Transplantation and Cellular Therapy 30 (2024) 712.e1–712.e12

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Infectious Disease

Listeria monocytogenes Infections in Hematopoietic Cell Transplantation Recipients: Clinical Manifestations and Risk Factors. A Multinational Retrospective Case-Control Study from the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation

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Partial results of this study were presented orally at the 48th virtual Annual EBMT Conference, 2022.

Financial disclosure: See Acknowledgments on page 712.e11.

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https://doi.org/10.1016/j.jtct.2024.04.008

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Article history:
Received 2 December 2023
Accepted 10 April 2024

Key words:
Listeriosis
Hematopoietic cell transplantation
Risk factors
Mortality
Cotrimoxazole prophylaxis

A B S T R A C T

Listeriosis is rare after hematopoietic stem cell transplantation (HCT). Little is known about listeriosis in this population. In this retrospective international case-control study, we evaluated 41 listeriosis episodes occurring between 2000 and 2021 in HCT recipients (111 transplant centers in 30 countries) and assessed risk factors for listeriosis by comparisons with matched controls. The 41 listeriosis episodes (all due to *Listeria monocytogenes* [LM]) occurred in 30 allogeneic (allo)-HCT recipients and 11 autologous (auto)-HCT recipients at a median of 6.2 months (interquartile range [IQR], 1.6 to 19.3 months) post-HCT. The estimated incidence was 49.8/100,000 allo-HCT recipients and 13.7/100,000 auto-HCT recipients. The most common manifestations in our cohort were fever (n = 39; 95%), headache (n = 9; 22%), diarrhea, and impaired consciousness (n = 8 each; 20%). Four patients (10%) presented with septic shock, and 19 of 38 (50%) were severely lymphocytopenic. Thirty-seven patients (90%) had LM bacteremia. Eleven patients (27%) had neurolisteriosis, of whom 4 presented with nonspecific signs and 5 had normal brain imaging findings. Cerebrospinal fluid analysis revealed high protein and pleocytosis (mainly neutrophilic). Three-month mortality was 17% overall (n = 7), including 27% (n = 3 of 11) in patients with neurolisteriosis and 13% (n = 4 of 30) in those without neurolisteriosis. In the multivariate analysis comparing cases with 74 controls, non-first HCT (odds ratio [OR], 5.84; 95% confidence interval [CI], 1.10 to 30.82; P = .038); and lymphocytopenia <500 cells/mm^3 (OR, 7.54; 95% CI, 1.50 to 37.83; P = .014) were significantly associated with listeriosis. There were no statistically significant differences in background characteristics, immunosuppression, and cotrimoxazole prophylaxis between cases and controls. HCT recipients are at increased risk for listeriosis compared to the general population. Listeriosis cause severe disease with septic shock and mortality. Neurolisteriosis can present with nonspecific signs and normal imaging. Lymphocytopenia and non-first HCT are associated with an increased risk of listeriosis, and cotrimoxazole was not protective.

INTRODUCTION

Listeria is a facultative intracellular bacillus that can infect humans following ingestion of contaminated food [1]. There are several species of *Listeria*, of which *Listeria monocytogenes* (LM) and (rarely) *Listeria ivanovii* can cause infection in humans [2]. Following gastrointestinal infection, *Listeria* can spread to the bloodstream and brain and is one of the most common etiologies of central nervous system (CNS) infection in immunocompromised patients [3]. The most common manifestation of listeriosis in the immunocompetent individuals is mild gastroenteritis. However, vulnerable populations, including immunocompromised patients, can experience severe life-threatening infections, such as sepsis and meningitis [2,4].

Listeriosis is rare following hematopoietic cell transplantation (HCT), with a reported incidence of .4% to .6% [5–7]. Little is known about its presentation and outcome. Literature on listeriosis in HCT recipients published since 1993 is limited to small case series (2 to 6 patients) and case reports [5–11]. We conducted this multicenter international retrospective study of listeriosis in HCT recipients to analyze its clinical, radiological, and microbiological characteristics and outcomes.

