RESEARCH ARTICLE

Risk Factors for Recurrent *Clostridium difficile* Infection in Pediatric Inpatients

Elyse M. Schwab, BS,[a] Jacob Wilkes, BS,[b] Kent Korgenski, MS,[b] Adam L. Hersh, MD, PhD,[b,c] Andrew T. Pavia, MD,[b,c] Vanessa W. Stevens, PhD[a,b]

ABSTRACT

OBJECTIVE: The purpose of this study was to identify the risk factors during the incident *Clostridium difficile* infection (CDI) episode, associated with developing recurrent CDI within 60 days, among hospitalized children that may be amenable to intervention.

METHODS: This was a retrospective cohort study of pediatric patients hospitalized at a freestanding children's hospital from January 1, 2003, to December 31, 2010. Patients were eligible if they were <18 years of age at admission and had a new diagnosis of CDI. Patients <1 year of age and those with a history of CDI in the previous 60 days were excluded. Age, gender, race, complex chronic conditions, and other information were collected. Multivariable logistic regression was used to evaluate predictors of recurrent CDI.

RESULTS: During the study period, there were 612 unique patients with an incident CDI episode; 65 (10.6%) experienced at least 1 recurrence. Patients with any complex chronic condition were 4.0 (95% confidence interval [CI]: 1.2–13.9) times more likely to experience recurrence. Patients with a malignancy and those who received non-CDI antibiotics at any time during CDI treatment were 2.3 (95% CI: 1.3–4.0) and 2.8 (95% CI: 1.2–6.9) times more likely to experience recurrence, respectively.

CONCLUSIONS: The presence of underlying comorbidities, malignancies, and treatment with non-CDI antibiotics during CDI treatment were the most important risk factors for recurrence. Efforts to reduce unnecessary courses of non-CDI antibiotics could lower the risk of CDI recurrence.

www.hospitalpediatrics.org
DOI:10.1542/hpeds.2015-0170

[a]*Pharmacotherapy Outcomes Research Center, University of Utah College of Pharmacy, Salt Lake City, Utah;* [b]*Department of Pediatrics, Primary Children's Hospital, Salt Lake City, Utah; and* [c]*Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah*

Address correspondence to Vanessa Stevens, PhD, Pharmacotherapy Outcomes Research Center, University of Utah College of Pharmacy, 30 South 2000 East, Rm 4961, Salt Lake City, UT 84121. E-mail: vanessa.stevens@pharm.utah.edu

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Ms Schwab carried out the initial analyses, drafted the initial manuscript, and revised the manuscript; Mr Wilkes designed the data collection instruments and reviewed the manuscript; Mr Korgenski coordinated and supervised data collection and reviewed the manuscript; Drs Pavia and Hersh critically reviewed and revised the manuscript; Dr Stevens conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

Clostridium difficile is a spore-forming, anaerobic, Gram-positive bacillus that is transmitted from the environment or by the fecal-oral route. *C difficile* is associated with 10% to 25% of all cases of antimicrobial-associated diarrhea[1] and is a common cause of hospital-associated infection among adults and children in the United States.[2] The incidence of *C difficile* infection (CDI) has been increasing in the United States since 1997.[3,4]

Oral vancomycin and metronidazole are the 2 most commonly prescribed medications for the treatment of CDI. Both are effective treatment options, but recurrence still occurs in ∼15% to 35% of adult patients[5] and ∼12% to 24% of children.[6–9] Patients with recurrent CDI tend to have a higher frequency of abdominal pain, fever, and colitis compared with the initial infection.[10] The majority of evidence on CDI recurrence has been gleaned from studies among adults, and information on risk factors among pediatric patients is limited. Antibiotic exposure, including the use of non-CDI agents during treatment of CDI, is the most important risk factor for recurrence. Other risk factors include a history of CDI and underlying comorbidities, particularly those associated with immune disfunction.[11,12]

CDI is less common in children than adults, and the major limitation of existing studies to examine risk factors for recurrent infection is the relatively small sample size and lack of power to evaluate potential predictors.[6,9] Therefore, the objective of this study was to describe risk factors for hospitalized children during the incident CDI episode that are associated with developing recurrent CDI within 60 days during hospitalization or after discharge.

