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ORIGINAL RESEARCH

Predictors of *Clostridium difficile* Infections in Hospitalized Children

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BACKGROUND: Recent studies report an increasing incidence of *Clostridium difficile* infections (CDIs) in children and suggest that CDIs may occur outside known populations at risk.

OBJECTIVE: To identify clinical factors associated with CDI in a hospitalized pediatric population.

METHODS: A retrospective case-control study was conducted with C difficile cases (CD) and controls (CTLs) in hospitalized children over a 2-year period. CDs (N = 134) and 2:1 age-matched CTLs (N = 274) with diarrheal illness were evaluated.

RESULTS: CDs and CTLs were similar in gender and race. Watery diarrhea was the most common type of diarrhea in CDs and CTLs. Immunodeficiency (46% vs 6%; P < 0.001), gastrointestinal (GI) disease (31% vs 18%; P = 0.005), and proton pump inhibitor (PPI) use (22% vs 7%; P < 0.001) were more frequent in CDs. Of CDs, 30% were defined as community acquired. Bloody diarrhea was more frequent in community-acquired CD (28% vs 4% P < 0.001); however, other clinical variables were not statistically different. No antibiotic exposure, recent hospitalization, prolonged hospitalization, or past history of CDI existed in 8% of CDs. Multivariate logistic regression demonstrated that antibiotic use (odds ratio [OR]: 2.80, P = 0.001), recent hospitalization (OR: 2.33, P = 0.007), and immunodeficiency (OR: 6.02, P < 0.001) were significantly associated with cases when controlling for PPI use, having GI disease, and history of abdominal surgery.

CONCLUSIONS: Clinical history is of greater value than symptoms in distinguishing CD, with immunodeficiency having the strongest association. An important percentage of CDs did not have any risk factors, confirming concerns that CDIs do occur in otherwise low-risk pediatric populations *Journal of Hospital Medicine* 2014;9:94–98. © 2013 Society of Hospital Medicine

Clostridium difficile is the single most common cause of nosocomial diarrhea in both adults and children.[1,2] *C difficile* infections (CDIs) can range from self-limited diarrhea to severe pseudomembranous colitis. Though widely distributed in the environment, hospitals and child care facilities are major reservoirs for *C difficile*. Traditionally, hospitalization and antibiotic use have been the 2 major risk factors for acquiring CDI.

Recent studies suggest *C difficile* epidemiology is shifting. In 2005, the Centers for Disease Control and Prevention (CDC) reported CDIs in 33 otherwise low-risk patients, 6 of whom were children.[3] Other studies have noted increasing incidence of pediatric CDIs,[4–7] 1 identifying 43% with no prior antibiotic use.[4] This emerging data led to the recent American Academy of Pediatrics policy statement on pediatric CDIs.[8] Data regarding associated clinical risk factors of CDIs in pediatric patients in light of the changing epidemiology are limited. Only 1 recent study looked at 6 clinical factors and found that antibiotic use, history of solid organ transplantation, gastrointestinal (GI) devices, and acid suppressing medications increased risk for CDIs.[9]

Data regarding the source of these infections are also limited. Three pediatric studies evaluating source found a significant amount of community-acquired disease (59%, 25%, and 19% of the study population, respectively).[4,9,10] However, only 1 of these studies provided clinical comparisons between community and hospital-acquired cases.[10] To date, no study has examined a comprehensive list of potential risk factors that might differentiate hospitalized pediatric patients with CDIs from those with acute gastroenteritis (AGE).

PATIENTS AND METHODS

We conducted an investigator-initiated, retrospective, case-control study examining risk factors associated with CDIs in a hospitalized pediatric population at Rady Children's Hospital San Diego (RCHSD). Rady Children's is a tertiary-care pediatric healthcare system and the sole pediatric referral center for San Diego, with a catchment of 850,000 children. RCHSD posts over 71,000 emergency department (ED) and 30,000 urgent care (UC) visits at 4 sites and over 15,000 admissions yearly. All system information is archived in 1 electronic database. We reviewed patient records for a 2-year period from June 1, 2008 through

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May 31, 2010. The study protocol was reviewed and approved by the institutional review board at the University of California San Diego.

