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Treatment compliance with European guidelines and prognosis of *Clostridium difficile* infection according to age

Adéquation de la prise en charge thérapeutique aux recommandations européennes et pronostic des infections à *Clostridium difficile* selon l'âge

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Mots clés : infections à *Clostridium difficile*, personne âgée, mortalité, recommandations

Abstract

Objective. Age >65 years is associated with the recurrence and poor prognosis of *Clostridium difficile* infection (CDI). Data on elderly patients (≥ 75 years) is scarce, and little is known about compliance with European guidelines in terms of specific treatment. We aimed to analyze the treatment and prognosis of CDI in two groups of patients aged < and ≥ 75 years.

Patients and methods. We performed a prospective survey from May 2014 to April 2015 in a university hospital including all patients presenting with microbiologically confirmed CDI. Sociodemographic and clinical data, treatment of CDI, recurrences (<8 weeks after CDI treatment completion), new episodes, and mortality were recorded. Follow-up was performed until February 2016.

Results. Overall, 101 patients were included; 45 were aged ≥ 75 years (44.6%). More than two-thirds of CDIs (71/101) were severe. Seven per cent of patients presenting with severe CDI and 10% of patients at increased risk of recurrence received the adequate treatment as per European guidelines. Mean follow-up was 15 ± 4 months (range: 10-22). Among patients aged ≥ 75 years, we observed the same number of recurrences and new episodes of CDI during the follow-up. The 3-month case fatality was significantly higher in the elderly group ($P < 0.001$). The one-year survival rate was 73.2% in younger patients and 45.7% in elderly patients ($P = 0.0004$).

Conclusion. This study confirms the poor prognosis of CDI in elderly patients and highlights the lack of compliance with treatment guidelines.

Résumé

Objectif. L'âge > 65 ans est associé à un risque de récurrence et de mauvais pronostic des infections à *Clostridium difficile* (ICD). Les données concernant les patients ≥ 75 ans sont limitées et l'adéquation de la prise en charge thérapeutique des ICD aux recommandations européennes a été peu étudiée. Analyse du traitement et du pronostic des ICD en comparant deux groupes de patients âgés de < et ≥ 75 ans (mai 2014-avril 2015).

Patients et méthodes. Nous avons inclus tous les cas d'ICD confirmés microbiologiquement. Les données sociodémographiques et cliniques, le traitement, les récurrences (< 8 semaines après la fin du traitement), les nouveaux épisodes et la mortalité ont été recueillis. La cohorte a été suivie jusqu'en février 2016.

Résultats. 101 patients ont été inclus ; 45 âgés de ≥ 75 ans (44,6 %). 71/101 patients étaient graves, 7 % des patients ayant une ICD grave et 10 % des patients ayant un risque élevé de récurrence ont reçu un traitement adapté selon les recommandations européennes. Avec une limite à 75 ans, le nombre de récurrences et d'épisodes ultérieurs d'ICD était identique dans les deux groupes. Le taux de mortalité à 3 mois était plus élevé chez les patients très âgés ($P < 0,001$). Le taux de survie à un an était de 73,2 % chez les patients < 75 ans et de 45,7 % chez ceux ≥ 75 ans ($P = 0,0004$).

Conclusion. Cette étude souligne le mauvais pronostic des ICD chez les personnes âgées et la faible adéquation aux recommandations thérapeutiques.

Introduction

Clostridium difficile (CD) is considered the first cause of nosocomial diarrhea. The incidence of CD infection (CDI) has increased in France to reach 3.6 cases per 10,000 patient-days in 2012, with an annual attributable cost of around 160 million euros [1-3]. The morbidity rate and case fatality of this infection are high, with a 30% risk of recurrence [4] and a 3-month case fatality of 20% [5]. European guidelines were published in 2014, but little is known about the compliance with these recommendations [6]. Older age is usually associated with poor prognosis in terms of severity, recurrence, and mortality [7-9]. Yet the age to consider risks of severe CDI and of recurrence in the literature is low, with a cut-off at the age of 65. Data focusing on patients aged over 75 years is scarce.

The aim of our study was to analyze the treatment and long-term prognosis of CDI in two groups of patients aged $<$ and ≥ 75 years.

