Infect Chemother. 2024 Jun;56(2):239-246
https://doi.org/10.3947/ic.2023.0102
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Original Article

Check for updates

Determination of Risk Factors for Infectious Diarrhea in Patients with Hematological Malignancy

Şükran Şahinkaya [1], Zeynep Ture [2], Ali Unal [3], Gamze Kalın Ünüvar [2], and Ayşegül Ulu Kılıç [2]

[1]Department of Infection Control Committee, Erciyes University, Kayseri, Turkey
[2]Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey
[3]Department of Hematology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

Open Access

ABSTRACT

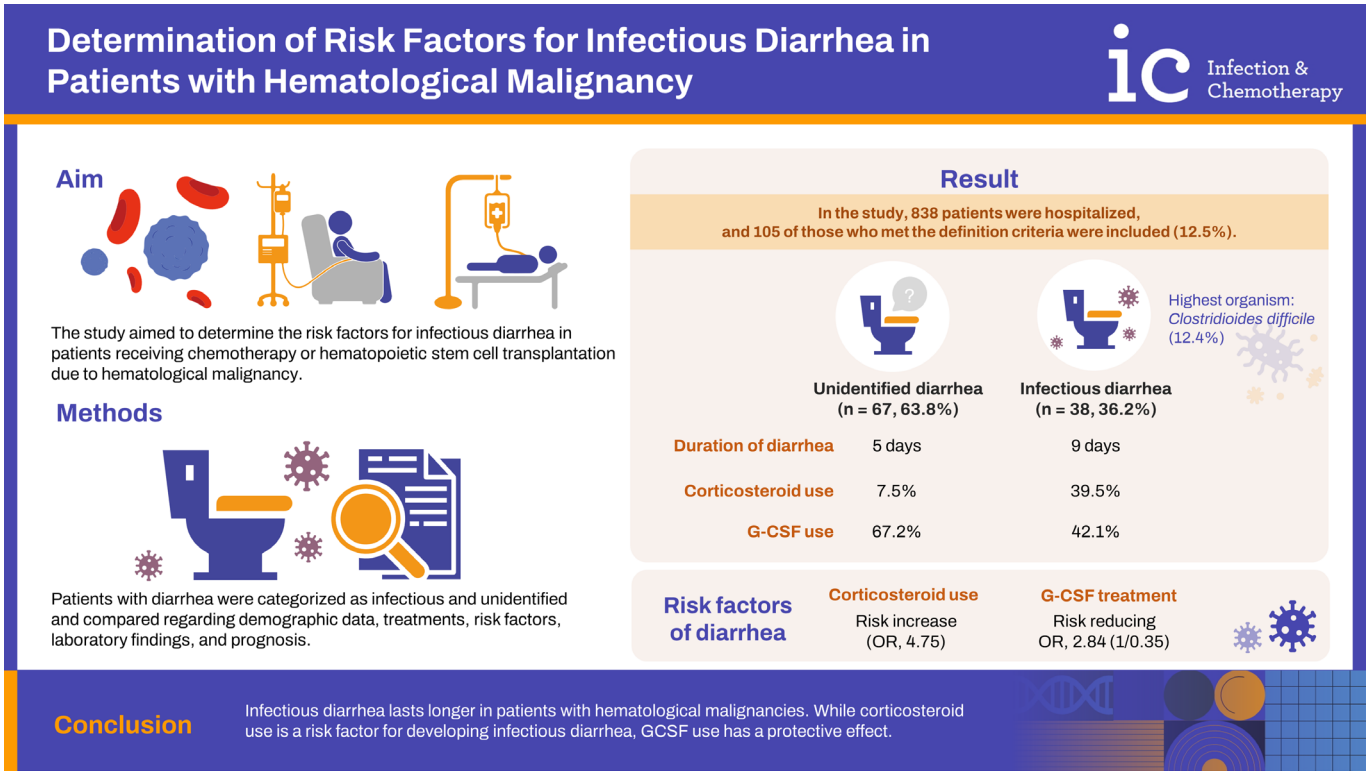
Background: This study aimed to determine the risk factors of infectious diarrhea in patients undergoing chemotherapy or hematopoietic stem cell transplantation for hematological malignancies.
Materials and Methods: This was a prospective, observational study. Patients in whom the infectious agent was determined by laboratory examination were considered to have infectious diarrhea. Patients with diarrhea were categorized as infectious or unidentified and compared in terms of demographic data, treatments, risk factors, laboratory findings, and prognosis.
Results: A total of 838 patients were hospitalized, among which 105 patients who met the inclusion criteria were included (12.5%). The patients were divided into two groups: 67 (63.8%) with unidentified diarrhea and 38 (36.2%) with infectious diarrhea. There were no differences between these groups in terms of age, sex, types of hematological malignancies, and presence of comorbidities. The most commonly isolated microorganism was *Clostridioides difficile* (12.4%). The rate of corticosteroid use was higher in the group with infectious diarrhea (39.5%) than in the group with unidentified diarrhea (7.5%) (P <0.001). The rate of granulocyte colony-stimulating factor (GCSF) use was higher in patients with unidentified diarrhea than in patients with infectious diarrhea (67.2% *vs.* 42.1%, P=0.022). The median duration of diarrhea was 9 (4–10) days in the group with infectious diarrhea and 5 (3–8) days in the group with unidentified diarrhea (P=0.012). According to the multivariate logistic regression model, corticosteroid treatment increased the risk of infectious diarrhea by a 4.75-fold (95% confidence interval [CI], 1.32–17.02) times. Moreover, the duration of diarrhea may result in a 1.15 (95% CI, 1.02–1.31) fold increase in the risk of infectious diarrhea, while GCSF treatment had a 2.84 (1/0.35) (95% CI, 0.12–0.96) fold risk-reducing effect against infectious diarrhea.
Conclusion: Infectious diarrhea lasts longer than unidentified diarrhea in patients with hematological malignancies. Although corticosteroid use is a risk factor for developing infectious diarrhea, GCSF use has a protective effect.