METHODS

Study Design and Settings

This international retrospective nested case-control study was performed by the Infectious Diseases Working Party (IDWP) of the European Society for Blood and Marrow Transplantation (EBMT). Our study population comprised HCT recipients (following allo-HCT and auto-HCT) who developed episodes of LM infection (ie, listeriosis) between January 1, 2000, and March 31, 2021. One reported case of *Listeria innocua*, a

nonpathogenic bacterium, was excluded [2]. Patients were recruited as follows. First, all EBMT-affiliated European HCT centers were invited to take part in the study. Those who agreed were asked to screen their microbiological and transplantation databases systematically and comprehensively. Next, the EBMT database was screened for listeriosis cases reported during the study period. Listeriosis was not systematically reported here, however, as it was not a predetermined item. For each case of listeriosis, 2 controls from the EBMT database were matched by IDWP EBMT study coordinators. Local investigators provided data regarding cases and control subjects, using the specially designed case report forms. The study met all relevant regulations in the participating countries, including approval by local Ethics Committees.

Inclusion Criteria

Adults (≥18 years) and children (0 to 17 years) who met the following criteria were eligible for inclusion: (1) history of allogeneic or autologous HCT (data on listeriosis following chimeric antigen receptor T cell therapy were not collected); (2) LM isolation in any clinical sample after the start of HCT conditioning; (3) suggestive clinical and/or radiological indications of listeriosis; and (4) diagnosis of listeriosis between January 1, 2000, and March 31, 2021.

Definition of Controls

The control–to–case ratio was 2:1 (ie, 2 controls per case). Controls (patients without evidence of LM infection) were defined as patients who received the same HCT type (allogeneic or autologous) and in the same institution and department (ie, pediatric controls for pediatric cases and adult controls for adult cases) as the listeriosis patient and as close in time as possible to the HCT of cases and who survived as long as the case until the development of listeriosis. For example, if listeriosis developed at 2 months after HCT, the control patient should have survived at least 2 months after HCT.

Study objectives were to describe the clinical, radiological, microbiological and outcome characteristics of listeriosis in the HCT recipients and to assess risk factors for listeriosis by comparison with the matched controls.

Microbiology

Laboratory diagnosis of listeriosis required growth of LM in a clinical sample. Antibiotic susceptibility testing was performed in local laboratories. The susceptibility testing methods (E-test, broth microdilution, other) were recorded.

Definitions

The date of diagnosis was defined as the day on which the clinical sample in which LM was first identified was collected. In control patients, the date of inclusion was based on that of the infected patient; the matched control of a patient who underwent HCT on January 1, 2010, and diagnosed with LM infection 151 days later, was given a date of inclusion of 151 days after their own HCT. Myeloablative and nonmyeloablative conditioning and engraftment were defined according to EBMT guidelines [12]. Severe neutropenia or lymphocytopenia was defined as a neutrophil or lymphocyte count <500 cells/mm^3. Low immunoglobulin level was defined as <600 mg/dL in adults and according to age-related norms in children [13].

Neurologic signs included the presence of at least one of the following: headache, impaired consciousness, focal neurologic signs, nuchal rigidity, abnormal movements, and abnormal speech. CNS infection (neurolisteriosis) was defined as the presence of neurologic signs or symptoms together with abnormal findings on cerebrospinal fluid (CSF) analysis or abnormal brain imaging at the time of LM bacteremia [14]. Meningeal involvement was defined clinically (presence of nuchal rigidity) or biologically (abnormal CSF WBC count and/or protein and/or LM growth in the CSF culture). Encephalitis was defined as the presence of at least one of the following with no alternative cause identified: altered consciousness, seizures, new onset of neurologic symptoms, and abnormality on electroencephalography consistent with encephalitis [15]. Brain stem involvement was defined as the presence of cranial neuropathy or brain stem lesions on imaging.