Methods

We performed a one-year prospective survey, from May 2014 to April 2015, in a university hospital (1,698 beds) with a geriatric department (490 beds: acute care, rehabilitation, long-term care). All cases of CD isolated from stool samples in our microbiology laboratory led to investigations in the clinical units, and only patients with a confirmed diagnosis of CDI were included. Cases were defined as described in the European guidelines [6]: a clinical picture compatible with CDI (diarrhea, ileus, or toxic megacolon) and microbiological evidence of free toxins and presence of *C. difficile* in unformed stool without reasonable evidence of another cause of diarrhea; or pseudomembranous colitis. A two-step algorithm is used at our hospital to detect CD: first with a glutamate dehydrogenase (GDH) test (C. DIFF QUIK CHEK[®]) [10] and positive GDH stool samples are then tested by

real-time polymerase chain reaction (Xpert[®] *C. difficile* on Cepheid GeneXpert[®] Dx System) assay to detect the presence of *tcdB*, binary toxin genes (*cdt*), and deletion nt 117 on *tcdC* gene characteristic of the BI/NAP1/O27 strain. A positive GDH and PCR sample is considered a positive microbiological test.

Data collection

A standardized questionnaire was filled in at baseline: demographic data and immunocompromised status (malignancy, chemotherapy or immunosuppressive treatment, corticosteroid therapy) were collected. The following risk factors associated with CDI were recorded: antibiotic exposure before and during the hospital stay, proton pump inhibitor therapy and number of hospitalizations in the previous year. Antibiotic exposure three months before hospitalization was recorded based on the patients' history and phone calls to family physicians. Duration of symptoms and specific treatment for CDI were recorded. As our hospital did not have any policy for CDI antibiotic administration, physicians were free to prescribe the treatment of their choice for CDI. Markers to determine severe CDI and increased risk of recurrence were collected, as per European guidelines [6]. Thus, fever $>38.5^{\circ}\text{C}$, albuminemia $<30\text{ g/L}$, leucocyte count $>15.10^9/\text{L}$, rise in serum creatinine level ($\geq 133\text{ }\mu\text{mol}$ or ≥ 1.5 times the pre-morbid level), and colitis (colonic ileus, peritonitis, CT scan complications, pseudomembranous colitis) were used to determine severe CDI. Age >65 years, history of previous CDI, antibiotic continuation after diagnosis of CDI, concomitant use of proton pump inhibitors, initial disease severity, and renal failure were used to determine an increased risk of recurrence. CDI was defined as community-acquired when occurring before hospital admission or within three days after admission without any overnight stay in a healthcare facility in the previous 12 weeks. Specific treatment,

compliance with treatments recommended in the European guidelines, and new episodes of CDI (recurrences within eight weeks after resolution of the initial episode and other episodes occurring more than eight weeks after resolution of the initial episode) were recorded. Follow-up and case fatality were assessed using a standardized process until February 2016 by calling family physicians and reviewing medical records on the same day. The protocol was approved by the local ethics committee.

Statistical analysis

Qualitative variables were compared by Fisher's exact test and quantitative variables by the Mann-Whitney test with the SAS system package. The survival analysis used the Kaplan-Meier method and logrank test. Statistical significance was considered if a 2-sided *P* value was ≤ 0.05 .

Results

A total of 1,525 stool samples were tested for CD during the 12-month enrolment period, of which 173 were positive by GDH test and 131 by PCR. No BI/NAP1/O27 strain was isolated. After clinical investigation, 101 patients with CDI diagnosis were included with a mean age of 68.1 ± 19.2 years and 45 patients aged ≥ 75 years (44.6%) (Figure 1). As 10.2% were diagnosed as community-acquired, the nosocomial incidence of CDI was estimated at 8.1 cases per 100,000 patient-days (95% CI: 6.6-9.9).

Elderly patients commonly lived in nursing homes (37.8%). Younger patients were significantly more immunosuppressed ($P=0.028$) according to our criteria, with more hospital stays in the previous year ($P=0.006$). The main causes of immunosuppression were neoplasia

(n=38, 27 patients <75 years), chemotherapy (n=23, 19 <75 years), and prolonged corticosteroid therapy (n=15, 12 <75 years) (Table I).

