JAMDA xxx (2019) 1–5

JAMDA

journal homepage: www.jamda.com

Original Study

Acute *Clostridioides difficile* Infection in Hospitalized Persons Aged 75 and Older: 30-Day Prognosis and Risk Factors for Mortality

Arnaud Caupenne MD [a,*], Pierre Ingrand MD, PhD [b,c], Isabelle Ingrand PhD [b,c], Emmanuel Forestier MD [d], Claire Roubaud-Baudron MD, PhD [e], Gaëtan Gavazzi MD, PhD [f], Marc Paccalin MD, PhD [a,c]

[a] *Pôle de Gériatrie, Centre Hospitalier Universitaire de Poitiers, Université de Poitiers, Poitiers, France*
[b] *Pôle Biologie, Pharmacie et Santé Publique, Centre Hospitalier Universitaire de Poitiers, Université de Poitiers, Poitiers, France*
[c] *Centre d'Investigation Clinique CIC 1402, INSERM, Centre Hospitalier Universitaire de Poitiers, Université de Poitiers, Poitiers, France*
[d] *Service de Maladies infectieuses, Centre hospitalier Métropole Savoie, Chambery, France*
[e] *Pôle de Gérontologie clinique, Hôpital Xavier Arnozan, Centre Hospitalier Universitaire de Bordeaux, Université Victor Segalen Bordeaux 2, Bordeaux, France*
[f] *Service de Gériatrie clinique, Centre hospitalier Universitaire Grenoble Alpes, Grenoble, France*

Keywords:
Older adult
Clostridioides difficile
infection
prognosis
recurrence
mortality

A B S T R A C T

Objectives: To assess the 30-day mortality predictive markers in the oldest patients with *Clostridioides difficile* infection (CDI) and to analyze the accuracy of the European severity risk markers in this population.
Design: Observational prospective multicenter cohort study conducted by the French Infectious Diseases Society and Geriatrics Society networks. An electronic questionnaire was sent to members of both societies regarding their participation. Each investigator used an online survey to gather the data.
Setting and participants: Patients aged ≥75 years hospitalized in French geriatric or infectious wards with confirmed diagnosis of CDI between March 1, 2016 and May 1, 2017.
Methods: Clinical and laboratory parameters included medical history and comorbidities with the Cumulative Illness Rating Scale (CIRS). Criteria increasing the risk of severe disease were recorded as listed in the European guidelines. Therapeutic management, recurrence, and mortality rates were assessed at day 30 after diagnosis.
Results: Included patients numbered 247; mean age was 87.2 years (SD 5.4). Most of the CDI incidences (66.4%) were health care–associated infections, with 81% diagnosed within 30 days of hospitalization; CIRS mean score was 16.6 (SD 6.6). Markers of severity ≥3 included 97 patients (39.3%). Metronidazole was the main initial treatment (51.0%). *C difficile* infection in the older adult was associated with a 30-day mortality of 12.6%. Multivariate analysis showed that baseline CIRS score [hazard ratio (HR) 1.06 per 1-point increase, 95% confidence interval (CI) 1.00-1.12] and evidence of cardiac, respiratory, or renal decompensation (HR 3.04, 95% CI 1.40-6.59) were significantly associated with mortality.
Conclusions and implications: European severity markers are adequate in the oldest old. Organ failure and comorbidities appeared to be the main markers of prognosis, and these should raise the awareness of practitioners. Although antibiotic treatment was not predictive of mortality, our results point out the lack of adherence to current guidelines in this population.