Combination therapy was defined as treatment with 2 antibiotics concomitantly for longer than 7 days. Determination of listeriosis as the cause of death was based on the judgment of the reporting physician.

Variables

Data were collected retrospectively by local investigators and sent to the EBMT/IDWP data office according to EBMT guidelines. Demographic and HCT-related data were obtained using the EBMT database. Variables collected for each listeriosis case are reported in the Supplementary Data.

Statistical Analysis

Continuous data were recorded as median (interquartile range [IQR]); categorical data, as number (%) of total. One-month all-cause survival was assessed using the Kaplan-Meier estimator and compared between groups with the log-rank test. A univariate Cox regression model was used to identify factors associated with 1-month all-cause survival. Variables with a P value <.05 on univariable analysis were included in a multivariable Cox regression model. A bilateral P value <.05 was considered statistically significant. Potential risk factors for listeriosis were compared between cases and controls (including only patients for whom 2 controls were provided) using a conditional logistic regression model. All analyses were performed using SAS v.9.4 statistical software (SAS Institute).

RESULTS

Participating Centers and Patients

A total of 111 centers from 30 countries responded to the invitation to participate. Among them, 19 centers from 10 countries (Belgium, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, Russia, Sweden) reported 41 listeriosis episodes in 30 allo-HCT recipients (73%) and 11 auto-HCT recipients (27%). During the study inclusion period, 60,241 allo-HCTs and 80,196 auto-HCTs were performed in the respondent centers; thus, the estimated incidence was 49.8/100,000 in allo-HCT recipients and 13.7/100,000 in auto-HCT recipients. The majority of cases (n = 31; 75.6%) were reported after 2010.

Patients' underlying diseases, HCT-related data, drug exposures, laboratory characteristics, and concomitant infections are presented in Table 1. No seasonal differences were observed (9 to 11 cases in each season).

Presentation of Listeriosis after HCT

Listeriosis occurred at a median of 6.2 months (interquartile range [IQR], 1.6 to 19.3 months) following HCT (Figure 1). The majority of cases (28 of 41; 68.3%) were community-acquired; the remaining 13 cases (31.7%) developed during hospitalization, which lasted a median of 10 days (IQR, 8 to 26 days) before the diagnosis of LM. In 9 cases, its presumed source was specific foods. No outbreaks were reported. The presentation of listeriosis in all patients, and separately in allo-HCT and auto-HCT patients, is summarized in Table 2.

The median time between the onset of symptoms and diagnosis was 2 days (IQR, 1 to 4 days). The most common signs and symptoms were fever (39 patients; 95%), headache (9 patients, 22%), and diarrhea and impaired consciousness (8 patients each; 20%). Four patients (10%) presented with septic shock. Diarrhea was more frequent in auto-HCT recipients compared to allo-HCT recipients (P = .02). Listeriosis occurred earlier after auto-HCT compared to allo-HCT, although the difference was not significant.

We separated cases based on their timing after HCT (every 3 months during the first year post-HCT and every 6 months thereafter) and observed that 18 cases (44%) occurred during the first 3 months (Figure 1), compared to 2 to 5 cases (5% to 12%) during each subsequent period. We compared the cases occurring during the first 3 months to the later cases (n = 18 [44%] and n = 23 [56%], respectively). The patients with listeriosis diagnosed during the first 3 months post-HCT had higher rates of severe neutropenia (4 of 18 [22%] versus 0 of 21 [0%]; P = .04), and severe lymphocytopenia (14 of 18 [78%] versus 5 of 20 [25%]; P = .001). There were no between-group differences in the other clinical or laboratory parameters, including in the rate of the CNS involvement and its outcomes.

In 37 of 41 patients (90%), blood cultures yielded LM. In one patient, presenting with cough, dyspnea, pleuritic pain and lung opacities on chest CT, LM was cultured from both blood and pleural fluid. In 7 bacteremic patients, LM was cultured from CSF as well. In 4 additional patients with negative blood cultures, LM was cultured solely in CSF. Repeat blood cultures were performed in 20 patients, of whom 5 had positive blood cultures for 2 to 9 days.

