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

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Für meine Familie

Inhaltsverzeichnis

Zusammenfassung der Publikation:

Univariate und multivariate Analyse potentieller Risikofaktoren für einen schweren Verlauf der Clostridium difficile-assozierten Diarrhoe:
Bedeutsamkeit der Komorbidität und des C-reaktiven Proteins (CRP)

Einleitung:

Die Clostridium difficile assoziierte Diarrhoe (CDAD) ist eine der häufigsten Ursachen für eine im Krankenhaus erworbene Diarrhoe.

Das Krankheitsspektrum dieser Erkrankung umfasst verschiedene Schweregrade, welche sich von einem asymptomatischen Trägerstatuts bis hin zu schweren Enterokolitiden oder sogar einem tödlichen Verlauf erstrecken können.

In zahlreichen Studien wurden Risikofaktoren für eine Infektion mit Clostridium difficile (CD) und anschließendes Auftreten einer Diarrhoe beschrieben, wie fortgeschrittenes Alter, schwere Komorbidität, Krankenhausaufenthalt, antibiotische oder immunsuppressive Therapie.

In Gegensatz dazu ist das Wissen über prädisponierende Faktoren für einen schweren Verlauf der CDAD begrenzt.

Material und Methoden:

Wir führten eine retrospektive Studie durch, um mögliche Risikofaktoren für einen schweren Verlauf der CDAD zu identifizieren.

Von Oktober 2003 bis August 2006 wurden alle Fälle mit einer positiven Stuhlprobe für CD Toxin B registriert.

In diesem Zeitraum registrierten wir 186 positive Stuhlproben für CD Toxin B bei 142 Patienten, welche die Kriterien der CDAD erfüllen.

Alle Patienten mit mehr als drei wässrigen Stuhlgängen an zwei aufeinander folgenden Tagen und einer positiven Stuhlprobe für CD Toxin wurden als CDAD diagnostiziert.

Nach Auswertung der Patientendaten wurden 18 Fälle von der weiteren Analyse ausgeschlossen.

Bei 5 Patienten kam es in dem oben genannten Zeitraum zu mehreren Krankenhausaufenthalten. In diesen Fällen wurde nur der erstmalige Aufenthalt berücksichtigt. Alle Patienten unter 18 Jahren wurden von dieser Studie ausgeschlossen (5 Patienten). In 8 Fällen waren die Daten unvollständig, so dass letztlich 124 Patienten zur weiteren Auswertung zur Verfügung standen.

Datenerhebung:

Wir ermittelten von den 124 Patienten demographische Daten wie Alter, Geschlecht etc..

Darüber hinaus wurde der Einfluss einer vorausgegangenen oder gegenwärtigen Medikation auf den Verlauf der CDAD untersucht.

Medizinische und chirurgische Interventionen vor Erkrankungsbeginn wurden erfasst.

Die Komorbidität der Patienten wurde mit Hilfe des Charlson Comorbidity Score kalkuliert, der wesentliche Begleiterkrankungen berücksichtigt.

Bei Diagnosestellung CDAD wurden die Vitalparameter (Blutdruck, Herzfrequenz, Körpertemperatur) sowie die Laborparameter (Leukozytenzahl, C-reaktives Protein, Natrium, Kalium, Kreatinin) erhoben.

Zusätzlich erfassten wir die Dauer des Krankenhausaufenthaltes, die Dauer bis zum Beginn einer spezifischen Therapie bei CDAD und die 30-Tage Mortalität nach Diagnosestellung.

CDAD wurde bei allen Patienten, die mehr als 72 Stunden nach Aufnahme an CDAD erkrankten, sowie bei denjenigen Patienten, die innerhalb der letzten 6 Wochen vor Aufnahme stationär behandelt wurden, als im Krankenhaus erworben definiert.

CDAD wurde als schwer klassifiziert, wenn ein positiver Schockindex (Herzfrequenz bpm/systolischer Blutdruck mmHg >1.5) bei Diagnosestellung vorlag.

Statistische Auswertung:

Die univariate statistische Analyse wurde mit Hilfe des Student t Test bzw. χ^2 oder Fisher Exakt Test durchgeführt. Diejenigen Variablen, die sich in der univariaten Analyse als statistisch signifikant ($p<0.05$) ergaben, wurden zusammen mit denjenigen Risikofaktoren, die in der Literatur beschrieben wurden, in die multivariate Analyse integriert. Die statistische Analyse wurde mit SPSS Version 14.0 durchgeführt (SPSS,Inc.,Chicago,IL,USA).