Clostridium difficile, recently reclassified as *Clostridioides difficile*, represents the most common pathogen cause of health care–associated diarrhea in developed countries.[1,2] Over the past 10 years, there has been an important increase in both incidence and severity of *C difficile* infection (CDI).[3] In a national study conducted in 2009, the incidence in France was estimated as up to 2.28 cases/10,000 patient-days in acute care and 1.14 cases/10,000 patient-days in rehabilitation and long-term care.[4] The risk of recurrence is estimated between 10% and 30%,[5–7] and all-cause CDI-related mortality ranges from 4.5% to 33.2%.[8–12] European guideline documents based on several studies report that older patients are at increased risk of recurrence and mortality.[13] Patients aged 65 and older represent 60%

This work was supported by Astellas Pharma France (Grant 10000€).
The authors declare no conflicts of interest.
* Address correspondence to Arnaud Caupenne, MD, Pôle de Gériatrie, CHU la Milétrie, 86021 Poitiers Cedex, France.
E-mail address: arnaud.caupenne@chu-poitiers.fr (A. Caupenne).

https://doi.org/10.1016/j.jamda.2019.07.002
1525-8610/

to 70% of CDI cases.[14–16] This age group is vulnerable because of more frequent and prolonged hospitalizations, senescence of immune mechanisms, and altered intestinal microbiota.[17–19] Still, few studies focused on patients older than 75 years,[10,20–22] and predictive markers for short-term mortality in this population are scarcely described.[8,23,24] We set up a national survey, named CLOdi, to assess the 30-day mortality predictive markers in the oldest patients and to analyze the accuracy of the European severity risk markers in this population.

Methods

CLOdi is a French observational prospective survey that included patients aged 75 years and older with diagnosis of CDI, hospitalized in geriatric and infectious wards between March 1, 2016, and May 1, 2017.

Data Collection

The study was conducted by the French Infectious Diseases Society and Geriatrics Society networks (Société de Pathologies Infectieuses de Langue Française and Société Française de Gériatrie et de Gérontologie) and approved by the French regulatory authorities, the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS; Consultative Committee on Information-Processing in Health Research) in September 2015, and the Commission Nationale Informatique et Libertés (CNIL; Commission for Protection of Private Data) in December 2015.

An electronic questionnaire was sent to the members of both societies regarding their participation on a voluntary basis. Each investigator who agreed to participate used an online survey to include patients at diagnosis, filled in the data during the course of CDI, and assessed case evolution 30 days after CDI diagnosis. The diagnosis of CDI was based on clinical symptoms and positivity of both CDI laboratory tests (glutamate dehydrogenase and toxins A or B) in stool samples. Health care–associated CDI was defined when infection occurred 48 hours or more after index hospitalization. When CDI was the cause of hospitalization or occurred within 48 hours of hospitalization, it was considered as community-acquired. The clinical and laboratory parameters were collected, as well as the markers of risk of severity and the CDI antibiotic sequences. The European markers of risk of severity are as follows: age $\geq$65 years, leukocyte count $>$15,000/mm^3, rise in serum creatinine level $\geq$50% of the premorbid level, and blood albumin $<$30 g/L and severe underlying disease.[13] Comorbidities were evaluated at admission by the Cumulative Illness Rating Scale (CIRS).[25,26] Total CIRS score was recorded at the onset of CDI. We decided to use the median score to define comorbidity as severe. Organ failure was arbitrarily assessed during the course of CDI, relying on intravenous use of loop diuretics for cardiac insufficiency, need for oxygen, or rise in serum creatinine level $\geq$50% of the premorbid level, for renal decompensation, according to the European guidelines documents.[13]

Treatment and outcome (length of hospital stay, recurrence of CDI, and mortality) were recorded. Recurrence was defined as new CDI confirmed after the onset of a previous episode, provided the symptoms from the previous episode resolved for at least 48 hours after completion of initial treatment.

Data Analysis

Descriptive statistics were expressed as mean $\pm$ standard deviation (SD) for continuous variables or absolute number and percentage for categorical variables. Unadjusted hazard ratios (HRs) and 95% confidence intervals (CI) were calculated from univariate Cox regression analysis. Adjusted HRs were calculated for significant variables ($P < .05$) from multivariate Cox analysis performed by stepwise elimination from an initial model including variables with univariate $P < .25$. The proportional risk assumption has been assessed. Analyses were performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

Investigators (63) included 247 hospitalized patients (mean age 87.2, SD 5.4, range 75-99) from 34 hospitals during the 14-month study period (Table 1); 31 (12.6%) patients came from nursing homes; CDI was diagnosed during an acute care or rehabilitation hospitalization; 195 (78.9%) patients were hospitalized in acute care hospitals and 52 (21.1%) in rehabilitation hospitals; CDI was community-acquired, including residents of nursing homes, in almost a third of patients. Main reasons for hospitalization were an infectious disease (27.1%), diarrhea (24.6%), and asthenia (8.5%). A past history of CDI was reported in 33 patients (13.4%).

