Open access • Journal Article • DOI:10.1017/ICE.2015.177

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Published on: 30 Jul 2015 - Infection Control and Hospital Epidemiology (University of Chicago Press)

Topics: Clostridium difficile and Intensive care unit

ORIGINAL ARTICLE

Impact of Toxigenic *Clostridium difficile* Colonization on the Risk of Subsequent *C. difficile* Infection in Intensive Care Unit Patients

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BACKGROUND. *Clostridium difficile* infection (CDI) in hospitalized patients is generally attributed to the current stay, but recent studies reveal high *C. difficile* colonization rates on admission.

OBJECTIVE. To determine the rate of colonization with toxigenic *C. difficile* among intensive care unit patients upon admission as well as acquired during hospitalization, and the risk of subsequent CDI.

METHODS. Prospective cohort study from April 15 through July 8, 2013. Adults admitted to an intensive care unit within 48 hours of admission to the Johns Hopkins Hospital, Baltimore, Maryland, were screened for colonization with toxigenic *C. difficile*. The primary outcome was risk of developing CDI.

RESULTS. Among 542 patients, 17 (3.1%) were colonized with toxigenic *C. difficile* on admission and an additional 3 patients were found to be colonized during hospitalization. Both colonization with toxigenic *C. difficile* on admission and colonization during hospitalization were associated with an increased risk for development of CDI (relative risk, 10.29 [95% CI, 2.24–47.40], $P = .003$; and 15.66 [4.01–61.08], $P < .001$, respectively). Using multivariable analysis, colonization on admission and colonization during hospitalization were independent predictors of CDI (relative risk, 8.62 [95% CI, 1.48–50.25], $P = .017$; and 10.93 [1.49–80.20], $P = .019$, respectively), while adjusting for potential confounders.

CONCLUSIONS. In intensive care unit patients, colonization with toxigenic *C. difficile* is an independent risk factor for development of subsequent CDI. Further studies are needed to identify populations with higher toxigenic *C. difficile* colonization rates possibly benefiting from screening or avoidance of agents known to promote CDI.

Infect. Control Hosp. Epidemiol. 2015;36(11):1324–1329

Clostridium difficile infection (CDI) is a major cause of healthcare-associated diarrhea.[1] In a recently published multistate prevalence survey, CDI was responsible for 12.1% of healthcare-associated infections,[2] pointing to its ongoing significance and the need for further investigation regarding prevention. In intensive care unit (ICU) patients, CDI has been associated with prolonged length of hospital and ICU stay, and increased need for skilled nursing care or rehabilitation following discharge.[3] CDI in hospitalized patients is generally attributed to the current hospital stay. Recent studies, however, challenge this concept and reveal high *C. difficile* colonization rates upon hospital admission.[4] In patients known to be colonized with toxigenic *C. difficile*, a key component for prevention of progression to CDI is to avoid, when possible, agents known to incite clinical expression of *C. difficile*—emphasizing the importance of antibiotic stewardship. If this principle is true, it is key to identify those patients who are colonized in order to define risk and optimal methods of patient-specific prevention interventions in high-risk populations.

We sought to determine the rate of colonization with toxigenic *C. difficile* both at hospital admission and acquired during hospitalization, as well as the risk of subsequent CDI, among a cohort of high-risk patients in the ICU.

METHODS

Design and Setting

We performed a prospective, observational cohort study of patients at least 18 years of age admitted to ICUs within

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Presented in part: 24th European Congress of Clinical Microbiology and Infectious Diseases; Barcelona, Spain; May 11, 2014 (Abstract P0773).

Received March 31, 2015; accepted July 5, 2015; electronically published July 30, 2015

 0899-823X/2015/3611-0011. DOI: 10.1017/ice.2015.177

48 hours of admission to the Johns Hopkins Hospital, a 900-bed tertiary care academic medical center in Baltimore, Maryland, from April 15 through July 8, 2013.