Ergebnisse:

CDAD hatte bei 22% der Patienten einen schweren Verlauf. Die 30-Tage Mortalität lag bei 10% (13/124). Alle gestorbenen Patienten waren älter als 70 Jahre.

Univariate Analyse:

Die univariate Analyse zeigte einen statistisch signifikanten Unterschied der beiden Gruppen (schwere vs. nicht-schwere CDAD) hinsichtlich einer immunsuppressiven Therapie, dem

Gebrauch von Laxanzien, der Körpertemperatur ≥38°C, der Länge des Krankenhausaufenthaltes >14 Tage, der 30-Tage Mortalität und der Komorbidität des Patienten. Darüber hinaus unterschieden sich die beiden Gruppen in den Laborparametern Leukozytenzahl, C-reaktives Protein und Kreatinin bei Diagnosestellung signifikant.
Die multivarite Analyse bestätigte einen signifikanten Zusammenhang zwischen schwerer CDAD und der Komorbidität des Patienten bzw. dem C-reaktiven Protein bei Diagnosestellung.

Diskussion:

Der Anteil an schweren Verläufen der CDAD war mit 22% der Fälle beachtlich. Eine schwere CDAD ist signifikant assoziiert mit einer hohen 30-Tage Mortalität und einem verlängerten Krankenhausaufenthalt >14 Tage.
Darüber hinaus konnte in dieser Studie die Komorbidität des Patienten (Charlson Comorbidty Score) und das C-reaktive Protein bei Diagnosestellung als unabhängige Risikofaktoren für einen schweren Verlauf der CDAD identifiziert werden.
Die wahrscheinlichste Erklärung für den relativ hohen Prozentsatz schwerer Verläufe der CDAD (22%) ist das fortgeschrittene Alter der Patienten (Median 76 Jahre), sowie die Vielzahl an Begleiterkrankungen (Median Charlson Comorbidty Score 4).
Der gefundene Zusammenhang zwischen schwerer CDAD und Komorbidität lässt sich in Einklang bringen mit einer Vielzahl von publizierten Studien, die einen Zusammenhang zwischen schwerer CDAD und speziellen Begleiterkrankungen beschrieben.
Das C-reaktive Protein war in dieser Studie ein weit nützlicherer Parameter bei der Evaluation der Erkrankungsschwere als die Leukozytenzahl, welche von anderen Studien favorisiert wurde.
Die Tatsache, dass sich in dieser Studie kein Zusammenhang zwischen dem Alter des Patienten und einem schweren Verlauf der CDAD zeigte, ist höchstwahrscheinlich auf das bereits fortgeschrittene Alter in unserer Population (Median 76 Jahre) zurückzuführen.
Darüber hinaus konnte kein Zusammenhang zwischen einem schweren Verlauf der CDAD und einer verlängerten Gabe eines Antibiotikums oder der Weitergabe des Antibiotikums nach Diagnosestellung bestätigt werden.
Auch zeigte sich kein statistisch fassbarer Zusammenhang zwischen schwerer CDAD und gastrointestinalen Interventionen oder chirurgischen Eingriffen vor Diagnosestellung. Man darf schlussfolgern, dass Patienten mit schweren Begleiterkrankungen und hoher Serum

Konzentration des C-reaktiven Proteins bei Diagnosestellung mit besonderer Aufmerksamkeit therapiert werden sollten.

Neben der nachfolgenden Publikation sind zur gleichen Thematik noch zwei Vorträge gehalten worden, die als Abstracts erschienen sind (Hardt et al., 2007; Hardt et al., 2008).

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RAPID COMMUNICATION

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

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Abstract

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

METHODS: We analysed risk factors for severe CDAD (associated with systemic signs of hypovolemia) in 124 hospitalised 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.

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

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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[1-5]. Recently, a new epidemic strain producing higher levels of toxin has emerged in Canada and the US[5-8] 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 hospitalised patients.