CDI diagnosis had occurred within 30 days following admission in 199 (81%) cases and within 90 days in 240 (98%) cases; 106 patients (42.9%) had antibiotic exposure at the time of CDI, mainly betalactamins (89%), which were discontinued in 68 cases (64.1%). Baseline CIRS mean score was 16.6 (SD 6.6, range 2-34, median 14), and 80 (32.4%) patients were classified with severe comorbidity (CIRS

Table 1
Characteristics of Patients With *Clostridioides difficile* Infection (N = 247)

Variables	Enrolled Patients (N = 147)
Women	162 (65.6)
Mean age, y, (SD)	87.2 (5.4)
Men	86.8 (5.4)
Women	87.4 (5.4)
Abode	
Community-dwelling	216 (87.4)
Nursing home	31 (12.6)
Baseline CIRS score, mean (SD)	12.6 (6.6)
Number of medications, mean (SD)	7.4 (3.5)
PPI	129 (52.2)
Antibiotic therapy at diagnosis	109 (44.1)
Penicillin	61 (56.0)
Cephalosporin	36 (33.0)
Health care–associated CDI	164 (66.4)
Organ failure during the course of CDI*	62 (25.1)
Use of intravenous loop diuretics	29 (46.8)
Renal failure	53 (85.5)
Respiratory failure	15 (24.2)
Mean duration of isolation precaution, d (range)	10 (2-82)
First-line treatment	
Metronidazole	126 (51)
Vancomycin	91 (36.9)
Fidaxomicin	25 (10.1)
Combination of antibiotics	4 (1.6)
Median duration of antibiotic therapy, d (range)	10 (1-40)
Severity risk markers ($\geq$3)	97 (39.3)
Age $>$65 y	247 (100)
Leukocyte count $>$15,000/mm^3	72 (29.1)
Rise in serum creatinine level†	53 (21.5)
Blood albumin $<$30 g/L	130 (52.6)
Severe comorbidity‡	182 (73.7)

PPI, proton pump inhibitors.
Values are n (%) unless otherwise noted. Severity risk markers were assessed according to the European guideline documents.[13]
*Organ failure was assessed when use of intravenous loop diuretics, rise in serum creatinine level $\geq$1.5 times the premorbid level, or need for oxygen.
†Rise in serum creatinine level $\geq$1.5 times the premorbid level.
‡Severe comorbidity (CIRS score $>$ 14).

Table 2
Risk Factors for Mortality at Day 30, in Patients With *Clostridioides difficile* Infection

