International Journal of Infectious Diseases 127 (2023) 17–22

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Infectious diarrhea after allogeneic hematopoietic cell transplantation assessed by a multiplex polymerase chain reaction assay

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ARTICLE INFO

Article history:
Received 4 August 2022
Revised 26 November 2022
Accepted 30 November 2022

Keywords:
Infectious diarrhea
Multiplex polymerase chain reaction assay
Allogeneic hematopoietic cell transplantation

ABSTRACT

Objectives: To determine the incidence of infectious diarrhea after allogeneic hematopoietic cell transplantation (HCT) using a multiplex polymerase chain reaction assay and assess risk factors for developing infectious diarrhea.

Methods: This was a single-center retrospective study of 140 consecutive allogeneic HCT recipients. Infectious diarrhea was assessed using a laboratory-developed multiplex polymerase chain reaction the first year after transplantation.

Results: The incidence rate of infectious diarrhea episodes was 47 per 100 person-years, with the highest rate observed in the pre-engraftment phase. Most episodes were seen as nosocomial infections (38%) and most affected patients (82%) had only one episode of infectious diarrhea. The cumulative incidence of at least one episode of infectious diarrhea was 32% after 1 year. Nonrelapse mortality was higher in transplant recipients with at least one episode of infectious diarrhea (hazard ratio (HR) 2.02, 95% CI = 1.07-3.80). The most frequently observed pathogens were *Clostridium difficile*, adenovirus, Enteropathogenic *Escherichia coli,* and *Campylobacter jejuni*. Patients with acute lower gastrointestinal graft-vs-host disease stage 3 or 4 (HR 3.68, 95% CI = 1.57-8.63) conferred a higher risk for a first infectious diarrhea episode.

Conclusion: Infectious diarrhea after allogeneic HCT was seen in about one-third of the patients, mostly as nosocomial infection in the pre-engraftment phase.

Introduction

Diarrhea is a frequently encountered complication of allogeneic hematopoietic cell transplantation (HCT), which can be provoked by different etiologies. Apart from drug toxicity and acute graft-vs-host disease (GvHD) of the lower gastrointestinal (GI) tract, numerous infectious pathogens have been identified as potential causes, including bacterial, viral, and protozoan agents [1,2]. The broad microbiological differential diagnosis of infectious diarrhea in HCT patients poses a challenge to the microbiology lab [3]. Recently, molecular tests that detect multiple GI pathogens simultaneously, including multiplex polymerase chain reaction (PCR) panels, have proven to be a useful asset by augmenting the diagnostic yield of the work-up without an increase in testing costs [4].

A seminal study conducted in the early eighties found that an episode of infectious diarrhea was associated with increased mortality in patients after allogeneic HCT [5]. However, no data have been published on the clinical outcome of infectious diarrhea detected of using these rapid, highly sensitive, and broad contem-

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https://doi.org/10.1016/j.ijid.2022.11.045

poraneous molecular multiparameter assays. Also, differences in the etiology between the pre- and post-engraftment period, and between ambulatory and hospitalized patients have not been described in detail.

Using a GI multiparameter PCR on microarray cards, this single-center study aimed to determine the incidence and causes of infectious diarrhea after allogeneic HCT and identify transplant-related risk factors. Furthermore, we examined the association of infectious diarrhea with nonrelapse mortality.

Methods

Study population

We included 140 consecutive patients aged 18 years and older undergoing allogeneic HCT from October 2016 to September 2020 in the AZ Sint-Jan Brugge-Oostende AV hospital. If a patient was transplanted multiple times, we only included the data from the last transplantation. Patient data were retrieved from the medical records. Pretransplant variables included demographics (age, sex, and ethnicity), HCT-specific comorbidity index (HCT-CI, which incorporates comorbidities associated with nonrelapse mortality [6]), cytomegalovirus (CMV) status, human leukocyte antigens match, conditioning (categorized as myeloablative, reduced intensity [RIC] or nonmyeloablative) and GvHD prophylaxis regimens. HCT-CI scores were categorized as follows: low risk, score of zero; intermediate-risk, one to two; and high-risk, three or more [7]. As part of standard clinical care, a stool sample was submitted to the clinical microbiology laboratory in case of a new diarrheal episode. The results of all stool tests and endoscopic biopsies were assessed from admission until 1 year after HCT. This study was approved by the Ethical Committee of AZ Sint-Jan Brugge-Oostende AV (advice number 2701).

