Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Original Article

Clinical characteristics associated with the severity of *Clostridium [Clostridioides] difficile* infection in a tertiary teaching hospital from Mexico

Laura Tijerina-Rodríguez [d], *Elvira Garza-González* [b,*], *Adrián Martínez-Meléndez* [d], *Rayo Morfín-Otero* [a], *Adrián Camacho-Ortiz* [c], *Esteban Gonzalez-Diaz* [a], *Hector Raul Perez-Gomez* [a], *Licet Villarreal-Treviño* [d], *Héctor Maldonado-Garza* [b], *Sergio Esparza-Ahumada* [a], *Eduardo Rodríguez-Noriega* [a]

[a] *Hospital Civil de Guadalajara, Fray Antonio Alcalde, Instituto de Patología Infecciosa y Experimental, Centro Universitario de Ciencias de La Salud, Universidad de Guadalajara, Mexico*

[b] *Servicio de Gastroenterología, Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Mexico*

[c] *Servicio de Infectología, Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Mexico*

[d] *Laboratorio de Microbiología General, Facultad de Ciencias Biológicas, Universidad Autónoma de Nuevo León, Mexico*

ARTICLE INFO

Article history:
Received 12 November 2018
Accepted 18 February 2021
Available online 23 February 2021

Keywords:
Severity
Clostridioides difficile
Recurrence
CDI

ABSTRACT

Background: Clostridium difficile infection (CDI) is a leading cause of healthcare-associated diarrhea worldwide. In this study, risk factors associated with the development of severe-complicated and recurrent outcomes in CDI patients in different age groups, including the non-elderly, were assessed in a third-level hospital.

Methods: CDI cases were detected by clinical data and polymerase-chain-reaction (PCR). Clinical, demographic, epidemiological, and microbiological risk factors for CDI were evaluated.

Results: During the study period, 248 out of 805 patients with nosocomial diarrhea were diagnosed with CDI and the majority were severe-complicated cases (87.90%). Female gender (OR 3.19, 95% CI 1.19–8.55, $p = 0.02$) and lymphoma (OR 3.95, 95% CI 1.03–15.13, $p = 0.04$) were risk factors for severe-complicated CDI. Mature adulthood (51–60 years) (OR 5.80, 95% CI 1.56–21.62, $p = 0.01$), previous rifampicin use (OR 7.44, 95% CI 2.10–26.44, $p = 0.00$), and neoplasm (solid malignant neoplasm or hematological malignancies) (OR 4.12, 95% CI 1.01–16.83, $p = 0.04$) were risk factors for recurrent infection. Autoimmune disorders (OR 6.62, CI 95% 1.26–34.73, $p = 0.02$), leukemia (OR 4.97, 95% CI 1.05–23.58,

* *Corresponding author*. Gastroenterology Service, Dr. José Eleuterio González University Hospital, New Autonomous University, Avenida Madero s/n Colonia Mitras Centro, Monterrey, Nuevo Leon 64460, Mexico.
E-mail address: elvira_garza_gzz@yahoo.com (E. Garza-González).

Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2021.02.007

$p = 0.04$), lymphoma (OR 3.79, 95% CI 1.03–12.07, $p = 0.04$) and previous colistin treatment (OR 4.97, 95% CI 1.05–23.58, $p = 0.04$) were risk factors for 30-day mortality.
Conclusion: Newly identified risk factors for recurrent CDI were rifampicin treatment and age between 51 and 60 years; colistin treatment was identified as a risk factor for 30-day mortality. Previously identified risk factors for severe-complicated CDI were confirmed, but with a major impact on non-elderly patients.

At a glance of commentary

Scientific background on the subject

Clostridium difficile infection (CDI) is a leading cause of healthcare-associated diarrhea worldwide. Some known risk factors for acquiring CDI are advanced age (>65 years), the use of broad-spectrum antibiotics, extended hospital stays, stay in the intensive care unit, cancer, leukemia, lymphoma, gastrointestinal procedures, and the use of immunosuppressive drugs, antacids and steroids.

What this study adds to the field

In our study, young (21–30 years) and mature adults (51–60 years) had the highest frequency of CDI. Colistin use was identified as a new risk factor for increased 30-day mortality, and the use of rifampin treatment was a new risk factor for the development of recurrent episodes.

Clostridium difficile (recently reclassified as *Clostridioides difficile*) infection (CDI) is a leading cause of healthcare-associated diarrhea worldwide. In 2011, there were an estimated 453,000 infections and 29,000 deaths resulting from CDI in the United States [1]. CDI may be a mild, self-limiting disease or a severe, complicated, life-threatening or recurrent disease [2].