Cases of *C difficile* (CDs) included pediatric patients ≤18 years of age with all of the following: International Classification of Diseases, 9th Revision (ICD-9) code for *C difficile* infection (08.45), a positive *C difficile* toxin A or B by enzyme immunoassay (EIA) (Meridian Bioscience, Inc., Cincinnati, OH), and the presence of diarrhea and/or abdominal pain. Randomly selected age-matched controls from the same time period with a discharge diagnosis of AGE (APR-DRG 249) and the presence of diarrhea served as controls (CTLs). In the ≤1 year age group, any patient with a positive *C difficile* toxin assay but no diagnosis of CDI was excluded from the CTL group to avoid potential confounding.

Records were reviewed for multiple potential risk factors based on limited past studies and other factors associated with CDI pathogenesis including age, race, ethnicity, antibiotic use within the previous 90 days (type, route, and duration), diarrhea type, abdominal pain, fever, proton pump inhibitor (PPI) use, sick contacts (diarrheal illness), recent travel, and hospitalization within the last 6 months. Diarrhea was defined as increase in stool frequency or volume. Past medical/surgical history abstracted included GI disease, past CDIs, abdominal surgery, immunodeficiency, renal disease, cardiac disease, nutritional deficiencies, and number of past hospitalizations (all cause). In addition, multiple factors during the hospital course were reviewed: length of stay (LOS), antibiotic therapy, diarrhea type, abdominal pain, fever, electrolyte levels, need for stool replacement fluid, and altered diet recommendations. Thirty-day return to ED/UC or readmission and cause for the return were also retrieved on all patients. An objective data collection form was used, and all records were reviewed by 1 researcher (W.S.) with a second reviewer (E.F.) reviewing 20% of the charts, with 90% initial concordance. Consensus was reached on all elements abstracted.

Three additional subanalyses were completed. The first subanalysis compared antibiotic prophylaxis (defined as daily use of an antibiotic for >28 days) in CDs versus CTLs. We reviewed charts to ensure extended antibiotic use was for prophylaxis and not treatment. The second subanalysis compared CDs to those CTLs with a negative *C difficile* toxin assay. This was done to evaluate whether using this control group would highlight a different set of risk factors. The third subanalysis separated CDs into community-acquired CD (CA-CD) and hospital-acquired CD (HA-CD). We defined CA-CD as any patient with symptoms either prior to or within the first 48 hours of the index admission and no past hospitalizations or with the last hospitalization >4 weeks prior to the index admission. Patients who developed symptoms at home or within 48 hours of the index admission, but had been hospitalized within the past 4 weeks, were defined as community-onset HA-CD. Patients who developed CDIs after 48 hours of the index admission were defined as hospital-onset HA-CD. These groupings are consistent with the CDI surveillance recommendations.[11]

All statistical analyses were performed with SPSS statistical software version 21.0 (SPSS Inc., Chicago, IL). Initial comparisons between CDs and CTLs were conducted using *t* tests for continuous variables and χ^2 tests for categorical variables. As CDI in infants is controversial, we analyzed our data with and without this cohort to eliminate extraneous, age-related differences. After confirming that there were no issues with tolerance among possibly related factors, a saturated multiple logistic regression model was used to determine which of the independent variables identified in the initial comparison were predictors of having *C difficile* when controlling for factors associated with chronic disease.

RESULTS

Descriptive characteristics of the 134 CDs and the 274 CTLs are provided in Table 1. CDs and CTLs were similar in gender and race. More CDs had recent hospitalization and antibiotic exposure, with 24% of CDs versus 3% of CTLs treated with 2 or more antibiotics. Watery stools were the most common type of diarrhea in both CDs and CTLs, and bloody stools did not differ significantly between the 2 groups. However, abdominal pain on admission was more common in CTLs. CDs were more likely to have a history of GI disease, abdominal surgery, and specifically GI surgery. Immunodeficiency and PPI use were far more frequent in CDs, whereas exposure to sick contacts was more common in CTLs. Although CDs had an overall higher rate of ED/UC return visits and readmissions, the rate of return due to GI symptoms was similar in both groups. Reanalysis of the data with the <1-year cohort removed showed persistent statistically significant findings in these variables. Hospital course, including electrolyte levels, need for intravenous fluids, or modified diets, did not significantly differ between CDs and CTLs (data not shown).