Definitions

Underlying disease risk groups at transplantation were classified as either standard or high-risk [8]. The high-risk group was defined as acute leukemia, chronic lymphoid leukemia, lymphoma, multiple myeloma, solid tumor not in remission, chronic myeloid leukemia in blast crisis, and all relapsed diseases after HCT. All other stages in any disease as well as myelodysplastic syndrome were categorized into the standard risk group The pre-engraftment phase was defined as the day of transplantation until the day of engraftment, which was considered as the first of 3 consecutive days of neutrophil count above 500/µl [9]. In absence of a neutropenic phase, day 30 was chosen as the end of this period. The early post-engraftment phase was defined as the day of engraftment until day 100 and the late post-engraftment phase as day 100 until 1 year after HCT. Acute GvHD was staged according to the MAGIC criteria [10]. Infectious diarrhea was defined as a diarrheal episode with the identification of an enteric pathogen in the stool or an endoscopic biopsy. Stool tests or biopsies performed within 14 days of a prior test were considered to be part of the same episode of infectious diarrhea [4]. A diarrheal episode was considered as nosocomial with an onset of more than 72 hours after admission [11].

Microbiological assays

All stool samples were tested in real-time by a laboratory-developed highly sensitive and specific molecular assay based on the Taqman Array Card technology [12] detecting nine bacterial pathogens, eight protozoan pathogens, and eight viral pathogens, the details of which are provided in Supplementary Table 1. For CMV colitis, a value of 0.006 IU CMV per cell on biopsy was considered indicative of CMV disease [13].

Table 1
Baseline characteristics and demographic of allogeneic hematopoietic stem cell transplant recipients (n = 140).

Age - mean (SD)	55.8 (12.6)
Male - no. (%)	70 (50.0)
Race - no. (%)	
Caucasian	137 (97.8)
Non-caucasian	3 (2.14)
Disease - no. (%)	
Acute leukemia	67 (47.8)
Hodgkin lymphoma	4 (2.9)
Myelodysplastic syndrome	41 (29.3)
Myeloproliferative disorder	11 (7.9)
Non-Hodgkin lymphoma	11 (7.9)
Other	6 (4.3)
Disease risk - no. (%)	
High	93 (66.4)
Standard	47 (33.6)
HCT-CI score - median (IQR)	2 (1-3)
HCT-CI score - no. (%)	
0	23 (16.4)
1-2	41 (29.3)
≥3	63 (45)
Graft-vs-host disease prophylaxis - no. (%)	
CNI	63 (45)
CNI and MMF	46 (32.9)
CNI, MMF and cyclophosphamide	7 (5.0)
CNI and methotrexate	11 (7.9)
Other	13 (9.3)
T cell-depleted transplant - no.(%)	
No	68 (48.6)
Yes	72 (51.4)
Conditioning regimen - no.(%)	
Myeloablative	22 (15.7)
Reduced intensity conditioning	118 (84.3)
Human leukocyte antigens match - no.(%)	
Haploidentical related	8 (5.7)
Matched unrelated	79 (56.4)
Matched related	53 (37.9)
Donor CMV status - no.(%)	
Negative	102 (72.9)
Positive	38 (27.1)
Recipient CMV status- no.(%)	
Negative	82 (58.6)
Positive	58 (41.4)

CNI, calcineurin inhibitor; CMV, cytomegalovirus; HCT-CI, hematopoietic stem cell transplant-specific comorbidity index; IQR; interquartile range; MMF, mycophenolate mofetil.