Variables	Alive Patients (n = 216)	Dead Patients (n = 31)	Univariate Analysis		Multivariate Analysis	
			P Value	HR (95% CI)	*P* Value	HR (95% CI)
Women	145 (67.1)	17 (54.8)	.19	1.62 (0.78, 3.27)	—	
Age, y, mean (SD)*	87.0 (5.4)	88.8 (4.9)	.09	1.06 (0.99, 1.13)	—	
Antibiotic therapy in previous 3 mo	130 (60.2)	13 (41.9)	.06	1.97 (0.97, 4.10)	—	
Number of medications, mean (SD)*	7.3 (3.6)	8.1 (3.5)	.25	1.06 (0.96, 1.16)	—	
Non-CDI antibiotic therapy at the time of diagnosis	91 (42.1)	18 (58)	.09	1.84 (0.90, 3.76)	—	
Health care–associated CDI	141 (65.3)	23 (74.2)	.21	1.67 (0.75, 4.22)	—	
CIRS score, mean (SD)*	12.1 (6.3)	16.0 (6.9)	.004	1.08 (1.03, 1.14)	.033	1.06 (1.00, 1.12)
Organ failures during the course of CDI†	46 (21.3)	16 (51.6)	<.001	3.64 (1.80, 7.36)	.0048	3.04 (1.40, 6.59)
Treatments during the course of infection						
Metronidazole	116 (53.7)	15 (48.4)	.54	0.80 (0.39, 1.63)	—	
Vancomycin	95 (43.9)	14 (45.2)	.89	1.05 (0.51, 2.13)	—	
Fidaxomicin	44 (20.4)	5 (16.1)	.56	0.76 (0.26, 1.82)	—	
Severity risk markers						
≥3 markers	77 (35.6)	20 (64.5)	.003	3.07 (1.50, 6.62)	—	
Age >65 y	216 (100)	31 (100)	—		—	
Leukocyte count >15,000/mm^3	61 (28.2)	11 (35.5)	.39	1.39 (0.64, 2.84)	—	
Rise in serum creatinine level‡	42 (19.4)	11 (35.5)	.048	2.18 (1.01, 4.46)	—	
Blood albumin <30 g/L	110 (50.9)	20 (64.5)	.15	1.71 (0.83, 3.69)	—	
Severe comorbidity§	64 (29.6)	16 (51.6)	.013	2.50 (1.22, 5.21)	—	

Unless otherwise noted, values are n (%). Severity risk markers were assessed according to the European guideline documents.[13]

*Per unit change.

†Organ failure was assessed when intravenous use of diuretics and/or rise in serum creatinine level ≥ 1.5 times the premorbid level and/or need for oxygen during the course of CDI.

‡Rise in serum creatinine level: ≥1.5 times the premorbid level.

§Severe comorbidity was assessed when baseline CIRS score > 14.

score > 14). The mean CIRS score was 14.4 (SD 6.5) in patients diagnosed and treated in a rehabilitation hospital and 12.2 (SD 6.4) in patients diagnosed and treated in an acute care hospital ($P = .023$). Sixty-two (25.1%) patients presented with either use of loop diuretics and/or rise in serum creatinine level ≥1.5 times the premorbid level and/or need for oxygen at the time of CDI, but none were admitted to intensive care. Ninety-seven (39.3%) had ≥3 severity risk markers. Metronidazole was the most common initial treatment (51.0%), administered intravenously in 16 patients (12.7%). Thirty-six (14.6%) patients had a second-line treatment with fidaxomicin (52.8%), vancomycin (41.7%), and metronidazole (the last in 2 cases).

Course of Infection

Median length of hospitalization was 26 days (range 5-254), with 89 patients (36%) staying more than 30 days. Ten patients died before 10 days of treatment. At day 30 after CDI diagnosis, mortality rate was 12.6%, with 58.1% of these patients dying during CDI treatment; mortality rate at day 30 was similar in acute care hospitals and rehabilitation hospitals ($P = .27$). One patient died before prescription of any CDI treatment; 38 patients did not have discontinuation of the likely offending antibiotic at the onset of CDI, with mortality rate of 28.9% at day 30 (11/38).

Recurrence rate at day 30 was 13%. When recurrence occurred, treatment was the same as the one for the first episode in 9 cases (28.1%), vancomycin was prescribed in 10 cases (31.2%), fidaxomicin in 7 cases (21.9%), and metronidazole in 1 case. Three patients (9.4%) were treated with combination of antibiotics and 2 did not have any therapeutic management. Among the 31 deaths at day 30, 9 (29%) patients had presented with a recurrence.

Univariate analysis showed that occurrences of organ failure, CIRS score, severe comorbidity (CIRS score >14) and a higher number of severity risk markers (≥3) were significantly associated with mortality (Table 2). Multivariate analysis showed that CIRS score (HR 1.06 per 1-point increase, 95% CI 1.00-1.12) and occurrence of organ failure as defined (HR 3.04, 95% CI 1.40-6.59) were significantly associated with mortality at day 30 (Table 2, Figures 1 and 2). Thus, an increase of 10 points of the CIRS score would increase the risk of mortality up to 78%.

