THE ROLE OF INTRAVENOUS TIGECYCLINE MONOTHERAPY IN THE TREATMENT OF SEVERE *CLOSTRIDIOIDES* (FORMERLY *CLOSTRIDIUM*) *DIFFICILE* INFECTION AMONG ADULT HOSPITALIZED PATIENTS

PhD thesis

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INTRODUCTION

In the dissertation, we review the current *state-of-the-art* knowledge on the microbiological and clinical aspects of human *C. difficile* infections (CDI) in adults, and presented original research, analysing the efficacy and treatment failure with intravenous tigecycline monotherapy among adult patients hospitalized with severe CDI.

C. difficile is a Gram positive obligate anaerobic rod, transmitted mainly by the faecal-oral route between humans, animals and the environment, and capable of producing endospores, thus surviving harsh ecological conditions both *ex vivo* and *in vivo*. Sporulation, toxin and biofilm formation are the main virulence factors of *C. difficile*. Patients with pathological gut microbiome changes might become colonized with non-toxigenic or toxigenic *C. difficile* strains. The former leads to asymptomatic carriage, while the latter may result in asymptomatic colonization or symptomatic infection, depending on the host immune response. Diagnosis of *C. difficle* infection relies on organism detection by enzyme immuno-assay (EIA), nucleic acid amplification tests or toxigenic culture from a stool sample during a clinically compatible case presentation, such as diarrhea, toxic megacolon or paralytic ileus. After considering clinical signs, endoscopic, laboratory and imaging findings, the appropriate anti-CDI treatment could be decided upon by risk stratification. *C. difficile* infections possess an overall high morbidity burden, and in severe and fulminant clinical forms of CDI, the prognosis is unfavourable, partially due to the lack of alternative therapeutic strategies.

AIMS

Our scientific aims during the studies presented in this dissertation were the following:

1) Our primary objective was to analyse the efficacy of intravenous tigecycline monotherapy compared to standard anti-CDI therapy (oral vancomycin + intravenous metronidazole) among adult patients hospitalized with severe CDI.

2) Our secondary objective was to assess characteristics and predictors of treatment failure with intravenous tigecycline monotherapy among adult patients hospitalized with severe CDI.

At our institution during the study period, we adhered to the 2014 *European Society of Clinical Microbiology and Infection* guideline and considered applying

tigecycline as a last-resort drug if the patient with severe CDI deteriorates or improvement of physical, laboratory and imaging findings attributable to ongoing CDI fails during standard therapy, and a surgical approach is not feasible.

METHODS

Study design and settings

A retrospective observational cohort study of consecutive adult patients (≥18 years at diagnosis) hospitalized at South Pest Central Hospital, National Institute of Hematology and Infectious Diseases with severe CDI between 2014 and 2018 was carried out. Our institution is a tertiary referral centre with >100 dedicated beds for infectious diseases and national catchment.

The study was carried out in two phases: in the first phase, a *pilot* study aiming the primary objective was executed between 2014 and 2015, while in the second phase, a study was completed with data generated between 2014 and 2018. The study was in accordance with institutional and national ethical standards, as well as the Helsinki Declaration (1975, revised in 2000 and 2008). The institutional review board approved the study protocol, informed consent was not necessary for this type of study.

Patient selection and data collection

To overcome selection bias, all eligible patients were identified through an electronic records search and evaluated for inclusion on a case-by-case basis, if a diagnosis of CDI was established at admission or during hospital stay (*International Classification of Diseases*, 10th Edition: A04.70). In the first phase following an *a priori* inclusion criterium, patients receiving anti-CDI treatment for severe CDI with intravenous tigecycline monotherapy for ≥48 hours were included in the tigecycline therapy group, while patients receiving oral vancomycin + intravenous metronidazole (standard therapy) without tigecycline for severe CDI were identified using a computer-generated random selection from the same time frame, and included in the standard therapy group in a 1:1 ratio. Patients were excluded from both groups if anti-CDI antibiotics were administered for <48 hours, for any reason. In the second phase, only one cohort was established from all eligible patients, consisting of included patients receiving intravenous tigecycline monotherapy, according to the same inclusion and exclusion criteria.

A database was established for the purpose of the study aims, by manually extracting data of included patients from hospital records, and anonymously transferring them to a standardized case report form. For both phases, variables extracted were: 1) age, and gender at baseline; 2) comorbidities at baseline (essential hypertension, chronic heart disease [ischaemic heart disease, cardiomyopathies], chronic pulmonary disease [COPD, intersticial lung diseases], chronic kidney disease [chronic renal insufficiency], diabetes mellitus, active oncohematological malignancy, long-term systemic corticosteroid therapy [≥15 mg/day prednisone or dose-equivalent for ≥3 months], chronic immunosuppression [congenital immunodeficiency, asplenia, HIV infection, solid organ or hematopoetic stem cell transplantation, chemotherapy or immunosuppressive therapy within ≤6 months, autoimmune disease, hepatic cirrhosis]); 3) documented risk factors for CDI at baseline (systemic antibiotic use in ≤3 months, hospitalization for ≥3 days in ≤6 months, long-term care facility residency, prior CDI episode or multiple CDI recurrences); 4) number and treatment of preceding CDI episodes at baseline; 5) characteristics of current CDI episode at baseline (first or recurrent appearance, onset time and place, symptoms, physical and laboratory results); 6) imaging and endoscopic findings at baseline; 7) durations and types of anti-CDI antibiotics and supportive therapies initiated after diagnosis; 8) need for intensive care unit (ICU) admittance and hospital length of stay (LOS); 9) clinical outcomes. Baseline variables were assessed on the day of CDI diagnosis, clinical outcomes were assessed at hospital discharge or upon patient death.