Statistical analyses

Incidence rates of diarrhea episodes per 100 person-years (PY) with 95% confidence intervals (CIs) are estimated based on the exact method using the Poisson distribution ("fmsb" package in R). Cumulative incidence curves of relapse and nonrelapse mortality were plotted. Predicted risks of pathogens with asymptotic 95% CIs were calculated using generalized estimating equations models for a binomial distribution with a logit link, taking into account multiple infections per patient through an exchangeable correlation structure. The association of acute infectious diarrhea with time to nonrelapse mortality, defined as death in the absence of disease relapse [14], was assessed by fitting an unadjusted cause-specific Cox proportional hazards model, where infectious diarrhea was treated as a time-dependent covariate; its value changed from the first episode of acute infectious diarrhea onwards. The associations between transplant-related variables and the time to the first development of infectious diarrhea were likewise assessed with unadjusted cause-specific Cox proportional hazards models using Efron's approximation for tied event times. Acute lower GI GvHD

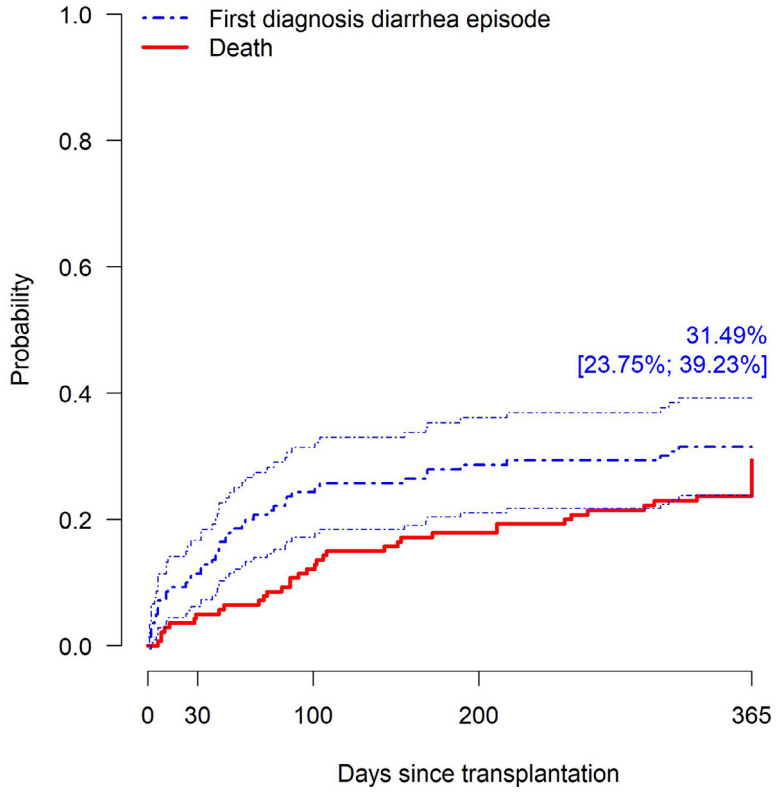

Figure 1. Cumulative incidence curves of diarrhea and mortality.
Boxed numbers indicate day-365 cumulative incidence rate (95% confidence interval).

was analyzed as a time-dependent covariate. Statistical analyses were performed in SPSS version 28 and R Studio version 4.1.2.

Results

Demographics and baseline characteristics

The demographics and baseline characteristics of the 140 included patients are summarized in Table 1. The median follow-up was 22 months (Interquartile range 5.0-34). A total of 98% of the patients were white and 50% were female. Overall 48% of the patients were transplanted for acute leukemia. Based on HCT-CI categorization, 18% were considered low risk, 32% intermediate-risk, and 50% high-risk. Conditioning was mostly performed as RIC with myeloablative conditioning only being used in 16% of the patients. Acute lower GI GvHD stage 1 or 2 was observed in 22 patients (16%) and grade 3 or 4 in 26 patients (19%). The estimated rate of nonrelapse mortality was 5% on day 30, 16% on day 100, and 29% on day 365.

