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BRIEF ARTICLE

Predictors of *Clostridium difficile* infection severity in patients hospitalised in medical intensive care

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Abstract

AIM: To describe and analyse factors associated with *Clostridium difficile* infection (CDI) severity in hospitalised medical intensive care unit patients.

METHODS: We performed a retrospective cohort study of 40 patients with CDI in a medical intensive care unit (MICU) at a French university hospital. We include patients hospitalised between January 1, 2007 and December 31, 2011. Data on demographics characteristics, past medical history, CDI description was collected. Exposure to risk factors associated with CDI within 8 wk before CDI was recorded, including previous hospitalisation, nursing home residency, antibiotics, antisecretory drugs, and surgical procedures.

RESULTS: All included cases had their first episode of CDI. The mean incidence rate was 12.94 cases/1000 admitted patients, and 14.93, 8.52, 13.24, 19.70, and 8.31 respectively per 1000 admitted patients annually from 2007 to 2011. Median age was 62.9 [interquartile range (IQR) 55.4-72.40] years, and 13 (32.5%) were women. Median length of MICU stay was 14.0 d (IQR 5.0-22.8). In addition to diarrhoea, the clinical symptoms of CDI were fever (> 38 ℃) in 23 patients, abdominal pain in 15 patients, and ileus in 1 patient. The duration of diarrhoea was 13.0 (8.0-19.5) d. In addition to diarrhoea, the clinical symptoms of CDI were fever (> 38 ℃) in 23 patients, abdominal pain in 15 patients, and ileus in 1 patient. Prior to CDI, 38 patients (95.0%) were exposed to antibiotics, and 12 (30%) received at least 4 antibiotics. Fluoroquinolones, 3rd generation cephalosporins, coamoxiclav and tazocillin were prescribed most frequently (65%, 55%, 40% and 37.5%, respectively). The majority of cases were hospital-acquired (n = 36, 90%), with 5 cases (13.9%) being MICU-acquired. Fifteen patients had severe CDI. The crude mortality rate within 30 d after diagnosis was 40% (n = 16), with 9 deaths (9 over 16; 56.3%) related to CDI. Of our 40 patients, 15 (37.5%) had severe CDI. Multivariate logistic regression showed that male gender [odds ratio (OR): 8.45; 95%CI: 1.06-67.16, P = 0.044], rising serum C-reactive protein levels (OR = 1.11; 95%CI: 1.02-1.21, P = 0.021), and previous exposure to fluoroquinolones (OR = 9.29; 95%CI:

1.16-74.284, P = 0.036) were independently associated with severe CDI.

CONCLUSION: We report predictors of severe CDI not dependent on time of assessment. Such factors could help in the development of a quantitative score in ICU's patients.

Key words: *Clostridium difficile*; Health-care associated infection; Hospital-acquired infection; Intensive care unit; Nosocomial infection; Severe *Clostridium difficile* infection

Core tip: We reported that male gender, rising serum C-reactive protein level, and previous exposure to fluoroquinolones were independently associated with severe *Clostridium difficile* infection (CDI) in medical intensive care unit. This could help in the development of a quantitative severity score that could fuel comparative effectiveness studies and prospective trials of CDI therapy in critically-ill patients.

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INTRODUCTION

Clostridium difficile (*C. difficile*) infection (CDI) has become a growing cause of nosocomial morbidity, high hospital costs and mortality in North America as well as in other areas of the world[1-6]. Hospital-acquired CDI has surpassed methicillin-resistant *Staphylococcus aureus* (*S. aureus*) in some hospitals as the leading source of healthcare-associated infections[7] and was ranked in the five most important scientific issues facing healthcare epidemiology[8]. Several mechanisms have been postulated to increase disease severity, including the emergence of specific strains with genetic polymorphisms that encode higher levels of bacterial toxins A and B as well as the production of a binary toxin[9-11]. Advanced age, severe co-morbidity, hospitalisation, antibiotic exposure, immunosuppressants and treatment with motility-influencing or acid-suppressive drugs have all been implicated as risk factors for CDI[12-17].