Keywords: Hematological cancer; Leukemia, infection; Diarrhea; Acute gastroenteritis, *Clostridioides difficile*

Received: Oct 11, 2023
Accepted: Nov 26, 2023
Published online: Apr 11, 2024

Corresponding Author:
Zeynep Ture, MD
Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Talas 38280, Kayseri, Turkey.
Tel: +90-546-436-9779, Email: dr.zeynepture@gmail.com

GRAPHICAL ABSTRACT



INTRODUCTION

Diarrhea is a common complication in patients with hematologic malignancies [1]. Cancer treatment-related diarrhea may be caused by several conditions, such as nutritional deficiencies, specific chemotherapies, proton pump inhibitors, antibiotics, immunotherapeutic methods, surgery, radiation, and graft versus host disease (GVHD), which significantly affect patient morbidity and mortality [2, 3]. The etiological spectrum of infectious diarrhea includes bacterial, viral, and parasitic agents. Although infectious diarrhea develops in immunocompetent adults with mild symptoms, it may cause complications such as neutropenic enterocolitis, sepsis, septic shock, or perforation in patients with hematological malignancies [4, 5]. Therefore, it is crucial to practice effective source control and implement appropriate isolation procedures because diarrheal agents such as viral gastroenteritis or *Clostridioides difficile,* can spread rapidly [6, 7]. Moreover, epidemics caused by infectious diarrheal factors in patients with cancer, disruptions in chemotherapy plans, and associated morbidities due to these epidemics have been reported [8]. Consequently, understanding the risk factors for infectious diarrhea in patients with hematological malignancies is critical for predicting epidemics, outcomes, and early initiation of appropriate empirical treatments [8, 9].

Therefore, this study aimed to determine the risk factors for infectious diarrhea in patients receiving chemotherapy or hematopoietic stem cell transplantation (HSCT) for hematological malignancies.

MATERIALS AND METHOD

This prospective study included patients diagnosed with malignancy at the Erciyes University Faculty of Medicine Hospital, hematology and bone marrow transplantation unit, hematology, and bone marrow transplantation unit between June 1, 2021, and November 30, 2022. Patients treated as inpatients in these units and those who developed diarrhea 72 h after admission to the hospital were included in the study.

1. Data collection

Patient demographic information, type and stage of hematological cancer, comorbidities, history of HSCT,

https://doi.org/10.3947/ic.2023.0102

presence and duration of neutropenia at the onset of diarrhea, chemotherapy regimen, use of corticosteroids, granulocyte colony-stimulating factor (GCSF), radiotherapy, and antibiotic treatment in the last 15 days before diarrhea occurred were recorded.

Acute gastroenteritis was described as unexplained loose or watery stools that occurred three times in a 24-hour period [9].

2. Ethics statement

This study was approved by the Clinical Research Ethics Committee of Erciyes University Faculty of Medicine (26.05.2021 /2021-381). Informed consent was obtained from all patients included in the study.