Infectious diarrhea incidence and outcomes

One year after transplantation, 31.4% of the patients (44 of 140) experienced at least one episode of infectious diarrhea. The estimated cumulative incidence of at least one episode of infectious diarrhea in 1 year with death as a competing risk was 31.5% (95% CI 23.8 to 39.2%) (Figure 1). Most affected patients (36 of 44) had only one episode of infectious diarrhea, whereas six patients had two episodes and two patients had three or more episodes. The incidence rate of infectious diarrhea episodes was 47.1 per 100 PY (95% CI 35.5 to 61.3). This rate was the highest in the pre-engraftment phase (217.2 per 100 PY; 95% CI 115.6 to 371.4), followed by the early post-engraftment phase (77.0 per 100 PY; 95% CI 50.3 to 112.8) and the late engraftment phase (14.3 per 100 PY; 95% CI 7.1 to 25.6). Most episodes were seen as nosocomial infections (38.2%) and to a somewhat lesser extent in an ambulatory setting or as a reason for admission (both in 30.9%). The presence of at least one episode of infectious diarrhea was significantly associated with a higher hazard of nonrelapse mortality (hazard ratio (HR) 2.02; 95% CI 1.07 to 3.80; *P*-value = 0.03). A patient who had his first infectious diarrhea episode at day 100, had a 13.1% estimated probability of nonrelapse death at day 180 and 24.4% at day 365, while a patient who survives until day 100 but never had infectious diarrhea, had an estimated probability of nonrelapse death of 6.7% at day 180 and 13.0% at day 365. Using a cause-specific Cox proportional hazard model adjusted for the HCT-CI score category and conditioning regimen, we found borderline significance for the association of infectious diarrhea and nonrelapse mortality (HR 1.99; 95% CI 0.99-3.99, *P*= 0.05).

Etiology of infectious diarrhea

The most frequently observed pathogens were *Clostridium difficile*, adenovirus, Enteropathogenic *Escherichia coli* (EPEC), *Campylobacter jejuni, Dientamoeba fragilis,* and astrovirus (Figure 2a). The risks for the six most frequently observed pathogens in the pre- and post-engraftment periods are shown in Figure 2b. The risk for *C. difficile* (41.2%) and adenovirus (21.4%) were the highest in the early post-engraftment period. For EPEC (22.8%) and astrovirus (11.9%), the risks were the highest in the late post-engraftment phase. The risk for *D. fragilis* was the highest in the pre-engraftment phase (26.0%), whereas the risk for *C. jejuni* was comparably high in the pre-engraftment as well in the late post-engraftment phase (15.5% and 17.1% respectively). The risks for these pathogens in patients who were ambulatory, admitted due to diarrhea or acquired nosocomial diarrhea are shown in Figure 2c. The risk for *C. difficile* was the highest in patients admitted due to diarrhea (47.6%). For EPEC (18.5%), astrovirus (18.9%) and *C. je-*