The cumulative mortality attributable to CDI for all patients typically ranges from 5.5% to 6.9% but can reach 16.7% during severe outbreaks[18-24]. In the United States, *C. difficile* is now the 9th leading gastrointestinal cause of death[25]. CDI is more common in the intensive care unit (ICU) setting, with an overall incidence of roughly 4%[26]. Up to 20% of ICU patients who develop symptomatic disease will progress to fulminant colitis with a mortality rate of nearly 60%[26]. In the United States, attributable costs range from $2871 to $4846 per case of primary CDI and from $13655 to $18067 for infection recurrence or relapse[18], with annual expenditures in excess of $3 billion[27]. A study of ICU patients disclosed gross costs of $11353 for CDI compared to $6028 without CDI[26].

CDI among critically-ill patients usually presents as diarrhoea, abdominal pain, hypotension, electrolyte perturbations, and fever[2,3,10,21,28,29]. Several studies have examined factors related to CDI acquisition and mortality in different medical units[30,31]. To the best of our knowledge, factors associated with CDI severity in medical ICUs (MICU) are poorly documented. We undertook a one-center cohort investigation to analyse factors linked with CDI severity and to report the prognosis of CDI in hospitalised MICU patients.

MATERIALS AND METHODS

Study population

This retrospective cohort study was performed at an 860-bed university-affiliated public hospital in Lyon, France. All adult patients with CDI diagnosed in a MICU (15 beds) between January 1, 2007 and December 31, 2011 were included. Patients were followed up until the last point of hospital contact. Thirty-day in-patient mortality from any cause was chosen as the primary endpoint. According to French law, a study like this one does not require ethics committee approval because it is observational and derives from a surveillance database approved under national regulations (*Comité National Informatique et Liberté*)[32]. Protocol design was approved by the hospital's institutional review board.

Data collection

After case identification, full medical files were reviewed and data collected through our institution's electronic medical database. The following data were analysed: age, sex, body weight, diagnosis on admission, co-morbidities, Glasgow coma score available on the day of ICU admission, nutritional status, parenteral nutrition administration, CDI symptoms and their duration, prior CDI history, results of microbiological tests, specific antibiotherapy for CDI, and evolution of infection. Exposure to risk factors associated with CDI within 8 wk before CDI was recorded, including previous hospitalisation, nursing home residency, antibiotics, antisecretory drugs (proton pump inhibitors, PPI), and surgical procedures (endoscopy, percutaneous gastrostomy, nasogastric feeding, gastrointestinal surgery). Leukocyte count, C-reactive protein, and serum albumin values were collected on days -2 to +2 relative to day 0 (the day the diarrhoeal sample was tested for CDI). Patient outcomes were analysed until in-patient death or last point of hospital contact.

Microbiological data

C. difficile testing was performed only on unformed stool samples from patients clinically suspected to have

CDI. Laboratory diagnosis of CDI was based on stool enzyme-linked immunosorbent assay (ELISA, Immuno-Card Toxins A and B, Meridian Biosciences, Cincinnati, OH, United States, Ref. 716060) coupled with toxigenic culture.

Definitions

All definitions were selected as part of routine CDI surveillance. Bacteriological cases of CDI were defined as positive enzyme linked immunosorbent assay (ELISA) results and/or positive toxigenic culture. Clinical CDI severity was considered when patients met at least 1 of the following criteria: endoscopically- or histologically-proven colitis or CDI-related complications, such as toxic megacolon, intestinal perforation, colectomy, septic shock, CDI requiring admission to ICU or related death in 30 d. It should be noted, however, that there are currently no prospectively-validated severity scores for CDI. Recurrence was defined as a new episode of diarrhoea and positive toxin assay within 8 wk after a first correctly-treated episode.

According to French guidelines, a nosocomial CDI was assumed if diarrhoea onset took place more than 2 d after admission to hospital or if hospital admission occurred within 4 wk of discharge and indeterminate or unknown if the patient had been discharged from a healthcare facility within the previous 4-12 wk. Cases were defined as community-acquired if CDI signs presented in the absence of previous hospitalisation within the last 12 wk in out- or in-patients within the first 48 h of admission[33]. French health authorities currently adopt a cut-off period of 48 h post-admission to define hospital-acquired infections. We considered fever as core temperature > 38 ℃, and leukocytosis as leukocyte count > 15×10^9/L. Malnutrition was defined according to the national recommendations[34]. The incidence rate was calculated as the number of CDI in MICU per 1000 admitted patients.