Neurolisteriosis was reported in 11 patients (27%), of whom 4 (36%) presented with nonspecific signs, including fever along with 1 or more of headache, vomiting, chills, septic shock (Supplementary Table S1);. All 11patients with neurolisteriosis underwent CNS imaging, including computed tomography (CT) in 10 patients and magnetic resonance imaging (MRI) in 7 patients. In 5 of the 11 patients (46%), CNS imaging (MRI in 3, CT in 4) was normal. CSF analysis in 10 patients revealed high protein (median, 1432 mg/L; IQR, 1220 to 1807 mg/L); pleocytosis (median WBC count, 172/mm^3; IQR, 91 to 623 cells/mm^3; n = 8; 2 missing data); a median neutrophil count of 82 cells/mm^3 (IQR, 47 to 431 cells/mm^3) with a median of 79% neutrophils (IQR, 25% to 92%) and a median lymphocyte count of 62/mm^3 (IQR, 21 to 144/ mm^3) (both n = 7; 3 missing data); and low glucose in 3 of 8 patients (38%). CSF culture yielded LM in eight patients. Two patients with

Table 1
Characteristics of Patients with Listeriosis and Controls

Characteristic	Cases (N = 37)	Controls (N = 74)	*P* Value
Demographics			
Male, n (%)	26 (70)	42 (57)	.2
Female, n (%)	11 (30)	32 (43)	
Age at HCT, yr, median (range)	54.1 (3.4-69.1)	53.5 (2.6-70.6)	.4
Children, n (%)	4 (11)	8 (11)	
Age at listeriosis diagnosis/inclusion for controls, yr, median (range)	55.2 (3.9-72.8)	54.1 (2.9-71.8)	.4
Underlying disease, n (%)			
Acute leukemia/ myelodysplastic syndrome	13 (35)	37 (50)	.09
Plasma cell disorders	13 (35)	17 (23)	
Lymphoma	7 (19)	7 (9)	
Chronic leukemia	2 (5)	4 (5)	
Inherited diseases	2 (5)	1 (1)	
Other*	0 (0)	8 (11)	
HCT type, n (%)			
Allogeneic	26 (70)	52 (70)	-
Autologous	11 (30)	22 (30)	
Most recent HCT, n (%)			
First	26 (70)	71 (96)	.003
Second or more	11 (30)	3 (4)	
Stem cell source, n (%)			
Bone marrow	3 (8)	15 (20)	.08
Peripheral blood	34 (92)	59 (80)	
HLA matching, n/N (%)			
Matched related/identical sibling	9/26 (35)	18/52 (35)	1
Matched unrelated	9/26 (35)	17/52 (33)	
Mismatched	2/26 (8)	2/52 (4)	
Unrelated, number of mismatches unknown	6/26 (23)	15/52 (29)	
Conditioning, n/N (%)			
Reduced	14/35 (40)	20/73 (27)	.1
Standard	21/35 (60)	53/73 (73)	
Total body irradiation, n (%)	11 (30)	19 (26)	.5
T cell depletion, n/N (%)	13/34 (38)	36/69 (52)	.04
Post-transplantation cyclophosphamide, n (%)	2 (5)	2 (3)	.4
Comorbidities at the time of listeriosis, n (%)	16 (43)	26 (35)	.4
Underlying disease treatment, n (%)	7 (19)	10 (14)	.3
Laboratory characteristics at listeriosis diagnosis, or inclusion for controls			
WBC count, median (IQR)	5200 (2030- 8510); n = 37	4500 (2230 - 6300); n = 71	.03
Neutropenia <500 cells/mm^3, n/N (%)	4/35 (11%)	10/65 (15)	.3
Lymphocyte count, median (IQR)	470 (100-740); n = 32	1480 (600-2220); n = 59	.008
Lymphopenia <500 cells/mm^3, n/N (%)	19/34 (56)	17/64 (27)	.004
CD4/CD8 ratio >1, n/N (%)	1/11 (9)	9/26 (35)	.7
Low IgG level, n/N (%)	16/24 (67)	10/44 (23)	.005
Risk factors before or at the time of listeriosis, or inclusion for controls, n/N (%)			
Gastric acid-suppressing medications	30 (81)	39/72 (54)	.006
Active acute GVHD grade II-IV	5/26 (19)	5/52 (10)	.1
Chronic GVHD	11/26 (42)	6/52 (12)	.01
Extensive chronic GVHD	6/26 (23)	3/52 (6)	.04
Liver chronic GVHD	5/26 (19)	2/52 (4)	.05
Immunosuppressive medications, n (%)	27 (7)	39 (53)	.02