Discussion

CDI is known as a severe disease, but data in the oldest old are scarce. Our study reports management and short-term prognosis in 247 patients hospitalized in geriatrics and infectious diseases wards with a mean age of 87.2 (SD 5.4) years. We wanted to focus the analysis

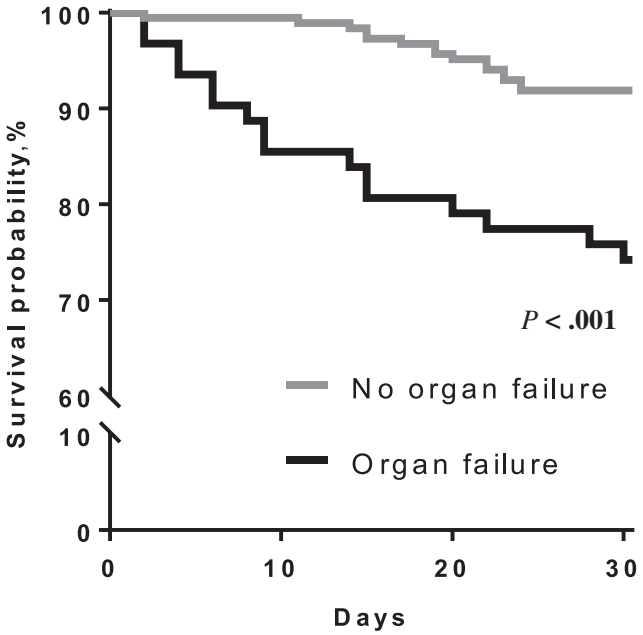

Fig. 1. Kaplan-Meier plot of 30-day survival probability after *Clostridioides difficile* infection diagnosis comparing patients with or without organ failure. Organ failure was assessed when there was use of diuretics, rise in serum creatinine level ≥1.5 times the premorbid level, or need for oxygen.

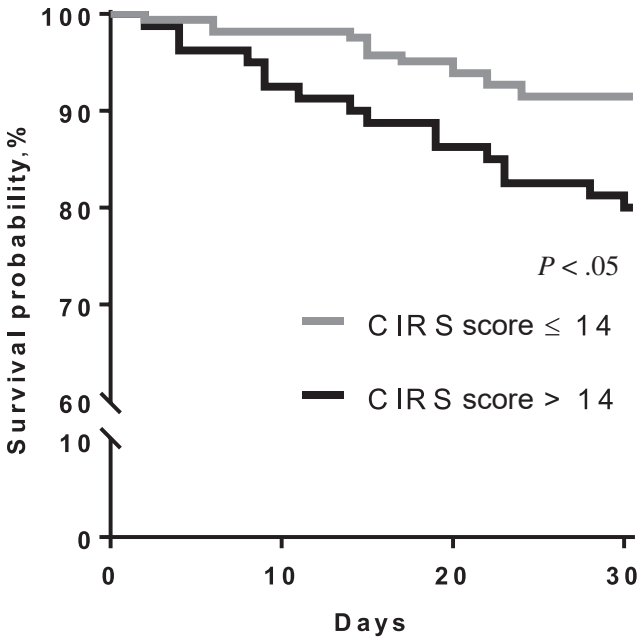

Fig. 2. Kaplan-Meier plot of 30-day survival probability after *Clostridioides difficile* infection diagnosis according to Cumulative Illness Rating Scale (CIRS) score (cutoff of 14).

within the 30-day interval after CDI diagnosis to better consider the weight of the infection at short term. Our results show a rate of 12.6% of all-cause mortality at day 30, 58.1% occurring during CDI episode treatment. The rate of mortality was the same in acute care hospitals and in rehabilitation hospitals. Important to note that in France, rehabilitation centers are considered as rehabilitation hospitals and a patient with CDI in a rehabilitation hospital is treated in the rehabilitation hospital. This rate is lower than 30-day mortality rates reported in literature, which were between 16.5% and 32.2% in patients older than 65 and 80 years, respectively.[21,27,28]