The two groups of patients were similar in terms of risk factor exposure. One-third had received antibiotics within three months before admission and nearly half of patients were treated with antibiotics at the time of CDI diagnosis, mainly penicillins and cephalosporins. Over two-thirds of CDIs (71/101) were considered severe (Table II). The mean numbers of markers determining a severe CDI and determining an increased risk of recurrence were similar, irrespective of age. Nevertheless, fever >38.5°C was more frequent in the younger group ($P=0.042$), whereas albuminemia <30 g/L was more frequent in patients aged ≥ 75 years ($P=0.041$). Among the 30 patients presenting with non-severe CDI, 28 presented with at least one risk factor for recurrence. Metronidazole was the first-line antibiotic prescribed to 87.3% of severe CDI patients and to 90% of non-severe CDI patients. First-line treatment failure was reported in 18 patients (17.8%). Second-line treatment included oral vancomycin in 13 patients, oral vancomycin combined with intravenous metronidazole in one patient, and fidaxomicin in one patient. A third-line treatment was prescribed to three patients: fidaxomicin (n=2) and oral vancomycin combined with parenteral metronidazole (n=1).

Mean duration of first-line treatment was 9.5 ± 3.2 days (similar in both groups). Mean duration of overall specific treatment was 11.6 ± 7.7 days in group 1 and 11.2 ± 4.5 days in group 2.

According to the European guidelines, 7% and 10% of patients respectively presenting with severe CDI and risk of recurrence received the adequate treatment regimen. The percentage of adequate treatments was higher in non-severe CDI cases (60%; 18/30).

Prognosis

The median duration of hospital stay was 21 days [0-158 days], similar in both groups. One

patient died before initiating the specific antibiotic treatment. Three patients died while treated with the first-line antibiotic. Fifteen recurrences were recorded during follow-up (seven in group 1) and were treated as per European guidelines in nine cases (60%). Seven patients presenting with recurrent CDI died (46.6%), on average 27.9 ± 19.1 days after the diagnosis of recurrence. Median follow-up of the cohort was 15 months (range 10-22). Another episode of CDI (>8 weeks after resolution of the initial episode) occurred in seven patients: six patients <75 years and 1 ≥ 75 years, respectively 6.3 ± 4.6 months and 9 months after the initial diagnosis. Overall, 22 patients relapsed after the first episode of CDI, 13 patients <75 years (23.2%) and nine ≥ 75 years (20%). The case fatality was 23.8% during the hospital stay and 32.7% after three months of follow-up, significantly higher in elderly patients (Table III). Ten additional deaths were recorded after the third month, with a mean time of 8.7 ± 5.3 months after the initial CDI diagnosis: six deaths (12.8%) in patients <75 years and four (19%) in patients ≥ 75 years. Median survival after CDI diagnosis was 3.3 months in patients ≥ 75 years. The one-year survival rate was $74 \pm 6\%$ in the younger patient group and $36.4 \pm 7.7\%$ in the elderly group ($P=0.0004$) (Figure 2).

Discussion

Clostridium difficile infection is associated with significant morbidity and mortality. As data on CDI in elderly patients is scarce, we aimed to compare the management and prognosis of this disease in two groups of patients aged <75 and ≥ 75 years. In this survey, CDI incidence was 0.81/10,000 patients-day, i.e. lower than the French CDI incidence reported at 3.6 ± 2.9 cases per 10,000 patient-days [2]. Metronidazole was the most often used antibiotic with a low compliance with European guidelines. The three-month survival rate was 67.3%, higher than the rates reported in previous studies [5, 11] and particularly unfavorable in elderly

patients. The one-year survival rate was also significantly lower in this same group ($P=0.0004$). In our study the number of markers determining severe CDI and increased risk of recurrence was the same in both groups. The cut-off age of 75 and the higher number of patients with criteria for immunodeficiency might explain this result differing from those of previous studies [3, 5, 6, 9, 10, 12-17]. It should also be noted that we did not collect any data on comorbidities such as heart failure, diabetes, or cognitive disorder that would probably be more frequent in patients aged ≥ 75 years. Age and immunosenescence are known to enhance the risk and the poor prognosis of CDI. In elderly people, structural changes occur in the ecosystem with decline of protective bacterial species and increase of detrimental ones, leading to the alteration of the microbiotas [18]. Antibiotics are well-known risk factor for CDI; they disrupt the natural protective microbiota enabling the overgrowth of *Clostridium difficile* and toxin expression. Advanced age is associated with higher antibiotic exposure and prolonged hospitalization. Immunodeficiency also contributes to the pathogenesis of CDI. Immunocompromised and cancer patients are often exposed to hospital environment, antibiotics, and gastric acid-suppressing medications. Chemotherapeutic agents alter the commensal flora and have an antimicrobial-like effect on the microbiota similar to antibiotics [19]. Gastric acid-suppressing medications, such as proton pump inhibitors prescribed to 54% of the cohort, alter the protective effect of gastric acid and increase the load of bacterial species leading to decreasing bacterial diversity and disrupting the gut microbiota [20]. Glucocorticoids, due to their anti-inflammatory and immunosuppressive effects, also increase the risk of CDI, all the more if patients received this treatment at the time of CDI [21].

