Univariate and multivariate analysis of risk factors for severe *Clostridium difficile*-associated diarrhoea: Importance of co-morbidity and serum C-reactive protein

Christian Hardt, Thomas Berns, Wolfgang Treder, Franz Ludwig Dumoulin

**Abstract**

AIM: To investigate risk factors for severe *Clostridium difficile* associated diarrhoea (CDAD) in hospitalized patients.

METHODS: We analysed risk factors for severe CDAD (associated with systemic signs of hypovolemia) in 124 hospitalized patients by retrospective chart review.

RESULTS: Severe CDAD was present in 27 patients (22%). Statistical analysis showed a significant association with a higher 30-d mortality (33% vs 4%, \( P < 0.001 \)) and a higher proportion of longer hospital stay exceeding 14 d (74% vs 52%, \( P = 0.048 \)). Charlson co-morbidity score (OR 1.29 for 1 point increment, \( P < 0.05 \)) and serum C-reactive protein at diagnosis (OR 1.15 for 10 mg/L increment, \( P < 0.001 \)) were independent predictors of severe CDAD.

CONCLUSION: Patients with a severe level of co-morbidity and high serum C-reactive protein levels at the time of diagnosis should receive particular attention.

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**Key words:** *Clostridium difficile*; Nosocomial diarrhoea; Co-morbidity; C-reactive protein; 30-day mortality

**Peer reviewer:** Hitoshi Asakura, Director, Emeritus Professor, International Medical Information Center, Shinanomachi Renga Bldg.35, Shinanomachi, Shinjukuku, Tokyo 160-0016, Japan

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**INTRODUCTION**

*Clostridium difficile* associated diarrhoea (CDAD) is the most common cause of healthcare-associated diarrhoea and results in a wide spectrum of disease severity ranging from asymptomatic carriage to life-threatening enterocolitis and death[1-3]. Recently, a new epidemic strain producing higher levels of toxin has emerged in Canada and the US[4-8] as well as in some European countries which results in CDAD with higher morbidity and mortality[9-13]. Many studies have investigated risk factors for infection with *Clostridium difficile* (C. difficile) and subsequent development of CDAD. Thus, advanced age, severe comorbidity[14], hospitalisation[15], antibiotic exposure, immunosuppressive therapy[16,17] and treatment with motility influencing or acid-suppressive drugs have all been reported as risk factors for CDAD[18-21]. In contrast, less is known about risk factors associated with a severe course of CDAD in hospitalized patients.

**MATERIALS AND METHODS**

We conducted a retrospective analysis of CDAD in hospitalized patients to identify possible risk factors for a severe clinical course. Our institution is a community hospital treating approximately 19 000 in-patients per year. Using a computer-based search, we identified 186 positive stool tests for *C. difficile* toxin B from 142 patients who fulfilled the case definition for CDAD between October 2003 and August 2006. After chart review 18 cases were excluded: 5 patients had multiple admissions and only the first admission was included, 5 patients were younger than 18 years and in 8 patients
Table 1  Patient characteristics

| Patient characteristics | Data          |
|-------------------------|---------------|
| Age (yr)                | 76 (18-95)    |
| Sex                     |               |
| Female                  | 71 (57%)      |
| Male                    | 53 (43%)      |
| Nursing home residency  |               |
|                         | 19 (15%)      |
| Charlson’s comorbidity  | 4 (0-10)      |
| GI procedures including | 13 (10%)      |
| Previous medication:    |               |
| Antibiotic therapy      | 101 (81%)     |
| Acid-suppressive therapy| 66 (53%)      |
| Immunosuppressive therapy| 25 (20%)     |
| Opioid use              | 57 (46%)      |
| Laxative use            | 30 (24%)      |
| Clinical features of CDAD|             |
| Hospital-acquired CDAD  | 101 (81%)     |
| Interval onset of diarrhoea to CDAD therapy ≥ 7 d | 45 (37%) |
| Body temperature ≥ 38°C | 56 (45%)      |
| Severe CDAD             | 27 (22%)      |
| Laboratory at diagnosis:|              |
| White blood cell count  | 14.1 (4.6-81.3)|
| CRP (mg/L)              | 118 (2-413)   |
| Creatinine (mg/L)       | 11.5 (3.1-110.5)|
| Sodium (mmol/L)         | 136 (114-145) |
| Potassium (mmol/L)      | 3.52 (2.43-5.07)|
| Continuation of initial antibiotic therapy despite CDAD | 71 (57%) |
| Antibiotic therapy for CDAD | 113 (91%) |
| Length of hospital stay > 14 d | 70 (56%) |
| 30-d mortality          | 13 (10%)      |

1Data are given as median (range) or number (percentage).