Organ failure, defined as relying on intravenous loop diuretics, need for oxygen, or rise in serum creatinine level ≥50% of the premorbid level, was the most predictive parameter of short-term mortality (HR 3.04, CI 95% 1.40-6.59). Among these criteria, renal failure occurring during the course of CDI illness and relying on rise in serum creatinine level ≥1.5 times the premorbid level was the most relevant (Table 2). These results underline the predictivity of a vulnerable status. Indeed, our results highlight the weight of comorbidities in this very old population having a CIRS score significantly associated with mortality ($P = .033$). Other studies conducted in similar-aged populations focused on mortality risk factors,[22,29–32] but none of them had assessed comorbidities with CIRS.[22,30–32] We used the criteria "CIRS score >14" to define the comorbidity as severe (Figure 2). Our results show that this criterion was significantly associated ($P = .013$) with mortality in univariate analysis. It confirms the central place of the CIRS score in CDI mortality prognosis in older adults. Despite its significance, we could not logically insert this median score in multivariate analysis with the CIRS continuous variable.

The adequacy of European markers of the risk of severity with mortality, including comorbidities, was already reported on in previous meta-analysis and retrospective studies.[7,29] Our results also showed that patients with ≥3 markers of risk of severity had a higher risk of mortality ($P = .022$).

Almost half of deaths (48.4%) occurred before 10 days of therapeutic management, verifying the weight of organ failure and questioning the adequacy of the initial antibiotic. Although antibiotic prescription was not associated with mortality at day 30, metronidazole was the most frequent initial treatment (51.0%), as reported in the literature.[16,33] Vancomycin and fidaxomicin were more frequently prescribed as a second-line treatment and on recurrence. This highlights the lack of adherence to the guidelines, which do not recommend prescription of metronidazole for patients profiled with disease severity markers.[13,34] Fidaxomicin represents a small part of the CDI initial treatment.[33] This molecule is recent, with a higher cost, which may be a barrier in clinical practice despite the lower risk of recurrence associated with this treatment.[35,36]

However, because of the weight of comorbidity and risk of organ failure in CDI short-term prognoses, our results enhance the need to better control modifiable risk factors of CDI, such as antibiotics prescription and hygiene control.

On the one hand, the practices that we observe adhere to European and US guidelines for diagnosis of CDI, as all patients had both clinical symptoms and positive laboratory tests. On the other hand, the practices deviate from treatment guidelines, as patients >65 years old with CDI should not be treated with metronidazole.[13,34]

Our study has some limitations. First, it is a survey. All older adult patients with CDI may not have been included by investigators during the study period. Second, a longer follow-up should be also performed to assess markers associated with recurrences and the real impact of CDI antibiotic treatment.

Conclusions and Implications

This prospective survey, in hospitalized patients aged ≥75 years with CDI, confirms the high risk of short-term mortality in older adults, with more than half of deaths occurring before the end of therapeutic management. European severity markers are adequate in the oldest old. Organ failure, mainly renal failure, and comorbidities appeared to be the main markers of prognosis. These markers should raise awareness of practitioners to anticipate prognosis of this infection. Although antibiotic treatment was not predictive of short-term mortality, our results point out the lack of adherence to current guidelines in this population.

