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# Clinical and Microbiological Characteristics of Hospitalized Adults Aged ≤45 Years With *Clostridioides* (Formerly *Clostridium*) *difficile* Infection: A Prospective Observational Cohort Study From Hungary

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**Keywords:** *Clostridioides difficile* | *Clostridium difficile* | diarrhea | nosocomial infection | young adult

## ABSTRACT

Studies focusing on young adults with *Clostridiodes* (formerly *Clostridium*) *difficile* infection (CDI) are scarce. Our objective was to assess characteristics and outcomes of CDI among hospitalized young adults between the ages of 18–45 years at diagnosis, compared to a subcohort of randomly selected older patients aged >45 years. We performed a prospective, observational cohort study by enrolling and stratifying 234 consecutive cases of first/recurrent CDI at our tertiary referral center between 2015 and 2019. At 30 days post-treatment initiation, young adults had a higher clinical cure (99.1% vs. 81.2%; $p<0.01$) and lower all-cause mortality (0.9% vs. 16.4%; $p<0.01$). Metronidazole was a common first-line choice (77.8% vs. 46.2%; $p<0.01$) with similar relapse rates (6.0% vs. 5.1%, $p=0.56$). We conclude that CDI in patients aged between 18 and 45 years was associated with fewer complications and higher clinical cure with metronidazole, compared to older patients.

## 1 | Introduction

*Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) is one of the leading causes of healthcare-associated infections in Northern America and Europe, and it is still associated with a significant burden of morbidity and mortality [1, 2]. Advanced age is a known risk factor for severe and recurrent CDI, and the majority of the infections occur in adults aged 65 years or older [3, 4]. A retrospective analysis of the United States National Hospital Discharge Surveys from 2001 to 2010, representing 2.3 million cases of CDI, found that mortality and the median hospital length-of-stay (LOS) were

**Abbreviations:** CA, community acquired; CDI, *Clostridioides* (formerly *Clostridium*) *difficile* infection; CO, community onset; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HA, hospital acquired; HO, hospital onset; ICU, intensive care unit; IQR, interquartile range; LOS, length-of-stay; NSAID, non-steroid anti-inflammatory drug; sCDI, severe *Clostridioides* (formerly *Clostridium*) *difficile* infection; SD, standard deviation; WBC, white blood cell.

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significantly different between age groups. Mortality was the highest for elderly adults (8.8%), followed by younger adults (6.9%) and pediatric (3.1%) populations. Median hospital LOS was also longer for elderly patients (8 days), as compared to younger adults (7 days) and children (6 days) [5]. Similarly, a survey study analyzing data of 509 patients from 34 European countries found that 63% of all hospitalized adult patients were 65 years or older, and advanced age was a significant risk factor for complicated CDI [6]. Although CDI has a larger burden on populations of the elderly, a relevant proportion of affected patients are younger; however, the number of publications focusing on these age cohorts, particularly those assessing treatment strategies is limited. Therefore, our objective was to assess the clinical and microbiological characteristics of CDI among hospitalized young adults between the ages of 18 and 45 years at diagnosis, compared to older patients.

## 2 | Methods

### 2.1 | Patient Identification and Inclusion

A prospective, observational cohort study was conducted by enrolling consecutive cases of adult (≥ 18 years of age at diagnosis) patients with first or recurrent CDI episodes, hospitalized between 2015 and 2019 in South Pest Central Hospital, National Institute for Hematology and Infectious Diseases (SPCH-NIHI), a tertiary referral center with > 100 dedicated beds for infectious diseases in Budapest, Hungary. Our study was conducted in accordance with the Helsinki Declaration and national ethical standards. The Institutional Review Board of SPCH-NIHI approved the study protocol (IKEB/17/2016). Informed consent for anonymized data collection was obtained from patients.

All patients were screened for inclusion on the day of CDI diagnosis. An eligible patient was included in the study if: (1) the clinical case presented with symptoms compatible with CDI (see later), and (2) microbiological verification of the presence of toxin-producing *C. difficile* from a stool sample was done, and (3) no alternative causes for clinical symptoms were identified during hospitalization. Patients aged ≤ 45 years were included in the young adult subcohort and were matched in a 1:1 ratio with another subcohort of randomized patients aged over 45 years. During the randomization process, all patients aged > 45 years and diagnosed or hospitalized with CDI in our Institute from the same time period were identified based on the national disease-specific digital codes (corresponding to codes of the International Classification of Diseases, 10th Revision) and then selected with computer-based randomization.