Assessment of diagnosis and severity

At our institution during the study period, diagnosis and severity of CDI was evaluated by the ESCMID guidelines (75, 51, 52). Each case was retrospectively re-assessed for correct diagnosis and severity classification of CDI. Briefly, a case of CDI was defined by the demonstration of toxigenic *C. difficile* from an unformed stool sample by EIA (C. DIFF Quik Chek Complete EIA, TechLab, USA), detecting glutamate dehydrogenase and toxins A+B during a clinically compatible case. If toxin production by EIA was not proven, a culture was performed (ChromID *C. difficile* Agar, bioMérieux, Spain), and the isolate was re-checked for toxin production. Laboratory tests and imaging (abdominal X-ray, computed tomography and ultrasonography) were done in each case at baseline and during follow-up, as deemed clinically necessary by recommendation of expert gastroenterologists and infectious disease specialists. Rectosigmoidoscopy or colonoscopy was only performed in ambiguous cases by recommendation of expert gastroenterologists and infectious

disease specialists. At least 4 bottles of blood cultures (BacT/ALERT aerobic and anaerobic Culture Media, bioMérieux, Spain) were taken from peripheral and/or central veins (if feasible) from patients with fever, or suspicion of sepsis or complicated CDI. At our centre, fresh stool samples are also sent from every patient with acute-onset diarrhea for routine bacterial culturing of *Salmonella sp*., *Yersinia sp*., *Campylobacter sp.* and *Shigella sp*. All clinical specimens are processed within 2 hours at the Core Microbiology Laboratory of our institution.

For case evaluation, diarrhea was defined by ≥3 unformed stools (Bristol type 5–7) in ≤24 hours for ≥2 consecutive days. Severe CDI was defined by a CDI episode with ≥2 of the following: fever (core body temperature ≥38.5°C) with or without chills, severe abdominal pain, respiratory failure (need for ventilatory support) or haemodynamic instability (need for circulatory support), peritonitis (muscle defense with rebound sensitivity), blood leukocytosis (WBC count >15x10^9/L), marked left-shift (>20% of bands), elevated serum creatinine (≥1.5-fold rise compared to premorbid levels), elevated serum lactate (≥5 mmol/L), reduced serum albumin (<30 g/L), colonic distension with wall thickening, ascites or pseudomembranous colitis. Complications of CDI were ileus, toxic megacolon or CDI associated sepsis. Ileus was defined as bowel passage absence for ≥24 hours and radiological features of abnormal bowel distension. Toxic megacolon was defined as colonic ileus with a transverse width of >6 cm for the ascending or transverse colon upon radiological evaluation. CDI associated sepsis was defined as a confirmed CDI with presence of sepsis according to *American College of Chest Physicians/Society of Critical Care Medicine*. Recurrent CDI was defined as ≥1 episode with documented clinical resolution before current disease onset. The ATLAS score and the Charlson Comorbidity Score was calculated at baseline for each case. Anti-CDI antibiotics were promptly initiated after establishment of CDI diagnosis, or if the clinical scenario was alarming for complications. Tigecycline was administered intravenously in monotherapy with a loading dose of 100 mg, followed by 50 mg twice daily. Vancomycin was administered orally with 125 mg four times daily. Metronidazole was administered intravenously with 500 mg three times daily. Efficacy and adverse reactions were assessed during daily visits of attending physicians.

Outcome measures

The primary outcome was clinical cure, defined by patient survival and complete resolution of all following characteristics of CDI at the end of treatment without the need for addition of a different anti-CDI therapy: 1) diarrhea; 2) abdominal pain; 3)

fever; 4) leukocytosis. Treatment failure was counted as persistence of any of the mentioned CDI characteristics, need for introduction of additional anti-CDI therapy or patient death occuring during anti-CDI therapy. For the first phase, clinical cure, and for the second phase, treatment failure was assessed.

Secondary outcomes were mortality, relapse, colectomy and complication rates. In the first phase, in-hospital outcomes were assessed by final clinical diagnoses at discharge (autopsy reports were not collected at this phase), while 90-day outcomes of discharged patients were ascertained through focused electronic record searches and telephone interviews up for 90 days. In the second phase, only in-hospital outcomes were assessed by final clinical diagnoses at discharge or autopsy reports. Relapse was defined as re-occurrence of diarrhea and any of the other CDI specific characteristics after completion of cure and before hospital discharge or within 90 days, without evidence for alternative causes. Colectomy was registered if surgical intervention done on the colon was performed during hospitalization due to CDI. Complicated disease course was counted if any complication occured during anti-CDI treatment.

Statistical analysis

Continuous variables are expressed as mean±standard deviation (SD) or median±interquartile range (IQR) with minimum–maximum ranges, comparison was done with Student's *t*-test or Mann–Whitney *U*-test, depending on distribution. Normality of continuous variables was checked using the D'Agostino–Pearson omnibus test. Categorical values are reported as absolute numbers (n) with percentages (%). For statistical comparison, *Fisher*'s exact test and *Pearson*'s χ^2 test were used.

In the first phase, the probability of occurrence of one of the binary outcomes was modelled. Due to the probability being constrained between values of 0 and 1, their logit transformation was used instead: $logit(p) = ln\frac{p}{1-p}$. For stratified analysis along the ATLAS scores, the regression model of $logit(p) = \beta + Ax + \beta Ax$ was employed, where β was the effect of treatment (tigecycline vs. standard therapy), A is the effect of the ATLAS score (x being the actual ATLAS score of the patient), and βA is the interaction effect between them. Model goodnes-of-fit was checked using deviance and Pearson residuals.

In the second phase, predictors of clinical failure were identified by uni- and multivariate binomial logistic regression. Univariate analysis was planned *a priori* to include patient demographics, comorbidities and case severity characteristics,

temporal parameters of hospitalization and tigecycline therapy as covariates. Parameters with a *p* value of ≤0.1 were loaded into forward stepwise multivariate logistic regression (entry criterion *p*=0.05, removal criterion *p*=0.1). The maximal number of independent predictors was approximated with a common rule-of-thumb. Linearity in the logit was tested by *Box–Tidwell* test, model goodness-of-fit was tested by *Hosmer–Lemeshow* test.