Patients were screened by means of rectal swabs for colonization with toxigenic *C. difficile* on admission to the ICU and weekly thereafter until discharge from the ICU. C. *difficile* screening results were not shared with clinicians. No enhanced infection control practices were undertaken for patients identified as colonized with toxigenic *C. difficile* on the basis of rectal swab results. Patients diagnosed with CDI within 48 hours of hospital admission were excluded from this study because the infection likely was acquired before admission.[5] Information regarding demographic variables, clinical characteristics, and exposures to established risk factors 4 weeks prior to admission and during hospitalization (up to development of CDI) was obtained by electronic medical chart review, including records on outpatient visits in Johns Hopkins–affiliated practices. Patients were longitudinally followed up for development of CDI during their hospital stay and up to 1 month after discharge by medical chart review. Data regarding symptoms and complications attributable to CDI were recorded. Results from all stool samples submitted for *C. difficile* testing as part of routine clinical care throughout the Johns Hopkins Hospital and its outpatient clinics as standard of care were collected. This study was approved by the Johns Hopkins University School of Medicine institutional review board with a waiver of informed consent.

Definitions and Categorization of Patients

Patients were considered colonized on admission if rectal swabs performed within 48 hours of admission were positive for toxigenic *C. difficile*. A patient was classified[6] as colonized with toxigenic *C. difficile* during hospitalization if (1) the rectal swab upon admission to the ICU was positive for toxigenic *C. difficile*, (2) a subsequent rectal swab during a patient's ICU stay was positive for toxigenic *C. difficile*, or (3) stool sent as part of routine clinical care was positive for toxigenic *C. difficile* in the absence of clinical findings suggestive of CDI.

CDI was defined using standard definitions.[5] Development of CDI was evaluated during hospitalization and during a 1-month follow-up period after hospital discharge.

Microbiological Analyses

Rectal surveillance swab specimens were obtained on ICU admission and weekly thereafter until ICU discharge and were immediately sent to the microbiology laboratory for processing. Both rectal swabs and stool specimens submitted for *C. difficile* detection as standard of care underwent polymerase chain reaction (PCR) analysis using the GeneOhm *C. difficile* assay (BD). Toxigenic bacterial culture was performed for PCR-positive samples. All isolated strains were prospectively collected.

PCR ribotyping was performed by capillary electrophoresis as described elsewhere.[7] Capillary electrophoresis was conducted using the automated sequencer ABI-PRISM 3130 Genetic Analyzer and fragments were analyzed using GeneMapper software (both, Applied Biosystems).

Statistical Analyses

Relative risks for colonization with toxigenic *C. difficile* on admission and development of CDI were estimated using univariable Poisson regression with robust error variance.[8] Only variables found to be significant in univariable analyses were included in a multivariable model. $P \leq .05$ was considered significant. The Pearson and deviance goodness-of-fit tests were performed to assess the fit of data to a Poisson distribution in the final regression model. A priori power calculations were performed using data from a prior study[9] that showed that 182 patients are necessary to detect a significant difference in the risk of CDI on the basis of toxigenic *C. difficile* colonization status, assuming a 2-sided significance level of.05 and power of 0.8. All analyses were performed using Stata, version 12.0 (StataCorp).

RESULTS

During the study period, 548 consecutive patients were screened for colonization with toxigenic *C. difficile* on admission. Six patients were excluded from further analyses because they were diagnosed with CDI during the first 48 hours of admission (Figure 1).

Reasons for ICU admission included monitoring after neurosurgery (239), respiratory failure (46), monitoring after cardiac surgery (33), sepsis (29), intracranial hemorrhage (28), trauma (25), stroke (24), monitoring after vascular surgery (23), cardiac failure (23), monitoring after abdominal surgery (17), gastrointestinal bleeding (16), encephalopathy (7), liver or renal failure (6), meningoencephalitis (6), seizures/status epilepticus (5), monitoring after thoracic surgery (4), and other reasons (11).