Acknowledgments

Laurence Maulin, MD, Guillaume Puigserver, MD (Aix); Thibaut Fraisse, MD (Alès); Aude Pignon, MD, Lucie Tremblay Nguyen, MD (Angers); Céline Jarry, MD (Angoulême), Emilie Piet, MD (Annecy); Emmanuel Bard, MD (Belley); Charles-Emmanuel Geffroy, MD, Patrick Friocourt, MD (Blois); Isabelle Bourdel-Marchasson, MD, PhD, Maria Dubos, MD, Claire Roubaud-Baudron, MD, PhD (Bordeaux); Emmanuel Forestier, MD (Chambery); Fanny-Nisrin Ghazali, MD (Châtellerault); Sylvie Dardalhon, MD, Claudine Hauler, MD (Colmar); Sylvain Dadet, MD (Clermont-Ferrand); Philippe Suel, MD (Dieppe); Christine Piroth, MD, PhD, Alain Putot, MD (Dijon); François Berode, MD (Dunkerque); Ana-Maria Dascalita, MD (St Etienne); Isabelle Carriere, MD (St Galmier); Gaetan Gavazzi, MD, PhD, Patricia Pavese, MD (Grenoble); Lenaig Merrien, MD (Landerneau); Gilles Albrand, MD, Chala Hayet, MD, Denis Federico, MD, Sylvain Gaujard, MD, Géraldine Martin-Gaujard, MD (Lyon); Claude Jeandel, MD, PhD, Aurélie Terminet, MD (Montpellier); Cyprien Arlaud, MD, Jean-Michel Turpin, MD (Nice); Maurice Viala, MD, Benoit de Wazières, MD, PhD (Nîmes); Sandrine Kahlifa, MD (Niort); Jean-Christophe Bourgeois, MD (Orléans); Alice Breining, MD, Bernard Durand-Gasselin, MD, Ségolène Greffe, MD, Sophie Moulias, MD, Elisabeth Rouveix, MD, PhD (Paris); Aurélia Eden, MD, Irène Silga, MD (Perpignan); Aribi El Heddi, MD (Plaisir); Antoine Chartier, MD (Rochefort); Karine Guignery-Kadri, MD, Aini Kloul, MD, Violaine Renaudier, MD (Rouen); Louis Bernard, MD, PhD, Marc Lamande, MD (Tours); François Marechal, MD, Carole Pietropaoli, MD (Trevoux); Ronan Fevrier, MD, Romain Decours, MD, Thomas Guimard, MD, Martine Martin, MD, Marine Morier, MD, Hélène Pelerin, MD (Hôpital de Vendée); Anne-Claire Jestin, MD (St Yvi).