A two-tailed *p*-value of <0.05 was considered statistically significant for all tests. When reported, odds ratios (OR) and their 95% confidence intervals (95%CI) are given for positive outcomes (clinical cure, survival, no relapse, no need for colectomy, uncomplicated disease course) with the treatment under investigation. Statistical analysis was done using IBM SPSS Statistics 23 (New York, USA). Results are reported by following the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) statement.

RESULTS

First phase: efficacy of intravenous tigecycline monotherapy compared to standard anti-CDI therapy

Baseline and clinical characteristics

After reviewing 602 patients hospitalized with CDI during the study period, 359 (59.6%) cases of severe CDI were found. Of these, 90 (25.1%) patients met study criteria, and 45–45 (12.5–12.5%) were assigned to the tigecycline and standard treatment groups, respectively.

Baseline patient characteristics are shown in *Table 1*. There was no difference in age and gender. Patients receiving tigecycline were more likely to suffer from chronic immunosuppression (53.3% vs. 28.9%; p=0.02), while chronic renal disease was more prevalent in the standard therapy group (22.2% vs. 53.3%; p=0.002). Altogether 75 (83.3%) patients received systemic antibiotics ≤3 months before disease onset. More patients had recurrent episodes in the tigecycline therapy group. However, previous administration of oral vancomycin for CDI was higher in this group (24.4% vs. 6.7%; p=0.02).

Table 1. Baseline characteristics of adult patients with severe *Clostridium difficile* infection included in the first phase, subgrouped by disease treatment

Characteristics	Tigecycline therapy group (n=45)	Standard therapy group (n=45)	*p* value
Age (years, mean±SD, min–max)	75.2±10.1 (51.4–94.6)	78.0±10.0 (55.4–94.1)	0.17
Male gender (n, %)	25 (55.6)	13 (28.9)	0.1

Comorbidities (n, %):			
- Arterial hypertension	38 (84.4)	44 (97.8)	0.05
- Chronic heart disease	33 (73.3)	36 (80.0)	0.45
- Chronic pulmonary disease	9 (20.0)	12 (26.7)	0.45
- Chronic renal disease	10 (22.2)	24 (53.3)	0.002
- Diabetes mellitus	13 (28.9)	14 (31.1)	0.81
- Active malignancy	15 (33.3)	8 (17.8)	0.09
- Chronic corticosteroid use	12 (26.7)	6 (13.3)	0.11
- Chronic immunosuppression	24 (53.3)	13 (28.9)	0.02
Charlson Comorbidity Score (mean±SD, min–max)	4.6±2.0 (1–11)	5.0±1.9 (1–9)	0.33
Risk factors for CDI (n, %):			
- Antibiotic use within 3 months	37 (82.2)	38 (84.4)	0.78
- Hospitalization for ≥3 days within 6 months	42 (93.3)	42 (93.3)	1.0
- Long-term care facility resident	13 (28.9)	17 (37.8)	0.37
Recurrent CDI episode (n, %)	17 (37.8)	13 (28.9)	0.37
No. of previous CDI episodes (mean±SD, min–max)	1.5±0.8 (1–4)	1.5±0.9 (1–4)	1.0
Treatment for for previous CDI episode (n, %):			
- Metronidazole	17 (37.8)	11 (24.4)	0.17
- Vancomycin	11 (24.4)	3 (6.7)	0.02
- Tigecycline	1 (2.2)	0 (0)	0.31

Clinical characteristics at diagnosis are shown in *Table 2*. Median ATLAS score was 8 in both groups. Significantly longer LOS (25.4±13.7 days vs. 13.5±11.5 days; p=0.001) and higher frequency of hospital-onset CDI (64.4% vs. 28.9%; p=0.001) were observed in the tigecycline treatment group, but rates of ICU admissions and ICU LOS were similar. Patients receiving tigecycline had prolonged symptoms before treatment initiation (15.9±12.7 days vs. 9.6±10.1 days; p=0.01). Initial physical and laboratory signs of severe CDI did not show any statistically significant difference. Imaging diagnostics more often detected signs of severity among receivers of tigecycline (91.1% vs. 66.7%; p=0.004). Although more endoscopic examinations were performed on patients treated with tigecycline (48.9% vs. 11.1%; p=0.004), and more blood cultures were taken from them (84.4% vs. 62.2.%; p=0.02), the rate of demonstrated pseudomembranous colitis and true bacteraemia did not differ between groups.

Table 2. Clinical characteristics of adult patients with severe *Clostridium difficile* infection included in the first phase, subgrouped by disease treatment

Characteristics	**Tigecycline therapy group (n=45)**	**Standard therapy group (n=45)**	***p* value**
CDI onset (n, %):			
- Hospital	29 (64.4)	13 (28.9)	0.001
- Long-term care facility	8 (18.8)	14 (31.1)	0.21
- Community	8 (18.8)	19 (42.2)	0.01
LOS at ward (days; median±IQR, min–max)	25.0±17.5 (2–60)	10.5±11.5 (2–51)	0.001
ICU admission (n, %)	10 (22.2)	12 (26.7)	0.62
LOS at ICU (days; median±IQR, min–max)	6.0±12.0 (1–25)	6.5±10.3 (1–34)	0.76
Symptom duration before admission (days; median±IQR, min–max)	14.0±13.0 (5–60)	6.0±10.0 (1–60)	0.01
Bristol stool score (median±IQR, min–max)	7.0±1.0 (6–7)	7.0±0.5 (6–7)	0.1