(*continued*)

Table 1 (*Continued*)

Characteristic	Cases (N = 37)	Controls (N = 74)	*P* Value
Steroids any dose	22 (59)	18 (24)	.0006
Steroids ≥1 mg/kg/day	6 (1%)	4 (5)	.07
Cyclosporine	7 (19)	24 (32)	.04
Tacrolimus	9 (24)	7 (9)	.02
Other	13 (35)	17 (23)	.1
None	10 (27)	35 (47)	.02
One drug	10 (27)	19 (26)	
Two or more drugs	17 (46)	20 (27)	
Underlying disease status after HCT, n/N (%)			
Continued complete remission	23/36 (64)	61 (82)	.02
Not in continued complete remission	13/36 (36)	13 (18)	
Ferritin level above normal	12/16 (75)	24/34 (71)	.1
Antibiotic exposure at the time of listeriosis, n/N (%)			
Trimethoprim-sulfamethoxazole	11/35 (31)	30/70 (43)	.2
Penicillin	4 (11)	3 (4)	.2
Fluoroquinolone	1 (3)	5 (7)	.4
Infections within 1 month before or after listeriosis/ inclusion, n (%)	13 (35)	15 (20)	.07
Bacterial	6 (16)†	9 (12)‡	.6
Invasive fungal infections	3 (8)§	2 (3%)‖	.2
Viral infections	10 (27%)⍰	8/73 (11%)**	.03

* Other diseases: bone marrow failure (n = 6), hemoglobinopathies (n = 2).

† Bacteremia with coagulase-negative *Staphylococcus* (n = 2), *Enterococcus faecium* (n = 1), *Enterobacter cloacae* (n = 1), *Streptococcus pneumoniae* (n = 1), and *Pseudomonas aeruginosa* pneumonia (n = 1).

‡ Bacteremia due to *Escherichia coli* (n = 2), *Citrobacter freundii* (n = 1), *Propionibacterium acnes* (n = 1), *Lactobacillus* spp. (n = 1), *Staphylococcus epidermidis* (n = 1), and *Enterobacter* spp. (n = 1); urinary tract infection due to *E. coli* (n = 2).

§ Lung infections due to aspergillosis (n = 2) or *Pneumocystis jirovecii* (n = 1).

‖ Lung infections due to aspergillosis (n = 2).

⍰ Viral infections (1 or more of): cytomegalovirus (CMV) reactivation (n = 7), Epstein-Barr virus (EBV) reactivation (n = 3, including 2 with post-transplantation lymphoproliferative disorder), adenovirus in gastrointestinal tract (n = 1). Respiratory infections: rhinovirus (n = 1), enterovirus (n = 1), and parainfluenza-4 (n = 1).

** CMV reactivation (n = 5), EBV reactivation (n = 1), upper respiratory tract infection due to adenovirus (n = 1) and respiratory syncytial virus (n = 1), and varicella zoster virus eruption (n = 1).