### 2.2 | Data Collection

Data from included patients were collected manually during daily patient visits and from the hospital electronic records, and then anonymously transferred to a standardized electronic case report form. The collected data included: (1) age, gender; (2) comorbidities; (3) relevant medications used prior to *C. difficile* episode; (4) number and treatment of prior CDI episodes; (5) characteristics of current CDI episode (onset, symptoms, findings on physical examination, laboratory, microbiological, imaging and endoscopic studies); (6) admission to ICU and length of stay; and (7) clinical outcomes.

### 2.3 | Diagnosis and Assessment of Severity

Diagnosis of CDI was performed in accordance with the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guideline [7]. Diagnosis was made by a clinically compatible case presentation (diarrhea, ileus, toxic megacolon or CDI associated sepsis) plus confirmation of a toxin-producing *C. difficile* strain from an unformed stool sample, using enzyme immuno-assay targeting glutamate dehydrogenase and toxins A + B (C. Diff Quik Chek Complete, TECHLAB Inc.) [8]. Diarrhea was defined as at least 3 stools (Bristol stool chart type 5–7) in ≤ 24 h for two consecutive Days [9]. Epidemiological classification was performed according to the European Centre for Disease Prevention and Control surveillance definitions [10]. An episode was defined as community-onset (CO) if typical CDI symptoms started outside of healthcare settings, or healthcare-onset (HO) if CDI symptoms presented during a stay in a healthcare facility. We defined an episode community-associated (CA) if symptoms started in the community or within the first 48 h after hospital admission, and the patient did not attend any healthcare facilities in the previous 12 weeks. Healthcare facilities in the previous 12 weeks. Healthcare-associated (HA) CDI was defined by symptoms starting 48 h after hospital admission, or if the patient has been discharged from a healthcare facility during the previous 4 weeks. An episode was marked unclassifiable if the documentation lacked relevant data necessary for further identification, or if the patient has been discharged from a healthcare setting for 4–12 weeks.

Severe disease (sCDI) was defined as confirmed CDI with at least two of the following: fever (core body temperature ≥ 38°C), respiratory or hemodynamic instability (requirement for ventilatory and/or circulatory support), abdominal pain with peritonitis (muscle guarding with rebound tenderness), peripheral blood leukocytosis (white blood cell [WBC] count $> 15 \times 10^9$/L) with marked left-shift (> 20% of band neutrophils), 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 or wall thickening, ascites, or pseudomembranous colitis. Disease severity was quantified using the ATLAS score for each patient at CDI diagnosis [11].

Complicated disease was defined as sCDI and presence of ileus, and/or toxic megacolon, and/or CDI associated sepsis resulting in the need for ICU admission, colectomy, or death. We used definitions from a previous publication from our group, based on the ESCMID definitions [12]. Briefly, ileus was defined as the absence of intestinal motility for ≥ 24 h, and radiological features of abnormal bowel distension. Toxic megacolon was defined as colonic ileus and radiological signs of extreme distension (> 6 cm in transverse width). *Clostridium difficile* sepsis was defined as CDI with at least two systemic inflammatory response syndrome adult criteria, according to the American College of Chest Physicians/Society of Critical

Care Medicine definition [13]. Each individual complication was counted separately per patient. Recurrent CDI was diagnosed after at least one previously documented CDI with clinical cure before the onset of the index episode within 8 weeks.

### 2.4 | Clinical Outcomes and Follow-Up

Primary outcome was clinical cure, defined as the complete resolution of CDI characteristics (diarrhea, abdominal pain, fever, and blood leukocytosis). Clinical failure was counted as patient death or persistence of any CDI symptoms. Secondary outcomes were all-cause mortality, relapse of CDI (recurrence of CDI symptoms without evidence for alternative causes), rates of colectomy (partial or total resection of the colon during hospitalization due to CDI) and a complicated disease course (occurrence of ≥1 CDI specific complication, as defined earlier). All primary and secondary outcomes were assessed at +30 days from anti-CDI treatment initiation. If the patient was discharged before +30 days, follow-up was carried out through ambulatory visits, e-mails, and phone calls.