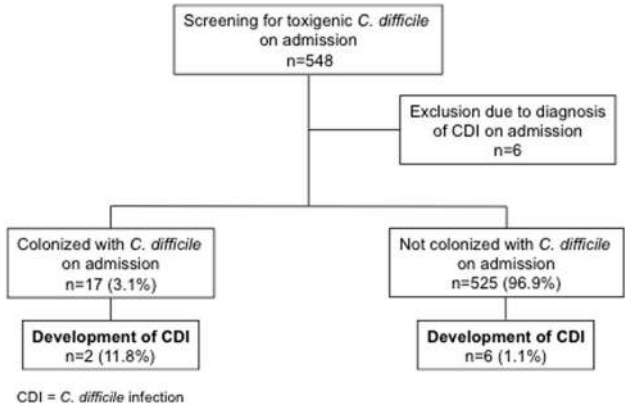

FIGURE 1. Colonization with toxigenic *Clostridium difficile* on admission and subsequent development of *C. difficile* infection.

TABLE 1. Risk Factors for Colonization With Toxigenic *Clostridium difficile* on Intensive Care Unit Admission

	Colonized on admission (n = 17)		Not colonized on admission (n = 525)				
Variable	Value		Value		Relative risk	95% CI	*P* value
Demographic							
Age, mean (SD), y	58.1	(16.2)	55.6	(17.0)	1.01	0.98–1.04	.540
Healthcare exposure							
Prior hospitalization <4 weeks	5	29.4	144	27.4	1.10	0.39–3.07	.857
Prior hospitalization 4-12 weeks	2	11.8	51	9.7	1.23	0.29–5.24	.779
Comorbidities							
Charlson comorbidity index, median (range)	4	(1–11)	4	(0–12)	1.12	0.95–1.31	.176
Cancer	3	17.6	150	28.6	0.55	0.16–1.87	.335
Immunosuppression	5	29.4	162	30.9	0.94	0.33–2.61	.899
Solid organ transplant	2	11.8	13	2.5	4.68	1.17–18.71	.029
Human Immunodeficiency virus	1	5.9	10	1.9	3.02	0.44–20.82	.263
Exposure 4 weeks prior to admission							
Antibiotics	2	11.8	4	8.4	1.44	0.34–6.10	.623
Proton pump inhibitors	4	23.5	88	16.8	1.51	0.50–4.52	.466
H2 Antagonists	1	5.9	7	1.3	4.17	0.63–27.83	.140

NOTE. Data are no. (%) of patients unless otherwise indicated.

Among the remaining 542 patients, 17 (3.1%) were colonized with toxigenic *C. difficile* on admission. Three of 35 patients with weekly follow-up swabs, after admission, were identified as subsequently colonized with toxigenic *C. difficile*. Follow-up information 1 month after discharge was available for 393 patients (72.5%). Patients with and without follow-up information on CDI status 1 month after discharge were similar regarding demographic characteristics, preexisting medical conditions, and exposures to known risk factors for the development of CDI (data not shown).

Neither age, nor prior exposure to healthcare (up to 12 weeks prior to admission), nor receipt of antibiotics or gastric acid suppressants were associated with an increased risk for colonization with toxigenic *C. difficile* on admission. Patients with solid organ transplant were more commonly colonized on ICU admission (relative risk, 4.68 [95% CI, 1.17–18.71]) (Table 1).

CDI developed in 8 patients (1.5%) during hospitalization (Figure 1). An additional 4 patients were diagnosed with CDI within 1 month after discharge (overall, 12 [2.2%] of 542 patients). None of the patients with CDI were diagnosed with severe complicated CDI (ie, septic shock, toxic megacolon) and no patients experienced a CDI-attributable death.

In univariable analyses, exposures to penicillins (82.1% being penicillin and beta-lactamase inhibitor combinations) or proton pump inhibitors during hospitalization were associated with an increased subsequent risk for CDI (Table 2). For each additional day in the ICU, there was a 4% increase in the risk of CDI (relative risk, 1.04 [95% CI, 1.01–1.07]).