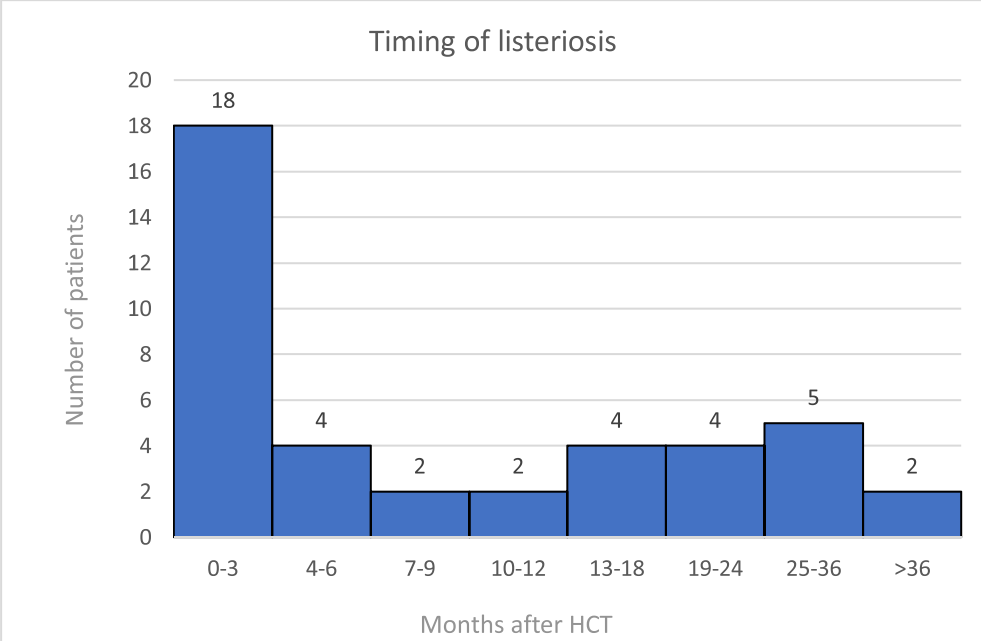


Figure 1. Timing of listeriosis after HCT.

Table 2
Listeriosis Presentation and Outcome

Variable	Total (N = 41)	Allo-HCT Recipients (N = 30)	Auto-HCT Recipients (N = 11)
Patients, n (%)			
Male	29 (71)	22 (73)	7 (36)
Female	12 (29)	8 (27)	4 (64)
Children	4 (10)	4 (13)	0 (0)
Adults	37 (90)	26 (87)	11 (100)
Time since HCT to listeriosis, mo, median (IQR)	6.2 (1.6-19.3)	9.3 (2.3-19.5)	2.4 (.1-6.6)
Time from onset of symptoms to diagnosis, d, median (IQR)	2 (1-4); n = 36	1 (1-3); n = 27	4 (2-5); n = 9
Clinical signs, n (%)			
Fever >38 ○C	39 (95)*	28 (93)*	11 (100)
Headache	9 (22)	6 (20)	3 (27)
Impaired consciousness	8 (20)	5 (17)	3 (27)
Diarrhea	8 (20)	3 (10)	5 (45)
Chills	7 (17)	6 (20)	1 (9)
Nausea and/or vomiting	5 (12)	4 (13)	1 (9)
Septic shock	4 (10)	3 (10)	1 (9)
Cough/dyspnea	4 (10)	2 (7)	2 (18)
Bacteremia, n (%)	37 (90)	29 (97)	8 (73)
Without organ involvement	21 (51)	18 (60)	3 (27)
With organ involvement	16 (39)	11 (37)†	5 (45)‡
CNS disease, n (%)	11 (27)	8 (27)	3 (27)
Laboratory parameters, n/N (%)			
Neutropenia <500 cells/mm^3	4/39 (10)	1/28 (4)	3 (27)
Lymphopenia <500 cells/mm^3	19/38 (50)	12/27 (44)	7 (64)
Lymphopenia <100 cells/mm^3	11/38 (29)	5/27 (19)	6 (55)
Hypogammaglobulinemia	18/27 (67)	14/19 (74)	4/8 (50)
High C-reactive protein	27/30 (90)	21/23 (91)	6/7 (86)
Outcome, n (%)			
ICU admission for listeriosis	6 (15)	5 (17)	1 (9)
30-day mortality	2 (5)	2 (7)	0 (0)
3-month mortality	7 (17)	7 (23)	0 (0)
Attributable mortality	3 (7)	3 (10)	0 (0)

ICU indicates intensive care unit.

