Reducing the risk of severe complications among patients with *Clostridium difficile* infection

Kamran Manek[1], Victoria Williams[1], Sandra Callery BScN MHSc CIC[1], Nick Daneman MD MSc FRCPC[1,2]

K Manek, V Williams, S Callery, N Daneman. Reducing the risk of severe complications among patients with *Clostridium difficile* infection. Can J Gastroenterol 2011;25(7):368-372.

BACKGROUND: The incidence and severity of *Clostridium difficile* infections are increasing, and there is a need to optimize the prevention of complicated disease.
OBJECTIVE: To identify modifiable processes of care associated with an altered risk of *C difficile* complications.
METHODS: A retrospective cohort study (with prospective case ascertainment) of all *C difficile* infections during 2007/2008 at a tertiary care hospital was conducted.
RESULTS: Severe complications were frequent (occurring in 97 of 365 [27%] *C difficile* episodes), with rapid onset (median three days postdiagnosis). On multivariable analysis, nonmodifiable predictors of complications included repeat infection (OR 2.67), confusion (OR 2.01), hypotension (OR 0.97 per increased mmHg) and elevated white blood cell count (OR 1.04 per 10^9 cells/L). Protection from complications was associated with initial use of vancomycin (OR 0.24); harm was associated with ongoing use of exacerbating antibiotics (OR 3.02).
CONCLUSION: *C difficile* infections often occur early in the disease course and are associated with high complication rates. Clinical factors that predicted a higher risk of complications included confusion, hypotension and leukocytosis. The most effective ways to improve outcomes for patients with *C difficile* colitis are consideration of vancomycin as first-line treatment for moderate to severe cases, and the avoidance of unnecessary antibiotics.

Key Words: Clostridium difficile; *Complications; Metronidazole; Risk factors; Vancomycin*

Réduire le risque de graves complications chez les patients ayant une infection à *Clostridium difficile*

HISTORIQUE : L'incidence et la gravité des infections à *Clostridium difficile* augmentent, et il est nécessaire d'optimiser la prévention des maladies complexes.
OBJECTIFS : Déterminer les processus modifiables de soins associés à une altération du risque de complications de *C difficile*.
MÉTHODOLOGIE : Les auteurs ont effectué une étude de cohorte rétrospective (comportant une évaluation prospective des cas) de toutes les infections à *C difficile* en 2007-2008 dans un hôpital de soins tertiaires.
RÉSULTATS : Les graves complications étaient fréquentes (se produisant dans 97 des 365 [27 %] épisodes de *C difficile*) et faisaient rapidement leur apparition (médiane de trois jours après le diagnostic). À l'analyse multivariée, les prédicteurs non modifiables de complications incluaient une infection répétée (RRR 2,67), une confusion (RRR 2,01), une hypotension (RRR 0,97 par mmHg accru) et une leucocytémie (RRR 1,04 par 10^9 cellules/L). La protection contre les complications s'associait à l'utilisation initiale de vancomycine (RRR 0,24); tandis que les dommages s'associaient à une utilisation continue d'antibiotiques qui exacerbaient la situation (RRR 3,02).
CONCLUSION : Les infections à *C difficile* se produisent souvent au début de l'évolution de la maladie et s'associent à de forts taux de complications. Les facteurs cliniques qui présagent un risque plus élevé de complications incluent la confusion, l'hypotension et la leucocytose. Les meilleurs moyens d'améliorer les issues des patients atteints de colite à *C difficile* consistent à envisager un traitement de première ligne à la vancomycine dans les cas modérés à graves et à éviter les antibiotiques inutiles.

Patients seek health care to improve their well-being; however, each year, more than 200,000 Canadians acquire an infection during a hospital stay, and approximately 8000 die from these illnesses (1). *Clostridium difficile* colitis has long been among the most burdensome of hospital-acquired infections and, increasingly so, given the emergence of the virulent NAP1/027 strain (2). Over the past decade, the incidence of *C difficile* infections has doubled (3), and the attributable mortality rate has quadrupled (4).