Since 2000, an increase in the overall incidence of CDI has been highlighted by outbreaks of more severe disease in the United States, Canada, England, some Asian countries, and Latin America, with rates five-fold higher in patients older than 65 years. The emergence of the strain *C. difficile* NAP1/BI/027 has been associated with an increased incidence, more severe infection, a high recurrence rate after 8 weeks of resolution, and higher 30-day mortality rates [3]. A limited number of effective antimicrobials have been approved for CDI treatment, and the highly virulent NAP1/BI/027 strain complicates current treatment protocols [2].

Known risk factors for acquiring CDI are advanced age (>65 years), the use of broad-spectrum antibiotics, extended hospital stays, stay at the intensive care unit, infection with the human immunodeficiency virus, cancer, leukemia, lymphoma, autoimmune disorders, pulmonary infections (tuberculosis or pneumonia), gastrointestinal procedures, arterial hypertension, and the use of immunosuppressive drugs, antacids and steroids [4–9].

The present study aimed to identify risk factors associated with the development of severe-complicated, and recurrent outcomes in CDI patients of different age groups, including the non-elderly, in a third-level hospital.

Materials and methods

Study setting and population

This was a retrospective study at the Hospital Civil de Guadalajara Fray Antonio Alcalde, a 1000-bed tertiary-care teaching hospital. The hospital has 31 wards housed in four separate buildings. The hospital provides services to Guadalajara in the state of Jalisco, Mexico, with approximately 30,000 admissions each year.

Patient demographics and CDI diagnosis

As part of the surveillance protocol for CDI, between November 2013 and December 2015, all hospitalized patients with a hospital stay more significant than 48 h who developed diarrhea (3 or more depositions in the last 24 h with a Bristol score of 6 or 7 or a recent hospitalization in the previous 12 weeks) were tested for *C. difficile* using the Cepheid Xpert *C. difficile*/Epi test (Cepheid, Sunnyvale CA).

Epidemiological and clinical data were reviewed in medical records from CDI patients
CDI was defined as complicated when one of the following criteria were present: admission to the intensive care unit, hypotension with or without the required use of vasopressors, fever ≥38.5 °C, ileus, significant abdominal distention, mental status changes, white blood cell (WBC) count ≥35,000 cells/mm^3 or <2000 cells/mm^3, or serum lactate levels >2.2 mmol/l [10]. CDI was defined as severe because of hypoalbuminemia (serum albumin <3 g/dl), WBC ≥15,000 cells/mm^3, or abdominal tenderness [10].

Cases not meeting the severe or complicated infection criteria were classified as having mild to moderate CDI (without additional symptoms)
Recurrent CDI was defined by the reoccurrence of diarrhea associated with clinical and laboratory evidence of CDI within eight weeks after completing therapy or resolution of the initial CDI, [10]. The study was reviewed and approved by the Ethics Committee of the "Hospital Civil de Guadalajara Fray Antonio Alcalde."

Table 1 Demographic and epidemiological characteristics of patients with confirmed CDI (N = 244[a]).

	N	%
Gender		
Male	154	63.10
Female	90	36.90
Age groups (years)		
11-20	29	11.88
21-30	46	18.85
31-40	25	10.25
41-50	37	15.16
51-60	45	18.44
61-70	32	13.11
71-80	21	8.60
>80	9	3.69
Severity of infection		
Severe-complicated	214	87.70
Moderate	30	12.29
Clinical data		
Abdominal pain	115	47.13
Fever (>38 °C)	103	42.21
Abdominal distention	102	41.80
Mucus in stool	102	41.80
Vomiting	37	15.16
Blood in stool	17	6.97
Pseudomembranes	9	3.69
Laboratory results		
Hypoalbuminemia	148	60.65
White blood cells (>15,000 cells//mm^3)	76	31.14
Comorbidities		
Arterial hypertension	93	38.11
Kidney disease	84	34.40
Diabetes mellitus	77	31.55
Neoplasm (solid malignant neoplasm or hematological malignancies)	63	25.82
Pneumonia	37	15.16
Lymphoma	11	4.51
Leukemia	8	3.28
Autoimmune disorder	6	2.46
Other	19	7.79
C. difficile strain characteristics		
NAP1/027 strain	127	52.05
non- NAP1/027	117	47.95
Recurrence		
At least one	22/84	26.19
Due to *C. difficile* NAP1/027 strain	10/22	45.45
Due to non-*C. difficile* NAP1/027 strain	12/22	54.55
Hospitalization		
General ward (before and after diagnosis)	222	90.98
In the previous 12 weeks	124	50.82
Intensive Care Unit	20	9.01
Antibiotic treatment before CDI diagnosis		
Overall	165	67.62
Clindamycin	128	77.58
Cephalosporins	89	53.94
Carbapenems	54	32.73
Metronidazole	35	21.21
Fluoroquinolones	23	13.94
Linezolid	21	12.73
Vancomycin	19	11.52
Rifampin	19	11.52
Amikacin	15	9.09
Piperacillin-tazobactam	15	9.09
Fluconazole	12	7.27
Others	27	16.36
Another drug treatment		
Histamine blockers	14	5.73
Proton pump inhibitors (PPI)	204	83.61
Immunosuppressors	36	14.75
CDI cases per year[b]		
2014	68	27.42
2015	177	71.37
30-day mortality		
Overall	38	15.57
12-month mortality		
Overall	69	28.27