Analysis of CDs without traditional risk factors was performed. To identify patients, we first selected the 46 (34%) without prior antibiotic exposure, then eliminated 19 who had been hospitalized within the past 6 months. Of the remaining 27 patients, 16 had a prolonged hospitalization (>5 days) at the time of CDI diagnosis. This left us with 11 patients (8% of CDs) without any common risk factors of antibiotic use, recent hospitalization, or prolonged hospitalization. None of these patients had a history of CDIs; 6 had significant medical histories. A detailed description of these 11 patients if provided in Table 2.

The first subanalysis evaluated antibiotic prophylaxis and found 51 (37%) in CDs versus 10 (4%) in CTLs. However, after controlling for immunodeficiency found in 40 of these CDs, we found no statistically significant

TABLE 1. Descriptive Characteristics of *Clostridium difficile* Cases and Controls

Characteristics	Cases, N = 134 (%)	Controls, N = 274 (%)	*P* Value
Age, y			
<1	28 (21)	58 (21)	
≥1–4	50 (37)	100 (37)	
≥5–9	21 (17)	44 (16)	
≥10	35 (26)	72 (26)	
Sex, male	68 (51)	141 (52)	
Race			
White	63 (46)	110 (40)	
Black	6 (4)	18 (7)	
Asian	11 (8)	15(6)	
Other	50 (37)	123 (45)	
Ethnicity, Hispanic	70 (52)	85 (31)	<0.001
Diarrhea*			
Admission	50 (37)	229 (83)	<0.001
Bloody	13/50 (26)	29/229 (13)	
Watery	37/50 (74)	200/229 (87)	
Hospitalization	128 (95)	185 (68)	<0.001
Bloody	16/128 (13)	10/185 (5)	
Watery	112/128 (88)	175/185 (95)	
Abdominal pain, admission	30 (23)	111 (41)	<0.001
PPI use	29 (22)	18 (7)	<0.001
Antibiotic use			
Past 90 days	88 (66)	55 (20)	<0.001
>2 antibiotics	32 (24)	9 (3)	<0.001
Antibiotic type			
Penicillin	10 (11)	19 (7)	0.84
Cephalosporins	29 (21)	19 (7)	<0.001
Sulfa	50 (37)	12 (4)	<0.001
Prophylaxis	51 (37)	10 (4)	<0.001
Sick contacts	4 (3)	52 (19)	<0.001
Hospitalization past 6 months	88 (66)	52 (19)	<0.001
Past CDI	12 (9)	8 (4)	0.013
GI disease†	41 (31)	50 (18)	0.005
Immunodeficiency‡	61 (46)	17 (6)	<0.001
Abdominal surgery§	41 (31)	43 (16)	0.001
GI surgery§	32 (24)	36 (13)	0.01
Return††	41 (31)	37 (14)	<0.001
Due to GI symptoms	12 (9)	22 (8)	0.85

NOTE: **Abbreviations:** CDI, *Clostridium difficile* infection; GI, gastrointestinal; PPI, proton pump inhibitor.

*Diarrhea was categorized as "bloody" if there was any mention of blood by patient, family, or staff.

†GI disease includes inflammatory bowel disease, hepatic disorders, motility disorders, and celiac disease.

‡Immunodeficiency includes those with immunosuppression due to malignancy, congenital syndromes, and chronic steroid use.

§Abdominal surgery includes all incisions into abdominal cavity; GI surgery is limited to incision into the bowel.

††Return to the emergency department or readmission to the hospital.

difference. There were insufficient numbers of those on prophylaxis for other reasons (eg, vesicoureteral reflux) to analyze prophylaxis independently.

The second subanalysis compared controls with a negative *C difficile* toxin assay (21% of CTLs) to CDs on a number of clinical factors. Results were compared to the primary analysis. Many factors remained significant: antibiotic use in the past 90 days was still more frequent in CDs (66% vs 35%, $P < 0.001$) as was immunodeficiency in CDs (46% vs 14%, $P < 0.001$). However, immunodeficiency in this subset of the controls was represented over twice as often as that of the baseline CTLs (14% vs 6%), whereas GI disease was similar between the 2 groups (37% vs 31%, $P < 0.40$). PPI use demonstrated a suggestive relationship (22% vs 11%, $P < 0.07$).

Data for the third subanalysis between CA-CD and HA-CD are shown on Table 3. We initially compared CA-CD, community-onset HA-CD, and hospital-onset HA-CD. However, when stratification was found to not be significant, we combined both categories of HA-CD into 1 group. CA-CD and HA-CD did not demonstrate significant difference in antibiotic use, type, prophylaxis, history of abdominal surgery, immunodeficiency, or GI disease. Bloody stools were more common in CA-CD.