Previous studies (5-12) suggested that the likelihood of *C difficile* treatment failure and complications are greater for patients of advanced age, with underlying illness, fever, cognitive impairment, leukocytosis, hypoalbuminemia, renal failure, bowel obstruction or ileus, imaging evidence of colitis, colonoscopic evidence of pseudomembranes or intensive care unit location. These predictors are useful in identifying patients who may require more intensive monitoring, more aggressive treatments and earlier surgical referral. However, these nonmodifiable factors do not offer direct avenues to improve the outcomes of patients infected with *C difficile*.

Therefore, the current study examined modifiable processes of care associated with an altered risk of complications among patients with *C difficile* infection.

METHODS

Study cohort

A retrospective cohort study (with prospective case ascertainment) was conducted at Sunnybrook Health Sciences Centre (SHSC) – a large, 700-bed academic health sciences centre in Toronto, Ontario. All consecutive cases of *C difficile* infection were prospectively identified by the Department of Infection Prevention and Control between January 1, 2007, and December 31, 2008. As per standard provincial guidelines, the case definition required laboratory confirmation of a positive toxin assay, together with diarrhea or visualization of pseudomembranes on sigmoidoscopy, colonoscopy or histopathology (13). Diarrhea was defined as two or more loose/watery bowel movements in a 24 h period that was unusual or different for the patient, and with no other recognized etiology (13). During the period examined in the present study, stool testing at SHSC was performed using enzyme immunoassay (EIA) for *C difficile* toxins A and B (TECHLAB, Inverness Medical, United Kingdom). Patients were excluded from analysis only in the rare event that they were enrolled in an investigational study of a novel *C difficile* therapy (n=3), or if their medical chart was unavailable for abstraction after three attempts (n=5).

[1]*Sunnybrook Health Sciences Centre;* [2]*Division of Infectious Diseases & Clinical Epidemiology, Department of Medicine, University of Toronto, Toronto, Ontario*
Correspondence: Dr Nick Daneman, Division of Infectious Diseases & Clinical Epidemiology, G-Wing Room 106, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5. Telephone 416-480-6100 ext 2791, fax 416-480-5808, e-mail nick.daneman@sunnybrook.ca
Received for publication August 19, 2010. Accepted January 11, 2011

TABLE 1
Complications among 365 episodes of *Clostridium difficile* infection

Complication	*C difficile* episodes with complication(s), n (%)
Severe hypokalemia*	19 (5.3)
Gastrointestinal bleeding†	6 (1.7)
Toxic megacolon	5 (1.4)
Bowel perforation	2 (0.6)
Transfer to intensive care unit‡	39 (13)
Colectomy	9 (2.5)
Death	50 (14)
Overall complication rate§	97 (27)

**Potassium level lower than 2.5 mM; †Requiring blood transfusion of one or more units of red blood cells; ‡Denominator does not include patients already in intensive care unit at diagnosis; §*C difficile *episodes involving at least one of the above complications*

Primary outcome measure

The primary outcome measure was a composite of severe complications including severe hypokalemia (potassium level lower than 2.5 mM), toxic megacolon (colonic distension of greater than 7 cm or cecal distension of greater than 12 cm), bowel perforation, lower gastrointestinal bleeding requiring blood transfusion, intensive care unit transfer or death before completion of treatment for an episode of *C difficile* infection (4). In secondary sensitivity analyses, the outcome definition was varied to exclude the least severe events (eg, hypokalemia) or least preventable complications (eg, outcome events occurring before positive diagnostic test results). Outcome events were adjudicated by retrospective chart review conducted by two of the study authors.

Nonmodifiable predictors (baseline characteristics and clinical presentation)

Extensive data regarding baseline patient characteristics were collected. Demographic data included age, sex and place of residence. The source of infection was determined prospectively and defined as nosocomial if the onset occurred more than 72 h after hospital admission, or was related to a previous admission to a health care facility within the previous eight weeks (13). Comorbidities of interest included the following: cardiac disease, lung disease, liver disease, renal disease, neurological disease, inflammatory bowel disease, malignancy, diabetes mellitus, HIV/AIDS, preceding surgery during the current admission and gastrointestinal tube feeding. The acuity of the clinical presentation during the first 48 h of illness was assessed by measurement of maximum heart rate, minimum systolic blood pressure (mmHg), maximum number of stools per day, presence of blood in stool, abdominal pain, confusion, maximum white blood cell count ($\times 10^9$cells/L), maximum creatinine level (mM) and minimum albumin level (g/L).