3. Stool testing

Stool samples from patients who met the definition of acute gastroenteritis were collected and sent to the laboratory within 30 min. After staining with Lugol's solution, the presence of leukocytes, erythrocytes, and parasites was determined via microscopic examination. Hekto Enteric Agar (Thermo Scientific) medium was used to culture *Salmonella* spp. and *Shigella* spp., and Thermo Scientific™ Butzler Agar was used for routine *Campylobacter* spp. culture. The toxin A+toxin B combination rapid test (CITES; CMC Medical, Spain) was performed for *C. difficile* detection.

Patients in whom diarrhea was persistent despite supportive or empirical treatment at the 72nd hour of the onset of acute gastroenteritis and whose etiology could not be determined by other laboratory tests were tested for cytomegalovirus (CMV) colitis using a stool CMV polymerase chain reaction (PCR) (Roche diagnostic, Cobas 6800 system) test. Stool specimens were tested also by the multiplex PCR method using the BD Max Enteric Viral Panel. The gastrointestinal pathogen panel includes sapoviruses, noroviruses, astroviruses, rotaviruses, and adenoviruses.

Colonoscopy was performed in patients whose etiology could not be determined by laboratory tests for two weeks, and the biopsy samples underwent histopathological examination. The presence of colitis was recorded when radiological imaging was performed during diarrhea. To determine the prognosis, improvement, follow-up in the intensive care unit, development of acute renal failure, perforation, and 28-day mortality were assessed.

Infectious diarrhea was defined as patients whose infectious agent was determined by laboratory examination.

Improvement was defined as stool consistency returning to normal and the number of daily defecations decreasing to three or fewer.

Patients were categorized as having infectious or unidentified diarrhea and were compared in terms of demographic data, treatments, risk factors, and prognosis.

4. Statistical analysis

Data were analyzed using SPSS 25 (IBM Corp., Armonk, NY, USA). The mean, standard deviation, median (Q1–Q3), minimum, maximum, frequency, and percentage values were presented for descriptive measurements. Normality was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Student's *t*-test and Mann–Whitney *U* test were used for pairwise comparisons, and adjusted Bonferroni values were used for repeated measurements. Chi-square (Pearson, Yates, Fisher's Exact, Likelihood Ratio) tests were used to evaluate categorical data. The risk coefficients and confidence intervals were calculated for the variables significant in the univariate. Statistical significance was set a $P < 0.05$ for all other tests except the pairwise comparison correction.

RESULTS

During the planned study period, 838 patients were hospitalized and received chemotherapy in the hematology or bone marrow transplant units. Among them, 105 patients who met the criteria for acute gastroenteritis were included in this study. The overall rate of diarrhea was 12.5%. Patients were divided into two groups: 67 (63.8%) had unidentified and 38 (36.2%) had infectious diarrhea. The rate of infectious diarrhea was 4.5%. A comparison of the groups in terms of demographic data, hematological malignancies, and treatments is presented in **Table 1**. The groups were similar in terms of demographic data, type of hematological malignancy, and presence of comorbidities. There were no significant differences between the groups in hematological malignancy stage, history, and type of HSCT, presence of neutropenia and neutropenic fever at the onset of diarrhea, or duration of neutropenia. In the three-month period before the onset of diarrhea, corticosteroid therapy was administered to 15 (39.5%) patients with infectious diarrhea and 5 (7.5%) patients with

https://doi.org/10.3947/ic.2023.0102

Table 1. Comparison of demographic data, hematological malignancies, and treatments of patients with infectious and unidentified diarrhea