Our study underlines the lack of knowledge or of consideration of guidelines. This lack of compliance with European guidelines needs to be highlighted as metronidazole was prescribed regardless of the severity or the risk of recurrence, while vancomycin or fidaxomicin are recommended. It is difficult to say if this non-compliance is associated with

the high case fatality, as literature data is heterogeneous [8, 22, 23]. Nevertheless, guideline-compliant therapy was associated with a significant reduction in recurrence and mortality on Day 30 [24]. The frequency of recurrences was 14.8%, close to literature data reporting figures between 18% and 25% [4, 5, 16, 25, 26]. However, the recurrence rate is identical in both groups, which is not consistent with previous literature data [4, 16, 25, 26]. The low sample size of our study, the cut-off age of 75, and the high rate of young immunocompromised patients may again explain this result. If we had chosen a cut-off age of 65, 11 patients ≥ 65 years would have developed recurrent CDI (within eight weeks after resolution of the initial episode), almost three times the number of recurrences ($n=4$) in patients <65 years. The association between age and poor prognosis is well known [6, 27, 28]. A recent review focusing on the 30-day case fatality reported an increased rate in patients aged >70 years [26]. CDI is associated with an almost twice higher mortality in adults aged >65 years ($P<0.001$) [12]. The median survival of patients aged ≥ 75 years in our cohort (3.3 months) is close to the result of a retrospective study also evaluating CDI in elderly patients (mean age 86 ± 4.8) [8]. A higher case fatality observed among elderly patients is not surprising. Although we did not collect the number of comorbidities, this group of patients was significantly more often institutionalized, which means that most of them were probably affected by multiple comorbidities. However, this higher case fatality cannot be attributable to CDI recurrences. A recent study reported a decreased case fatality attributable to CDI particularly in elderly patients, due to the reduced transmission of virulent strains thanks to infection control measures and improved testing allowing for an earlier treatment [29]. The lack of compliance with guidelines could be explained by the lack of local policy to treat CDI. Although all patients were symptomatic, thus reducing the risk of including colonized patients and although we used a high cut-off for age, our study has several limitations. It was a monocenter study with a low sample size. Results thus cannot be generalized to the overall

population. We did not collect any score of comorbidities, which could have influenced the prognosis. The causes of death were not recorded, and we were not able to determine how many deaths were attributable to CDI.

Conclusion

The occurrence of CDI and severe CDI was as often described in patients aged <75 years as in patients aged ≥ 75 years, and the number of recurrences was not different. As expected, the case fatality was significantly higher in elderly patients. Our study highlights the lack of compliance with treatment guidelines.

Contributions of author

Dr M. Lauda-Mailen designed the study protocol, collected the data, analyzed the data, and wrote the article.

Dr E. Liuu analyzed the data and reviewed the article.

Dr M. Catroux analyzed the data and reviewed the article.

Dr A. Caupenne designed the study protocol, analyzed the data, and reviewed the article.

Dr M. Priner designed the study protocol, analyzed the data, and wrote the article.

Pr F. Cazenave-Roblot analyzed the data and reviewed the article.

Pr C. Burucoa analyzed the data and reviewed the article.

Pr P. Ingrand analyzed the data, performed the statistical analysis, and reviewed the article.

Pr M. Paccalin designed the study protocol, analyzed the data, and wrote the article.