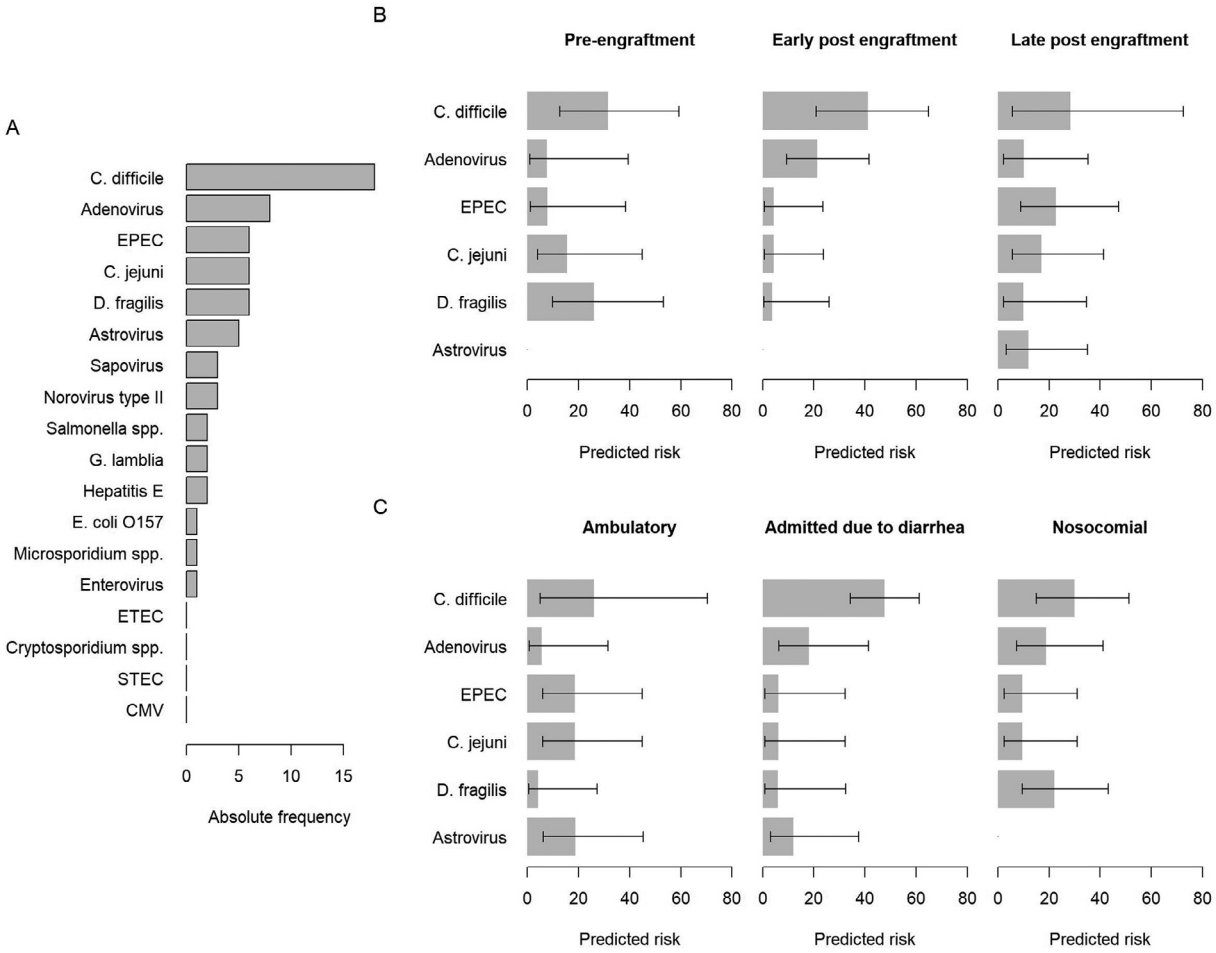

Figure 2. Frequency of pathogens.
Panel a shows the overall frequency of pathogens. Horizontal bar charts of absolute frequencies of pathogens are given. Panels b and c shows the predicted risks of the six most frequently observed pathogens according to the post-transplant phase and patient settings, with asymptotic 95% CI calculated using generalized estimating equations models taking into account multiple infections per patient and displayed using horizontal bar charts.
CMV, cytomegalovirus; EPEC, Enteropathogenic *Escherichia Coli*; ETEC, Enterotoxigenic *E. Coli*; STEC, Shiga toxin-producing *E. coli*.

juni (18.5%) the risks were the highest in the ambulatory setting, whereas the risk for *D. fragilis* was the highest in nosocomial acquired diarrhea (22.1%).

Risk factors for infectious diarrhea

Table 2 shows the results of unadjusted cause-specific Cox proportional hazards models on time to first infectious diarrhea episode. We found that patients with an intermediate-risk HCT-CI category (HR 2.97; 95% CI 1.00 to 8.78; $P = 0.049$) had a higher risk than low risk category patients. Also, acute lower GI GvHD disease stage 3 or 4 (HR 3.68; 95% CI 1.57 to 8.63; $P= 0.003$) conferred a higher risk for infectious diarrhea episode compared to the absence of acute lower GI GvHD.