Variables	Infectious diarrhea (n=38)	Unidentified diarrhea (n=67)	*P*	Multivariate regression analysis OR (95% CI), *P*
Age, Median (Q1-Q3)	51.9±13.5 (19-71)	47±14.3 (18-79)	0.144	
Male sex	26 (68.4)	35 (52.2)	0.106	
Type of malignancy			0.260	
ALL	4 (10.5)	5 (7.5)		
AML	6 (15.8)	12 (17.9)		
MM	13 (34.2)	22 (32.8)		
HL	5 (13.2)	13 (19.4)		
NHL	9 (23.7)	7 (10.4)		
Other	1 (2.6)	8 (11.9)		
Presence of comorbidity	8 (21.1)	24 (35.8)	0.174	
Malignancy phase				
New diagnosis	2 (5.3)	4 (6.0)		
Remission	16 (42.1)	24 (35.8)	0.817	
Refractory	20 (52.6)	39 (58.2)		
HSCT	30 (78.9)	52 (77.6)	>0.999	
Type of HSCT				
Autologous	23 (60.5)	39 (58.2)		
Allogeneic	7 (18.4)	13 (19.4)	>0.999	
Presence of neutropenia	20 (52.6)	44 (65.7)	0.268	
Presence of neutropenic Fever	10 (26.3)	17 (25.4)	>0.999	
Duration of neutropenia, Median (Q1-Q3)	5 (3-12)	6 (4-8)	0.930	
The time until diarrhea after chemotherapy or HSCT, Median (Q1-Q3)	6 (2-30)	5 (2-14)	0.820	
Anthracycline	2 (5.3)	4 (6.0)	>0.999	
Antimetabolite	4 (10.5)	9 (13.4)	0.766	
Corticosteroid	15 (39.5)	5 (7.5)	<0.001	4.75 (1.32-17.02), 0.017
GCSF	16 (42.1)	45 (67.2)	0.022	0.35 (0.12-0.96), 0.042
Radiotherapy	2 (5.3)	1 (1.5)	0.296	
GVHD	4 (10.5)	0		
Any antibiotic	34 (89.5)	55 (82.1)	0.466	
Piperacillin tazobactam	17 (44.7)	30 (44.8)	>0.999	
Carbapenem	8 (21.1)	17 (25.4)	0.794	
Levofloxacin	21 (55.3)	34 (50.7)	0.656	
Moxifloxacin	2 (5.3)	4 (6.0)	>0.999	
Aminoglycoside	13 (34.2)	25 (37.3)	0.915	
Tigecycline	2 (5.3)	1 (1.5)	0.296	
Glycopeptide	9 (23.7)	17 (25.4)	>0.999	
Any antifungal	28 (73.7)	59 (88.1)	0.108	
Fluconazole	20 (52.6)	51 (76.1)	0.024	
Voriconazole	8 (21.1)	6 (9.0)	0.146	
Amphotericin_B	5 (13.2)	5 (7.5)	0.490	
Echinocandin	1 (2.6)	3 (4.5)	>0.999	
Posaconazole	2 (5.3)	2 (3.0)	0.619	
Antiviral	31 (81.6)	59 (88.1)	0.534	

OR, odds ratio; CI, confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MM, multiple myeloma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; HSCT, hematopoietic stem cell transplantation; GCSF, granulocyte colony stimulation factor; GVHD, graft versus host disease.

unidentified diarrhea (*P* <0.001). The rate of G-CSF use was higher in patients with unidentified diarrhea than in those with infectious diarrhea (67.2% *vs.* 42.1%, *P*=0.022). When antimicrobial treatments were evaluated, the rate of fluconazole use was higher in the unidentified diarrhea group than in the infectious diarrhea group (76.1% *vs.* 52.6%) (*P*=0.024).

Stool microscopy was performed for all 105 patients; leukocytes were observed in 26 patients, erythrocytes in three patients, and yeast in one patient. Parasitic stool examination was performed in 78 patients; *Blastocstis hominis* was detected in three patients, *Entamoeba histolytica* in five patients, and *Giardia intestinalis* in 2 patients. *C. difficile* screening was performed in 87 patients and was found to be positive in 13 patients. CMV

Table 2. Evaluation of diagnostic examinations

Variables	Positive/total test number
Stool microscopy (n=105)	
Leukocyte	26/105
Erythrocyte	3/105
Yeast	1/105
Parasitic diagnostic tests	
Blastocystis hominis	3/78
Entamoeba histolytica	5/78
Giardia intestinalis	2/78
Stool culture (*Salmonella* spp.)	3/105
Clostridioides difficile	13/87
Stool CMV PCR	8/22
Adenovirus PCR	3/22
Abdominal USG	
Neutropenic colitis	1/7
Abdominal CT	
Neutropenic colitis	14/31
Enteritis	3/31
Colonoscopy	
GVHD	3/3

CMV, cytomegalovirus; USG, ultrasonography; CT, computed tomography; GVHD, Graft Versus Host Disease.

colitis was detected in eight patients. A gastrointestinal pathogen panel was examined in 22 patients which revealed adenovirus PCR positivity in three patients. One patient was diagnosed with neutropenic colitis using abdominal ultrasound. Abdominal computed tomography was performed in 31 patients, 14 of whom had neutropenic colitis, while three patients had enteritis. Colonoscopy was performed in three patients, and histopathological examination of the biopsy was compatible with GVHD (**Table 2**). All 13 patients who were *C. difficile* positive had a history of antibiotic use in the last 15 days involving carbapenem (6 patients), glycopeptide (6 patients), piperacillin-tazobactam (4 patients), and quinolone (4 patients). The empirical antibiotic treatments are listed in **Table 3**. Accordingly, 89.5% of patients with infectious diarrhea and 77.6% with unidentified diarrhea were administered empirical antibiotic treatment. Metronidazole was the most commonly used empiric antibiotic, which was administered in 92.1% of patients with infectious diarrhea and 77.3% with unidentified diarrhea.