[a] Clinical data were available for 244 patients only.
[b] 2013 frequency was not included since only 2-month period data was available for this year.

Statistical analyses

The patients were classified into the following age group: 11–20, 21–30, 31–40, 41–50, 51–60, and >60 years of age. For the analyses of categorical variables, Pearson's chi-squared and Fisher's exact tests were used; for continuous variables, the Mann–Whitney U test was used. The Kruskal–Wallis test was performed for comparison between severe-complicated and recurrent CDI, as well as NAP1/027-associated CDI, 30-day, and 12-month mortality frequencies among age groups.

A multivariable logistic regression was conducted over two stages: a univariable analysis to identify significant associations between independent variables and outcomes. Odds ratios with a 95% confidence interval were determined. Variables identified in the univariate analysis with odds ratios>1.0 and $p < 0.25$ were included in a binary logistic regression model. Variables with a $p < 0.05$ were considered as independent risk factors.

We examined multi-collinearity using linear regression to study the tolerance index (Ti) and the variance inflation factor (VIF) for the absence of multicollinearity issues between independent variables by the Statistical Package for the Social Sciences (SPSS), software version 23.

Results

Epidemiological and clinical data

During the study period, 805 patients presented with nosocomial diarrhea, and 248 were confirmed to have CDI by PCR (62.10% were males, and 75% were <60 years old). Most patients with CDI were young adults (age, 21–30 years; n = 46, 18.85%) or mature adults (51–60 years of age; n = 45, 18.44%) [Table 1].

Most patients presented with severe-complicated disease (87.70%). Hypoalbuminemia n = 148, 60.65%), abdominal pain (n = 115, 47.13%), fever >38.5 °C (n = 103, 42.21%), abdominal distension (n = 102, 41.80%), and mucus in stool (n = 102, 41.80%) were the most common signs and symptoms associated with CDI. The most frequently observed comorbidities

Table 2 Risk factors for the development of severity, recurrence, and 30-day mortality.

Dependent	Variable	Univariate analysis		Binary logistic regression	
		U-OR[d] (95% CI)	p-value	A-OR[e] (95% CI)	p-value
Severe CDI[a]	Gender (females)	2.58 (1.00–6.51)	0.03*	3.19 (1.19–8.55)	0.02*
	Lymphoma	1.33 (0.89–1.99)	0.04*	3.95 (1.03–15.13)	0.04*
	Age (21–30 years)	1.51 (0.98–1.35)	0.03*	2.41 (1.00–5.78)	0.05
	Infection with 027 strain	1.67 (0.77–3.64)	0.13	0.56 (0.25–1.26)	0.16
Recurrence[b]	Age (51–60 years)	6.54 (2.07–20.68)	0.00**	5.80 (1.56–21.62)	0.01*
	Antibiotics intake	2.19 (0.57–8.44)	0.19	1.42 (0.31–6.43)	0.64
	Rifampin	4.37 (0.89–21.37)	0.07	7.44 (2.10–26.44)	0.00**
	Neoplasm	2.42 (0.79–7.47)	0.10	4.12 (1.01–16.83)	0.04*
	Fluoroquinolones	2.74 (0.74–10.12)	0.11	2.55 (0.55–11.73)	0.23
	Hypertension	1.23 (0.46–3.29)	0.67	1.62 (0.48–5.49)	0.23
30-day-mortality[c]	Autoimmune disorder	5.09 (0.97–26.24)	0.03*	6.62 (1.26–34.73)	0.02*
	Leukemia	3.90 (0.84–18.24)	0.09	4.97 (1.05–23.58)	0.04*
	Lymphoma	2.62 (0.75–9.21)	0.12	3.79 (1.03–12.07)	0.04*
	Colistin	3.79 (0.81–17.70)	0.10	4.97 (1.05–23.58)	0.04*