No. of stools per day (median±IQR, min–max)	6.0±4.0 (3–20)	7.0±3.0 (3–20)	0.83
ATLAS score (mean±SD, min–max)	7.8±1.3 (5–10)	8.0±1.1 (5–10)	0.25
Physical signs of CDI (n, %):			
- Fever (≥38.5 °C)	37 (82.2)	42 (93.3)	0.11
- Chills	18 (40.0)	19 (42.2)	0.83
- Abdominal pain	12 (26.7)	13 (28.9)	0.81
- Meteorism (tympanites)	9 (20.0)	14 (31.1)	0.23
- Respiratory failure	16 (35.6)	21 (46.7)	0.28
- Haemodynamic instability	36 (80.0)	31 (68.9)	0.23
- Peritonitis	4 (8.9)	6 (13.3)	0.5
Laboratory signs of CDI (n, %):			
- White blood cell count >15x10^9/L	38 (84.4)	43 (95.6)	0.08
- Band neutrophil cells >20%	36 (80.0)	39 (86.7)	0.39
- Serum creatinine ≥1.5x premorbid level	20 (44.4)	25 (55.6)	0.29
- Serum lactate >5 mmol/L	19 (42.2)	19 (42.2)	1.0
- Serum albumin <30 g/L	36 (80.0)	41 (91.1)	0.14
Imaging signs of CDI (n, %):			
- Dystension of colon (>6 cm)	30 (66.7)	25 (55.6)	0.28
- Mural thickening of colon	31 (68.9)	23 (51.1)	0.08
- Ascites	29 (64.4)	15 (33.3)	0.003
Patients with performed endoscopy[2] (n, %)	22 (48.9)	5 (11.1)	0.004
No. of pseudomembranous colitis (n, %)	19 (86.4)	4 (80.0)	0.71
Patients with performed blood cultures (n, %)	38 (84.4)	28 (62.2)	0.02
Patients with detected bloodstream-infections (n, %)	10 (26.3)	6 (21.4)	0.64

[1] Abdominal X-ray and ultrasonography for all patients.
[2] Sigmoidoscopy or total colonoscopy for all patients.

Clinical outcomes

Clinical outcomes are displayed in *Table 3*. Clinical cure was significantly higher in the tigecycline treatment group: 34 (75.6%) patients met the *a priori* defined criteria for recovery, compared to 24 (53.3%) patients in the standard treatment group (p=0.02). No significant differences were detected among mortality and relapse rates between the observed groups. Colectomy was not performed on any tigecycline recipients; 2 (4.4%) patients had colectomies in the standard treatment group (p=0.15). In total, complicated disease course occured in 13 (28.9%) patients treated with tigecycline, compared to 24 (53.3%) patients receiving standard treatment (p=0.02). CDI sepsis was more frequent among patients with standard treatment (15.6% vs. 40.0%, p=0.009). Rates of ileus and toxic megacolon showed no statistically significant difference. In the *logit* regression model, outcomes of clinical cure, complicated disease course and CDI sepsis remained significantly different between treatment groups (*Table 3*.).

Table 3. Clinical outcomes of adult patients with severe *Clostridium difficile* infection included in the first phase, subgrouped by disease treatment and stratified by *logit* regression analysis

Outcome measures (n, %)	Tigecycline therapy group	Standard therapy group	*p* value, nonstratified	OR, nonstratified (95%CI)[1]	*p* value, stratified	OR, stratified (95%CI)[1]

	(n=45)	(n=45)				
Clinical cure	34 (75.6)	24 (53.3)	0.02	2.7 (1.1–6.6)	0.02	11.9 (0.01–999<)
Mortality:						
- In-hospital	15 (33.3)	16 (35.6)	0.82	0.9 (0.4–2.2)	0.83	0.03 (0.001–42.66)
- 90-day	17 (37.8)	21 (46.7)	0.39	0.7 (0.3–1.6)	0.40	0.01 (0.001–12.46)
Relapse:						
- In-hospital	3 (6.7)	4 (8.9)	0.69	0.73 (0.2–3.5)	0.72	0.58 (0.001–31.55)
- 90-day	7 (15.6)	8 (17.8)	0.78	0.8 (0.3–2.6)	0.75	0.52 (0.001–999<)
Colectomy rate	0	2 (4.4)	0.15	0.2 (0.01–4.1)	NA	NA
Complicated disease:						
- Any manifestation	13 (28.9)	24 (53.3)	0.02	0.4 (0.2–0.8)	0.04	0.001 (0–36.24)
- Sepsis	7 (15.6)	18 (40.0)	0.009	0.3 (0.1–0.8)	0.008	0.01 (0–191.79)
- Ileus	5 (11.1)	4 (8.9)	0.72	1.3 (0.3–5.1)	0.73	9.28 (0.001–999<)
- Toxic megacolon	3 (6.7)	3 (6.7)	1.0	1.0 (0.2–5.2)	1.0	1.0 (0.01–999<)

[1] ORs and 95%CIs are reported for positive outcomes with tigecycline treatment.

Time to different outcomes are shown in *Table 4*. Only time to cure and in-hospital mortality from admission was significantly longer in the tigecycline treatment group.

Table 4. Time to different outcomes of adult patients with severe *Clostridium difficile* infection included in the first phase, subgrouped by disease treatment

Time elapsed (days; median±IQR, min–max)	Tigecycline therapy group (n=45)	Standard therapy group (n=45)	*p* value
To cure from admission	19.5±8.8 (8–45)	10.5±3.5 (7–20)	<0.001
To cure from treatment initiation	10.0±4.8 (5–24)	10.0±1.8 (7–18)	0.5
To in-hospital mortality from admission	13.0±12.5 (2–60)	3.0±9.0 (2–21)	0.007
To mortality from hospital discharge	36.0±29.0 (7–65)	25.0±9.0 (22–55)	0.75
To in-hospital relapse from admission	20.0±7.0 (11–25)	19.5±3.3 (12–22)	1.0
To relapse from hospital discharge	22.0±7.0 (10–30)	38.5± 26.8 (12–80)	0.19

Characteristics of anti-CDI antibiotic regimens

Course of tigecycline therapy was started 8.2±7.1 (0–38) days after hospital admittance with a mean treatment duration of 10.3±4.4 (2–22) days. Seven (15.6%) patients received tigecycline as first-line treatment without initial standard therapy. Tigecycline was given to 38 (84.4%) patients as an alternative after clinical failure of standard treatment was acknowledged. Among them, initial vancomycin was given for 8.9±4.7 (2–23) days compared to 9.0±5.4 (2–21) days to patients receiving standard therapy alone (p=0.79), and metronidazole was administered for 6.2±4.6 (2–18) days compared to 6.5±4.8 (2–21) days (p=0.92).