Statistical analysis

The data were analysed in 2 stages. First, univariate analysis identified significant differences between severe and non-severe CDI cases. Continuous variables were compared by the Mann-Whitney *U* test. The χ^2 or Fisher's exact test compared categorical variables. Second, a multivariate logistic regression model identified factors associated with CDI severity. The distribution of continuous variables was checked. All potential risk factors significant at the 0.2 level in univariate analysis were entered into the model. Multivariate analysis was performed with models that were judged a priori to be clinically sound. This was prospectively determined to be necessary to avoid producing spuriously significant results with multiple comparisons. The goodness-of-fit was assessed by the Hosmer-Lemeshow test. For all tests performed, 2-tailed *P* values < 0.05 were regarded as denoting statistical significance. Statistical data were analysed with statistical package for the social sciences (version 17.0 for Windows, SPSS, Inc., Chicago, IL).

RESULTS

A total of 40 adult patients suffering from CDI-related diarrhoea diagnosed in MICU from January 2007 and December 2011 were included. The mean incidence rate was 12.94 cases/1000 admitted patients, and 14.93, 8.52, 13.24, 19.70, and 8.31 respectively per 1000 admitted patients annually from 2007 to 2011 ($P = 0.99$). The demographics and outcomes of these patients are summarised in Table 1. Median age was 62.9 [interquartile range (IQR) 55.4-72.40] years; 13 (32.5%) were women, and 24 (60%) were admitted directly to MICU. Median length of MICU stay was 14.0 d (IQR 5.0-22.8). Twenty-nine patients (72.5%) presented symptoms after MICU admission, and 15 patients (37.5%) developed CDI 10 d or less after MICU admission. Based on the inclusion criteria, ELISA was positive in 35 patients (87.5%), with the remaining 5 patients (12.5%) being diagnosed by toxigenic culture. Median time between onset of symptoms and microbiological diagnosis was 2 d for ELISA and 10 d for toxigenic culture. The mean interval between onset of symptoms and *C. difficile* laboratory test results was 7.2 ± 16.5 d. The duration of diarrhoea was 13.0 (8.0-19.5) d. In addition to diarrhoea, the clinical symptoms of CDI were fever (> 38 ℃) in 23 patients, abdominal pain in 15 patients, and ileus in 1 patient. At the time of diagnosis, median leukocyte count was 14.4 (9.45-21.73), with leukocytosis (> 20 × 10^9/L) in 12 patients (30%). C-reactive protein was 117 mg/L (60-193), and albumin was 26.0 g/L (20.0-28.0). Prior to CDI, 38 patients (95.0%) were exposed to antibiotics, and 12 (30%) received at least 4 antibiotics. Fluoroquinolones, 3rd generation cephalosporins, coamoxiclav and tazocillin were prescribed most frequently (65%, 55%, 40% and 37.5%, respectively). During MICU stay, 12 patients received parenteral nutrition due to malnutrition and impossible intake. The majority of patients had hospital-acquired CDI (90%), with 5 cases (13.9%) being MICU-acquired. Metronidazole was administered as a single agent to 25 patients and vancomycin to 2 (5%). Eight patients (20%) received a combination of 2 CDI medications during the course of treatment. Five patients were given no antimicrobials against CDI.

Of our 40 patients, 15 (37.5%) had severe CDI. Table 1 shows characteristics of severe and non-severe patients. Univariate analysis showed that Glasgow coma score, gender, diabetes mellitus, previous exposure to fluoroquinolones, PPI or coamoxiclav, and C-reactive protein were statistically different between severe and non-severe patients. Multivariate analysis indicated that male gender, C-reactive protein levels, and fluoroquinolones were independently associated with severe CDI (Table 2).