METHODS

Study Design and Participants

We conducted a retrospective cohort study among hospitalized patients at Primary Children's Hospital (PCH), a freestanding academic children's hospital in Salt Lake City, Utah. PCH is the primary referral center for pediatric patients in the Mountain West region. PCH provides care for patients from Utah, Idaho, Wyoming, and Nevada, as well as specialized care for patients across the United States. PCH is a not-for-profit hospital within the Intermountain Healthcare (IHC) system, which includes 22 hospitals and 185 clinics. All data from patients admitted to PCH is stored in the Intermountain Healthcare Enterprise Data Warehouse (EDW), which is a data repository for clinical and administration data from all IHC facilities.

Patients were included if they were hospitalized at PCH from January 1, 2003, to December 31, 2010; were <18 years of age at admission; and had a new laboratory-confirmed diagnosis of CDI. A laboratory-confirmed diagnosis of CDI was defined as a positive laboratory test, including toxin A and B enzyme immunoassay or cytotoxicity assay for toxigenic *C difficile*. Patients were excluded if they had a history of CDI. Information on demographics, CDI treatment courses, medication use, and other clinical characteristics were extracted from the EDW. For the purposes of the current study, the cohort was restricted to the first hospitalization with CDI and the first recurrence experienced by the patient either during hospitalization or after discharge as an outpatient. Patients <1 year of age were excluded because of the high rate of asymptomatic colonization and the unclear significance of positive tests in this age group. Approval for this study was obtained from the Institutional Review Board at the University of Utah and the Privacy Board at PCH.

Clinical Characteristics

Patient demographic information was collected, including age at the time of CDI, gender, race, ethnicity, and underlying comorbidities. Underlying comorbidities were classified according to Feudtner's Complex Chronic Condition.[13] Medication dispensing information was collected for acid-suppressive therapy including proton pump inhibitors, histamine-2 blockers, and antibiotics received not used to treat CDI.

Episode Definitions

During the study period *C difficile* was identified at PCH by initial use of enzyme immunoassay for *C difficile* toxin A. All enzyme immunoassay–negative specimens were tested by cell culture cytotoxicity B assay. PCH did not start using polymerase chain reaction (PCR) testing until after 2010. To keep our results consistent, we used data from before PCR testing was introduced. We were unable to assess the presence of symptoms of CDI. The diagnosis of CDI was based on a positive stool test by toxin A enzyme immunoassay or cytotoxin B assay. Positive tests that were >14 days after the initial episode but <60 days were classified as a recurrent episode. Because recurrences are often treated in the outpatient setting, we followed patients for positive *C difficile* tests conducted at all Intermountain Healthcare Facilities using the system-wide EDW. The initial episodes were classified into the following epidemiologic groups: health care–associated CDI, community-associated CDI, or community onset-associated with health care.[14]

Antibiotics Definitions

Agents for the treatment of CDI in the 48 hours before a positive test and 48 hours after a positive test return were recorded, including vancomycin and metronidazole. Patients who received CDI antibiotics other than vancomycin and metronidazole were combined into another treatment group (probiotics, rifampin, rifaximin, or nitazoxanide). We were unable to evaluate individual treatments because of the small number of patients who received vancomycin or other treatments.

We evaluated non-CDI antibiotics received in the 30 days before the index CDI and in the 60 days after completion of CDI treatment during the inpatient stay. Patients who received ≥3 days of antibiotic therapy after discharge were not recorded. Antibiotic received during CDI treatment was defined as the receipt of at least 1 dose of any non-CDI antibiotic for any period of time during CDI treatment. We conducted a subsequent analysis where only non-CDI antibiotic courses that were received for at least 3 days during CDI treatment, while hospitalized, were classified as concomitant antibiotics. This more restrictive definition was applied to capture only those antibiotics that were given for longer periods of time during CDI treatment as an inpatient. The reference group was also hospitalized for at least 3 days.