Discussion

GI infections are among the many causes of diarrhea encountered after allogeneic HCT. Using a contemporaneous multiplex GI PCR panel, we found that about one-third of a patient series developed at least one episode of infectious diarrhea the first year after transplantation. Similar to a study performed in the early 80, our study showed that the nonrelapse mortality was higher after a first episode of infectious diarrhea. Incidence was the highest in the pre-engraftment phase and patients with an intermediate-risk HCT-CI category or GI GvHD disease stage 3 or 4 conferred a higher risk for a first episode of infectious diarrhea.

Our data provide valuable insights into the epidemiology of infectious diarrhea after allogeneic HCT. Overall, most episodes were caused by *C. difficile*, adenovirus, EPEC, *C. jejuni, D. fragilis,* and astrovirus. These observations somewhat overlap with a recent study in both autologous and allogeneic HCT recipients using the FilmArray GI PCR Panel, reporting *C. difficile*, norovirus, EPEC, *Yersinia enterocolitica, Campylobacter* spp., and CMV as most frequently documented pathogens [4]. Of note, our assay detects all adenovirus types, whereas the FilmArray GI PCR only captures serotypes 40 and 41. Another series in allogeneic HCT found *C. difficile* and adenovirus to be the most common cause of infectious diarrhea [3]. The high incidence of *D. fragilis* in the pre-engraftment phase is an unexpected finding of our study and warrants further investigation. Epidemiological studies in otherwise healthy individuals have linked this flagellate protozoan parasite to gastrointestinal symptoms of diarrhea and abdominal pain, but some carriers are asymptomatic [15]. The incidence of infectious diarrhea in our study was the highest in the pre-engraftment phase with *C. difficile, D. fragilis*, norovirus type 2, and *C. jejuni* as the most frequent documented pathogens. In the post-engraftment period, *C. difficile* remained the most important pathogen, followed by viral agents including adenovirus, astrovirus, and sapovirus. Most episodes were nosocomial acquired with the predominance of *C.*

Table 2
Unadjusted analyses on time to first infectious diarrhea episode.

	Hazard ratio (95% confidence interval)
Age, per year	0.99 (0.97 to 1.01)
Sex	
Male	Reference
Female	0.86 (0.48 to 1.56)
Hematopoietic stem cell transplant-specific comorbidity index score	
0	Reference
1-2	**2.97 (1.00 to 8.78)**
≥3	1.93 (0.66 to 5.67)
GvHD prophylaxis	
CNI	Reference
CNI and MMF	0.89 (0.46 to 1.73)
CNI, MMF and cyclophosphamide	1.48 (0.51 to 4.32)
CNI and methotrexate	0.68 (0.2 to 2.29)
Other	0.21 (0.03 to 1.56)
T cell-depleted transplant	
No	Reference
Yes	1.31 (0.72 to 2.37)
Conditioning regimen	
Myeloablative	Reference
Reduced intensity conditioning	0.99 (0.44 to 2.21)
Human leukocyte antigens match	
Matched related	Reference
Haploidentical related	1.96 (0.66 to 5.84)
Matched unrelated	0.97 (0.52 to 1.82)
Donor CMV status	
Negative	Reference
Positive	1.1 (0.57 to 2.14)
Recipient CMV status	
Negative	Reference
Positive	0.99 (0.54 to 1.81)
Acute lower gastrointestinal GvHD	
Absent	Reference
Stage 1-2	0.26 (0.04 to 1.97)
Stage 3-4	**3.68 (1.57 to 8.63)**

CNI, calcineurin inhibitor; CMV, cytomegalovirus; GvHD, graft-vs-host disease; MMF mycophenolate mofetil.

difficile, D. fragilis, adenovirus, EPEC, and *C. jejuni* in this setting. Of note, the treatable pathogens hepatitis E and *Giardia lamblia* were each identified as the cause of infectious diarrhea in 3.6% of all episodes. Multiplex PCR assays should thus be designed to include these pathogens as to maximize their diagnostic yield.