Modifiable predictors related to processes of care

Emphasis was placed on modifiable care processes relevant to the diagnosis and treatment of patients with *C difficile* infection. Important diagnostic measures included the duration of symptoms before diagnosis (days), laboratory stool assay turnaround time (same day or longer), negative stool EIA results preceding a positive stool EIA result (as a measure of impact of imperfect test sensitivity), and the use of abdominal x-ray testing or abdominal computed tomography scans. Treatment measures included the following: delays in treatment beyond 24 h from the time of the positive *C difficile* test result, any use of metronidazole, any use of oral/rectal vancomycin, inclusion of vancomycin in the initial therapeutic regimen, adjunctive use of probiotics (*Saccharomyces boulardii* or *Lactobacillus* preparations), use of potentially exacerbating antibiotic treatments after *C difficile* diagnosis and the use of antimotility agents (diphenoxylate or loperamide).

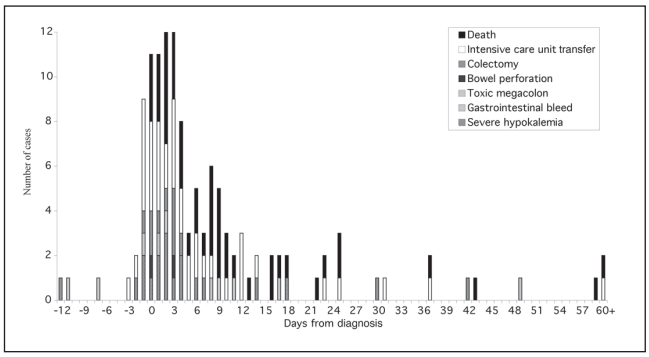

Figure 1) *Timing of* Clostridium difficile *complications. The median time to* C difficile*-related complications was three days following microbiological diagnosis (interquartile range one to nine days). Fifteen (16%) of the complications preceded the date of diagnosis*

Statistical analysis

Univariate analysis was undertaken to compare each modifiable and nonmodifiable predictor variable among *C difficile* episodes with and without severe acute complications. The χ^2 test was used to assess differences for binary predictors, while Wilcoxon rank-sum tests were used to examine differences for continuous variables. Multivariable logistic regression was the primary analysis used to assess the incremental impact of modifiable and nonmodifiable predictors on the risk of severe complications during an episode of *C difficile* infection. Assuming a baseline complication rate of 22%, a power of 85% (alpha = 0.05) was estimated to detect a 15% increased risk of complications associated with each predictor (4,14). Generalized estimating equations were used to account for the fact that some patients experienced multiple *C difficile* episodes (15). Variable reduction was accomplished by backward selection after including significant predictors on univariate analysis (ie, $P<0.1$) as well as prespecified inclusion of initial vancomycin therapy. Laboratory tests (albumin), imaging tests (x-ray and computed tomography scans) and endoscopy were not performed in the majority of patients and, therefore, could not be included in multivariable models. To assess the robustness of the results, secondary multivariable analysis was also repeated with variations in the composite outcome (as described above). All analyses were performed using SAS version 9.1 (SAS Institute, USA). The study was approved by the research ethics board of the SHSC.

RESULTS

General characteristics of the cohort

The cohort included 305 individual patients who experienced a total of 365 episodes of *C difficile* infection. Almost all infections were associated with diarrhea (n=360 [99%]), and almost all were diagnosed on the basis of a positive stool EIA performed at the SHSC (n=361 [99%]). The majority of cases were nosocomial (n=335 [91%]), attributed to the current hospital admission (n=291 [80%]), a previous SHSC admission (n=26 [7%]) or a previous admission to another health care facility (n=16 [4%]). A minority of infections (n=30 [8%]) were community acquired. Most patients were elderly (mean [± SD] 71±16 years of age), with at least one underlying illness (n=327 [90%]).