Time to cure from treatment initiation was equal between observed groups (10.7±4.2 days vs. 10.7±2.7 days; p=0.97), while time to in-hospital mortality from admission was longer among patients receiving tigecycline (18.7±14.4 days vs. 7.2±6.6 days; p=0.007). Adverse drug reactions attributable to tigecycline treatment were not observed. In contrast, 6 (13.3%) patients complained of nausea after initiation of metronidazole from the standard therapy group (p=0.02). Discontinuation of therapy was not necessary due to spontaneous resolution of complaints.

In a limited subgroup analysis of 38 patients who received tigecycline as salvage treatment (excluding those who received tigecycline without initial standard therapy [n=7]), selected characteristics measured on the day of standard therapy initiation and tigecycline initiation were compared (*Table 5.*). It was demonstrated that on the day tigecycline initiation was decided upon, most clinical and laboratory parameters corresponded to severe ongoing *C. difficile* infection.

Table 5. Clinical characteristics of study patients who received tigecycline as salvage treatment after failure of standard therapy by treatment initiation days. Characteristics represent paired observations of same patients. Patients receiving tigecycline first without initial standard therapy (n = 7) were not included in the analysis.

Characteristics	**Day of tigecycline initiation (n = 38)**	**Day of standard therapy initiation (n = 38)**	***p* value**
Duration of symptoms (days; median±IQR, min–max)	24.6±14.5 (9–68)	15.4±13.2 (5–60)	0.001
Patients with symptoms for ≥14 days (n, %)	29 (76.3)	12 (31.6)	0.001
Bristol stool score (median±IQR, min–max)	6.5±0.5 (6–7)	6.6±0.5 (6–7)	0.3
No. of stools per day (median±IQR, min–max)	9.3±4.0 (2–16)	6.9±3.2 (3–15)	0.007
Physical signs of sCDI (n, %):			
- total	38 (100)	36 (94.7)	0.15
- abdominal pain	27 (71.1)	30 (78.9)	0.42
- fever (≥38.5 °C)	28 (73.7)	14 (36.8)	0.001
- chills	14 (36.8)	8 (21.1)	0.12
- respiratory failure	11 (28.9)	6 (15.8)	0.13
- haemodynamic instability	23 (60.5)	13 (34.2)	0.02
- meteorism (tympanites)	33 (86.8)	29 (76.3)	0.23
- peritonitis	4 (10.5)	3 (7.9)	0.69
Laboratory signs of sCDI (n, %):			
- total	38 (100)	36 (94.7)	0.49
- WBC >15x10^9/L	38 (100)	34 (89.5)	0.04
- band neutrophils >20%	38 (100)	31 (81.6)	0.005
- serum creatinine ≥1.5x premorbid level	32 (84.2)	18 (47.3)	0.001
- serum lactate >5 mmol/L	27 (71.1)	15 (39.5)	0.005
- serum albumin <30 g/L	34 (89.5)	32 (84.2)	0.49
WBC (x10^9/L; median±IQR, min–max)	34.0±7.3 (21.0–45.5)	24.1±10.3 (2.1–52.0)	<0.001
Relative neutrophilia (%;median±IQR, min–max)	92.7±3.6 (88–98)	85.6±12.1 (29–98)	0.002
CRP (mg/L; median±IQR, min–max)	307.5±110.3 (101–550)	206.8±103.4 (62–520)	<0.001
Serum creatinine (μmol/l/1.73 m^2; median±IQR, min–max)	361.0±179.4 (117–729)	215.1±155.9 (44–653)	0.001
Serum lactate (mmol/L; median±IQR, min–max)	6.3±1.8 (3.0–9.5)	5.3±3.1 (2.1–16.9)	0.09
Serum albumin (g/L; median±IQR, min–max)	21.9± 5.1 (14–30)	25.3±3.4 (19–33)	0.001

Second phase: characteristics and predictors of treatment failure with intravenous tigecycline monotherapy

Baseline and clinical characteristics

During the study period, 2718 CDI episodes were found (with any severity), and from these, 1148 (42.2%) severe CDI cases were identified. Of these, 110 cases met study criteria and were included in the cohort, 62.7% (69/110) had treatment success, 37.3% (41/110) had treatment failure.

Baseline and clinical characteristics are shown in *Table 6*. Median age was 75.0±14.4 years, and there was a tendency for treatment success among males (38/69, 55.1% vs. 18/41, 43.9%, p=0.32). Among patients with treatment failure, chronic heart (50/69, 72.5% vs. 38/41, 92.7%, p=0.01) and pulmonary diseases (13/69, 18.8% vs. 17/41, 41.5%, p=0.01) were more common, other comorbidities were balanced. Risk factors for CDI and ATLAS scores were statistically comparable between the two groups.