### 2.5 | Statistical Analysis

Continuous variables are expressed as median ± interquartile range (IQR), with minimum–maximum ranges; comparison was done with Student's t-test or Mann–Whitney *U* test, depending on distribution. Categorical variables are presented as absolute numbers (*n*) and percentages (%), Fisher's exact test was used for statistical analysis. A two-tailed *p* value of $<0.05$ was considered to be statistically significant for all tests. All statistical analysis was done on IBM SPSS 23.0. For reporting, we adhered to the "STrengthening the Reporting of OBservational studies in Epidemiology" Statement (www.strobe-statement.org).

## 3 | Results

During the study period, 3381 cases of CDI in 2718 patients were screened, and from these, 117 (4.3%) patients were included in the young adult subcohort. Baseline and demographic characteristics of the included patients are shown in Table 1. Among young adults, the ratio of male patients was

**TABLE 1** | Demographic and baseline characteristics of adult patients with CDI included in the study, grouped by subcohorts of age.

| Characteristics | Total cohort (*n* = 234) | Young adults[a] (*n* = 117) | Older adults[a] (*n* = 117) | *p* |
|---|---|---|---|---|
| Age at diagnosis (years, median ± IQR, min–max) | 43.2 ± 42.3 (19–95) | 33.6 ± 10.6 (19–42) | 76.0 ± 15.1 (45–95) | **<0.01** |
| Male patients (*n*, %) | 55 (23.5) | 10 (8.5) | 45 (38.5) | **<0.01** |
| Comorbidities (*n*, %) | | | | |
| Essential hypertension | 91 (38.9) | 7 (6.0) | 84 (71.8) | **<0.01** |
| Chronic heart disease | 49 (20.9) | 2 (1.7) | 47 (40.2) | **<0.01** |
| Chronic pulmonary disease | 31 (13.2) | 4 (3.4) | 27 (23.1) | **<0.01** |
| Chronic hepatological disease | 13 (5.6) | 8 (6.8) | 5 (4.3) | 0.57 |
| Chronic gastrointestinal disease | 31 (13.2) | 10 (8.5) | 21 (17.9) | **0.03** |
| Chronic renal disease | 26 (11.1) | 11 (9.4) | 15 (12.8) | 0.3 |
| Chronic cerebral disease | 31 (13.2) | 10 (8.5) | 21 (17.9) | **0.03** |
| Chronic immunosuppression | 23 (9.8) | 12 (10.3) | 11 (9.4) | 0.82 |
| Active malignancy | 32 (13.7) | 12 (10.3) | 20 (17.1) | 0.12 |
| Diabetes mellitus | 26 (11.1) | 1 (0.9) | 25 (21.4) | **<0.01** |
| Documented risk factors for CDI[b] (*n*, %) | | | | |
| Recent hospitalization | 136 (58.1) | 52 (44.4) | 84 (71.8) | **<0.01** |
| Recent systemic antibiotic therapy | 169 (72.2) | 89 (76.1) | 80 (68.4) | 0.18 |
| Recent surgery | 23 (9.8) | 11 (9.4) | 12 (10.3) | 0.82 |
| Recent immuno-chemotherapy | 15 (6.4) | 9 (7.7) | 6 (5.1) | 0.42 |
| Systemic corticosteroids | 59 (25.2) | 29 (24.8) | 30 (25.6) | 0.88 |
| Number of recent episodes | 1 ± 1 (1–6) | 1 ± 0.5 (1–6) | 1 ± 1 (1–4) | 0.05 |

[a]Younger adults were defined as 18–45 years of age, older patients were >45 years of age, at diagnosis of CDI.
[b]Within 90 days prior to the onset of the CDI episode.

significantly lower (8.5% vs. 38.5%; $p < 0.01$). The rates of chronic liver (6.8% vs. 4.3%; $p = 0.57$) and renal diseases (9.4% vs. 12.8%; $p = 0.3$), as well as chronic immunosuppression (10.3% vs. 9.4%; $p = 0.82$) and active malignancies (10.3% vs. 17.1%; $p = 0.12$) were statistically similar between the subcohorts. Among documented risk factors for CDI, the only statistically significant difference was present in respect of recent hospitalization (44.4% vs. 71.8%, $p < 0.01$).