Odds ratio (OR) was calculated for association of individual risk factors for disease between CDs and CTLs (Table 4). Our model controlled for antibiotics use in the past 90 days, PPI use, treatment with 2 or more antibiotics, recent hospitalization, past history of CDIs, history of GI disease, history of abdominal surgery, and being immunodeficient. Antibiotic use within the past 90 days (OR: 2.80, $P = 0.001$), recent hospitalization (OR: 2.33, $P = 0.007$), and immunodeficiency (OR: 6.02, $P < 0.001$) were associated with having *C difficile*. A similar logistic regression was conducted using a model comparing community- and hospital-acquired cases, but no difference was found among risk factors.

DISCUSSION/CONCLUSION

Our study shows that in addition to traditional risk factors of antibiotic use and recent hospitalization, immunodeficiency is a significant key factor associated with the diagnosis of CD. We found that traditional risk factors are not present in all hospitalized pediatric patients with CD. Our study does not support routine testing for *C difficile* in patients with diarrhea; however, it does suggest testing children with persistent or severe diarrheal symptoms even if traditional risk factors are absent, especially in the presence of immunodeficiency. The intervals we used for antibiotic exposure (past 90 days) and recent hospitalization (past 6 months) were longer compared to other studies,[9,12] making our findings even more meaningful. Although some of the 11 patients without traditional risk factors had the presence of clinical factors shown in previous studies to be more common in patients with CDIs (GI disease, GI surgery, gastric tube/nasogastric feeding),[12,13] we still find 4 patients >1 year of age with CDIs and no risk factors. This echoes the CDCs concerns of CDIs in low-risk patients.[3]

Unlike clinical history, we found clinical symptoms and basic electrolyte testing may not help to distinguish CD from AGE patients. Although abdominal pain and diarrhea on admission were significantly more common in CTLs, when including abdominal pain and diarrhea during hospitalization, this finding was no longer valid. Additionally, although overall

TABLE 2. Cases Without History of Antibiotics Use, Past or Prolonged Hospitalization, or History of Past Infection

Case No.	Age, y	Sex	Symptom Development*	Bloody Diarrhea	Past Medical History
37	≥10	Female	0	Present	None
49	≥1–4	Female	0	None	History of bowel perforation, prior bowel resection, GT
63	≥10	Female	0	None	Status post-renal transplant on antivirals only
97	≥1–4	Male	0	None	Polycystic kidney disease, on nasogastric feeds
98	<1	Male	2–5 days	None	Congenital heart disease
101	<1	Male	2–5 days	None	None
102	≥10	Male	2–5 days	None	Neurofibromatosis type 2, GT
107	≥5–9	Female	0	Present	None
108	≥10	Male	0	None	Cerebral palsy, GT
116	≥1–4	Female	2–5 days	None	None
126	≥10	Female	1–2 days	None	None

NOTE: **Abbreviations:** GT, gastric tube.

*When symptoms developed in relation to index admission; 0 = symptoms developed at home.

return rate was higher for CDs, the return rate for GI symptoms specifically was not different. The former was instead most often due to complications associated with comorbid conditions (GI disease, immunodeficiency). We did assess LOS for both CDs and CTLs; however, due to the high percentage of CDs with malignancy and other severe illnesses, it was difficult to ascertain the effect of CDIs on LOS. Severe CD is described as admission to the intensive care unit due to *C difficile* complications, colectomy, and death secondary to *C difficile*.[11] Although our study did not look at severe CDI as a direct outcome, we did not have any cases of colectomy or death secondary to CDI.