We also recorded the number and class (eg, fluoroquinolone) of concomitant antibiotics that each patient received.

Data Analysis

Characteristics of patients with and without recurrences were compared using χ^2 or Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests for continuous, nonnormally distributed variables. Characteristics that were associated with recurrence ($P < .20$) on bivariate analysis, and those identified from the literature as important predictors of recurrence in pediatric patients were considered for inclusion in a final multivariable model. Multivariable logistic regression modeling was used to predict first recurrence as a function of patient characteristics. Because of the small number of events, we eliminated from the model any variables that did not significantly contribute to the prediction of recurrent CDI based on the likelihood ratio test using manual backward elimination. We conducted an exploratory analysis of the impact of concomitant antibiotic exposure on the risk of recurrence. Three separate models were constructed in which various measures of concomitant antibiotic use (ie, any concomitant antibiotic receipt, at least 3 days of concomitant antibiotic receipt, number of antibiotics, class, and duration) were entered along with the other variables identified from the final model.

To assess the impact of possible misclassification of case status due to our inability to assess for symptoms, we conducted a sensitivity analysis using patients with a positive *C difficile* laboratory result and an *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis for CDI. The use of ICD-9 codes with laboratory results has shown to be a reliable and accurate method for identifying pediatric patients with CDI according to Shaklee et al.[15] In the sensitivity analysis, patients who did not have an ICD-9 diagnosis code for CDI and a positive laboratory result were removed from the sample population. All statistical analyses were then repeated on the patients who met the stricter case definition.

The predictive ability of the model (discrimination) was assessed using the *c* statistic, and the model fit (calibration) was assessed using the Hosmer-Lemeshow goodness-of-fit statistic. Variance inflation factors were used to evaluate the potential for multicollinearity between predictors, and variance inflation factors <10 were considered to indicate lack of serious multicollinearity.[16] Unless otherwise specified, statistical analyses were performed in SAS V9.3 (SAS Institute, Cary, NC) assuming a 2-sided α of .05.

RESULTS

From January 1, 2003, to December 31, 2010, there were 1143 unique incident episodes of CDI from patients with a hospitalization at PCH. After selection of the first qualifying hospitalization and exclusion of the patients younger than 1 year, 612 unique inpatients with incident episodes of CDI remained. Of those, 65 (10.6%) patients experienced at least 1 recurrence. Recurrent infection developed during the index admission in 4 (6.2%) of the patients.

The demographic and clinical characteristics of patients with and without recurrence are demonstrated in Table 1. The median (interquartile range) age of patients in the study was 4.8 (9.3) years, and patients with recurrence tended to be older than patients without recurrence (7.2 vs 4.6 years, $P = .16$). Nearly half of the initial episodes were community acquired CDI, but more patients with hospital-acquired CDI had recurrences than community acquired (46.2% vs 29.2%, $P = .01$). Malignancy was present in 200 (33%) patients of the study population diagnosed with the first incident of CDI, and 74% had at least 1 complex chronic condition (CCC). On bivariate analysis, patients with a malignancy and any CCC were 3.9 (95% confidence interval [CI]: 2.3–6.6) and 8.5 (95% CI: 2.6–27.4) times more likely to experience recurrence, respectively. Approximately 40% of all patients in the study received any non–CDI concomitant antibiotics during the CDI treatment period. Patients who received non-CDI antibiotics at any time during CDI treatment were 4.9 times (95% CI: 2.1–11.5) more likely to experience recurrence than those that did not. The most common non-CDI antibiotics received were aminoglycosides (17.3%), cephalosporins (14.4%), intravenous vancomycin (13.6%), and penicillins (12.6%).