Table 6. Baseline and clinical characteristics of adult patients with severe *Clostridium difficile* infection included in the second phase, subgrouped by response to tigecycline treatment

Parameter	Total (n=110)	Treatment success (n=69)	Treatment failure (n=41)	*p* value
Age (years, median±IQR, min–max)	75.0±14.4 (40–94)	73.3±15.2 (45–94)	76.9±11.9 (40–93)	0.71
Male gender (n, %)	56 (50.9)	38 (55.1)	18 (43.9)	0.32
Comorbidities (n, %)				
- Arterial hypertension	99 (90.0)	61 (88.4)	38 (92.7)	0.53
- Chronic heart disease	88 (80.0)	50 (72.5)	38 (92.7)	0.01
- Chronic pulmonary disease	30 (27.3)	13 (18.8)	17 (41.5)	0.01
- Chronic renal disease	43 (39.1)	24 (34.8)	19 (46.3)	0.31
- Diabetes mellitus	43 (39.1)	26 (37.7)	17 (41.5)	0.84
- Active malignancy	32 (29.1)	22 (31.9)	10 (24.4)	0.51
- Chronic corticosteroid use	18 (16.4)	12 (17.4)	6 (14.6)	0.79
- Chronic immunosuppression	42 (38.2)	31 (44.9)	11 (26.8)	0.06
No. of comorbidities per patient (mean±SD, min–max)	3.6±1.5 (0–8)	3.5±1.5 (0–7)	3.8±1.4 (1–8)	0.21
Charlson Comorbidity Score (mean±SD, min–max)	6.5±2.1 (1–10)	6.4±2.0 (1–10)	6.8±2.2 (2–10)	0.3
Risk factors for CDI (n, %):				
- Antibiotic use within 3 months	95 (86.4)	60 (87.0)	35 (85.4)	1.0
- Hospitalization for ≥3 days within 6 months	101 (91.8)	65 (94.2)	36 (87.8)	0.29
- Long-term care facility resident	21 (19.1)	15 (21.7)	6 (14.6)	0.45
Recurrent CDI episode (n, %)	43 (39.1)	26 (37.7)	17 (41.5)	0.84
No. of previous CDI episodes (median±IQR, min–max)	0±1 (0–5)	0±1 (0–4)	0±1 (0–5)	0.61
Treatment for previous CDI episode (n, %):				
- Metronidazole	35 (31.8)	22 (31.9)	13 (31.7)	1.0
- Vancomycin	31 (28.2)	17 (24.6)	14 (34.1)	0.38
- Tigecycline	2 (1.8)	1 (1.4)	1 (2.4)	1.0
CDI onset (n, %):				
- Hospital	64 (58.2)	40 (62.3)	24 (58.5)	1.0

- Community	14 (12.7)	10 (14.5)	4 (9.8)	0.66
- Long-term care facility	32 (29.1)	19 (27.5)	13 (31.7)	0.56
Symptom duration before admission (days, median±IQR, min–max)	10.0±11.0 (1–60)	12.0±14.0 (2–60)	7.0±9.8 (1–60)	0.01
No. of stools per day (median±IQR, min–max)	7.0±4.5 (1–20)	7.0±4.5 (1–20)	6.0±4.0 (2–17)	0.41
Bristol stool score (median±IQR, min–max)	6.0±1.0 (6–7)	7.0±1.0 (6–7)	6.0±1.0 (6–7)	0.43
Physical signs of CDI (n, %):				
- Fever (≥38.5 °C)	38 (34.5)	21 (30.4)	17 (41.5)	0.31
- Chills	18 (16.4)	11 (15.9)	7 (17.1)	1.0
- Abdominal pain	75 (68.2)	48 (69.6)	27 (65.9)	0.86
- Meteorism (tympanites)	83 (75.5)	52 (75.4)	31 (75.6)	1.0
- Respiratory failure	16 (14.5)	6 (8.7)	10 (24.4)	0.05
- Haemodynamic instability	18 (16.4)	12 (17.4)	6 (14.6)	0.79
- Peritonitis	11 (10.0)	2 (2.9)	9 (22.0)	<0.01
Imaging signs of CDI (n, %):				
- Dystension of colon (>6 cm)	55 (50.0)	30 (43.5)	25 (61.0)	0.11
- Mural thickening of colon	76 (69.1)	49 (71.0)	27 (65.9)	0.68
- Ascites	69 (62.7)	42 (60.9)	27 (65.9)	0.67
Patients with performed endoscopy (n, %)	63 (57.3)	42 (60.9)	21 (51.2)	0.42
No. of pseudomembranous colitis (n, %)	54 (49.1)	38 (55.1)	16 (39.0)	0.11
Patients with blood cultures (n, %)	79 (71.8)	52 (75.4)	27 (65.9)	0.38
Patients with bloodstream-infections (n, %)	17 (15.5)	9 (13.0)	8 (19.5)	0.41
ICU admission (n, %)	21 (19.1)	7 (10.1)	14 (34.1)	0.01
LOS at ICU (days, median±IQR, min–max)	5.0±13.0 (1–53)	9.0±12.0 (1–25)	5.0±10.3 (1–53)	0.45
LOS at ward (days, median±IQR, min–max)	22.0±17.0 (1–173)	24.5±16.5 (9–173)	20.0±21.0 (1–124)	0.01
ATLAS score (mean±SD, min–max)	6.9±1.4 (5–10)	6.8±1.3 (5–10)	7.2±1.4 (5–10)	0.16

Among patients with subsequent treatment failure, symptom duration before admission was shorter (12.0±14.0 vs. 7.0±9.8 days, p=0.01), peritonitis was more frequent (2/69, 2.9% vs. 9/41, 22.0%, p<0.01), and median CRP values (157.0±107.0 mg/dL vs. 191.0±135.0 mg/dL, p=0.03) were higher. Other physical and laboratory findings of severe CDI were statistically similar between groups. The rate of bloodstream-infections was higher (9/52,17.3% vs. 8/27, 29.6%, p=0.25), whereas pseudomembranes were detected less frequently (38/42, 90.5% vs. 16/21, 76.2%, p=0.14) in the failure group. Patients with clinical failure had higher ICU admittance rates (7/69, 10.1% vs. 14/41, 34.1%, p=0.01, and lower LOS (24.5±16.5 days vs. 20.0±21.0 days, p=0.01). Bacterial and fungal pathogens of detected bloodstream-infections are shown in *Table 7*. Most breakthrough bloodstream-infections were caused by *Escherichia coli*, and interestingly, there was a trend for higher incidence among patients with treatment success (5.8% vs. 2.4%). Among Gram positive pathogens, infections caused by *Enterococcus faecalis* and *Enterococcus faecium* were prevalent. Only one case of bloodstream-infection was caused by an acquired multidrug-resistant organism, namely *Acinetobacter baumannii*, in a patient treated at the ICU.