The prognosis of CDI was good in 18 patients. A total of 12 patients (30%) experienced complications due to their infection with 2 cases (16.7%) of pseudomembranous colitis (PMC) and 4 cases (33.3%) of colitis. In one patient, CDI was marked by hyper-leukocytosis (53

Table 1 Comparison of the characteristics of severe and non-severe *Clostridium difficile* infection patients hospitalised in medical intensive care unit between January 2007 and December 2011

	Total *n* = 40	Severe CDI *n* = 15	Non-severe CDI *n* = 25	*P* value
Age (yr)	62.9 (55.3-72.4)	59.52 (54.8-77.3)	64.27 (56.1-72.2)	0.99
Male gender	27 (67.5)	13 (86.7)	14 (56.0)	0.045
Origin of patient				0.61
Home	14 (35.0)	6 (40)	8 (32)	
Other ward and/or other hospital	26 (65.0)	9 (60)	17 (68)	
Diagnosis at MICU admission				0.39
Respiratory disease	15 (37.5)	3 (20)	12 (48)	
Septic shock	12 (30.0)	6 (40)	6 (24)	
Renal disease	3 (7.5)	1 (6.7)	2 (8)	
Gastrointestinal disease	3 (7.5)	1 (6.7)	2 (8)	
Neurological disease	3 (7.5)	1 (6.7)	2 (8)	
Other	4 (10.0)	3 (20)	1 (4)	
Clinical symptoms and biological features at diagnosis				
Fever	23 (57.5)	8 (53.3)	15 (60.0)	0.75
Abdominal pain	15 (37.5)	7 (46.7)	8 (32.0)	0.35
Duration of diarrhoea (d)	13.0 (8.0-19.5)	18 (5-29)	13 (8-17)	0.38
C-reactive protein (mg/L)	117 (60-193)	185 (73-339)	105 (39-127)	0.01
Albumin count (g/L)	26.0 (20.0-28.0)	23 (17-27)	26 (21-28)	0.30
Leukocyte count (x 10^9/L)	14.4 (9.5-21.7)	17.9 (10.6-33.4)	12.4 (9.0-21.1)	0.17
Previous exposure to CDI risk factors within 8 wk before onset of symptoms				
Hospitalisation	28 (70.0)	10 (66.7)	18 (72.0)	0.72
Exposure to PPI	21 (52.5)	10 (66.7)	11 (44.0)	0.17
Chemotherapy	12 (30)	5 (33.3)	7 (28.0)	0.72
Gastrointestinal procedures	23 (57.5)	9 (60.0)	14 (56.0)	0.80
Antibiotic treatment	38 (95.0)	15 (100)	23 (92)	0.26
Cephalosporins 3rd generation	22 (55)	8 (53.3)	14 (56)	0.87
Clindamycin	2 (5)	1 (6.7)	1 (4)	0.71
Coamoxiclav	16 (40)	8 (53.3)	8 (32)	0.18
Fluoroquinolones	26 (65)	13 (86.7)	13 (52)	0.026
Treatment				0.06
No treatment	5 (12.5)	2 (13.3)	3 (12.0)	
Only metronidazole	25 (62.5)	6 (40)	19 (76)	
Only vancomycin	2 (5)	2 (13.3)	0 (0)	
Metronidazole+vancomycin	8 (20)	5 (33.3)	3 (12.0)	
Duration of hospital stay (d) and outcomes				
LOS in hospital	27.0 (13.5-50.8)	16 (5-48)	28.0 (16.0-55.5)	0.26
LOS in MICU	14.0 (5.0-22.8)	8 (2-21)	16.0 (6.0-25.5)	0.27
Death in 30 d	16 (40)	9 (60)	7 (28)	0.046

Data represent *n* (%) of patients for categorical variables and median (interquartile range) for continuous variables. CDI: *Clostridium difficile* infection; LOS: Length of stay; MICU: Medical intensive care unit; PPI: Proton pump inhibitor; WBC: White blood cells.

g/L), PMC, renal failure and intestinal perforation. The patient died 56 d after CDI diagnosis.

Overall mortality was 52.5%; 12 patients expired in MICU and 9 in-hospital after MICU discharge. The mortality rate within 30 d after diagnosis was 40%; 9 deaths (56.3%) were CDI-related according to the physician in charge of the patient.

DISCUSSION

C. difficile acquisition and severe CDI development are primarily associated with healthcare, although severe, community-acquired infections among persons previously thought to be at low risk have been reported[35,36]. CDI management has become more daunting over the past decade because of alarming increments in CDI incidence and severity. These increases have caused significant, concomitant escalation of the healthcare economic burden from CDI and will likely translate into excessive ICU admissions and attributable mortality. Up to 20% of critically-ill patients may suffer from ileus without the diarrhoea typically associated with CDI[37]. The absence of diarrhoea coupled with the inability of critically-ill patients to communicate with care providers make the diagnosis of CDI extremely difficult[38]. The objectives of this study were to analyse factors associated with CDI severity and to describe the prognosis of CDI in hospitalised MICU patients.