Risk and timing of severe complications

Severe complications occurred in 97 of 365 (27%) episodes of *C difficile* infection. Table 1 summarizes the rates of each individual complication. These complications occurred rapidly (median three days post-diagnosis, interquartile range one to nine days), and 15 (16%) preceded the positive stool assay (Figure 1).

Individual nonmodifiable predictors of *C difficile* complications

Different baseline characteristics were demonstrated between patients who experienced uncomplicated and complicated episodes of *C difficile*

TABLE 2
Baseline characteristics of patients with uncomplicated or complicated episodes of *Clostridium difficile* infection

	C difficile episodes		
Baseline characteristic	Without complications (n=268)	With complications (n=97)	P*
Age, years, mean ± SD	70±17	74±15	0.05
Sex (% female)	137 (51)	39 (40)	0.07
Location before admission			
Home	216 (81)	75 (77)	0.49
Health care facility	52 (19)	22 (23)	
Source of *C difficile* infection			
Nosocomial	236 (88)	87 (90)	0.67
Community acquired	32 (12)	10 (10)	
Cardiac disease	102 (38)	51 (53)	0.01
Lung disease	47 (18)	21 (22)	0.37
Liver disease	5 (1.9)	4 (4.1)	0.22
Inflammatory bowel disease	10 (3.7)	0 (0.0)	0.05
Diabetes mellitus	51 (19)	22 (23)	0.44
Renal disease	13 (4.9)	8 (8.2)	0.22
Malignancy	103 (38)	37 (38)	0.96
Neurological disease	75 (28)	39 (40)	0.03
HIV/AIDS	5 (1.9)	2 (2.1)	0.90
Gastrointestinal tube feeding	43 (16)	19 (20)	0.44
Preceding surgery	99 (37)	29 (30)	0.19

*Data presented as n (%) unless otherwise indicated. *Reflects Wilcoxon rank-sum test for continuous variables and χ^2 test for differences in proportions*

infection (Table 2). Severe complications were more common among older patients, and those with underlying cardiac or neurological disease. Clinical presentation also differed between uncomplicated and complicated cases (Table 3). A greater risk of severe complications was associated with tachycardia, hypotension, confusion, recurrent episodes of infection, leukocytosis, elevated creatinine levels and hypoalbuminemia. Results were similar when recurrent episodes of *C difficile* infection were excluded from the analysis (data not shown).

Modifiable predictors of *C difficile* complications

Diagnosis of *C difficile* infection was delayed beyond four days of diarrhea symptoms in 20% of patients; however, there was no difference in diarrhea duration between uncomplicated and complicated episodes (Table 4). Laboratory results were not available on the same calendar day as specimen collection for 93 (25%) episodes, with no differences between uncomplicated and complicated episodes. An initial stool assay was negative before the positive result in 59 (16%) episodes, which was associated with a delay in diagnosis (7±8 days versus 3±5 days; P<0.0001), but not with an increased risk of complications. Abdominal x-rays and computed tomography scans were more frequently obtained for patients with complicated compared with uncomplicated disease; however, the proportion of abnormal imaging findings was similar in both groups.

Initiation of effective antibiotic therapy (metronidazole or vancomycin) was delayed more than one calendar day from the positive stool assay result for 20% of episodes; however, the likelihood of delayed therapy was similar between complicated and uncomplicated

TABLE 4
Investigation and treatment in uncomplicated and complicated episodes of *Clostridium difficile* infection