Both acute and chronic GvHD disease has been linked with increased infectious risk due to immune dysfunction and enhanced immunosuppression [16]. There is a raised susceptibility for reactivation of endogenous infections (herpes- & adenoviruses, hepatitis E virus, etc.) as well as exogenously acquired infections, including respiratory viruses, encapsulated bacteria, *Pneumocystis jiroveci*, and other inhaled mold infections. Furthermore, lower GI GvHD may decrease the barrier function of the gut. Unsurprisingly, we found that patients with acute lower GI GvHD stage 3 of 4 were at higher instantaneous risk for a first infectious diarrhea episode. Also, patients in the intermediate-risk and high-risk (although not significantly) HCT-CI categories conferred a higher risk, possibly related to their comorbid conditions.

In accordance with a historic study, we found a higher nonrelapse mortality in patients with at least one episode of infectious diarrhea. Although this association remained significant after adjustment for condition regimen and HCT-CI score category, we were not able to fully explore the link between infectious diarrhea and nonrelapse mortality due to the limited number of patients included in our study. Larger cohort studies are required to establish whether this association is not confounded by other transplant-related risk factors.

Strategies to prevent GI infections include hand hygiene, patient cohorting and isolation precautions, use of personal protective equipment, environmental cleaning, and prophylactic administration of vancomycin for *C. difficile* infection [17,18]. The latter, however, is currently not recommended by any guideline and remains to be investigated with a randomized controlled trial as retrospective studies provided inconclusive evidence. The prolonged asymptomatic fecal shedding of many enteric viruses, including adenovirus and norovirus, has been documented in HCT recipients and may result in a longer duration of infectiousness [19]. Rotavirus vaccination is currently contraindicated in HCT recipients [20].

Limitations of this study include its retrospective design and inclusion of patients in only one single center. Given diarrheal episodes were not monitored prospectively, some episodes of infectious diarrhea in ambulatory setting might have been missed. Furthermore, the etiology of some episodes might have been multifactorial, and documentation of a pathogen by molecular techniques does not always prove causal inference.

In summary, we report that about one-third of allogeneic HCT recipients had at least one episode of infectious diarrhea in the first year after transplantation, with the highest incidence in the pre-engraftment phase and a higher risk in patients with grade 3 or 4 GI tract GvHD. Importantly, these patients had a higher nonrelapse mortality. Future studies should focus on the prevention and treatment of these episodes in this vulnerable population.

Declarations of competing interest

The authors have no competing interests to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors are indebted to Isabel Moyaert for excellent logistical support.

Author contributions

JVP and MR designed the study. JVP, AH, EDK, SS, SVD, TL, AS, DS and MR collected the data. JVP and SDB analyzed the data. SDB made the figures. JVP drafted the paper. All authors approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.11.045.

References

[1] Cox GJ, Matsui SM, Lo RS, Hinds M, Bowden RA, Hackman RC, et al. Etiology and outcome of diarrhea after marrow transplantation: a prospective study. *Gastroenterology* 1994;**107**:1398–407. doi:10.1016/0016-5085(94)90542-8.

[2] van Kraaij MG, Dekker AW, Verdonck LF, van Loon AM, Vinjé J, Koopmans MP, et al. Infectious gastro-enteritis: an uncommon cause of diarrhoea in adult allogeneic and autologous stem cell transplant recipients. *Bone Marrow Transplant* 2000;**26**:299–303. doi:10.1038/sj.bmt.1702484.

[3] Kamboj M, Mihu CN, Sepkowitz K, Kernan NA, Papanicolaou GA. Work-up for infectious diarrhea after allogeneic hematopoietic stem cell transplantation: single specimen testing results in cost savings without compromising diagnostic yield. *Transpl Infect Dis* 2007;**9**:265–9. doi:10.1111/j.1399-3062.2007.00230.x.

[4] Rogers WS, Westblade LF, Soave R, Jenkins SG, van Besien K, Singh HK, et al. Impact of a multiplexed polymerase chain reaction panel on identifying diarrheal pathogens in hematopoietic cell transplant recipients. *Clin Infect Dis* 2020;**71**:1693–700. doi:10.1093/cid/ciz1068.