Table 3. Comparison of antibiotics used in the empirical treatment of infectious and unidentified diarrhea

Variables	Unidentified diarrhea (n=67)	Infectious diarrhea (n=38)	*P*
Any antibiotic	52 (77.6)	34 (89.5)	0.210
Metronidazole	51 (76.1)	35 (92.1)	0.098
Vancomycin	10 (14.9)	10 (26.3)	0.257
Ciprofloxacin	6 (9.0)	3 (7.9)	>0.999

The comparison of prognoses of patients with infectious and unidentified diarrhea is summarized in **Table 4**. Accordingly, while the duration of diarrhea was 9 days in patients with infectious diarrhea, it was 5 days in patients with unidentified diarrhea; this difference was statistically significant (*P*=0.012). Acute renal failure developed in 42.1% patients with infectious diarrhea and 38.8% patients with unidentified diarrhea; however, none of these patients required hemodialysis during follow-up. No perforations were observed in any patient. Diagnostic laparoscopy was required in only one patient with unidentified diarrhea. While the 28-day mortality rate was 7.9% in patients with infectious diarrhea, it was only 3% in those without infectious diarrhea.

A multivariate logistic model was constructed to investigate the effects of infectious diarrhea on risk factors, treatments, laboratory findings, and prognosis. Accordingly, corticosteroid treatment was found to increase the risk of infectious diarrhea odds ratio, 4.75 (95% confidence interval [CI], 1.32–17.02) times. GCSF treatment had 2.84 (OR, 0.352; 95% CI, 0.12–0.96)-fold protective (risk-reducing) effect against infectious diarrhea, whereas an increase in the duration of diarrhea was found to increase the risk of infectious diarrhea by 1.15 (95% CI, 1.02–1.31)-fold (**Table 1**, **Table 4**).

DISCUSSION

New cytotoxic treatment regimens and supportive treatment options have improved the prognosis of

Table 4. Comparison of prognosis in patients with infectious and unidentified diarrhea

Variables	Infectious diarrhea (n=38)	Unidentified diarrhea (n=67)	*P*	Multivariate regression analysis OR (95% CI), *P*
Duration of the diarrhea	9 (4–10)	5 (3–8)	0.012	1.15 (1.02–1.31), 0.023
Improvement	35 (92.1)	64 (95.5)	0.665	
Acute Kidney Failure	16 (42.1)	26 (38.8)	0.901	
Surgical intervention	0	1 (1.5)	-	
28-Day mortality	3 (7.9)	2 (3.0)	0.350	

OR, odds ratio; CI, confidential interval.
Data are presented as median (Q1–Q3), and n (%). Mann–Whitney ***U*** and Chi-square tests were used.

https://doi.org/10.3947/ic.2023.0102

patients with hematological malignancies. However, as an inevitable effect of this development, the risk of severe infections has increased significantly owing to deeper immunosuppression [10]. The frequency of diarrhea in patients with hematological malignancies varies from 4.8 – 41.0% [11, 12], and may be as high as 83% in patients who underwent allogeneic HSCT [13]. Therefore, understanding the causes of diarrhea according to risk factors in patients with hematological malignancies, prophylaxis, and empiric treatment practices are crucial to prevent the development of complications [1]. The present study examined hospitalized patients with hematological malignancies or stem cell transplantation for infectious or unidentified diarrhea.

Comparing patients with infectious and unidentified diarrhea revealed that the rate of GCSF use was higher in patients with unidentified diarrhea, indicating that GCSF use had a protective effect against infectious diarrhea. Mhaskar et al. demonstrated that GCSFs did not significantly reduce overall mortality or infection-related mortality compared with empirical antibiotics alone [14]. However, the duration of hospitalization exceeding 10 days, duration of neutropenia, and duration of antibiotic use were significantly lower in patients receiving GCSF. A prospective cohort study reported the incidence and risk factors of neutropenic enterocolitis in 317 neutropenic episodes in 215 patients. Accordingly, the rate of GCSF use was found to be lower in patients with neutropenic enterocolitis (18.2%) than in those with diarrhea (27.1%) [15]. It was considered that the long duration of neutropenia in severe chemotherapy protocols applied to refractory and relapsed patients would also affect the GCSF dose and duration of use. Thus, owing to the positive effect of GCSF use on the duration of neutropenia, GCSF has a protective effect against infectious diarrhea.