Our investigation comprised 40 CDI patients diagnosed at a MICU between 2007 and 2011, with a mean incidence rate of 12.94 cases/1000 admitted patients. All included cases had their first episode of CDI. The majority were hospital-acquired (90%), with 5 cases (13.9%) being MICU-acquired. In this work, we compared the characteristics of a group of 15 cases of severe CDI with a group of 25 patients without severe CDI in our MICU.

Table 2 Factors independently associated with severe *Clostridium difficile* infection among patients in medical intensive care unit

Variables	Unadjusted OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Glasgow coma score	1.16 (0.99-1.36)	0.15	-	
Diabetes mellitus	4.89 (1.00-23.93)	0.04	-	
Previous PPI exposure	2.55 (0.67-9.66)	0.17	-	
Coamoxiclav (in the previous 8 wk)	2.43 (0.65-9.07)	0.18	-	
Fluoroquinolones (in the previous 8 wk)	6.0 (1.12-32.28)	0.026	9.29 (1.16-74.28)	0.036
C-reactive protein (mg/L; 10 mg/L increments)	1.10 (1.02-1.18)	0.014	1.11 (1.02-1.21)	0.021
Male gender	5.11 (0.95-27.55)	0.045	8.45 (1.06-67.16)	0.044

Exposure to fluoroqionolones, C-reactive protein level and gender were included in the multivariate model [The value of the likelihood was 34.56 with 3 df, and χ^2 test: 18.37 ($P < 0.0001$)]. OR: Odds ratios; PPI: Proton pump inhibitor.

In univariate analysis, gender, BMI, diabetes mellitus, fluoroquinolone use and C-reactive protein were associated with CDI severity. Multivariate logistic regression modelling showed that male gender, C-reactive protein, and previous exposure to fluoroquinolones were independently linked with severe CDI. Exposure to specific antimicrobial drugs, notably fluoroquinolones, clindamycin, and cephalosporins, has been linked to severe CDI in some studies[3,21] but not in others[14].

Malnutrition, reported to be as high as 40%, is prevalent in ICU patients and is associated with increased morbidity and mortality[39], but to the best of our knowledge, this observation has not been made in CDI patients. The majority of patients were not referred to a dietitian. Among patients consulting a dietitian, 87.5% required parenteral nutrition, which was not associated with 1-month survival in our study. This is consistent with the findings of a previous meta-analysis of 26 randomised trials[40]. The investigators showed that, in critically-ill patients, parenteral nutrition did not influence overall mortality.

Underlying illness is moderately associated with severe CDI[14], an effect not observed in our study and could be related to the homogeneity of our study population. Recent investigations have disclosed a potential role of acid suppression in CDI acquisition and relapse[41,42]. Hardt *et al*[43] noted an association between these agents and severe CDI, although their definition of severe CDI was different. Also, significant linkage has been reported in a recently-published paper[44]. This effect was not seen in our study, but may be related to our study population, and PPIs did not play a role in CDI severity in MICU. Previous works have identified few clinical characteristics that consistently predict severe CDI. Different findings, such as fever, abdominal pain, decreased albumin, and significant leukocytosis (often > 20 g/L), are likely in severe colitis[45,46]. Such outcomes often precede multi-organ dysfunction and should prompt urgent consideration of CDI as a possible cause[47,48]. In our study, these variables were not different between severe and non-severe cases. Ananthakrishnan *et al*[49] demonstrated that serum albumin < 3 g/dL, haemoglobin < 9 g/dL and creatinine > 1.5 g/dL were independent predictors of severe CDI and may have prognostic significance in patients with inflammatory bowel disease. We also identified rising serum C-reactive protein levels as being independently associated with severe CDI. As the distribution of C-reactive protein was normal, our multivariate result suggested that an increase by 10 mg/L lead to an increase of the risk of severe CDI by 10%. In fact, serum C-reactive protein was a far better predictor of severe CDI than white blood cell count, which has been implicated by others[43,50-52]. Perhaps more sensitive markers of inflammation, such as procalcitonin, might be especially useful in the evaluation of disease severity. Male gender was associated with severe CDI; to the best of our knowledge, this has not been found in other series. However, a similar effect was reported in a Canadian study, where women were less likely to develop severe CDI, but it was indicated by univariate analysis and was not significant[53]. Our study provides data on the initial treatment courses chosen by care providers. The majority of patients were treated with metronidazole. Only 7 (46.7%) with severe disease received vancomycin. However, information regarding antibiotherapy (duration and dosage) of CDI was not fully captured; thus, the treatment response could not be analysed in our study. Although current guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America urge vancomycin as first-line therapy in severe disease among adult patients[54], a major portion of our study period predated the publication of these recommendations. In contrast, severe CDI was not associated with nursing home residency, the presence of hospital-acquired CDI or increasing age.