Comparisons between the two groups of severe and non-severe CDAD were performed by Student t test for normally distributed data, proportions were analysed by χ² or F test as appropriate. A two-sided error level of P < 0.05 was considered statistically significant. Variables significantly associated with severe CDAD in univariate analysis together with risk factors reported in the literature were entered into a multivariate analysis. Statistical analysis was computed with SPSS version 14.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Demographics and results of initial evaluation

Patient characteristics are summarised in Table 1. Many patients had a comorbidity resulting in a median Charlson comorbidity score of 4. The majority of patients had hospital-acquired CDAD, 27 patients (22%) had severe CDAD, the overall 30-d mortality was 10% (13/124); all patients who died were >70 years.

Analysis of possible risk factors

Univariate analysis for comparison of patients with non-severe (n = 97) and severe CDAD (n = 27) revealed that immunosuppressive therapy, laxative use, body temperature ≥ 38°C, length of hospital stay > 14 d, 30-d mortality, Charlson comorbidity score, white blood cell count, serum levels of C-reactive protein and creatinine were all significantly associated with severe CDAD (Table 2).
A borderline statistically significant association was found for comedication with acid-suppressive therapy or opioids. By contrast, severe CDAD was not associated with nursing home residency, presence of hospital-acquired CDAD, continuation of the initial antibiotic therapy after diagnosis or increasing age. Multiple logistic regression analysis confirmed a significant association of severe CDAD and Charlson comorbidity score (OR 1.29 for 1 point increment, \( P < 0.05 \)) and levels of serum C-reactive protein (OR 1.15 for 10 mg/L increment, \( P < 0.001 \); Tables 2 and 3).

### DISCUSSION

The major findings in this retrospective analysis were a 22% rate of severe CDAD significantly associated with relatively high 30-d mortality (33% vs 4%, \( P < 0.001 \)) and a higher proportion of a hospital stay exceeding 14 d (74% vs 52%, \( P < 0.05 \)). In addition, comorbidity assessed by the Charlson comorbidity score (\( P < 0.05 \)) and serum C-reactive protein at the time of diagnosis (\( P < 0.001 \)) were identified as independent risk factors for severe CDAD in multivariate analysis.

The rate of severe CDAD and associated 30-d mortality in this study are relatively high. Infection with the recently emerging strain BI/NAP1 associated with severe courses of CDAD\(^{[2,8-11]}\) is an unlikely explanation, since this strain had not been documented in Germany at the time of our retrospective analysis\(^{[25]}\). Therefore the most likely explanation are advanced age (median 76 years) and high comorbidity (median Charlson score of 4) of our cohort. The observed association of disease severity with comorbidity assessed by the Charlson comorbidity score is in line with reports on an association of severe CDAD with cognitive impairment\(^{[26]}\), number of chronically affected organ systems\(^{[26]}\), cardiac disease, malignancy, chronic obstructive pulmonary disease, pre-existing renal failure and other severe disease\(^{[27,28]}\). Our data support the hypothesis that comorbidity is an important risk factor for severe CDAD and the Charlson comorbidity score, which includes most of these conditions, might be a useful tool to identify patients at particular risk for severe CDAD. We also identified serum levels of C-reactive protein as independently associated with severe CDAD. In fact, serum C-reactive protein was a far better predictor of severe CDAD than white blood cell count, which has been described by others\(^{[28,29]}\).

Thus, at the median Charlson comorbidity score of our cohort (4 points) a C-reactive protein level of 250 mg/L at diagnosis predicted a higher than 50% probability for severe CDAD. Perhaps more sensitive markers of inflammation such as procalcitonin might be even more useful in the evaluation of disease severity.