[5] Yolken RH, Bishop CA, Townsend TR, Bolyard EA, Bartlett J, Santos GW, et al. Infectious gastroenteritis in bone-marrow-transplant recipients. *N Engl J Med* 1982;**306**:1010–12. doi:10.1056/NEJM198204293061701.

[6] Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005;**106**:2912–19. doi:10.1182/blood-2005-05-2004.

[7] Abramson MH, Gutgarts V, Zheng J, Maloy MA, Ruiz JD, Scordo M, et al. Acute kidney injury in the modern era of allogeneic hematopoietic stem cell transplantation. *Clin J Am Soc Nephrol* 2021;**16**:1318–27. doi:10.2215/CJN.19801220.

[8] Seo S, Campbell AP, Xie H, Chien JW, Leisenring WM, Englund JA, et al. Outcome of respiratory syncytial virus lower respiratory tract disease in hematopoietic cell transplant recipients receiving aerosolized ribavirin: significance of stem cell source and oxygen requirement. *Biol Blood Marrow Transplant* 2013;**19**:589–96. doi:10.1016/j.bbmt.2012.12.019.

[9] Cornell RF, Hari P, Drobyski WR. Engraftment syndrome after autologous stem cell transplantation: an update unifying the definition and management approach. *Biol Blood Marrow Transplant* 2015;**21**:2061–8. doi:10.1016/j.bbmt.2015.08.030.

[10] Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai acute GVHD international consortium. *Biol Blood Marrow Transplant* 2016;**22**:4–10. doi:10.1016/j.bbmt.2015.09.001.

[11] Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;**16**:128–40. doi:10.1016/0196-6553(88)90053-3.

[12] Van Praet JT, Steyaert S, Vandecasteele S, Van Den Bergh B, Mahieu H, De Buyser S, et al. Mycoplasma genitalium acquisition and macrolide resistance after initiation of HIV pre-exposure prophylaxis in men who have sex with men. *Sex Transm Infect* 2020;**96**:396–8. doi:10.1136/sextrans-2019-054335.

[13] Ganzenmueller T, Henke-Gendo C, Schlué J, Wedemeyer J, Huebner S, Heim A. Quantification of cytomegalovirus DNA levels in intestinal biopsies as a diagnostic tool for CMV intestinal disease. *J Clin Virol* 2009;**46**:254–8. doi:10.1016/j.jcv.2009.08.008.

[14] Tanaka Y, Kurosawa S, Tajima K, Tanaka T, Ito R, Inoue Y, et al. Analysis of non-relapse mortality and causes of death over 15 years following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2016;**51**:553–9. doi:10.1038/bmt.2015.330.

[15] Garcia LS. Dientamoeba fragilis, one of the Neglected intestinal Protozoa. *J Clin Microbiol* 2016;**54**:2243–50. doi:10.1128/JCM.00400-16.

[16] Nathan S, Ustun C. Complications of stem cell transplantation that affect infections in stem cell transplant recipients, with analogies to patients with hematologic malignancies. *Infect Dis Clin North Am* 2019;**33**:331–59. doi:10.1016/j.idc.2019.01.002.

[17] Misch EA, Safdar N. Clostridioides difficile infection in the stem cell transplant and hematologic malignancy population. *Infect Dis Clin North Am* 2019;**33**:447–66. doi:10.1016/j.idc.2019.02.010.

[18] Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Bone Marrow Transplant* 2009;**44**:453–5. doi:10.1038/bmt.2009.254.

[19] Roddie C, Paul JP, Benjamin R, Gallimore CI, Xerry J, Gray JJ, et al. Allogeneic hematopoietic stem cell transplantation and Norovirus gastroenteritis: a previously unrecognized cause of morbidity. *Clin Infect Dis* 2009;**49**:1061–8. doi:10.1086/605557.

[20] Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;**58**:309–18. doi:10.1093/cid/cit816.