In the final multivariable logistic regression model (Table 2), any CCC (adjusted odds ratio [aOR]: 4.0, 95% CI: 1.2–13.9, $P = .02$), malignancy (aOR: 2.3, 95% CI: 1.3–4.0, $P = .004$), or concomitant antibiotics received during treatment (aOR: 2.8, 95% CI: 1.2–6.9, $P = .02$) were independently associated with recurrent CDI. The *c* statistic was 0.734, and the Hosmer-Lemeshow test had a *P* value of .321.

A subanalysis was conducted on the associations between various classifications of concomitant antibiotic exposures and the risk of recurrent CDI as a target for antimicrobial stewardship. The results of that subanalysis are presented in Table 3. When we restricted the definition of concomitant antibiotics to include only those courses lasting ≥3 days, patients who received concomitant antibiotics were 2.2 times more likely to develop recurrence (95% CI: 1.3–3.7, $P = .03$). However, using the stricter definition of receipt of at least 3 days of concomitant antibiotics was no longer an independent risk factor after adjusting for the effects of any CCC and malignancy. Patients who received ≥4 different concomitant agents of at least 3 days each were at a 2.4-fold increased risk for recurrence compared with patients who did not receive any concomitant antibiotics (95% CI: 1.1–5.5, $P = .04$) even after adjusting for malignancy and any complex chronic condition. Vancomycin intravenous (OR: 2.3, 95% CI: 1.3–4.3), aminoglycosides (OR: 1.9, 95% CI: 1.1–3.6), cephalosporins (OR: 2.2, 95% CI: 1.2–3.9), and sulfamethoxazole/trimethoprim (OR: 3.4, 95% CI: 1.8–6.6) were associated with an increased risk of recurrence on bivariate analysis, but these did not remain significant in the final multivariable model.

We conducted a sensitivity analysis requiring a positive *C difficile* laboratory result and an ICD-9 code during admission for a case definition of CDI. The analysis showed that chronic comorbid conditions and malignancy still increased the risk of recurrent CDI (OR: 3.7, 95% CI: 1.1–13.3, OR: 2.1, 95% CI: 1.1–4.0, respectively). Non-CDI antibiotics received during CDI

TABLE 1 Demographic and Clinical Characteristics of 612 Inpatients, With and Without Recurrent CDI at PCH, 2003–2010

	Patients With Recurrence		Patients Without Recurrence		Unadjusted OR (95% CI)	*P*
	n or Age	% (or IQR)	*n* or Age	% (or IQR)		
Total	65	10.6	547	89.4		
Median age, y (IQR)	7.2	(10.4)	4.6	(8.8)	1.0 (0.9–1.1)	.16
Race						
Other	10	15.4	48	8.8	1.9 (0.9–3.9)	.09
Hispanic/Latino	4	6.2	43	7.9	0.8 (0.3–2.4)	.73
White, non-Hispanic	51	78.5	456	83.4	1.0 (Ref)	
Gender						
Male	33	50.8	276	50.5	1.0 (0.6–1.7)	.96
Female	32	49.2	271	49.5	1.0 (Ref)	
Epidemiologic classification						
Health care associated, community onset	16	24.6	75	13.7	3.0 (1.5–6.2)	.002
Hospital acquired	30	46.2	201	36.8	2.1 (1.7–3.9)	.014
Community acquired	19	29.2	271	49.5	1.0 (Ref)	
Any CCC	62	95.4	388	70.9	8.5 (2.6–27.4)	<.001
Antibiotics received during CDI treatment	59	90.8	366	66.9	4.9 (2.1–11.5)	<.001
Malignancy	40	61.5	160	29.3	3.9 (2.3–6.6)	<.001
History of CDI	5	7.7	27	4.9	1.6 (0.6–4.3)	.35
Acid-suppressive therapy						
Proton pump inhibitor	30	46.2	202	36.9	1.5 (0.9–2.5)	.15
Histamine-2 receptor blocker	26	40	221	40.4	0.9 (0.6–1.7)	.95
Initial CDI treatment						
Metronidazole	58	89.2	408	74.6		
Vancomycin	0	0	4	0.7		
Combination	1	1.5	18	3.3		
Other treatment group	0	0	29	5.3		
No initial treatment	6	9.2	88	16.1		

IQR, interquartile range.

treatment was no longer statistically significantly associated (OR: 1.8, 95% CI: 0.7–5.1).