Our study has some limitations which need to be considered when interpreting the data. Our sample size was limited and the study was conducted in one single hospital. Therefore we would not be able to extrapolate our results to other groups. Other potential predictors of severe CDI were unable to provide complete risk scores. There was no validated definition of severe CDI; thus, we applied criteria of severe CDI without a scoring system. A larger, multi-center study would be required to validate any definition of severe CDI. Our patients were assembled from a MICU in a tertiary hospital and may not be generalisable to patients in community hospitals or outpatient settings. Our study population consisted of a significant proportion of patients with multiple co-morbidities, which may reflect tertiary care settings. However, these

centers may be ideal to investigate severe CDI, as patients at risk of severe disease are usually found in tertiary care facilities. The number of antibiotic days should be considered as a potential risk factor for severity, which was not available in our data. Nevertheless, we could not detail the antibiotic consumption. Instead we simply noted if antibiotics were used in the last 2 mo preceding CDI.

We performed this study with the aim of identifying factors that predict severe outcomes associated with CDI in MICU patients. Our results indicate that low C-reactive protein, male gender and previous use of fluoroquinolones are independent predictors of severe CDI in hospitalised MICU patients. In the majority of published studies, factors for a severity score index of CDI were assessed within 48 h after laboratory reporting of test results positive for *C. difficile*. This is problematic in terms of reproducibility in deciding the severity score index of CDI, because the time window from CDI diagnosis to the evaluation of severe CDI is variable. We reported predictors of severe CDI not dependent on the timing of their assessment except for C-reactive protein; in our study, however, values were obtained from the day of CDI diagnosis which made these results valid in clinical practice.

Identification of such factors would foster the development of a quantitative severity score that could drive comparative effectiveness investigations and prospective trials of CDI therapy in these patients. Clinicians need to maintain a high index of suspicion and must often rely on physical examinations and laboratory findings to make the diagnosis. Vancomycin is recognized as the first-line treatment of severe CDI and should be preferred in the ICU setting. Rigorous attention to infection control measures and vigorous antimicrobial stewardship are essential to prevent *C. difficile* transmission. Improved diagnostic methods and new therapeutic tools are required to help clinicians to manage severe CDI cases.

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COMMENTS

Background

Clostridium difficile infection (CDI) has become a growing cause of nosocomial morbidity, high hospital costs and mortality over the world. Several mechanisms have been postulated to increase disease severity, including the emergence of hypervirulent strains. Critically-ill patients are at particularly high risk of CDI due to the prevalence of multiple risk factors in the patient population. However, factors associated with CDI severity in medical intensive care unit (MICU) are poorly documented.

Research frontiers

Current data are dealing with many aspects related to CDI. The list of hotspots, not exhaustive in any standards, would include measures of prevention, modalities of diagnosis and treatment, and standardization of basic definitions including severity and evaluation scales. Defining a set of approved prognostic factors would help us dealing with aforementioned topics.

Innovations and breakthroughs

The authors reported predictors of severe CDI no matter the timing of assessment except for C-reactive protein. Nevertheless, values were obtained from the day of CDI diagnosis which made these results valid in clinical practice.

Applications

Identification of some factors would foster the development of a quantitative severity score that could drive comparative effectiveness investigations and prospective trials of CDI therapy in patients hospitalised in MICU. Intensivists need to maintain a high index of suspicion and must often rely on physical examinations and laboratory findings to make the diagnosis.

Peer review

Risk factor assessment limited due to small sample size, but a tremendous time investment into the statistical analysis of this small sample makes the manuscript interesting. The study design is simple and reasonable and statistics are excellent.

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