In this study, the use of corticosteroids increased the risk of infectious diarrhea 5.73 times. A meta-analysis by Bloomfield et al. evaluated the risk factors of *C. difficile* colitis and defined corticosteroid use in the previous month as a risk factor [16]. Quintero et al. examined invasive gastrointestinal mold infections in immunosuppressed patients and reported that long-term use of systemic steroids may be a major risk factor for infection [17]. In line with these results, in the present study, corticosteroids were the most commonly used immunosuppressive agents (59.0%) [17]. Moreover, a study conducted in a group of patients receiving solid organ transplant determined that corticosteroid use in the last month increased the risk of *C. difficile* induced-colitis threefold [18]. According to our study, opportunistic microorganisms were able to proliferate owing to the immunosuppressive effects of corticosteroids, which led to a high rate of corticosteroid use in patients with infectious diarrhea.

In this study, the rate of antibiotic use within 15 days before diarrhea onset was >80% in both patient groups. Likewise, the rate of antifungal and antiviral drug use was > 70%. Levofloxacin and piperacillin-tazobactam usage rates were higher among the antibiotics. All patients diagnosed with *C. difficile*-associated colitis had a history of antibiotic use in the last 15 days. Thus, antibiotic-associated diarrhea may be self-limiting in immunocompetent patients; however, the risk of diarrhea-related complications increases with the use of immunosuppressants [19]. A broad spectrum of beta-lactam antibiotics, such as piperacillin-tazobactam, have an anti-anaerobic effect that limit the dissemination of some bacteria in the flora while stimulating the growth of bacteria like *Clostridioides* spp. [16]. Aksoy et al. evaluated the risk factors for patients with neutropenic enterocolitis and reported that the rate of aminoglycoside, cephalosporin, penicillin, and carbapenem use was higher in the group with neutropenic enterocolitis compared to the group of patients who did not develop neutropenic enterocolitis [15]. Another study examining infectious gastroenteritis in children who underwent allogeneic HSCT reported that all children were administered an antipseudomonal beta-lactamase inhibitor before the gastroenteritis attack [8]. Therefore, considering the history of intensive antibiotic use in the patient group included in the study, *C. difficile* and antibiotic-associated diarrhea should also be considered in the preliminary diagnosis. First, revision of antibiotics is crucial for rational antibiotic use.

In our study, *C. difficile* was the most common cause of infectious diarrhea (11.0%). Moreover, *C. difficile* is known to cause mild diarrhea, pseudomembranous colitis, and toxic megacolon, with mortality rates of up to 25–40% [20, 21]. A prospective cohort study by Cannon et al. reported that the rate of *C. difficile* colonization was as high as 9.3% in patients with hematological malignancies, and symptomatic disease developed during hospitalization in 13.3% of the colonized patients [22]. In a 2016–2017 European point prevalence study, *C. difficile* was concluded to be the sixth most common

https://doi.org/10.3947/ic.2023.0102

microorganism responsible for healthcare-associated infections [23]. Thus, a high prevalence of *C. difficile* colonization, frequent antibiotic use, decreased immune function, higher exposure to healthcare environments, and immunocompromised individuals may be risk factors for a major *C. difficile* infection burden [24]. However, because the patient group included in the study had many risk factors, such as being a sensitive population, using corticosteroids and chemotherapeutic drugs, and broad-spectrum antibiotics, it was vital to perform further investigations on *C. difficile* in prolonged diarrhea.

According to our results, the duration of diarrhea was longer in patients with infectious diarrhea than in those with unidentified diarrhea (5 days *vs.* 9 days). In a study examining the frequency of *C. difficile* infection and risk factors in patients undergoing HSCT, the duration of infection and hospital stay were longer in patients with *C. difficile* infections (22 *vs.* 24.5 days) [25]. In this study, CMV and other parasitic agents were detected as infectious diarrheal agents. Among these factors, the duration of diarrhea is prolonged and may progress to complications.

The limitation of this study was its single center design and limited sample size. Further, due to the observational and non-interventional study design, diagnostic tests could not be performed. Therefore, risk factors identified in this study can be further validated using multicenter studies with larger numbers of patients. Consequently, algorithms for the diagnosis and empirical treatment of diarrhea can be developed.

In conclusion, the duration of infectious diarrhea was longer than unidentified diarrhea in patients with hematological malignancies. In patients with hematological malignancies who continue to have diarrhea despite symptomatic and empirical treatments, further investigations should be performed to identify opportunistic infectious agents. Corticosteroid use has been determined to be a risk factor for the development of infectious diarrhea. In patients receiving high-dose corticosteroids in the chemotherapy protocol and those with diarrhea, further examination and empirical treatment with infectious diarrheal agents should be planned accordingly. The use of G-CSF has a protective effect against the development of infectious diarrhea and should be considered in patients with severe immunosuppressive therapy and associated long-term neutropenia.