Other known risk factors for CDAD\(^{[2,18,30]}\) might also be relevant for severe CDAD. In line with these data we found comedication with laxatives, opioids and acid-suppressive therapy associated with severe CDAD in univariate analysis although these risk factors could not be confirmed in multivariate analysis. In contrast, a variety of other putative risk factors for severe CDAD could not be confirmed. Thus, we did not detect an association of severe CDAD with increased age\(^{[27,30]}\), which is probably due to the already advanced median age of our cohort. Moreover, prolonged antibiotic use per se, continuation of the antibiotic therapy after the diagnosis of CDAD, gastrointestinal procedures or surgery, which have all been reported as risk factors for \( C. \) difficile colonisation and CDAD\(^{[2,17]}\) were not associated with severe disease in this study.

In conclusion, comorbidity and serum levels of serum C-reactive protein were identified as predictors of severe CDAD. Patients with strong comorbidity and high serum C-reactive protein levels at the time of diagnosis should be treated with particular attention.

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### COMMENTS

#### Background

Clostridium difficile associated diarrhoea (CDAD) is the most common cause of healthcare-associated diarrhoea. It results in a wide spectrum of disease severity ranging from asymptomatic carriage to life-threatening enterocolitis and death with associated health care costs.

#### Research frontiers

A variety of studies has investigated risk factors for the development of CDAD. Thus, advanced age, severe comorbidity, hospitalisation, antibiotic exposure, immunosuppressive therapy as well as treatment with motility influencing or acid-suppressive drugs were identified as risk factors for CDAD. However, little is known about risk factors for associated with a severe course of CDAD in hospitalized patients.

#### Innovations and breakthroughs

The major findings reported are a 22% rate of severe CDAD which was significantly associated with relatively high 30-d mortality and a higher proportion of a hospitalstay exceeding 14 d. Moreover, comorbidity assessed by the Charlson comorbidity score and levels of serum C-reactive protein at the time of diagnosis were identified as independent risk factors for severe CDAD.
in multivariate analysis.

**Applications**

The major findings of this study should help to identify hospitalized patients with a particular risk for a severe course of CDAD. An early identification of patients at risk would allow a more timely intervention probably improving both morbidity and mortality.

**Peer review**

The paper describes important risk factors for a severe course of CDAD in hospitalized patients which have a potential for everyday clinical practice. It's an interesting paper.

**REFERENCES**

1. Loo VG, Libman MD, Miller MA, Bourgault AM, Frynette CH, Kelly M, Michaud S, Nguyen T, Poirier L, Vibiens A, Horn R, Laflamme PJ, Rene P. Clostridium difficile: a formidable foe. *CMAJ* 2004; 171: 47-48

2. Bartlett JG. Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. *Ann Intern Med* 2006; 145: 758-764

3. Aslam S, Musher DM. An update on diagnosis, treatment, and prevention of Clostridium difficile-associated disease. *Gastroenterol Clin North Am* 2006; 35: 315-335

4. McFarland LV. Diarrhoea associated with antibiotic use. *BMJ* 2007; 335: 54-55

5. McFarland LV. Update on the changing epidemiology of Clostridium difficile-associated disease. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5: 40-48

6. Miller MA. Clinical management of Clostridium difficile-associated disease. *Clin Infect Dis* 2007; 45 Suppl 2: S122-S128

7. Warny M, Pepin J, Fang A, Killigore G, Thompson A, Brazier J, Frost E, McDonald L. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. *Lancet* 2005; 366: 1079-1084

8. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frynette C, Kelly M, Vibiens A, Brassard P, Feen S, Dewar K, Hudson TJ, Horn R, Rene P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; 353: 2442-2449

9. Bartlett JG, Perl TM. The new Clostridium difficile—what does it mean? *N Engl J Med* 2005; 353: 2503-2505

10. Ricciardi R, Rothenberger DA, Madoff RD, Baxter NN. Increasing prevalence and severity of Clostridium difficile colitis in hospitalized patients in the United States. *Arch Surg* 2007; 142: 624-631; discussion 631

