ICU	1.9	1.9-2.4	<.001	2.0	1.7-2.4	<.001
ECS ≥ 4	1.6	1.4-2.0	<.001	1.7	1.4-2.0	<.001
Age ≥ 40 years	1.6	1.1-2.4	.02	1.7	1.2-2.4	.004
Operation in prior 30 days	1.0	0.7-1.4	.99	1.0	0.8-1.4	.80
Female	0.8	0.6-0.9	.001	0.7	0.6-0.9	<.001

CI, confidence interval; *ECS*, Elixhauser comorbidity score; *ICU*, intensive care unit; *OR*, odds ratio.

Table 3
Multivariate analysis of patient characteristics on odds of laxative receipt before *Clostridium difficile* testing

Patient characteristic	24 hours			48 hours		
	OR	95% CI	P	OR	95% CI	P
Residence on a surgical service	2.5	2.1-3.1	<.001	2.7	2.3-3.2	<.001
ECS ≥4	1.4	1.1-1.7	.002	1.4	1.2-1.7	<.001
Residence in an ICU	1.3	1.0-1.6	.04	1.3	1.1-1.6	.009
Female	0.8	0.7-1.0	.07	0.8	0.7-0.99	.04
Age ≥ 40 years	1.4	0.9-2.0	.14	1.4	1.0-2.0	.06

CI, confidence interval; *ECS*, Elixhauser comorbidity score; *ICU*, intensive care unit; *OR*, odds ratio.
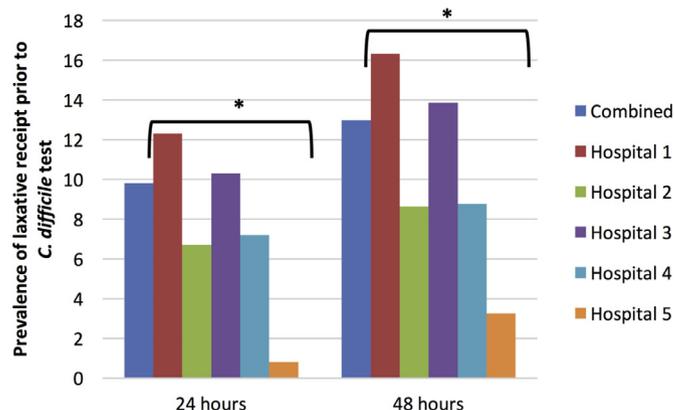
Fig 1. Prevalence of laxative receipt before *Clostridium difficile* testing. *Differences in prevalence of laxative receipt before *C difficile* test by hospital were significant at *P* < .05 level according to χ^2 test.

estimates reported here and elsewhere demonstrate that the practice of ordering *C difficile* tests while a patient's diarrhea may be attributable to recent laxative receipt is common both geographically and between different types and sizes of hospitals.[15-20] It is quite likely that this excess testing accounts for some false-positive test results that reflect *C difficile* colonization as opposed to infection. Although this study did not examine whether patients with positive test results were treated for CDI and whether this differed based on whether the patient had received laxatives before testing, it is likely that excess false-positive results lead to inappropriate treatment of *C difficile* colonization in these hospitals.[23] Surprisingly, among 898 positive *C difficile* tests, laxatives were continued in 99 (11%) episodes for at least 48 hours after testing.

This multicenter case-control study also sought to identify patient subpopulations in which this *C difficile* test ordering practice occurs more frequently. It is not surprising that patients with a greater number of underlying medical conditions (those with ECS ≥ 4) and patients residing in an ICU have significantly greater odds of having received laxatives in the 24 and 48 hours before testing. It is likely that a greater percentage of these patients are receiving laxatives at any given time than patients with a lower ECS or patients residing in a non-ICU. It is also possible that providers may be more concerned about the development and outcomes of CDI in these patient populations, thus ordering *C difficile* testing more frequently.