Both colonization with toxigenic *C. difficile* on admission and colonization during hospitalization were associated with an increased risk for development of CDI in univariable analyses (Table 3). After adjusting for exposures to penicillins and length of ICU stay before CDI, colonization with toxigenic *C. difficile* upon admission or hospitalization remained associated with an increased risk of development of CDI during hospitalization (Table 3) and for up to 1 month after discharge (data not shown).

The Pearson and deviance goodness-of-fit tests for the multivariable regression models revealed insignificant *P* values indicating adequate model-fit ($\chi^2 = 419.2$, $P > .99$, and $\chi^2 = 57.7$, $P > .99$, respectively, for the model including colonization with toxigenic *C. difficile* on admission; $\chi^2 = 548.1$, $P = .372$, and $\chi^2 = 59.7$, $P > .99$, respectively, for the model including colonization during hospitalization). Receipt of proton pump inhibitors during hospitalization was not included in the multivariable regression model because all patients with CDI were exposed.

Strains were available for ribotyping from 14 of 17 patients found to be colonized on admission. PCR ribotypes 001 and 027 were most commonly identified, accounting for 4 (29%) and 3 (21%) of the 14 strains, respectively. Ribotype 014 was determined in 2 patients and ribotypes 126, 056, 015, 003, and 002 in 1 patient each.

DISCUSSION

In ICU patients, colonization with toxigenic *C. difficile* on admission or during hospitalization increases the risk for development of CDI during hospitalization and up to 1 month after discharge.

The rate of colonization with toxigenic *C. difficile* on admission identified in our study was low—reflecting colonization rates described for the general population[10] but also

TABLE 2. Risk Factors for Development of *Clostridium difficile* Infection (CDI) During Hospitalization

Variable	CDI during hospitalization (n = 8) Value		No CDI during hospitalization (n = 534) Value		Relative risk	95% CI	*P* value
Demographic							
Age, mean (SD), y	61.6	(20.1)	55.6	(16.9)	1.02	0.97–1.08	.405
Prior hospitalization <4 weeks	4	50.0	145	27.2	2.64	0.67–10.42	.167
ICU stay							
CVSICU	1	12.5	70	13.1	0.95	0.12–7.60	.960
MICU	3	37.5	89	16.7	2.94	0.71–12.08	.136
NCCU	4	50.0	289	54.1	0.85	0.21–3.37	.817
SICU	0	0.0	86	16.1	N/A	N/A	N/A
Length of ICU stay prior to CDI, mean (SD), d	7.3	(4.8)	4.5	(5.9)	1.04	1.01–1.07	.010
Comorbidities							
Charlson comorbidity index, median (range)	5	(1–9)	4	(0–12)	1.13	0.88–1.44	.346
Cancer	1	12.5	152	28.5	0.36	0.05–2.93	.342
Immunosuppression	1	12.5	166	31.1	0.32	0.04–2.59	.286
Solid organ transplant	0	0.0	15	2.8	N/A	N/A	N/A
Human Immunodeficiency Virus	0	0.0	11	2.1	N/A	N/A	N/A
Exposures during hospitalization							
Antibiotics							
Penicillins	4	50.0	80	15.0	5.45	1.39–21.40	.015
Cephalosporins	7	87.5	356	66.7	3.45	0.43–28.0	.245
Carbapenems	1	12.5	37	6.9	1.89	0.24–15.03	.545
Quinolones	1	12.5	26	4.9	2.72	0.35–21.40	.340
Macrolides	1	12.5	42	7.9	1.66	0.21–13.19	.633
Clindamycin	0	0.0	63	11.8	N/A	N/A	N/A
Others	1	12.5	40	7.5	1.75	0.22–13.87	.598
Antacids							
Proton pump inhibitors	8	100.0	445	83.3	N/A	N/A	N/A
H2 antagonists	0	0.0	44	8.2	N/A	N/A	N/A

NOTE. Data are no. (%) of patients unless otherwise indicated. CVSICU, cardiovascular surgical intensive care unit; ICU, intensive care unit; MICU, medical intensive care unit; NCCU, neuroscience critical care unit; SICU, surgical intensive care unit.