11. Kato H, Kato H, Nakamura M, Nakamura A. A case of toxic megacolon secondary to Clostridium difficile-associated diarrhea worsened after administration of an antimotility agent and molecular analysis of recovered isolates. *J Gastroenterol* 2007; 42: 507-508

12. Pepin J, Valiquette L, Gagnon S, Routhish S, Brazeau I. Outcomes of Clostridium difficile-associated disease treated with metronidazole or vancomycin before and after the emergence of NAP1/027. *Am J Gastroenterol* 2007; 102: 2781-2788

13. Gould CV, McDonald LC. Bench-to-bedside review: Clostridium difficile colitis. *Crit Care* 2008; 12: 203

14. Cunney RJ, Magee C, McNamara E, Smyth EG, Walshe J. Clostridium difficile colitis associated with chronic renal failure. *Nephrol Dial Transplant* 1998; 13: 2842-2846

15. McFarland LV, Surawicz CM, Stamm WE. Risk factors for Clostridium difficile carriage and C. difficile-associated diarrhea in a cohort of hospitalized patients. *J Infect Dis* 1990; 162: 678-684

16. Kyne L, Merry C, O’Connell B, Kelly A, Keane C, O’Neill D. Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. *Age Ageing* 1999; 28: 107-113

17. Dial S, Delaney JA, Schneider V, Suisse S. Proton pump inhibitor use and risk of community-acquired Clostridium difficile-associated disease defined by prescription for oral vancomycin therapy. *CMJ* 2006; 175: 745-748

18. Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial Clostridium difficile diarrhea. *Infect Control Hosp Epidemiol* 2002; 23: 653-659

19. Thorson MA, Bliss DZ, Savik K. Re-examination of risk factors for non-Clostridium difficile-associated diarrhea in hospitalized patients. *J Adv Nurs* 2008; 62: 354-364

20. van der Koop T, Koningstein M, Lindemans A, Notermans DW, Kuiper E, van den Berg R, Boshaizen H, Filius PM, van den Hof S. Antibiotic use and other risk factors at hospital level for outbreaks with Clostridium difficile PCR ribotype 027. *J Med Microbiol* 2008; 57: 709-716

21. Carignan A, Allard C, Pepin J, Cossette B, Nault V, Valiquette L. Risk of Clostridium difficile infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. *Clin Infect Dis* 2008; 46: 1838-1843

22. Charleston ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373-383

23. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. *BMJ Cancer* 2004; 4: 94

24. Mushker DM, Manhas A, Jain P, Nuila F, Waqar A, Logan N, Marino B, Graves EA. Detection of Clostridium difficile toxin: comparison of enzyme immunoassay results with results obtained by cytotoxicity assay. *J Clin Microbiol* 2007; 45: 2737-2739

25. Reichardt C, Chaberny IJ, Kola A, Mattner F, Vonberg RP, Gastmeier P. [Dramatic increase of Clostridium difficile-associated diarrhea in Germany: has the new strain PCR ribotype 027 already reached us?] *Dtsch Med Wochenschr* 2007; 132: 222-228

26. Andrews CN, Raboud J, Kassen BO, Enns R. Clostridium difficile-associated diarrhea: predictors of severity in patients presenting to the emergency department. *Can J Gastroenterol* 2003; 17: 369-373

27. Dharmarajan T, Sipalay M, Shyamsundar R, Norkus E, Pitchumoni C. Co-morbidity, not age predicts adverse outcome in clostridium difficile colitis. *World J Gastroenterol* 2006; 12: 198-201

28. Rubin MS, Bodenstein LE, Kent KC. Severe Clostridium difficile colitis. *Dis Colon Rectum* 1995; 38: 350-354

29. Moskowitz M, Ben-Baruch E, Kline Z, Shimoni Z, Niven M, Konikoff F. Risk factors for severity and relapse of pseudomembranous colitis in an elderly population. *Colonol Rect Dis* 2007; 9: 173-177

30. Dial S, Delaney JA, Barkun AN, Suisse S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; 294: 2989-2995

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