MATERIALS AND METHODS

We conducted a retrospective analysis of CDAD in hospitalised 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[1] (yr)	76 (18-93)
Sex	
Female	71 (57%)
Male	53 (43%)
Nursing home residency	19 (15%)
Charlson´s comorbidity score	4 (0-10)
GI procedures including PEG and surgery	13 (10%)
Previous medication:	
Antibiotic therapy within 6 wk prior to onset CDAD	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℃	56 (45%)
Severe CDAD	27 (22%)
Laboratory at diagnosis:	
White blood cell count (G/L)	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%)

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

Table 2 Univariate analysis of risk factors for severe CDAD

Variable	Non-severe CDAD (n = 97)	Severe CDAD (n = 27)	P
Male sex	41/42	12/44	
Nursing home residency	12/12	7/26	
Hospital-acquired CDAD	76/78	25/93	
Immunosuppressive therapy	15/15	10/37	< 0.05
Previous antibiotic therapy	78/80	23/85	
Acid-suppressive therapy	47/48	19/70	
Therapy with opioids	40/41	17/63	
Laxative use	19/20	11/41	< 0.05
GI procedures including PEG and surgery	13/13	0/0	
Continuation of initial antibiotic therapy	52/54	19/70	
Antibiotic treatment for CDAD	88/91	25/93	
Body temperature ⩾ 38℃	38/39	18/67	< 0.05
Therapy ⩾ 7 d after onset diarrhoea	33/34	12/44	
Length of hospital stay > 14 d	50/52	20/74	< 0.05
30-d mortality	4/4	9/33	< 0.001
Age (yr)	74 ± 12	77 ± 12	
Charlson´s score (points)	3.4 ± 2.2	5 ± 2.6	< 0.001
White blood cell count (G/L)	15.3 ± 9.9	21.6 ± 10.4	< 0.01
C-reactive protein (mg/L)	109 ± 79	223 ± 92	< 0.001
Creatinine (mg/L)	14 ± 13	24 ± 17	< 0.01
Sodium (mmol/L)	135 ± 5	133 ± 7	
Potassium (mmol/L)	3.6 ± 0.5	3.4 ± 0.5	

data were incomplete, leaving 124 patients for further analysis. We recorded patient age, sex, nursing home residency, comorbidity to calculate the Charlson comorbidity score[22,23] previous and concomitant medication (systemic antibiotic treatment within 6 wk preceding diagnosis, continuation of the initial antibiotic therapy after diagnosis of CDAD, use of opioids or laxatives), predisposing medical or surgical procedures (endoscopy, percutaneous gastrostomy, nasogastric tubes, chemotherapy or radiotherapy) as well as vital signs (heart rate, blood pressure and body temperature) and laboratory parameters (white blood cells, C-reactive protein, sodium, potassium, creatinine) at the time of diagnosis. In addition, we recorded the length of hospital stay, the period until beginning therapy for CDAD after the onset of diarrhoea, whether a specific antibiotic therapy for CDAD was instituted or not and the 30-d mortality after initial diagnosis of CDAD.

Patients with more than three loose stools per day on more than two consecutive days with a positive stool test for *C. difficile* toxin were diagnosed as CDAD[16,24]. Hospital-acquired CDAD was assumed if the onset of diarrhoea was > 72 h after hospital admission or if there had been a hospital admission for CDAD within the previous 6 wk. Severe CDAD was defined as profuse diarrhoea associated with a positive shock index (heart rate bpm/systolic blood pressure mmHg >1.5) at initial diagnosis[10]. All other patients were classified as non-severe CDAD.

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 χ^2 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℃, 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).

Table 3 Multivariate analysis of possible risk factors for severe CDAD

	P	OR; 95% CI
Variable (unit)		
Charlson´s score (points; 1-point increments)	< 0.05	1.39; 1.06-1.83
Body temperature ⩾ 38℃		1.15; 0.35-3.83
Immunosuppressive therapy		1.84; 0.45-7.49
Acid-suppressive therapy		1.28; 0.39-4.21
Opioid use		2.50; 0.80-7.84
Laxative use		2.66; 0.79-8.97
C-reactive protein (mg/L; 10 mg/L increments)	< 0.01	11.2; 10.3-12.1
White blood cell count (G/L; 1 G/L increments)		1.01; 0.96-1.06
Creatinine level (mg/L; 10 mg/L increments)		12.5; 9.2-16.8
Reduced Model		
Charlson´s score (points; 1-point increments)	< 0.05	1.29; 1.02-1.61
C-reactive protein (mg/L; 10 mg/L increments)	< 0.001	1.15; 1.08-1.22

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[16], 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 hospitalised 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 hospital stay 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.

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