TABLE 3. Crude and Adjusted Relative Risks (RRs) for Development of *Clostridium difficile* Infection (CDI) During Hospitalization

Variable	Crude RR	Crude 95% CI	Crude *P* value	Adjusted[a] RR	Adjusted[a] 95% CI	Adjusted[a] *P* value
Colonization with toxigenic *C. difficile* on admission	10.29	2.24–47.40	.003	8.62	1.48–50.25	.017
Length of ICU stay prior to CDI	1.04	1.01–1.07	.010	1.00	0.94–1.06	.931
Exposure to penicillins during hospitalization	5.45	1.39–21.40	.015	4.96	0.96–25.64	.056
	Crude			Adjusted[b]		
	RR	95% CI	*P* value	RR	95% CI	*P* value
Colonization with toxigenic *C. difficile* during hospitalization	15.66	4.01–61.08	< .001	10.93	1.49–80.20	.019
Length of ICU stay prior to CDI	1.04	1.01–1.07	.010	0.98	0.95–1.03	.526
Exposure to penicillins during hospitalization	5.45	1.39–21.40	.015	4.56	0.97–21.42	.055

NOTE. ICU, intensive care unit.

[a]The multivariable model includes exposure to penicillins during hospitalization, length of ICU stay prior to CDI, and colonization with toxigenic *C. difficile* on admission.

[b]The multivariable model includes exposure to penicillins during hospitalization, length of ICU stay prior to CDI, and colonization with toxigenic *C. difficile* during hospitalization.

similar to the 4% reported in a large multicenter trial conducted in Canada.[11] One explanation for the low proportion of patients colonized upon admission may be the high proportion of patients without prior exposure to healthcare facilities and with none or few comorbid conditions, reflected by the low mean Charlson comorbidity index identified in our

study. We cannot rule out that our low prevalence of toxigenic *C. difficile* upon hospital admission may be due to the use of rectal swab rather than stool specimens and the use of PCR rather than anaerobic culture for detection.[12] Other studies report asymptomatic carriage with toxigenic *C. difficile* on admission for up to 14% of patients.[13–18] Even higher rates of colonization with *C. difficile* have been identified on admission to rehabilitation facilities, with 16% of stool samples testing positive.[19] Similarly, a *C. difficile* colonization rate of 15% has been described in general medical and surgical patients.[10]

Although earlier studies revealed recent exposure to antibiotics and healthcare facilities as important risk factors for colonization with toxigenic *C. difficile* on hospital admission,[11,13,15,17,18] both our study and another recent investigation[10] were not able to replicate these findings. Apart from solid organ transplantation, we were not able to identify any risk factors for colonization with toxigenic *C. difficile* on admission; however, we cannot rule out that our sample size is too small to detect such associations. Nevertheless, a growing body of knowledge points to *C. difficile* being acquired in the community setting without any clear antibiotic or healthcare exposures[20]—affecting patients previously considered as being at low risk as otherwise healthy people without prior exposure to antibiotics[21,22] as well as peripartum women[23,24] and children.[25] Possible sources may arise from the food chain; there is growing concern that *C. difficile* may be acquired from ingestion of spores in contaminated foods.[26]

Importantly in this study, colonization with toxigenic *C. difficile* on admission was identified as a strong and independent predictor for development of subsequent CDI. This finding suggests that traditional infection control measures may not suffice to avoid further increase in disease-burden. For patients colonized with toxigenic *C. difficile*, the challenge for disease prevention is not to prevent exposure but to reduce the risk of *C. difficile* toxin expression by restricting use of antibiotics,[11] acid-suppressive agents,[27] and narcotics.[28]