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Figure 1. Flow chart

Figure 1. Diagramme de flux

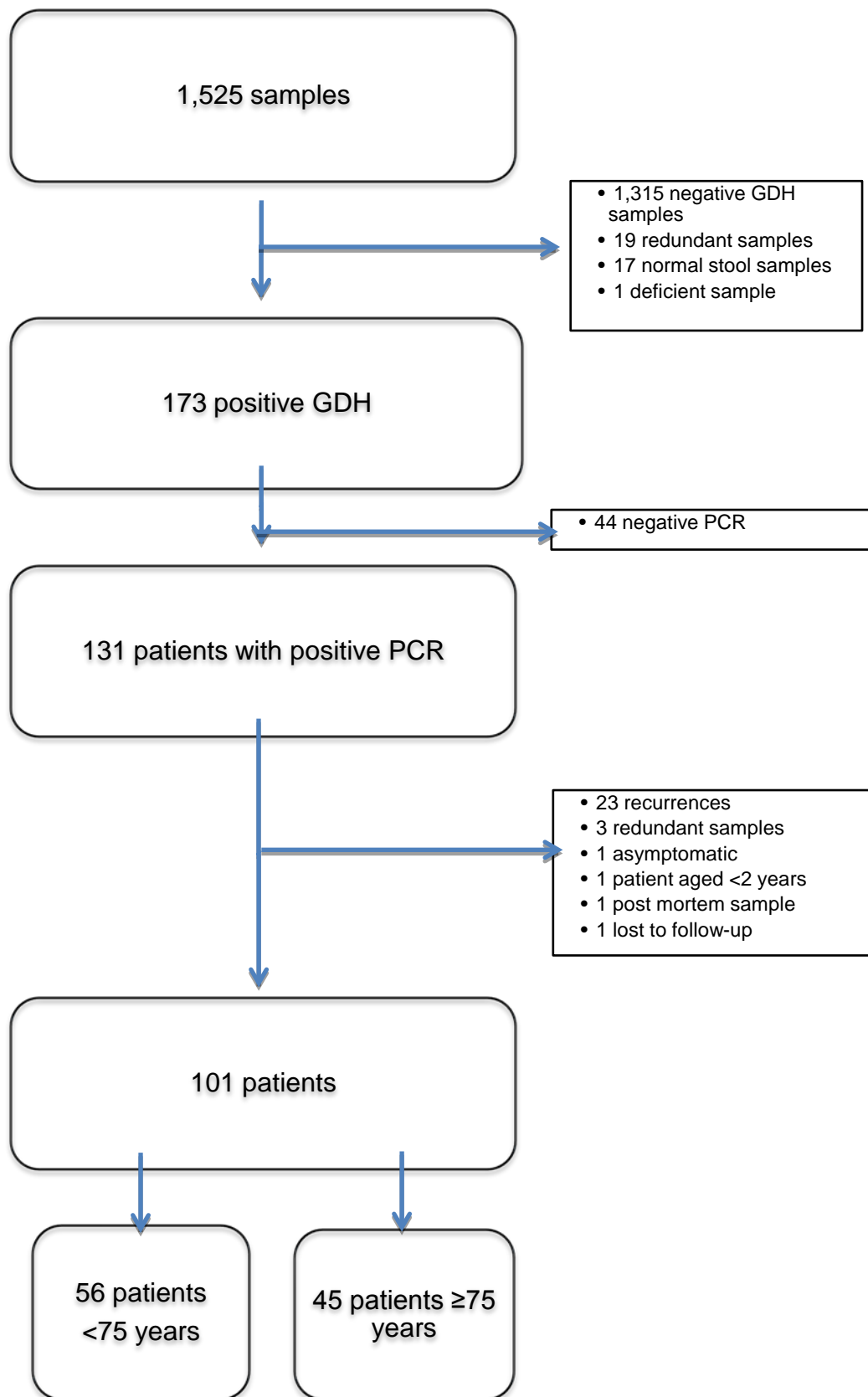


Figure 2. Kaplan-Meier survival estimates

Figure 2. Courbes de survie de Kaplan-Meier

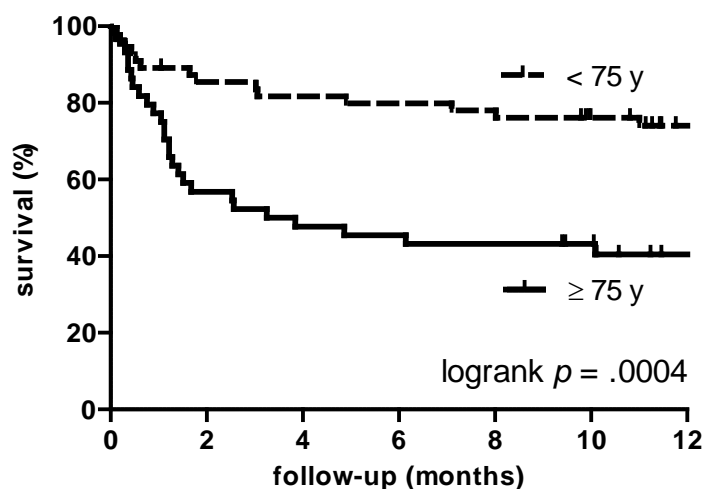


Table I. Characteristics of patients and exposure to risk factors

Tableau I. Caractéristiques des patients et exposition aux facteurs de risque

	<75 years	≥75 years	
n	56	45	<i>P</i>
Age (years)	55.5 ± 2.2	83.8 ± 1.0	
Men (%)	34 (60.7)	14 (31.1)	.0048
Living at home (%)	52 (92.9)	28 (62.2)	.0002
Living in nursing homes (%)	4 (7.1)	16 (36.4)	.0004
Community-acquired CDI (%)	4 (7.1)	6 (13.3)	.33
Median duration (days) of hospital stay before symptom onset	6 (0-13)	5 (0-15)	.91
Antibiotic exposure 3 months before hospitalization (%)	34 (60.7)	32 (71.1)	.30
Antibiotic exposure in hospital (%)	42 (75.0)	32 (72.7)	.82
Antibiotics at the time of symptoms (%)	30 (53.6)	22 (48.9)	.69

Continued use of antibiotics after diagnosis of CDI (%)	27 (48.2)	20 (44.4)	.84
Immunosuppression (%)	35 (62.5)	18 (40.0)	.029
Concomitant use of proton pump inhibitor (%)	29 (51.8)	26 (57.8)	.69
Number of medications	7.45 ± 4.99	7.93 ± 2.95	.48
Number of hospital stays in the last year	2.18 ± 2.22	1.09 ± 1.53	.004
Median time (days) since the last hospital stay	28 (10-103)	17 (9-69)	.54

Continuous variables were expressed as mean ± SD or median (interquartile range: 25%-75%).

CDI: *Clostridium difficile* infection.