Clinical characteristics are presented in Table 2. Most episodes of CDI were classifiable as CO-CA versus CO-HA among young adults versus elderly patients, respectively. The median time from symptom onset to CDI diagnosis was 5.5 ± 12.0 days, and 19.7% of all episodes were recurrent. Anti-motility agents were used at similar rates before hospitalization (10.3% vs. 5.1%; $p = 0.17$). With respect to symptoms, abdominal pain was more frequent (47.9% vs. 32.5%, $p < 0.01$), while respiratory (0.9% vs. 4.3%, $p = 0.91$) and hemodynamic failure (0.0% vs. 9.4%, $p < 0.01$) were less prevalent among young adults. The presence of fever was similar in the two subgroups (26.5% vs. 22.2%; $p = 0.36$). Although ATLAS scores (3.0 ± 1.0 vs. 4.0 ± 3.0; $p = 0.06$) and rates of ICU admissions (1.7% vs. 3.4%; $p = 0.04$) were comparable between subcohorts, older patients were more likely to be diagnosed with fulminant episodes of CDI (0.9% vs. 10.3%; $p < 0.01$), and complications such as ileus (0.9% vs. 6.0%; $p < 0.01$) or CDI associated sepsis (2.6% vs. 12.8%; $p < 0.01$). Furthermore, the presence of documented bloodstream infections (1.7% vs. 4.3%; $p = 0.25$) and pseudomembranous colitis (4.3% vs. 10.3%; $p = 0.07$) did not show a statistically significant difference between the two subgroups.

**TABLE 2** | Clinical and microbiological characteristics of adult patients with CDI included in the study, grouped by subcohorts of age.

| Characteristics | Total cohort ($n = 234$) | Young adults[a] ($n = 117$) | Older adults[a] ($n = 117$) | $p$ |
|---|---|---|---|---|
| Symptom duration before CDI diagnosis (days, median ± IQR, min–max) | 5.5 ± 12.0 (1–90) | 5.0 ± 9.0 (1–60) | 6.5 ± 12.0 (1–90) | 0.31 |
| Drugs for symptom alleviation before hospitalization (*n*, %) | | | | |
| Proton pump inhibitors | 62 (26.5) | 18 (15.4) | 44 (37.6) | **< 0.01** |
| NSAIDs | 34 (14.5) | 3 (2.6) | 31 (26.5) | **< 0.01** |
| Anti-motility agents | 18 (7.7) | 12 (10.3) | 6 (5.1) | 0.14 |
| Probiotics | 39 (16.7) | 27 (23.1) | 12 (10.3) | **< 0.01** |
| Recurrent CDI episode (*n*, %) | 46 (19.7) | 19 (16.2) | 27 (23.1) | 0.18 |
| First symptoms of CDI (*n*, %) | | | | |
| Diarrhea | 234 (100.0) | 117 (100.0) | 117 (100.0) | n.a. |
| Fever (≥ 38°C) | 57 (24.4) | 31 (26.5) | 26 (22.2) | 0.36 |
| Abdominal pain | 94 (40.2) | 31 (26.5) | 38 (32.5) | **0.01** |
| Respiratory failure | 6 (2.6) | 1 (0.9) | 5 (4.3) | 0.91 |
| Haemodynamic failure | 11 (4.7) | 0 | 11 (9.4) | **0.01** |
| Severity of CDI (*n*, %) | | | | |
| Non-severe | 143 (61.1) | 83 (70.9) | 60 (51.3) | **< 0.01** |
| Severe | 78 (33.3) | 33 (28.2) | 45 (38.5) | 0.09 |
| Fulminant | 13 (5.6) | 1 (0.9) | 12 (10.3) | **< 0.01** |
| ATLAS score (median ± IQR, min–max) | 3.0 ± 2.0 (2–10) | 3.0 ± 1.0 (2–6) | 4.0 ± 3.0 (2–10) | 0.27 |
| Epidemiological classification of the CDI episode (*n*, %) | | | | |
| Community-onset | 174 (74.4) | 103 (88.0) | 71 (60.7) | **< 0.01** |
| Healthcare-onset | 60 (25.6) | 18 (15.4) | 42 (35.9) | **< 0.01** |
| Community-associated | 88 (37.6) | 65 (55.6) | 23 (19.7) | **< 0.01** |
| Healthcare-associated | 146 (62.4) | 47 (40.2) | 99 (84.6) | **< 0.01** |
| Unclassifiable | 0 | 0 | 0 | n.a. |