Furthermore, it needs to be acknowledged that, in contrast to these recent findings, an earlier study, based on data collected in the 1980s and early 1990s, reported that primary symptomless *C. difficile* colonization was associated with a decreased risk of CDI. Risk reduction was found with colonization with either nontoxigenic or toxigenic strains.[29] Novel diagnostic approaches—including real-time PCR—and changing epidemiology may explain these conflicting results. One possible underlying mechanism for the finding of *C. difficile* colonization as a protective factor for CDI-development may be that lack of IgG against *C. difficile* toxins was described as an important risk factor for CDI for hospitalized patients with *C. difficile* colonization.[16,30] Subsequent studies also showed monoclonal antibodies to *C. difficile* toxins A and B to be protective against CDI relapse, indicating the defensive role of serologic response and thus suggesting a mechanism for carriage plus risk without CDI.[31]

Our study has some important limitations. These include its conduction at a single center and its reliance on clinical chart review to identify both exposures to known risk factors for development of CDI and diagnosis of CDI. We used the definitions outlined in the Society for Healthcare Epidemiology of America/ Infectious Diseases Society of America guidelines[5] to differentiate CDI likely acquired before hospital admission rather than during hospitalization, suggesting a cut-off of 48 hours from admission. Our results and conclusions, however, did not change when applying the National Healthcare Safety Network reporting criteria for healthcare facility onset of CDI of greater than 3 days from admission. The low number of patients colonized with toxigenic *C. difficile* in our population may result in the study being underpowered for detection of risk factors for colonization and limits the precision of our point estimates, reflected by broad confidence intervals. We were not able to assess the interaction between carriage at admission and subsequent exposure to antibiotics because all 17 patients colonized on admission received antibiotics during their hospital stay. Due to the short mean duration of ICU stay, weekly follow-up swabs could be performed in only a very small proportion of patients. Toxigenic *C. difficile* strains identified at diagnosis of CDI in the 2 patients found to be colonized at admission were not available for ribotyping, therefore identity of strains could not be assessed. Further, follow-up information was missing at 1 month after discharge for 149 (27.5%) of the 542 patients included in this study and we cannot rule out that CDI was missed in some patients with symptom onset after discharge. We were, however, not able to identify any differences in baseline characteristics, exposures, or colonization with toxigenic *C. difficile* between patients with and without follow-up information.

In conclusion, in ICU patients, colonization with toxigenic *C. difficile* is an independent risk factor for development of subsequent CDI. The low rate of colonization found in a general ICU population questions the utility of this screening strategy for identification of patients at risk for *C. difficile* in this setting. Further studies are needed to identify populations with higher toxigenic *C. difficile* colonization rates possibly benefiting from screening or avoidance of agents known to promote CDI.

ACKNOWLEDGMENTS

Financial support. The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Division of Infectious Diseases of the Johns Hopkins University School of Medicine.

Potential conflicts of interest. S.T.-S. reports that she is funded by the Swiss National Science Foundation; the Medical Division of the Lichtenstein Foundation of the University of Basel, Switzerland; and the Scientific Society Basel, Switzerland.

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

Disclaimer: This publication was made possible by support from the Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Division of Infectious Diseases of the Johns Hopkins University School of Medicine. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Fisher Center or Johns Hopkins University School of Medicine.