Table 7. Isolated bacterial and fungal pathogens of detected bloodstream-infections in adult patients with severe *Clostridium difficile* infection included in the second phase, subgrouped by response to tigecycline treatment

Isolated pathogens* (n, %)	Total (n=110)	Treatment success (n=69)	Treatment failure (n=41)	*p* value
Escherichia coli	5 (4.6)	4 (5.8)	1 (2.4)	0.69
Enterococcus faecalis	3 (2.7)	0	3	0.05
Enterococcus faecium	3 (2.7)	2 (2.9)	1 (2.4)	1.0
Klebsiella pneumoniae	2 (1.8)	1 (1.5)	1 (2.4)	1.0
Proteus mirabilis	2 (1.8)	2 (2.9)	0	0.52
Pseudomonas aeruginosa	2 (1.8)	1 (1.5)	1 (2.4)	1.0
Staphylococcus aureus	2 (1.8)	1 (1.5)	1 (2.4)	1.0
Acinetobacter baumannii	1 (0.9)	1 (1.5)	0	1.0
Enterococcus gallinarum	1 (0.9)	1 (1.5)	0	1.0
Enterobacter aerogenes	1 (0.9)	1 (1.5)	0	1.0
Klebsiella oxytoca	1 (0.9)	0	1 (2.4)	0.37
Staphylococcus epidermidis	1 (0.9)	1 (1.5)	0	1.0
Staphylococcus lugdunensis	1 (0.9)	0	1 (2.4)	0.37
Candida inconspicua	1 (0.9)	1 (1.5)	0	1.0
Candida albicans	1 (0.9)	1 (1.5)	1 (2.4)	0.37

* Six patients had mixed bloodstream-infections, the isolates are reported individually.

Clinical outcomes and therapeutic measures

Clinical outcomes and therapeutic measures are shown in *Table 8*, and *Figures 1-2.* In-hospital all-cause mortality was lower in the treatment success group (7.2% vs. 75.6%, p<0.01), in-hospital relapse (4.3% vs. 4.9%, p=1.0) and sepsis (13.0% vs. 26.8%, p=0.07) rates were similar. Among patients with treatment failure, CDI specific mortality was 34.1%, ileus (7.2% vs. 26.8%, p=0.01) and toxic megacolon (1.4% vs. 24.4%, p<0.01) were prevalent, colectomy was occasionally needed (0 vs. 12.2%, p<0.01). There was no statistically significant difference regarding the rate of patients receiving standard therapy, or the duration of standard therapy before tigecycline (*Figure 1.*). Tigecycline was started earlier in patients with subsequent failure (6.0±7.0 days vs. 2.5±4.0 days, p=0.19), treatment duration was shorter (10.0±2.0 days vs. 8.5±5.0 days, p=0.01), possibly explained by more patients dying during the first few days of therapy. In addition, total parenteral nutrition (20.3% vs. 46.3%, p=0.01) and vasopressor support (15.9% vs. 36.6%, p=0.02) were more commonly administered among them (*Figure 2.*).

Table 8. Clinical outcomes and therapeutic measures of adult patients with severe *Clostridium difficile* infection included in the second phase, subgrouped by response to tigecycline treatment

Parameter	Total (n=110)	Treatment success (n=69)	Treatment failure (n=41)	*p* value
In-hospital mortality, all-cause* (n, %)	36 (32.7)	5 (7.2)	31 (75.6)	<0.01
In-hospital mortality, CDI specific (n, %)	14 (13.6)	0	14 (34.1)	<0.01
In-hospital relapse (n, %)	5 (4.5)	3 (4.3)	2 (4.9)	1.0
Colectomy rate (n, %)	5 (4.5)	0	5 (12.2)	<0.01
Complicated disease course (n, %):				
- Any manifestation	38 (34.6)	16 (23.2)	22 (53.7)	<0.01
- Sepsis	20 (18.2)	9 (13.0)	11 (26.8)	0.07
- Ileus	16 (14.5)	5 (7.2)	11 (26.8)	0.01
- Toxic megacolon	11 (10.0)	1 (1.4)	10 (24.4)	<0.01
Duration of standard therapy before tigecycline** (days, median±IQR, min–max):				
- Metronidazole	4.0±6.8 (1–18)	4.0±6.0 (1–18)	3.0±3.0 (1–13)	0.24
- Vancomycin	7.0±6.0 (0–38)	8.0±5.3 (0–38)	6.0±7.5 (1–21)	0.06
Tigecycline therapy characteristics (days, median±IQR, min–max):				
- Starting day from diagnosis	4.0±6.0 (0–19)	6.0±7.0 (1–19)	2.5±4.0 (0–14)	0.19
- Duration of therapy	10.0±3.0 (2–22)	10.0±2.0 (4–22)	8.5±5.0 (2–21)	0.01

* Including CDI specific deaths.