ORCID iDs
Şükran Şahinkaya
https://orcid.org/0000-0003-1256-2548
Zeynep Ture
https://orcid.org/0000-0001-6895-0318
Ali Unal
https://orcid.org/0000-0001-7011-3412
Gamze Kalın Ünüvar
https://orcid.org/0000-0001-7209-8826
Ayşegül Ulu Kılıç
https://orcid.org/0000-0002-5105-1348

Funding
None.

Conflict of Interest
No conflict of interest.

Author Contributions
Conceptualization: ZT, ŞŞ, AU. Data curation: ZT, ŞŞ, GKU. Investigation: ZT, AU, ŞŞ. Methodology: ŞŞ, ZT, AU, GKU, AUK. Writing - original draft: ŞŞ, ZT. Writing - review & editing: ZT, AUK, AU.

REFERENCES

1. Bossi P, Antonuzzo A, Cherny NI, Rosengarten O, Pernot S, Trippa F, Schuler U, Snegovoy A, Jordan K, Ripamonti CI; ESMO guidelines committee. Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol 2018;29 (Suppl 4):iv126-42. PUBMED | CROSSREF
2. Maschmeyer G, Bullinger L, Garcia-Vidal C, Herbrecht R, Maertens J, Menna P, Pagano L, Thiebaut-Bertrand A, Calandra T. Infectious complications of targeted drugs and biotherapies in acute leukemia. Clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN). Leukemia 2022;36:1215-26. PUBMED | CROSSREF
3. Da Silva R, Casella T. Healthcare-associated infections in patients who are immunosuppressed due to chemotherapy treatment: a narrative review. J Infect Dev Ctries 2022;16:1784-95. PUBMED | CROSSREF
4. Babakhanlou R, Ravandi-Kashani F, Kontoyiannis DP. Neutropenic enterocolitis: an uncommon, but fearsome complication of leukemia. J Hematol 2023;12:59-65. PUBMED | CROSSREF
5. Kelly CR, Fischer M, Allegretti JR, LaPlante K, Stewart DB, Limketkai BN, Stollman NH. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol 2021;116:1124-47. PUBMED | CROSSREF
6. Schuster JE, Johnston SH, Piya B, Dulek DE, Wikswo ME, McHenry R, Browne H, Gautam R, Bowen MD, Vinjé J, Payne DC, Azimi P, Selvarangan R, Halasa N, Englund JA. Infectious causes of acute gastroenteritis in US children undergoing allogeneic hematopoietic cell transplant: a longitudinal, multicenter study. J Pediatric Infect Dis Soc 2020;9:421-7. PUBMED | CROSSREF
7. Payne DC, Vinjé J, Szilagyi PG, Edwards KM, Staat MA, Weinberg GA, Hall CB, Chappell J, Bernstein DI, Curns AT, Wikswo M, Shirley SH, Hall AJ, Lopman B, Parashar UD. Norovirus and medically attended gastroenteritis in U.S. children. N Engl J Med 2013;368:1121-30. PUBMED | CROSSREF