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REFERENCES

1. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. *Clin Infect Dis* 2002;34:346–353.
2. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014;370:1198–1208.
3. Micek ST, Schramm G, Morrow L, et al. *Clostridium difficile* infection: a multicenter study of epidemiology and outcomes in mechanically ventilated patients. *Crit Care Med* 2013;41:1968–1975.
4. McDonald LC. Vital signs: preventing *Clostridium difficile* infections. *MMWR Morb Mortal Wkly Rep* 2012;61:157–162.
5. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;31:431–455.
6. Deutsches Institut für Normung EN. Chemische Desinfektionsmittel und Antiseptika. Hygienische Händedesinfektion. Prüfverfahren und Anforderungen (Phase 2/Stufe 2). 1997.
7. Stubbs SL, Brazier JS, O'Neill GL, Duerden BI. PCR targeted to the 16S-23S rRNA gene intergenic spacer region of *Clostridium difficile* and construction of a library consisting of 116 different PCR ribotypes. *J Clin Microbiol* 1999;37:461–463.
8. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702–706.
9. Hung YP, Tsai PJ, Hung KH, et al. Impact of toxigenic *Clostridium difficile* colonization and infection among hospitalized adults at a district hospital in southern Taiwan. *PLoS One* 2012;7:e42415.
10. Alasmari F, Seiler SM, Hink T, Burnham CA, Dubberke ER. Prevalence and risk factors for asymptomatic *Clostridium difficile* carriage. *Clin Infect Dis* 2014;59:216–222.
11. Loo VG, Bourgault AM, Poirier L, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med* 2011;365:1693–1703.
12. Curry SR, Schlackman JL, Hamilton TM, et al. Perirectal swab surveillance for *Clostridium difficile* by use of selective broth preamplification and real-time PCR detection of tcdB. *J Clin Microbiol* 2011;49:3788–3793.
13. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. *N Engl J Med* 1989;320:204–210.
14. Brazier JS, Fitzgerald TC, Hosein I, et al. Screening for carriage and nosocomial acquisition of *Clostridium difficile* by culture: a study of 284 admissions of elderly patients to six general hospitals in Wales. *J Hosp Infect* 1999;43:317–319.
15. Hutin Y, Casin I, Lesprit P, et al. Prevalence of and risk factors for *Clostridium difficile* colonization at admission to an infectious diseases ward. *Clin Infect Dis* 1997;24:920–924.
16. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000;342:390–397.
17. Leekha S, Aronhalt KC, Sloan LM, Patel R, Orenstein R. Asymptomatic *Clostridium difficile* colonization in a tertiary care hospital: admission prevalence and risk factors. *Am J Infect Control* 2013;41:390–393.
18. Samore MH, DeGirolami PC, Tlucko A, Lichtenberg DA, Melvin ZA, Karchmer AW. *Clostridium difficile* colonization and diarrhea at a tertiary care hospital. *Clin Infect Dis* 1994;18:181–187.
19. Marciniak C, Chen D, Stein AC, Semik PE. Prevalence of *Clostridium difficile* colonization at admission to rehabilitation. *Arch Phys Med Rehabil* 2006;87:1086–1090.
20. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *Am J Gastroenterol* 2012;107:89–95.
21. Severe *Clostridium difficile*–associated disease in populations previously at low risk—four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005;54:1201–1205.
22. Surveillance for community-associated *Clostridium difficile*—Connecticut, 2006. *MMWR Morb Mortal Wkly Rep* 2008;57:340–343.
23. Garey KW, Jiang ZD, Yadav Y, Mullins B, Wong K, Dupont HL. Peripartum *Clostridium difficile* infection: case series and review of the literature. *Am J Obstet Gynecol* 2008;199:332–337.
24. Rouphael NG, O'Donnell JA, Bhatnagar J, et al. *Clostridium difficile*–associated diarrhea: an emerging threat to pregnant women. *Am J Obstet Gynecol* 2008;198:635.e1–6.
25. Benson L, Song X, Campos J, Singh N. Changing epidemiology of *Clostridium difficile*–associated disease in children. *Infect Control Hosp Epidemiol* 2007;28:1233–1235.
26. Hoover DG, Rodriguez-Palacios A. Transmission of *Clostridium difficile* in foods. *Infect Dis Clin North Am* 2013;27:675–685.
27. Deshpande A, Pant C, Pasupuleti V, et al. Association between proton pump inhibitor therapy and *Clostridium difficile* infection in a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:225–233.
28. Dubberke ER, Reske KA, Olsen MA, et al. Evaluation of *Clostridium difficile*–associated disease pressure as a risk factor for *C. difficile*–associated disease. *Arch Intern Med* 2007;167:1092–1097.
29. Shim JK, Johnson S, Samore MH, Bliss DZ, Gerding DN. Primary symptomless colonisation by *Clostridium difficile* and decreased risk of subsequent diarrhoea. *Lancet* 1998;351:633–636.
30. Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *Lancet* 2001;357:189–193.
31. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *N Engl J Med* 2010;362:197–205.