Two recent studies[9,14] showed a high percentage of acid suppression medication use in patients with CDIs, with 1 study reporting 60% using PPIs and 21% using histamine blockers. Our study initially found similar high levels of PPI use among patients with CDIs; however, no significance was found when controlling for chronic disease. Prescriptions of PPIs for pediatric patients have risen dramatically recently,[15] as have reported all-cause complications.[16]

TABLE 3. Comparison of Community-Acquired and Hospital-Acquired Cases

Characteristics	Community-Acquired Cases, N = 40, No. (%)	Hospital-Acquired Cases, N = 94, No. (%)	*P* Value
Age, y			
<1	4 (10)	24 (26)	
≥1–4	17 (43)	33 (35)	
≥5–9	4 (10)	18 (19)	
≥10	15 (38)	20 (21)	
Sex, male	19 (48)	49 (52)	0.71
Race, white	19 (48)	44 (47)	0.99
Ethnicity, Hispanic	21 (53)	49 (52)	0.99
Bloody diarrhea	11 (28)	4 (4)	<0.001
Abdominal pain	17 (43)	24 (26)	0.07
PPI use	12 (30)	17 (18)	0.17
Antibiotic use	27 (68)	61 (65)	0.84
≥2 antibiotics	9 (23)	23 (24)	0.99
Antibiotic type			
Penicillin	4 (10)	6 (6)	0.49
Cephalosporin	8 (20)	21 (22)	0.82
Sulfa	12 (30)	38 (40)	0.33
Prophylaxis	12 (30)	39 (41)	0.14
Hospitalization, past 6 months	17(43)	71 (76)	<0.001
Past CDI	5 (13)	7 (7)	0.34
GI disease*	16 (40)	25 (26)	0.15
Immunodeficiency†	14 (35)	47 (51)	0.13
Past abdominal surgery	15 (38)	26 (27)	0.31

NOTE: **Abbreviations:** CDI, *Clostridium difficile* infection; GI, gastrointestinal; PPI, proton pump inhibitor.

*GI disease includes inflammatory bowel disease, hepatic disorders, motility disorders, and celiac disease.

†Immunodeficiency includes those with immunosuppression due to malignancy, congenital syndromes, and chronic steroid use.

TABLE 4. Association of Individual Risk Factors With Disease

	Odds Ratio	*P* Value
Variable		
Antibiotic use (90 days)	7.69	<0.001
Proton pump inhibitors	4.17	<0.001
>2 antibiotics	9.26	<0.001
Hospitalization, past 6 months	8.20	<0.001
History CDI	3.27	0.012
Gastrointestinal disease*	1.98	0.005
Immunodeficiency†	12.66	<0.001
History abdominal surgery	2.37	0.001
Saturated logistic regression model		
Antibiotics (90 days)	2.80	0.001
Proton pump inhibitors	2.06	0.068
>2 antibiotics	2.23	0.092
Hospitalization, past 6 months	2.33	0.007
History CDI	1.03	0.956
Gastrointestinal disease*	1.31	0.432
Immunodeficiency†	6.02	<0.001
History abdominal surgery	1.16	0.675

NOTE: **Abbreviations:** CDI, *Clostridium difficile* infection.

*Gastrointestinal disease includes inflammatory bowel disease, hepatic disorders, motility disorders, and celiac disease.

†Immunodeficiency includes those with immunosuppression due to malignancy, congenital syndromes, and chronic steroid use.

Further studies are needed to evaluate the independent risks of PPI use and CDIs in children. We were unable to analyze the influence of antibiotic use at prophylactic levels on CD rates, as the majority our CDs were on prophylaxis due to immunodeficiency.

Our study is unique in many ways. It is the first study to evaluate hospitalized pediatric patients with a comprehensive list of potential risk factors for CDIs, looking at clinical data on admission and during hospitalization. Additionally, as our site archives all clinical information in 1 database, we were able to identify ED/UC return and hospital readmissions. Although it is possible patients may have been evaluated outside of our healthcare system, this would be uncommon due to our referral patterns and UC sites. Our study used age-matched patients with diarrheal symptoms and AGE discharge diagnosis as the control group. This differs from the 1 previous study looking at risk factors for CDIs in children.[9] In that study, researchers used patients with negative *C difficile* toxin testing as controls. Our subanalysis of CTLs with a negative toxin assay found much higher rates of underlying GI disease and immunodeficiency. Whereas previous studies compared patients already at high risk for CDI and assessed the differences between those with and without the infection, our study looked at what clinical factors distinguish CDI from AGE in a hospitalized population.

Similar to other pediatric studies, our study found a significant number of CA-CD. However our study is 1 of the first to compare pediatric CA-CD with HA-CD based on clinical factors. Of the 9 demographic and clinical variables assessed, the only significant difference found was presence of bloody diarrhea. It may be that bloody diarrhea prompted the patients to be admitted as opposed to evaluated in the ambulatory setting.