DISCUSSION

In this 8-year study, 10.6% of pediatric inpatients with CDI experienced a recurrent infection within 60 days. We found multiple risk factors associated with increased risk for recurrence, including the presence of any CCC, malignancy, and the receipt of concomitant non-CDI antibiotics for any duration during CDI treatment.

Our results add to the understanding of CDI recurrence in children and are largely in agreement with the results of 2 other recent studies.[6,9] Consistent with our understanding of risk factors for recurrent disease among adults, sicker patients and those with diminished immune function are more susceptible to recurrence. In our study, the presence of any CCC was associated with a four-fold increase in risk, and patients with malignancy were more than twice as likely to develop recurrence as patients without malignancies. Our results are supported by a study by Nicholson et al,[9] which demonstrated that malignancy increased the risk by 3.4 times.

The first recommendation in the guidelines for treatment of CDI is to discontinue other antibiotic use, if possible.[17] In our study, 69% of all patients received a concomitant antibiotic at any time during their CDI regimen. We also found that patients who received concomitant antibiotics were almost 3 times more likely to experience a recurrence than patients who received no other antibiotics during CDI treatment. Our results are consistent with existing evidence. Tschudin-Sutter et al and Nicholson et al reported concomitant antibiotic use rates of 52% and 80%, respectively. Concomitant antibiotic use was associated with a significant increase in the risk of recurrence in both studies.[6,9]

Using the restrictive definition of ≥3 days of antibiotics during CDI treatment, while hospitalized, we found that exposed patients were 1.5 times more likely to have a recurrence compared with patients without any concomitant antibiotics after adjusting for CCCs and malignancy. This value was not statistically significant. The reference group was also hospitalized. The association between concomitant antibiotics would be due to the exposure and length of hospital

TABLE 2 Final Multivariable Logistic Regression Model

	Adjusted OR (95% CI)	*P*
Any CCC	4.0 (1.2–13.9)	.02
Antibiotics received during CDI treatment	2.8 (1.2–6.9)	.02
Malignancy	2.3 (1.3–4.0)	.004

stay would not be a confounder for recurrence.

Increasing the number of concomitant antibiotics received was associated with an increased risk of recurrence. Patients who received 1 to 3 concomitant antibiotics were 1.8 times more likely to have a recurrence. Risks increased by as much as 4.6 times if ≥4 concomitant antibiotics were received for >3 days each during treatment. These values were statistically significant. Our results are similar to what Nicholson et al found, which was a 30% increase in the risk of recurrence for each additional antibiotic class received.[9] On bivariate analysis of the effects of concomitant antibiotic classes, sulfamethoxazole/trimethoprim, vancomycin, cephalosporins, and aminoglycosides were all associated with an increased risk of recurrence; however, these classes did not remain independently associated with recurrence in the multivariable model, possibly because of limited power.

Our study did not find a statistically significant association between the use of acid-suppressive therapy and recurrence. A recent study by Nylund et al showed an increased risk of recurrence with proton pump inhibitors and histamine-2 blocker.[4] Their study used a different definition of recurrence compared with our study, which may explain the discrepancies between their study and ours.

This study has several limitations. It is a retrospective single-center study and may not be representative of CDI from other geographic regions. Our study was able to follow all patients admitted to PCH for CDI that had an outpatient laboratory at another IHC facility. However, we were unable to follow a patient cared for outside of an IHC facility. Our study was only able to evaluate concomitant antibiotics during the inpatient stay, which may result in nondifferential misclassification of concomitant antibiotic exposure status and therefore underestimate the actual risk of recurrent CDI associated with concomitant antibiotics.