Table II. Criteria for severe *Clostridium difficile* infection (CDI) according to the European guidelines [6]

Tableau II. Critères de sévérité des infections à *Clostridium difficile* (ICD) selon les recommandations européennes

	<75 years n=56	≥75 years n=45	P
Severe CDI (%)	40 (71.5)	31 (68.9)	.83
Number of prognostic markers of severity	1.36 ± 1.23	1.53 ± 1.41	.58
Decreased blood albumin <30 g/l (61 samples)	11 (36.7)	20 (64.5)	.041
Leucocyte count >15x10⁹/L	17 (30.4)	17 (37.8)	.53
Rise in serum creatinine level (>133 µM/l or >50% above the baseline)	13 (23.2)	14 (31.1)	.50
Fever >38.5°C	28 (50.0)	13 (28.9)	.042
Colonic ileus	2	1	-
Peritonitis	0	0	-
CT scan complications (22 imaging tests)	7	3	-
Pseudomembranous colitis (6 colonoscopies)	0	1	-

Continuous variables were expressed as mean (\pm SD)

CDI: *Clostridium difficile* infection

Table III. Follow-up of patients

Tableau III. Suivi des patients

	<75 years n=56	≥75 years n=45	P
Length of hospital stay (days)	21 (9-34)	22 (15-40)	.40
Number of recurrences (<8 weeks) (%)	7 (12.5)	8 (17.8)	.58
Hospital case fatality (%)	8 (14.3)	16 (35.6)	.018
Three-month case fatality (%)	9 (16.1)	24 (53.3)	<.0001
New CDI episodes (%)	13 (23.2)	9 (20)	.68

CDI: *Clostridium difficile* infection

New CDI episode: all episodes occurring during the follow-up after the initial CDI, episode within eight weeks after resolution of the initial episode (recurrence), and other episodes occurring more than eight weeks after resolution of the initial episode.