(Continues)

**TABLE 2** | (Continued)

| Characteristics | Total cohort ($n=234$) | Young adults[a] ($n=117$) | Older adults[a] ($n=117$) | $p$ |
|---|---|---|---|---|
| Endoscopy during CDI ($n$, %) | | | | |
| Number of performed endoscopies[b] | 32 (13.7) | 12 (10.3) | 20 (17.1) | 0.35 |
| Pseudomembranous colitis | 17 (7.3) | 5 (4.3) | 12 (10.3) | 0.07 |
| Abdominal CT during CDI episode ($n$, %) | | | | |
| Number of performed scans[b] | 93 (39.7) | 40 (34.2) | 53 (45.3) | 0.08 |
| Perforation | 0 (0.0) | 0 (0.0) | 0 (0.0) | n.a. |
| Wall thickening | 43 (18.4) | 15 (12.8) | 28 (23.9) | **0.02** |
| Ascites | 28 (12.0) | 10 (8.5) | 18 (15.4) | 0.1 |
| Blood cultures during CDI episode ($n$, %) | | | | |
| Number of performed samplings[b] | 55 (23.5) | 17 (14.5) | 38 (32.5) | **<0.01** |
| True positive bacteremia | 7 (3.0) | 2 (1.7) | 5 (4.3) | 0.25 |
| Complications during CDI episode ($n$, %) | | | | |
| Ileus | 8 (3.4) | 1 (0.9) | 7 (6.0) | **<0.01** |
| Toxic megacolon | 4 (1.7) | 1 (0.9) | 3 (2.6) | 0.31 |
| CDI associated sepsis | 18 (7.7) | 3 (2.6) | 15 (12.8) | **<0.01** |
| Anti-CDI treatment ($n$, %) | | | | |
| Metronidazole | 145 (62.0) | 91 (77.8) | 54 (46.2) | **<0.01** |
| Vancomycin | 111 (47.4) | 34 (29.1) | 77 (65.8) | **<0.01** |
| Tigecycline | 3 (1.3) | 1 (0.9) | 2 (1.7) | 0.56 |
| Fidaxomicin | 4 (1.7) | 3 (2.6) | 1 (0.9) | 0.31 |
| Fecal microbiome transplantation | 7 (3.0) | 2 (1.7) | 5 (4.3) | 0.25 |
| ICU admission ($n$, %) | 6 (2.6) | 2 (1.7) | 4 (3.4) | 0.4 |
| LOS (days, median ± IQR, min–max) | 7.0 ± 7.5 (1–35) | 5.0 ± 4.0 (2–33) | 9.5 ± 6.5 (1–35) | **<0.01** |
| ICU LOS (days, median ± IQR, min–max) | 9.0 ± 5.5 (1–34) | 3.0 ± 2.0 (1–5) | 11.0 ± 6.8 (7–34) | 0.13 |

Abbreviations: ICU, intensive care unit; LOS, length of stay; n.a., not applicable; NSAID, non-steroidal anti-inflammatory drug.
[a]Younger adults were defined as 18–45 years of age, older patients were > 45 years of age, at diagnosis of CDI.
[b]Interventions were counted as single events per patient.

In the subgroup of young adults, metronidazole was commonly chosen as first therapy (77.8% vs. 46.2%; $p<0.01$), while the administration of vancomycin was more frequent among older patients (29.1% vs. 65.8%; $p<0.01$). The requirement for therapy change was similar (10.3% vs. 13.7%; $p=0.67$). Fecal microbiota transplantation was performed in a small proportion of the cohort (1.7% vs. 4.3%; $p=0.25$). Clinical outcomes are presented in Table 3. Clinical cure was significantly higher (99.1% vs. 81.2%; $p<0.01$), while all-cause mortality was lower among young adult patients (0.9% vs. 16.4%; $p<0.01$). Although the complicated disease course was more frequent among older patients (2.6% vs. 15.4%; $p<0.01$), colectomies were rarely required in this subcohort (0% vs. 1.7%; $p=0.15$). Relapse rates were similar (6.0% vs. 5.1%, $p=0.56$).