Patients residing on a surgical service had 2.5 to 2.7 times greater odds of having received laxatives before *C difficile* testing than patients residing on a medical service. This important finding demonstrates that the practice of ordering *C difficile* tests when a patient is receiving or has recently received laxatives occurs significantly more frequently in surgical services than in medical services. Although these differences may reflect differences in the prevalence of laxative use in surgical and medical services, they are also large enough to suggest marked differences in *C difficile* test ordering practices between physicians caring for surgical patients versus those caring for medical patients.

Ordering *C difficile* tests while a patient is receiving, or has recently received laxatives is common. We speculate that, by reducing the number of inappropriate tests that are ordered when a patient is experiencing diarrhea that may be attributable to laxative receipt, hospitals may be able to reduce the total number of tests, the number of false-positive results for CDI, and the inappropriate treatment of these false-positive results that represent *C difficile* colonization as opposed to infection.[13] Improving diagnostic stewardship around *C difficile* testing will likely save money and other resources; reduce inappropriate use of antibiotics and combat the development of antibiotic resistance; prevent CDI treatment from inducing CDI or *C difficile* spore shedding in a patient who is colonized; prevent placing a colonized patient in unnecessary contact precautions; and reduce the hospital's CDI rate, improving reimbursement from the Centers for Medicare and Medicaid Services.

We propose 2 complementary methods by which hospitals may reduce the practice of ordering *C difficile* tests while a patient is receiving or has recently received laxatives. The first is education for all providers who order *C difficile* tests, especially those who work on surgical services and ICUs. Effective educational campaigns should include information on the frequency of *C difficile* colonization in hospitalized patients and that *C difficile* tests do not distinguish between CDI and *C difficile* colonization; the negative results of treating a colonized patient for CDI; the prevalence of this practice and that this practice may occur significantly more frequently in patients residing on a surgical service or in an ICU; and the importance of considering whether a patient is receiving or has recently received laxatives in conjunction with evaluation of other clinical indicators (ie, leukocytosis, fevers, abdominal pain) that their diarrhea may be clinically significant when ordering a *C difficile* test. Recent work has shown that educational interventions for providers are effective at reducing inappropriate *C difficile* testing in pediatric populations.[24]

An additional method is to create electronic *C difficile* test ordering cascades that include soft stops if the patient is receiving or has recently received laxatives. In this case, the provider will be alerted by the *C difficile* test ordering cascade that the patient has recently received laxatives and prompted to consider this, as well as any other clinical indicators that the diarrhea may be clinically significant in deciding to order the test. Similar electronic interventions have been successful in reducing inappropriate *C difficile* testing in both pediatric and adult popualtions.[13,24,25]

The primary strength of this study is that the study population was drawn from 5 different hospitals that represent a range of sizes and hospital types. This increases the generalizability compared with that of prior studies, of which only 1 had a population size comparable to this study.[15-20] Drawing from 5 hospitals allowed us to analyze a total of 5,452 *C difficile* tests, giving the study sufficient power to detect significant differences in *C difficile* test ordering practices between different clinical services and patient types.

The major limitation of this study was that it did not examine whether patients were treated for CDI after a positive *C difficile* test result and whether the prevalence of treatment differed between patients who had received antecedent laxatives and patients who had not. It also did not examine the EMR of patients who received laxatives before their *C difficile* test to determine whether their diarrhea was indeed attributable to the laxative or whether the diarrhea was otherwise clinically significant and warranted ordering a *C difficile* test. With this information, the prevalence of inappropriate treatment of *C difficile* colonization could be characterized to understand better the extent to which inappropriate *C difficile* testing for patients who have recently received laxatives results in inappropriate treatment of colonization with *C difficile*.

In summary, among patients tested for *C difficile*, antecedent laxative use was common. Improving diagnostic stewardship around *C difficile* testing, particularly in surgical and ICU patients, is a significant opportunity and priority for quality improvement.

Acknowledgments

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