References

1. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372:825–834.
2. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care–associated infections. N Engl J Med 2014;370:1198–1208.
3. Evans CT, Safdar N. Current trends in the epidemiology and outcomes of *Clostridium difficile* infection. Clin Infect Dis 2015;60:66–71.
4. Eckert C, Coignard B, Hebert M, et al. Clinical and microbiological features of *Clostridium difficile* infections in France: The ICD-RAISIN 2009 national survey. Med Mal Infect 2013;43:67–74.
5. Mizusawa M, Doron S, Gorbach S. *Clostridium difficile* diarrhea in the elderly: Current issues and management options. Drugs Aging 2015;32:639–647.
6. Surawicz CM. *Clostridium difficile* infection: Risk factors, diagnosis and management. Curr Treat Options Gastroenterol 2015;13:121–129.
7. Garey KW, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. J Hosp Infect 2008;70:298–304.
8. Hensgens MPM, Goorhuis A, Dekkers OM, et al. All-cause and disease-specific mortality in hospitalized patients with *Clostridium difficile* infection: A multicenter cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am 2013;56:1108–1116.
9. Cober Eric D, Malani Preeti N. *Clostridium difficile* infection in the “oldest” old: Clinical outcomes in patients aged 80 and older. J Am Geriatr Soc 2009;57:659–662.
10. Lee HC, Kim KO, Jeong YH, et al. Clinical outcomes in hospitalized patients with *Clostridium difficile* infection by age group. Korean J Gastroenterol 2016;67:81–86.
11. Roncarati G, Dallolio L, Leoni E, et al. Surveillance of *Clostridium difficile* infections: Results from a six-year retrospective study in nine hospitals of a North Italian local health authority. Int J Environ Res Public Health 2017;14:16.
12. Shorr AF, Zilberberg MD, Wang L, et al. Mortality and costs in *Clostridium difficile* infection among the elderly in the United States. Infect Control Hosp Epidemiol 2016;37:1331–1336.
13. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: Update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect 2014;20:1–26.
14. Bauer MP, Notermans DW, van Benthem BHB, et al. *Clostridium difficile* infection in Europe: A hospital-based survey. Lancet 2011;377:63–73.
15. Asempa T, Nicolau D. *Clostridium difficile* infection in the elderly: An update on management. Clin Interv Aging 2017;12:1799–1809.
16. Leffler DA, Lamont JT. *Clostridium difficile* infection. N Engl J Med 2015;372:1539–1548.
17. Shin JH, High KP, Warren CA. Older is not wiser, immunologically speaking: Effect of aging on host response to *Clostridium difficile* infections. J Gerontol A Biol Sci Med Sci 2016;71:916–922.
18. Shin JH, Gao Y, Moore JH, et al. Innate immune response and outcome of *Clostridium difficile* infection are dependent on fecal bacterial composition in the aged host. J Infect Dis 2018;217:188–197.
19. Trifan A, Girleanu I, Stanciu C, et al. *Clostridium difficile* infection in hospitalized octogenarian patients. Geriatr Gerontol Int 2017;18:315–320.
20. Marshall LL, Peasah S, Stevens GA. *Clostridium difficile* infection in older adults: Systematic review of efforts to reduce occurrence and improve outcomes. Consult Pharm 2017;32:24–41.
21. Leibovitz A, Yarovoy A, Sharshar N, et al. *Clostridium difficile*-associated disease: A primary clinical evaluation of elderly patients in a geriatric hospital. Am J Infect Control 2016;44:1158–1160.
22. Leibovici-Weissman Y, Atamna A, Schlesinger A, et al. Risk factors for short- and long-term mortality in very old patients with *Clostridium difficile* infection: A retrospective study. Geriatr Gerontol Int 2017;17:1378–1383.
23. McGowan AP, Lalayiannis LC, Sarma JB, et al. Thirty-day mortality of *Clostridium difficile* infection in a UK National Health Service Foundation Trust between 2002 and 2008. J Hosp Infect 2011;77:11–15.
24. Miller M, Gravel D, Mulvey M, et al. Health care-associated *Clostridium difficile* infection in Canada: Patient age and infecting strain type are highly predictive of severe outcome and mortality. Clin Infect Dis 2010;50:194–201.
25. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified Cumulative Illness Rating Scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926–1931.
26. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: Application of the Cumulative Illness Rating Scale. Psychiatry Res 1992;41:237–248.
27. Karas JA, Bradshaw S, Mahmud W, et al. Mortality in hospitalized older adults associated with *Clostridium difficile* infection at a district hospital. Infect Dis Rep 2010;2:e8.
28. Wenisch JM, Schmid D, Kuo HW, et al. Hospital-acquired *Clostridium difficile* infection: Determinants for severe disease. Eur J Clin Microbiol Infect Dis 2012;31:1923–1930.
29. Abou Chakra CN, Pepin J, Sirard S, et al. Risk factors for recurrence, complications and mortality in *Clostridium difficile* infection: A systematic review. PLoS One 2014;9:e98400.
30. Bhangu S, Bhangu A, Nightingale P, et al. Mortality and risk stratification in patients with *Clostridium difficile*-associated diarrhoea. Colorectal Dis 2010;12:241–246.
31. Lungulescu OA, Cao W, Gatskevich E, et al. CSI: A severity index for *Clostridium difficile* infection at the time of admission. J Hosp Infect 2011;79:151–154.
32. Welfare MR, Lalayiannis LC, Martin KE, et al. Co-morbidities as predictors of mortality in *Clostridium difficile* infection and derivation of the ARC predictive score. J Hosp Infect 2011;79:359–363.
33. Lefevre-Tantet-Etchebarne D, Sivadon-Tardy V, Davido B, et al. Community-acquired *Clostridium difficile* infections in emergency departments. Med Mal Infect 2016;46:372–379.
34. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66:987–994.
35. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422–431.
36. Louie TJ, Miller MA, Crook DW, et al. Effect of age on treatment outcomes in *Clostridium difficile* infection. J Am Geriatr Soc 2013;61:222–230.