Goodness of fit test: Hosmer y Lemeshow, [a] $x^2 = 3.878$, $p = 0.567$, [b] $x^2 = 4.657$, $p = 0.702$, [c] $x^{2=}$ 0.167, $p = 0.683$. *$p < 0.05$, **$p < 0.01$. [d] Unadjusted odds-ratio, [e] Adjusted odds-ratio.

were arterial hypertension (n = 93, 38.11%), kidney disease, including patients that presented urinary infection or creatinine levels >1.5 mg/dl (n = 84, 34.40%), and diabetes (n = 77, 31.55%) [Table 1].

The hypervirulent *C. difficile* NAP1/027 strain was detected in 127 (52.04%) patients, and 84 of these patients were followed for the next eight weeks; among them, 22 patients (26.19%) developed at least one recurrent episode. From the recurrent episodes, 10/22 (45.40%) were caused by the *C. difficile* NAP1/027 strain and 12/22 (54.50%) by a non-NAP1/027 strain.

Most patients (n = 222) were housed in the general ward, and among them, 124 had been hospitalized during the 12 weeks previous to CDI. Twenty patients had been admitted to the intensive care unit when CDI was diagnosed. The remaining two patients were in other wards. All patients with the first episode of mild to moderate CDI were treated with metronidazole, and recurrent episodes were treated with metronidazole in combination with vancomycin according to the American College of Gastroenterology guidelines and the Guidelines for *C. difficile* Infection in Adults and Children of the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Second-line therapies, such as fidaxomicin treatment or a fecal microbiota transplant, were not used due to their unavailability at that time in our hospital.

Almost two-thirds of the patients had previously received antibiotic treatment (n = 165, 67.62%), most commonly clindamycin (n = 128, 77.58%) and cephalosporins (n = 89, 53.94%); metronidazole and vancomycin were previously administered in 21.21% and 11.52% of the cases, respectively which are usually administered for CDI treatment [Table 1]. From the CDI 248 cases, 3 (1.21%) occurred in 2013, 68 (27.42%) in 2014, and 177 (71.37%) in 2015.

Risk factors detected for CDI

Female gender (OR 3.19, 95% CI 1.19–8.55, $p = 0.02$) and lymphoma (OR 3.95, 95% CI 1.03–15.13, $p = 0.04$) were independent risk factors for severe CDI [Table 2].

Mature adulthood (51–60 years) (OR 5.80, 95% CI 1.56–21.62, $p = 0.01$), rifampin consumption (OR 7.44, 95% CI 2.10–26.44, $p = 0.00$) and neoplasm (solid malignant neoplasm or hematological malignancies) (OR 4.12, 95% CI 1.01–16.83, $p = 0.04$) were independent risk factors for the development of recurrent CDI [Table 2].

We identified the following independent risk factors for 30-day mortality rates: autoimmune disorders (OR 6.62, CI 95% 1.26–34.73, $p = 0.02$), leukemia (OR 4.97, 95% CI 1.05–23.58, $p = 0.04$), lymphoma (OR 3.79, CI 95% 1.03–12.07, $p = 0.04$) and previous colistin treatment (OR 4.97, 95% CI 1.05–23.58, $p = 0.04$) [Table 2].

Discussion

Our study addressed risk factors among patients with CDI, and we detected that 89.0% of the patients developed severe CDI. In contrast to previous reports that identified the elderly (>60 years) to be the most vulnerable age group [3,11–16], in our study, young (age 21–30 years) and mature adulthood (age 51–60 years) adults had the highest frequency of CDI, respectively 18.55% and 18.15%. Previous studies conducted in Mexico reported that patients <65 years of age had a higher risk of recurrent CDI [17–19]. This Mexican study identified mature adulthood (51–60 years) as an independent risk factor for the development of recurrent CDI. The different conclusions with respect to the most vulnerable age group may be explained by the fact that most CDI surveillance studies have focused primarily on the elderly, excluding younger adults and children [3,20,21]. Furthermore, the healthcare facility where the study was conducted also provided medical attention mainly to traumatized younger patients and was better equipped to identify this novel, at-risk population.