	C difficile episodes		
	Without complications (n=268)	With complications (n=97)	P*
Diagnosis-related processes of care			
Duration (days) of diarrhea before diagnosis, mean ± SD	4±6	3±4	0.73
Initial negative assay before positive	42 (16)	17 (18)	0.67
Greater than 24 h laboratory turnaround time	71 (28)	22 (23)	0.49
Abdominal x-ray obtained	73 (27)	47 (48)	0.0001
Abnormal findings on x-ray	28/73 (38)	18/47 (38)	0.99
Abdominal CT scan obtained	62 (23)	37 (38)	0.005
Abnormal findings on CT	44/62 (71)	28/37 (76)	0.61
Colonoscopy/sigmoidoscopy obtained	6 (2.2)	4 (4.1)	0.68
Abnormal findings on endoscopy	11/17 (65)	4/4 (100)	0.16
Treatment-related processes of care			
Greater than 24 h delay in antibiotics†	55 (22)	17 (19)	0.59
Oral or intravenous metronidazole	246 (92)	90 (93)	0.76
Oral or rectal vancomycin treatment	71 (26)	33 (34)	0.16
Vancomycin as part of initial regimen	22 (8.3)	4 (4.1)	0.18
Probiotic use after diagnosis	21 (7.8)	9 (9.3)	0.66
Exacerbating antibiotics after diagnosis	142 (54)	75 (78)	<0.0001
Antimotility agent use after diagnosis	20 (7.5)	7 (7.2)	0.94

*Data presented as n (%) unless otherwise indicated. *Reflects Wilcoxon rank-sum test for continuous variables and χ^2 test for differences in proportions; †From positive test result to physician order for vancomycin or metronidazole. CT Computed tomography*

TABLE 3
Clinical presentation in uncomplicated and complicated episodes of *Clostridium difficile* infection

	C difficile episodes		
Clinical presentation	Without complications (n=268)	With complications (n=97)	P*
Index episode is a recurrence, n (%)	46 (17)	25 (26)	0.07
Stools per day	5±3	5±2	0.08
Blood in stool, n (%)	19 (7.1)	8 (8.3)	0.70
Abdominal pain, n (%)	53 (20)	24 (25)	0.29
Fever, n (%)	76 (29)	25 (26)	0.63
Maximum temperature, °C	37.4±0.9	37.3±0.9	0.52
Heart rate, beats/min	99±19	106±22	0.02
Systolic blood pressure, mmHg	109±16	100±20	0.003
Confusion, n (%)	48 (18)	27 (28)	0.04
White blood cell count, $\times 10^9$ cells/L	14.0±9.3	20.7±15.8	<0.0001
Creatinine, mM	115±133	157±135	0.0005
Albumin, g/L	27.0±5.5	22.0±6.1	<0.0001

Data presented as mean ± SD unless otherwise indicated. *Reflects Wilcoxon rank-sum test for continuous variables and χ^2 test for differences in proportions*

cases (Table 4). Almost all *C difficile* infections were treated with metronidazole (92%), and only a minority of cases were treated with vancomycin at some point in their course (28%). There was a trend toward greater use of vancomycin in the initial treatment regimen for uncomplicated versus complicated episodes (8.3% versus 4.1%; P=0.18). The use of probiotics and antimotility agents was similar between complicated and uncomplicated episodes, but the continued use of exacerbating antibiotics after diagnosis was far more common among patients who experienced complicated episodes of infection (78% versus 54%; P<0.0001).

Multivariable analysis: Independent predictors of severe *C difficile* complications

Multivariable analysis yielded six independent predictors of severe *C difficile* complications, including four nonmodifiable factors and two potentially modifiable factors (Table 5). Nonmodifiable factors included repeat infection (OR 2.67 [95% CI 1.23 to 5.80]), confusion (OR 2.01 [95% CI 1.05 to 3.83), systolic hypotension (OR 0.97 [95% CI 0.95 to 0.98] per increased mmHg) and elevated white blood cell count (OR 1.04 [95% CI 1.02 to 1.07] per 10^9 cells/L). Inclusion of vancomycin in the initial therapeutic regimen was protective (OR 0.24 [95% CI 0.08 to 0.71]), while the use of exacerbating antibiotics was hazardous (OR 3.02 [95% CI 1.56 to 5.86]). These findings were unchanged in sensitivity analyses, which excluded the least severe outcome (hypokalemia) and the least preventable outcomes (those developing before the date of positive stool specimen) (data not shown).