## 4 | Discussion

In this study, we aimed to assess the clinical and microbiological characteristics of *C. difficile* infection in hospitalized adults aged ≤45 years, compared to older patients. Our findings revealed significant differences in outcomes between the two subcohorts. Among young adults, a higher rate of clinical cure was achieved, coupled with an infrequency of CDI-associated complications. Only one fatal case was documented, and colectomy was not required in this subcohort. During the study period, metronidazole was the most common treatment choice with similar relapse rates between subgroups, aligning with the actual ESCMID guideline that recommended first-line metronidazole for non-severe CDI during the study period [14]. However, it is important

**TABLE 3** | Clinical outcomes at 30 days after anti-CDI treatment initiation of adult patients with CDI included in the study, grouped by subcohorts of age.

| Clinical outcome | Total cohort ($n=234$) | Young adult patients[a] ($n=117$) | Older patients[a] ($n=117$) | $p$ |
|---|---|---|---|---|
| Clinical cure ($n$, %) | 211 (90.2) | 116 (99.1) | 95 (81.2) | $<0.01$ |
| All-cause mortality ($n$, %) | 20 (8.6) | 1 (0.9) | 19 (16.4) | $<0.01$ |
| CDI relapse ($n$, %) | 14 (5.9) | 8 (6.8) | 6 (5.1) | 0.56 |
| Colectomy performed ($n$, %) | 2 (0.9) | 0 (0.0) | 2 (1.7) | 0.15 |
| Complicated disease course ($n$, %) | 21 (9.0) | 3 (2.6) | 18 (15.4) | $<0.01$ |

[a]Younger adults were defined as 18–45 years of age, older patients were > 45 years of age, at diagnosis of CDI.

to highlight that according to the current ESCMID guideline, vancomycin is recommended as a first-line option, and metronidazole is only considered as an alternative in the absence of fidaxomicin or vancomycin [8, 15]. Additionally, severe *C. difficile* colitis and first-line treatment failure were more prevalent in patients aged ≥ 65 years, consistent with similar studies [16–19]. Recurrence rates were similar between the two groups (6.8% vs. 5.1%, $p=0.56$), and was lower in the complete cohort compared to literature reports. This difference might be accounted for by the shorter follow-up period and our single-center design, although a study from the same time period and similar geographic location with a larger patient cohort found a recurrence rate of 11.3% within a 12-week long follow-up period [20].

Among young adults, the majority of CDI cases were community-onset and community-associated, a trend which might be correlated with findings from the National Nosocomial Surveillance Report of Hungary during the same period [21]. The phenomenon of CDI affecting younger age groups regardless of prior healthcare admissions was also observed by Bauer et al. and Esteban-Vasallo et al. [22, 23]. Another population-based survey in the USA indicated that among patients aged 18–44 years, the incidence of community-associated CDI surpassed that of healthcare-associated cases (28.7 vs. 18.3 cases per 100,000 persons), while for those aged ≥ 65 years, community-associated CDI was less prevalent compared to healthcare-associated CDI (146.2 vs. 485.1 cases per 100,000 persons) [1]. A retrospective cohort study among U.S. veterans conducted between 2011 and 2016 also demonstrated an overall upward trend in CDI incidence among younger age cohorts, particularly in the 18–34 years and 35–49 years subgroups [24].

Major limitations to our study include the single-center nature and low patient numbers. Nonetheless, we hope that our findings could still provide useful information about the differences of CDI between these patient cohorts, and facilitate the design of new studies focusing on more targeted treatment strategies among them.

In summary, the characteristics and expected outcomes of *C. difficile* infections affecting younger age cohorts suggest that at least some of these patients may profit from a different clinical approach, by optimizing prognostic markers and treatment strategies, in comparison to patients from older cohorts.

## 5 | Conclusion

In this study, adult patients aged ≤ 45 years with *C. difficile* infection were more likely to acquire community-associated disease with fewer complications and a higher treatment success rate using metronidazole when compared to older patients aged > 45 years.


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### Ethics Statement

The study was in accordance with the Helsinki Declaration and national ethical standards. The Institutional Review Board of South Pest Central Hospital, National Institute for Hematology and Infectious Diseases (Budapest, Hungary) approved the study protocol (IKEB/17/2016). Informed consent for anonymized data collection was obtained from patients.

### Consent

Written informed consent was obtained from each patient before study inclusion.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

Anonymized data of patients are available from the corresponding author on reasonable request.

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