** If combination was used, durations were counted separately for each drug.

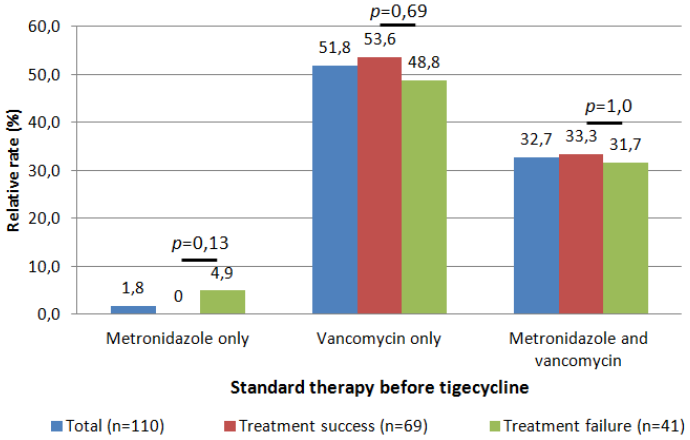

Figure 1. Standard therapy administered before tigecycline among adult patients with severe *Clostridium difficile* infection included in the second phase, subgrouped by response to tigecycline treatment

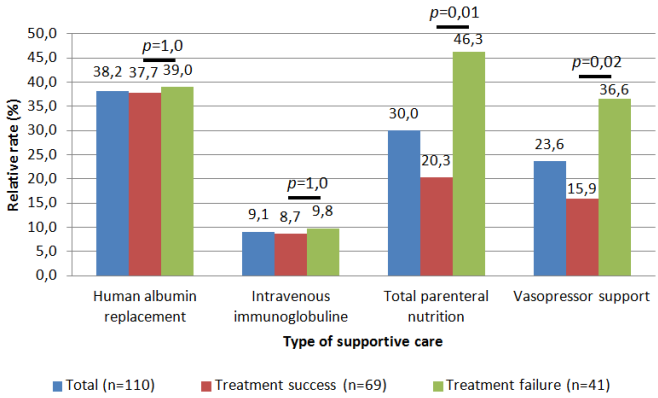

Figure 2. Supportive care among adult patients with severe *Clostridium difficile* infection included in the second phase, subgrouped by response to tigecycline treatment

Predictors of tigecycline treatment failure

Predictors for tigecycline treatment failure in uni- and multivariate logistic regression analysis are shown in *Table 9.* In univariate analysis, 11 possible covariates were selected, and in the final multivariate model, chronic pulmonary disease (OR 3.48, 95%CI 1.06–11.49, p=0.04), development of ileus (OR 2.38, 95%CI 0.53–10.75, p=0.01), need for total parenteral nutrition (OR 7.04, 95%CI 2.02–24.56, p<0.01) and duration of therapy (OR 0.81, 95%CI 0.69–0.94, p<0.01) were retained as independent predictors of treatment failure.

Table 9. Predictors for tigecycline treatment failure among adult patients with severe *Clostridium difficile* infection included in the second phase, subgrouped by uni- and multivariate logistic regression analysis

Parameter	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*p value*	*OR (95%CI)*	*p value*
Age at diagnosis	1.0 (0.96–1.04)	0.86		
Male gender	0.64 (0.29–1.41)	0.25		
Chronic heart disease	5.0 (1.33–20.0)	0.01	–	–
Chronic pulmonary disease	3.13 (1.29–7.69)	0.01	3.48 (1.06–11.49)	0.04
No. of comorbidities per patient	1.19 (0.91–1.56)	0.21		
Charlson index	1.10 (0.91–1.33)	0.29		
ATLAS score at diagnosis	1.25 (0.94–1.67)	0.12		
Peritonitis at diagnosis	10.0 (1.92–50.0)	0.01	–	–
Appearance of CDI associated sepsis	2.43 (0.92–6.67)	0.07	–	–
Appearance of ileus	4.76 (1.52–14.28)	0.01	2.38 (0.53–10.75)	0.01
Appearance of toxic megacolon	25.0 (2.71–100.0)	0.01	–	–
Presence of bloodstream-infection	1.61 (0.57–4.55)	0.37		
Recurrent CDI episode	0.85 (0.38–1.88)	0.69		
ICU admission	4.55 (1.67–12.5)	0.01	–	–

LOS at ward (not ICU)	0.99 (0.97–1.01)	0.47		
Symptom duration before admission*	0.95 (0.91–1.0)	0.05	n.a.	
White blood cell count at diagnosis	0.99 (0.96–1.02)	0.66		
Serum albumin at diagnosis	0.96 (0.91–1.02)	0.17		
Serum CRP at diagnosis	0.99 (0.98–1.0)	0.02	–	–
Starting day of tigecycline therapy from diagnosis	1.09 (1.02–1.19)	0.02	–	–
Duration of tigecycline therapy	0.85 (0.76–0.96)	0.01	0.81 (0.69–0.94)	<0.01
Need for total parenteral nutrition	3.39 (1.45–7.93)	0.01	7.04 (2.02–24.56)	<0.01
Need for vasopressor support	3.04 (1.23–7.52)	0.01	–	–

* The parameter was not included in the final model as co-linearity was not proven by the *Box-Tidwell* test ($p < 0.05$)
n.a. Not applicable

CONCLUSIONS

To assess the role of intravenous tigecycline monotherapy among adult patients hospitalized with severe CDI, we designed a two-phase retrospective observational cohort study at our tertiary referral centre.

In the first phase of our study, we described the clinical cure of severe CDI among hospitalized adult patients treated with intravenous tigecycline monotherapy. Favourable outcomes suggest that intravenous tigecycline might be a reasonable therapeutic choice for cases of severe CDI refractory to oral vancomycin + intravenous metronidazole therapy. Further research, particularly a prospective, randomized controlled trial is warranted for *proof-of-concept* validation and additional evidence.

In the second phase of our study, we described charateristics and predictors of treatment failure with intravenous tigecycline monotherapy administered among hospitalized adult patients with severe CDI. Our data suggests that a higher probability for clinical failure might be identified by some independent predictors, such as chronic pulmonary disease, development of ileus and need for total parenteral nutrition, while longer duration of therapy might be a protective factor against treatment failure.

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