TABLE 5
Predictors of *Clostridium difficile* complications on multivariable analysis

	Adjusted OR	95% CI
Relapse (versus initial) episode	2.67	1.23–5.80
Confusion	2.01	1.05–3.83
Systolic blood pressure, per increased mmHg	0.97	0.95–0.98
Elevated WBC, per 10^9 cells/L	1.04	1.02–1.07
Vancomycin as initial treatment	0.24	0.08–0.71
Other exacerbating antibiotics	3.02	1.56–5.86

WBC White blood cell count

DISCUSSION

Our study highlights the gravity of *C difficile* infection among hospitalized patients, as well as prospects to improve their outcomes. Severe complications were common among patients with *C difficile* infections, occurring in more than one in four episodes, and corroborated the findings of a recent national surveillance study (4). These complications occurred rapidly, often even before confirmatory test results, thereby emphasizing the importance of infection prevention and control measures to prevent new cases of infection (16). However, recent literature suggests that high-performing institutions are distinguished not only by their prevention of iatrogenic illnesses, but also by their capacity to detect and manage them (17). Our study revealed some ways that detection and treatment of *C difficile* episodes can be more effectively optimized.

Occasionally, diagnosis of *C difficile* infection is delayed, with 20% of patients experiencing more than four days of diarrhea before diagnosis, due in part, to the imperfect sensitivity of the EIA and initial negative test results before a positive specimen. However, neither initial negative assay results nor delayed diagnosis were associated with an increased risk of complications, suggesting that there is little yield in improved diagnostic strategies.

In contrast, our data indicated that there is substantial room for improving *C difficile* outcomes by optimizing treatment. The use of vancomycin as initial therapy was associated with a 76% reduction in the risk of severe complications. Our findings confirm the results of a recent randomized controlled trial that demonstrated the superior efficacy of vancomycin over metronidazole (18), and suggests that vancomycin should be considered as first-line therapy in patients with moderate-to-severe *C difficile* infections. There is a theoretical risk of increasing colonization rates of vancomycin-resistant *Enterococci* by promoting vancomycin to first-line therapy for *C difficile*; however, this has not been confirmed in recent clinical studies (19). Reserving vancomycin use for patients who do not respond to metronidazole therapy may also be inappropriate, given the rapid tempo of illness and early onset of complications.

Perhaps even more important than the selection of the best anti-*C difficile* agent is the discontinuation and avoidance of other exacerbating antibiotic agents. Ongoing or newly started antibiotics hinder restoration of bowel flora and, in our study, were associated with a threefold higher risk of severe complications. More than one-third of hospital antibiotic use is unnecessary or inappropriate (20,21). Patients diagnosed with *C difficile* infection warrant targeted attention by antibiotic stewardship programs. In contrast, there was no detectable hazard associated with the use of antimotility agents, which theoretically can increase colonic exposure to *C difficile* toxins A and B. Given that the use of these medications is uncommon, our study was not powered to test this association. Nevertheless, our findings are consistent with postmarketing surveillance information for loperamide and diphenoxylate, which revealed no adverse outcomes among patients who were concurrently receiving metronidazole or vancomycin (22).

Although our focus was on modifiable predictors, we did detect several nonmodifiable characteristics associated with a higher risk of *C difficile* complications including recurrent episodes of infection, hypotension, confusion, leukocytosis and hypoalbuminemia. These findings were consistent with the literature, and confirm that these factors identify higher-risk patients who may benefit from more aggressive monitoring and treatment.

Our study was limited to a single tertiary care centre, and processes of care may differ at other institutions. However, we believe that our data provide broad lessons for the care of *C difficile* patients that are likely generalizable to most hospital settings. As with all retrospective studies, there was a potential for nondifferential misclassification of predictor and outcome variables that would attenuate OR estimates toward the null. We attempted to overcome this issue by selecting objective measurements. Moreover, a prospective study of care processes may not be more helpful due to inevitable Hawthorne effects. A prospective study, however, would be especially helpful in accurately determining the appropriateness of other antibiotic therapies and defining attributable causes of death. Finally, we lacked data regarding *C difficile* strains; however, this information is not available to clinicians and, therefore, would not be relevant to risk prediction in the setting of routine patient care.