TABLE 3 Analysis of Antibiotics as a Risk Factor for Recurring CDI

	Unadjusted OR (95% CI)	aOR[a] (95% CI)	*P*
CAs received	2.2 (1.3-3.7)	1.5 (0.9-2.6)	.14
No. CA received			
5	1.7 (0.2-14.6)	0.9 (0.1-7.6)	.91
4	7.2 (3.0-17.1)	3.7 (1.5-9.2)	.004
3	2.2 (0.9-5.3)	1.4 (0.5-3.4)	.51
2	1.9 (0.9-3.8)	1.5 (0.7-3.0)	.32
1	1.5 (0.6-3.5)	1.1 (0.5-2.7)	.82
0	1.0 (Ref.)	1.0 (Ref.)	
Class of CA received			
Penicillin β-lactamase inhibitor	2.2 (0.8-6.1)	3.1 (0.9-10.3)	.07
Clindamycin	2.5 (0.5-12.0)	2.8 (0.5-16.4)	.25
Sulfamethoxazole/trimethoprim	3.4 (1.8-6.6)	1.7 (0.8-3.7)	.15
Cephalosporin	2.2 (1.2-3.9)	1.4 (0.7-2.8)	.07
Vancomycin	2.3 (1.3-4.3)	1.0 (0.5-2.2)	.91
Aminoglycoside	1.9 (1.1-3.6)	0.9 (0.4-2.0)	.88

CAs, concomitant antibiotics.
[a] Multivariable model included the variables "malignancy" and "any CCC."

Our study was also limited by our inability to assess the presence of diarrhea among patients, which may result in misclassification of CDI. However, the misclassification of CDI is unlikely to be differential by exposure status (ie, concomitant antibiotic exposure), which would result in a conservative estimate of the relationship between concomitant antibiotics and the risk of recurrence. In addition, the rates of recurrence in our study were consistent with the observations of 2 other studies conducted at single institutions that included CDI diagnosis as a positive *C difficile* laboratory and presence of diarrhea. Suggesting that misclassification resulting from lack of symptom data may not have a large impact on study results.[6,9] To further investigate this possibility; we also conducted a sensitivity analysis using positive *C difficile* laboratory results and an *ICD-9* diagnosis for CDI. The analysis found chronic comorbid conditions and malignancy were still significantly associated with recurrent CDI. However, the risk associated with non-CDI antibiotics received during CDI treatment was attenuated. The risk with non-CDI antibiotics was still elevated but no longer statistically significant in this analysis, likely as a result of reduced power.

Our study was limited by the type of diagnostic assay used in the microbiology laboratory during the study period. Enzyme immunoassay and cell culture cytotoxicity assay have not been shown to be as sensitive as nucleic acid amplification PCR testing.[18] However, these testing methods were used consistently across the study period and would likely have underestimated our rate of CDI. An insufficient number of patients receiving vancomycin limited our ability to conduct a rigorous comparative effectiveness analysis to evaluate the potential impact of treatment choice on the risk of recurrence.

Our study also has several notable strengths. This study had a larger sample size than previously conducted studies and because of that was able to capture more episodes of recurrence during the study period. To the best of our knowledge, this is 1 of the few existing studies, and now the

largest, to evaluate risk factors for recurrent CDI among pediatric patients. Our results provide support for previous work and serve as a foundation for larger studies in the future.

CONCLUSIONS

During an 8-year study period, CDI recurred in ∼11% of pediatric inpatients. Any CCC, malignancy, and non-CDI antibiotics received for any duration during CDI treatment were found to be independent predictors for recurrence. Antimicrobial stewardship efforts focused on limiting the use of non-CDI antibiotics during CDI treatment may reduce the risk of recurrent infection. Additional research is needed to evaluate risk factors of recurrent CDI in pediatric populations where symptoms of the study population are known and nucleic acid amplification diagnostic testing data are available.