Our study had some limitations. We used ICD-9 discharge diagnosis codes to identify our patients; however, thorough chart review found clinical indices (diarrhea and abdominal pain) that correlated well with CDI diagnosis in addition to positive laboratory test. The EIA *C difficile* toxin assay was the standard of care during our study period. However, a recent study has shown false positives using EIA testing in pediatric populations.[17] In our primary analysis, we did not exclude patients with a past history of CDIs. Recurrent CDI is defined as having symptoms within 8 weeks after the primary infection. Of our patients with a history of CDIs, only 2 met this definition. Due to the small number, excluding these patients would not have changed our results significantly. Last, as with any retrospective study, we relied on caregiver reports regarding clinical history, especially in the CA-CD cohort.

Based on our comprehensive analysis of pediatric patients, there should be increased suspicion for CDI in children with baseline immunodeficiency. Our study also supports testing children with persistent or severe GI symptoms even in the absence of traditional risk factors. These elements, coupled with history of antibiotic use, recent hospitalization, GI disease, and abdominal surgery could be used to create an assessment tool to assist clinicians in the diagnosis of CDIs in pediatric patients. A significant percentage of CDIs continues to be CA-CD. HA-CD and CA-CD patients have similar clinical features. Further studies are needed to determine the effect of PPI use and prophylactic antibiotics on CDIs in children.

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References

1. Dubberke ER, Gerding DN, Classen D, et al. Strategies to prevent clostridium difficile infections in acute care hospitals. *Infect Control Hosp Epidemiol*. 2008;29(suppl 1):S81–S92.
2. Langley JM, LeBlanc JC, Hanakowski M, Goloubeva O. The role of Clostridium difficile and viruses as causes of nosocomial diarrhea in children. *Infect Control Hosp Epidemiol*. 2002;23(11):660–664.
3. Centers for Disease Control and Prevention. Severe Clostridium difficile-associated disease in populations previously at low risk—four states, 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54(47):1201–1205.
4. Benson L, Song X, Campos J, Singh N. Changing epidemiology of Clostridium difficile-associated disease in children. *Infect Control Hosp Epidemiol*. 2007;28(11):1233–1235.
5. Zilberberg MD, Tillotson GS, McDonald C. Clostridium difficile infections among hospitalized children, United States, 1997–2006. *Emerg Infect Dis*. 2010;16(4):604–609.
6. 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.
7. Sammons JS, Toltzis P, Zaoutis TE. Clostridium difficile infection in children. *JAMA Pediatr*. 2013;167(6):567–573.
8. Schutze GE, Willoughby RE; Committee on Infectious Diseases; American Academy of Pediatrics. Clostridium difficile infection in infants and children. *Pediatrics*. 2013;131(1):196–200.
9. Sandora TJ, Fung M, Flaherty K, et al. Epidemiology and risk factors for Clostridium difficile infection in children. *Pediatr Infect Dis J*. 2011;30(7):580–584.
10. Tschudin-Sutter S, Tamma PD, Naegeli AN, Speck KA, Milstone AM, Perl TM. Distinguishing community-associated from hospital-associated Clostridium difficile infections in children: implications for public health surveillance. *Clin Infect Dis*. 2013;57(12):1665–1672.
11. McDonald LC, Coignard B, Dubberke E, et al. Recommendations for surveillance of Clostridium difficile-associated disease. *Infect Control Hosp Epidemiol*. 2007;28(2):140–145.
12. 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.
13. Kelsen JR, Kim J, Latta D, et al. Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(1):50–55.
14. Kim YG, Graham DY, Jang BI. Proton pump inhibitor use and recurrent Clostridium difficile-associated disease: a case-control analysis matched by propensity score. *J Clin Gastroenterol*. 2012;46(5):397–400.
15. Barron JJ, Tan H, Spalding J, Bakst AW, Singer J. Proton pump inhibitor utilization patterns in infants. *J Pediatr Gastroenterol Nutr*. 2007;45(4):421–427.
16. Tolia V, Boyer K. Long-term proton pump inhibitor use in children: a retrospective review of safety. *Dig Dis Sci*. 2008;53(2):385–393.
17. Toltzis P, Nerandzic MM, Saade E, et al. High proportion of false-positive Clostridium difficile enzyme immunoassays for toxin A and B in pediatric patients. *Infect Control Hosp Epidemiol*. 2012;33(2):175–179.