The prevalence of the NAP1/027 *C. difficile* strain in about half of our CDI patients is consistent with reports from other countries where prevalence was between 45 and 61% [19].

The present study confirmed previously described risk factors for complicated or recurrent CDI [3,12,22,23], e.g.,

middle-aged adulthood and neoplasm illness were independent risk factors for recurrent CDI, whereas lymphoma was an independent risk factor for complicated CDI.

As far as we know, we are the first to report that rifampin and colistin are independent risk factors for recurrent CDI and 30-day mortality, respectively. It should be noted, though, that only seven patients received colistin therapy before the CDI diagnosis. This risk factor is significant because recent studies have reported infections due to multidrug-resistant strains that were only susceptible to colistin. This antibiotic was not used until recently because of its nephrotoxicity. However, during the last decade, it has been reintroduced to treat critical illnesses such as pneumonia, bacteremia, meningitis, obstructive pulmonary disease, and cystic fibrosis [24–26]. However, in the treatment of pneumonia, bacteremia, and other critical diseases related to the development of CDI, a high mortality rate (61.9%) has been attributed to colistin therapy (OR, 1.99 to 8.2; $p < 0.001$) [24,25].

It should be mentioned that our hospital had an outbreak of carbapenem-resistant enterobacteria during the study period; thus, the use of tigecycline and colistin was increased. Regarding colistin as an independent risk factor for mortality, we must consider that these patients had severe clinical conditions, and the high mortality rate may be due to the underlying infection. In this regard, a prediction model using logistic regression for CDI in hospitalized patients identified an underlying infection as an independent predictor of CDI [27].

Still, this newly described risk factor for the development of CDI reinforced the need for control of other hospital-acquired infectious diseases as an additional means of preventing CDI. As a result, in our hospital, quinolone was reduced, and the use of levofloxacin was eliminated from almost all wards except for the hematology and urology wards.

We used the Xpert *C. difficile/Epi* assay to confirm CDI. This assay detects the genes *tcdB* and *cdt and* the 18-bp deletion in *tcdC*, but it does not identify the *tcdA* gene. Therefore, it is possible that patients infected with strains that only produced *tcdA* were not identified. On the other hand, it seems that the production of only toxin A is rare. A study that compared CDI detection by either the Xpert *C. difficile* with detection by the *tcdA*-based Illumigene *C. difficile* assay (Meridian Bioscience, Inc.) found that 157 samples were negative in both tests, 35 were positive in both assays, 7 were positive by GeneXpert but negative by the Illumigene assay, and in one case, the Genexpert was positive. However, the result of illumigene was invalid [28]. Thus, the lack of detection of *tcdA* by the GeneXpert may have had a minimal effect in our study.

The major limitation of our study was that it was performed at a single site, and results may not apply to other hospitals. The high number of complicated CDI infections in our hospital and their associated risk factors may be advocated by increased infections caused by carbapenem-resistant enterobacteria during the study period.

Conclusion

In summary, in our study, CDI was mainly prevalent among patients <60 years, who were also more vulnerable to severe CDI. The use of colistin was identified as a new risk factor for increased 30-day mortality rates, while the use of rifampin treatment was a new risk factor for the development of recurrent episodes in patients between the ages of 51 and 60 years.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors report no conflicts of interest.

Ethics in publishing

This study was reviewed and approved by the Ethics Comitee of “Hospital Civil de Guadalajara, Fray Antonio Alcalde”.

REFERENCES

[1] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med 2015;372:825–34.
[2] Sun X, Hirota SA. The roles of host and pathogen factors and the innate immune response in the pathogenesis of Clostridium difficile infection. Mol Immunol 2015;63:193–202.
[3] Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Society for Healthcare Epidemiology of A, Infectious Diseases Society of A. 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;31:431–55.
[4] Balassiano IT, Yates EA, Domingues RM, Ferreira EO. Clostridium difficile: a problem of concern in developed countries and still a mystery in Latin America. J Med Microbiol 2012;61:169–79.
[5] Marcon AP, Gamba MA, Vianna LA. Nosocomial diarrhea in the intensive care unit. Braz J Infect Dis 2006;10:384–9.
[6] Legaria MC, Lumelsky G, Rosetti S. Clostridium difficile-associated diarrhea from a general hospital in Argentina. Anaerobe 2003;9:113–6.
[7] Fernandez Canigia L, Nazar J, Arce M, Dadamio J, Smayevsky J, Bianchini H. Clostridium difficile diarrhea: frequency of detection in a medical center in Buenos Aires, Argentina. Rev Argent Microbiol 2001;33:101–7.
[8] Herrera P, Cotera A, Fica A, Galdo T, Alvo M. High incidence and complications of Clostridium difficile diarrhea among patients with renal diseases. Rev Med Chil 2003;131:397–403.
[9] Garcia C, Velarde J, Cedron H, Ferrufino JC, Seas C, Bussalleu A, et al. Clostridium difficile and cytomegalovirus involved in a case of pseudomembranous colitis. Rev Gastroenterol Peru 2007;27:408–10.
[10] Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 2013;108:478–98.