8. Ariza-Heredia EJ, Chemaly RF. Update on infection control practices in cancer hospitals. CA Cancer J Clin 2018;68:340-55. PUBMED | CROSSREF
9. Sato H, Kato H, Koiwai K, Sakai C. A nosocomial outbreak of diarrhea caused by toxin A-negative, toxin B-positive *Clostridium difficile* in a cancer center hospital. Kansenshogaku Zasshi 2004;78:312-9. PUBMED | CROSSREF
10. Hansen BA, Wendelbo Ø, Bruserud Ø, Hemsing AL, Mosevoll KA, Reikvam H. Febrile neutropenia in acute leukemia. Epidemiology, etiology, pathophysiology and treatment. Mediterr J Hematol Infect Dis 2020;12:e2020009. PUBMED | CROSSREF
11. Majeed A, Larriva MM, Iftikhar A, Mushtaq A, Campbell P, Nadeem Malik M, Rafae A, Zar MA, Kamal A, Lakhani M, Khalid NR, Zangeneh TT, Anwer F. A single-center experience and literature review of management strategies for *Clostridium difficile* infection in hematopoietic stem cell transplant patients. Infect Dis Clin Pract (Baltim Md) 2020;28:10-5. PUBMED | CROSSREF
12. Pala C, Kaynar L, Buyukoglan R, Kurnaz F, Metan G, Yazar S, Durmaz S, Sakioglu A, Sivgin S, Eser B, Unal A, Cetin M. Diarrhea in peripheral stem cell transplant recipients: a developing country's experience. J Infect Dev Ctries 2014;8:635-41. PUBMED | CROSSREF
13. Castro MD, Chebli JM, Costa LJ, Alves KRL, Atalla A, Neto AEH. Infectious diarrhea in autologous stem cell transplantation: high prevalence of coccidia in a South American center. Hematol Transfus Cell Ther 2018;40:132-5. PUBMED | CROSSREF
14. Mhaskar R, Clark OA, Lyman G, Engel Ayer Botrel T, Morganti Paladini L, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced Febrile neutropenia. Cochrane Database Syst Rev 2014;2014:CD003039. PUBMED
15. Aksoy DY, Tanriover MD, Uzun O, Zarakolu P, Ercis S, Ergüven S, Oto A, Kerimoglu U, Hayran M, Abbasoglu O. Diarrhea in neutropenic patients: a prospective cohort study with emphasis on neutropenic enterocolitis. Ann Oncol 2007;18:183-9. PUBMED | CROSSREF
16. Bloomfield MG, Sherwin JC, Gkrania-Klotsas E. Risk factors for mortality in *Clostridium difficile* infection in the general hospital population: a systematic review. J Hosp Infect 2012;82:1-12. PUBMED | CROSSREF
17. Quintero O, Allard L, Ho D. Invasive mold infection of the gastrointestinal tract: A case series of 22 immunocompromised patients from a single academic center. Med Mycol 2022;60:myac007. PUBMED | CROSSREF
18. Len O, Rodríguez-Pardo D, Gavaldà J, Aguado JM, Blanes M, Borrell N, Bou G, Carratalà J, Cisneros JM, Fortún J, Gurguí M, Montejo M, Cervera C, Muñoz P, Asensio A, Torre-Cisneros J, Pahissa A; Spanish research network for the study of infection in transplantation. Outcome of Clostridium difficile-associated disease in solid organ transplant recipients: a prospective and multicentre cohort study. Transpl Int 2012;25:1275-81. PUBMED | CROSSREF
19. Yin J, M P, Wang S, Liao SX, Peng X, He Y, Chen YR, Shen HF, Su J, Chen Y, Jiang YX, Zhang GX, Zhou HW. Different dynamic patterns of β-lactams, quinolones, glycopeptides and macrolides on mouse gut microbial diversity. PLoS One 2015;10:e0126712. PUBMED | CROSSREF
20. Bamba S, Nishida A, Imaeda H, Inatomi O, Sasaki M, Sugimoto M, Andoh A. Successful treatment by fecal microbiota transplantation for Japanese patients with refractory *Clostridium difficile* infection: a prospective case series. J Microbiol Immunol Infect 2019;52:663-6. PUBMED | CROSSREF
21. Wu KS, Syue LS, Cheng A, Yen TY, Chen HM, Chiu YH, Hsu YL, Chiu CH, Su TY, Tsai WL, Chen WY, Huang CH, Hung HM, Huang LJ, Kuo HJ, Lin PC, Yang CH, Hong PL, Lee SS, Chen YS, Liu YC, Huang LM; Infectious Diseases Society of TaiwanMedical Foundation in Memory of Dr. Deh-Lin ChengFoundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and EducationCY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines5th Guidelines Recommendations for Evidence-based Antimicrobial agents use in Taiwan (GREAT) working group. Recommendations and guidelines for the treatment of *Clostridioides difficile* infection in Taiwan. J Microbiol Immunol Infect 2020;53:191-208. PUBMED | CROSSREF
22. Cannon CM, Musuuza JS, Barker AK, Duster M, Juckett MB, Pop-Vicas AE, Safdar N. Risk of *Clostridium difficile* infection in hematology-oncology patients colonized with toxigenic *C. difficile*. Infect Control Hosp Epidemiol 2017;38:718-20. PUBMED | CROSSREF
23. Suetens C, Latour K, Kärki T, Ricchizzi E, Kinross P, Moro ML, Jans B, Hopkins S, Hansen S, Lyytikäinen O, Reilly J, Deptula A, Zingg W, Plachouras D, Monnet DL; healthcare-associated infections prevalence study group. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017. Euro Surveill 2018;23:1800516. PUBMED | CROSSREF
24. Revolinski SL, Munoz-Price LS. *Clostridium difficile* in immunocompromised hosts: a review of epidemiology, risk factors, treatment, and prevention. Clin Infect Dis 2019;68:2144-53. PUBMED | CROSSREF
25. Ford CD, Lopansri BK, Coombs J, Webb BJ, Asch J, Hoda D. Are *Clostridioides difficile* infections being overdiagnosed in hematopoietic stem cell transplant recipients? Transpl Infect Dis 2020;22:e13279. PUBMED | CROSSREF