REFERENCES

1. Bartlett JG. Clostridium difficile: history of its role as an enteric pathogen and the current state of knowledge about the organism. *Clin Infect Dis*. 1994;18(suppl 4):S265–S272
2. Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the burdens of hospital-onset, healthcare facility-associated *Clostridium difficile* Infection and of healthcare-associated infection due to methicillin-resistant *Staphylococcus aureus* in community hospitals. *Infection Control & Hospital Epidemiology*. 2011;32(4):387–390
3. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of *Clostridium difficile*–associated disease among inpatients at children's hospitals in the United States, 2001–2006. *Pediatrics*. 2008;122(6):1266–1270
4. Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. *Clostridium difficile* infection in hospitalized children in the United States. *Arch Pediatr Adolesc Med*. 2011;165(5):451–457
5. Mandell GL, Douglas RG, Bennett JE. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 4th ed. New York, NY: Churchill Livingstone; 1995
6. Tschudin-Sutter S, Tamma PD, Milstone AM, Perl TM. Predictors of first recurrence of *Clostridium difficile* infections in children. *Pediatr Infect Dis J*. 2014;33(4):414–416
7. Khanna S, Baddour LM, Huskins WC, et al. The epidemiology of *Clostridium difficile* infection in children: a population-based study. *Clin Infect Dis*. 2013;56(10):1401–1406
8. Kim J, Shaklee JF, Smathers S, et al. Risk factors and outcomes associated with severe *Clostridium difficile* infection in children. *Pediatr Infect Dis J*. 2012;31(2):134–138
9. Nicholson MR, Thomsen IP, Slaughter JC, Creech B, Edwards KM. Novel risk factors for recurrent *Clostridium difficile* infection in children. *J Pediatr Gastroenterol Nutr*. 2015;60(1):18–22
10. Fekety R, McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Mulligan ME. Recurrent *Clostridium difficile* diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. *Clin Infect Dis*. 1997;24(3):324–333
11. Abou Chakra CN, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in *Clostridium difficile* infection: a systematic review. *PLoS One*. 2014;9(6):e98400
12. Garey KW, Sethi S, Yadav Y, DuPont HL. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. *J Hosp Infect*. 2008;70(4):298–304
13. Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980–1997. *Pediatrics*. 2000;106(1 pt 2):205–209
14. Rupnik M, Wilcox MH, Gerding DN. *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. *Nat Rev Microbiol*. 2009;7(7):526–536
15. Shaklee J, Zerr DM, Elward A, et al. Improving surveillance for pediatric *Clostridium difficile* infection: derivation and validation of an accurate case-finding tool. *Pediatr Infect Dis J*. 2011;30(3):e38–e40
16. Craney TA, Surles JG. Model-dependent variance inflation factor cutoff values. *Qual Eng*. 2002;14(3):391–403
17. 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). *Infection Control & Hospital Epidemiology*. 2010;31(5):431–455
18. Longtin Y, Trottier S, Brochu G, et al. Impact of the type of diagnostic assay on *Clostridium difficile* infection and complication rates in a mandatory reporting program. *Clin Infect Dis*. 2013;56(1):67–73

Risk Factors for Recurrent *Clostridium difficile* Infection in Pediatric Inpatients

Elyse M. Schwab, Jacob Wilkes, Kent Korgenski, Adam L. Hersh, Andrew T. Pavia and Vanessa W. Stevens

Hospital Pediatrics 2016;6;339
DOI: 10.1542/hpeds.2015-0170 originally published online May 4, 2016;

Hospital Pediatrics®

AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Risk Factors for Recurrent *Clostridium difficile* Infection in Pediatric Inpatients

Elyse M. Schwab, Jacob Wilkes, Kent Korgenski, Adam L. Hersh, Andrew T. Pavia and Vanessa W. Stevens

Hospital Pediatrics 2016;6;339
DOI: 10.1542/hpeds.2015-0170 originally published online May 4, 2016;