Given the frequency, severity and early onset of *C difficile* complications, it is important to identify patients who are at increased risk of these outcomes. In this regard, useful markers include confusion, hypotension, leukocytosis and hypoalbuminemia. However, the simplest and most effective way to optimize the management of patients with *C difficile* infection is to consider the use of vancomycin as first-line therapy for moderate to severe cases, and discontinue or avoid the use of unnecessary antibiotics.

ACKNOWLEDGEMENTS: The authors acknowledge Ted Winkle for abstraction of pharmacy treatment data, and Laura Rosella for statistical advice.

FINANCIAL SUPPORT: Dr Nick Daneman is supported by a Clinician Scientist award from the Canadian Institutes of Health Research, and a Patient Safety Scholar Award from Sunnybrook Health Sciences Centre.

CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

REFERENCES

1. Zoutman DE, Ford BD, Bryce E, et al. The state of infection surveillance and control in Canadian acute care hospitals. Am J Infect Control 2003;31:266-72.
2. Kelly CP, LaMont JT. *Clostridium difficile* – more difficult than ever. N Engl J Med 2008;359:1932-40.
3. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996-2003. Emerg Infect Dis 2006;12:409-15.
4. Gravel D, Miller M, Simor A, et al. Health care-associated *Clostridium difficile* infection in adults admitted to acute care hospitals in Canada: A Canadian Nosocomial Infection Surveillance Program Study. Clin Infect Dis 2009;48:568-76.
5. Ramaswamy R, Grover H, Corpuz M, et al. Prognostic criteria in *Clostridium difficile* colitis. Am J Gastroenterol 1996;91:460-4.
6. Nair S, Yadav D, Corpuz M, et al. *Clostridium difficile* colitis: Factors influencing treatment failure and relapse – a prospective evaluation. Am J Gastroenterol 1998;93:1873-6.
7. Kyne L, Merry C, O'Connell B, et al. Factors associated with prolonged symptoms and severe disease due to *Clostridium difficile*. Age Ageing 1999;28:107-13.
8. Fernandez A, Anand G, Friedenberg F. Factors associated with failure of metronidazole in *Clostridium difficile*-associated disease. J Clin Gastroenterol 2004;38:414-8.
9. Drew RJ, Boyle B. RUWA scoring system: A novel predictive tool for the identification of patients at high risk for complications from *Clostridium difficile* infection. J Hosp Infect 2009;71:93-4.
10. Henrich TJ, Krakower D, Bitton A, et al. Clinical risk factors for severe *Clostridium difficile*-associated disease. Emerg Infect Dis 2009;15:415-22.
11. Gujja D, Friedenberg FK. Predictors of serious complications due to *Clostridium difficile* infection. Aliment Pharmacol Ther 2009;29:635-42.
12. Valiquette L, Pepin J, Do XV, et al. Prediction of complicated *Clostridium difficile* infection by pleural effusion and increased wall thickness on computed tomography. Clin Infect Dis 2009;49:554-60.
13. Provincial Infectious Diseases Advisory Committee. Best Practices Document for the Management of *Clostridium difficile* in all health care settings. 2009. Ontario Ministry of Health and Long Term Care. <http://www.health.gov.on.ca/english/providers/program/infectious/diseases/best_prac/bp_cdiff.pdf> (Accessed May 2010).
14. Hintze JL. PASS 2005. NCSS, LLC. Kaysville, Utah, USA. <www.ncss.com>.
15. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121-30.
16. 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.
17. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361:1368-75.
18. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45:302-7.
19. Miller M, Bernard L, Thompson M, Grima D, Pepin J. Lack of increased colonization with vancomycin-resistant *Enterococci* during preferential use of vancomycin for treatment during an outbreak of healthcare-associated *Clostridium difficile* infection. Inf Cont Hosp Epi 2010;31:710-5.
20. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.
21. Hecker MT, Aron DC, Patel NP, et al. Unnecessary use of antimicrobials in hospitalized patients: Current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch Intern Med 2003;163:972-8.
22. Koo HL, Koo DC, Musher DM, et al. Antimotility agents for the treatment of *Clostridium difficile* diarrhea and colitis. Clin Infect Dis 2009;48:598-605.