[11] Kyne L, Farrell RJ, Kelly CP. Clostridium difficile. Gastroenterol Clin N Am 2001;30:753–77.
[12] Pepin J, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 2005;41:1254–60.
[13] Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M, et al. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. Arch Surg 2009;144:433–9.
[14] Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 2010;170:772–8. Erratum in: Arch Intern Med 2010;170:1100.
[15] Welfare MR, Lalayiannis LC, Martin KE, Corbett S, Marshall B, Sarma JB. Co-morbidities as predictors of mortality in Clostridium difficile infection and derivation of the ARC predictive score. J Hosp Infect 2011;79:359–63.
[16] Reacher M, Verlander NQ, Roddick I, Trundle C, Brown N, Farrington M, et al. Excess mortality attributable to Clostridium difficile and risk factors for infection in an historic cohort of hospitalised patients followed up in the United Kingdom death register. PloS One 2016;11:e0149983.
[17] Camacho-Ortiz A, Lopez-Barrera D, Hernandez-Garcia R, Galvan-De Los Santos AM, Flores-Trevino SM, Llaca-Diaz JM, et al. First report of Clostridium difficile NAP1/027 in a Mexican hospital. PloS One 2015;10:e0122627.
[18] Morfin-Otero R, Garza-Gonzalez E, Aguirre-Diaz SA, Escobedo-Sanchez R, Esparza-Ahumada S, Perez-Gomez HR, et al. Hospital Civil de Guadalajara FAACdT. Clostridium difficile outbreak caused by NAP1/BI/027 strain and non-027 strains in a Mexican hospital. Braz J Infect Dis 2016;20:8–13.
[19] 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:e98400.
[20] Pepin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004;171:466–72.
[21] Lessa FC, Winston LG, McDonald LC. Emerging infections program CdST. Burden of Clostridium difficile infection in the United States. N Engl J Med 2015;372:2369–70.
[22] Camacho-Ortiz A, Galindo-Fraga A, Rancel-Cordero A, Macias AE, Lamothe-Molina P, Ponce de Leon-Garduno A, et al. Factors associated with Clostridium difficile disease in a tertiary-care medical institution in Mexico: a case-control study. Rev Invest Clin 2009;61:371–7.
[23] Lopez-Urena D, Quesada-Gomez C, Miranda E, Fonseca M, Rodriguez-Cavallini E. Spread of epidemic Clostridium difficile NAP1/027 in Latin America: case reports in Panama. J Med Microbiol 2014;63:322–4.
[24] Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic. Clin Microbiol Infect 2005;11:115–21.
[25] Paul M, Bishara J, Levcovich A, Chowers M, Goldberg E, Singer P, et al. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother 2010;65:1019–27.
[26] Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar AE, Garcia-Garmendia JL, Bernabeu-Wittel IM, et al. Treatment of multidrug-resistant Acinetobacter baumannii ventilator-associated pneu -monia (VAP) with intravenous colistin: a comparison with mipenem-susceptible VAP. Clin Infect Dis 2003;36 :1111–8.
[27] van Werkhoven CH, van der Tempel J, Jajou R, Thijsen SF, Diepersloot RJ, Bonten MJ, et al. Identification of patients at high risk for Clostridium difficile infection: development and validation of a risk prediction model in hospitalized patients treated with antibiotics. Clin Microbiol Infect 2015;21:786. e1-8.
[28] Pancholi P, Kelly C, Raczkowski M, Balada-Llasat JM. Detection of toxigenic Clostridium difficile: comparison of the cell culture neutralization, Xpert C. difficile, Xpert C. difficile/Epi, and Illumigene C. difficile assays. J Clin Microbiol 2012;50:1331–5.