* Two patients presented without fever; one presented with hypothermia 34.6 °C, and the other had a normal temperature but presented with poor general feeling, cough, and dyspnea.

† Seven patients with CNS involvement, 3 patients with gastrointestinal tract involvement (diarrhea), and 1 patient with lung involvement.

‡ Four patients with gastrointestinal tract involvement (diarrhea) and 1 patient with lung involvement, in whom *Listeria* was cultured from pleura and blood.

negative CSF cultures presented with fever, limb paralysis, CSF pleocytosis and high protein, and focal lesions on brain imaging. One of them developed listeriosis during treatment with penicillin that had been started before the onset of listeriosis; blood cultures yielded LM in both patients. In the eleventh patient, CSF was not obtained; he presented with septic shock, impaired consciousness, and abnormal electroencephalogram. MRI revealed leukoencephalopathy. LM was cultured from his blood, and he died 17 days later while being treated with piperacillin/tazobactam and metronidazole. Seven of the 11 patients (64%) with neurolisteriosis had encephalitis, and all 10 patients for whom data were available had meningeal involvement.

Microbiological Characteristics

The method used for microbiological identification of LM was reported in 31 cases (74%): matrix-

assisted laser desorption/ionization time-of-flight mass spectrometry in 25 patients (81%), a biochemical method in 4 (12%), and a molecular method in 2 (7%). The LM serotype was reported for 11 isolates: 4b in 5 patients, 1/2a in 3; 1/2b in 2, and 11a in 1.

Tested isolates were sensitive to ampicillin (n = 34), trimethoprim-sulfamethoxazole (n = 31), meropenem (n = 16), erythromycin (n = 8), gentamicin (n = 16), and linezolid (n = 3). Intermediate susceptibility was reported in 1 of 2 isolates to moxifloxacin and in 1 of 3 isolates to levofloxacin. One of 9 isolates was resistant to penicillin. The method of antimicrobial susceptibility testing was reported in 28 patients (68%), including an E-test in 24 (86%), disc diffusion in 4 (14%), and broth microdilution in 3 (11%).

Management of Listeriosis

Data on antibiotic therapy are summarized in Supplementary Table S2. All patients received antibiotics intravenously, and 8 patients switched to oral antibiotics. The most frequently used antibiotics were penicillins (n = 38; 93%). Fifteen patients (37%) received combination therapy for longer than 7 days, mainly beta-lactam and aminoglycoside (13 of 41; 32%). Three of 11 patients (27%) with neurolisteriosis and 12 of 30 (40%) without neurolisteriosis received combination therapy. The median duration of treatment was 20 days (IQR, 15 to 25 days) among the 38 patients alive at the end of treatment, including 24 days (IQR, 21 to 41 days) in the 8 patients with neurolisteriosis and 20 days (IQR, 14 to 22 days) in the 29 patients without neurolisteriosis (missing data for 1 patient). Three patients with neurolisteriosis died during treatment that lasted between 15 and 53 days from diagnosis. Steroids were not used to treat listeriosis in any patient.

Outcome of Listeriosis

Seven patients (17%) died within 3 months after diagnosis of listeriosis, all following allo-HCT,. The median time from diagnosis to death was 40 days (range, 15 to 88 days). Three deaths were considered to be due to listeriosis. Two patients (5%), who developed neurolisteriosis by 19 months post-HCT, died within 30 days after diagnosis. In another HCT recipient, who died 53 days after diagnosis of neurolisteriosis, listeriosis was considered to have contributed to death. Three-month overall mortality was 37% (3 of 11) in the patients with neurolisteriosis, and 13% (4 of 30) in those without neurolisteriosis (Figure 2). There was no mortality among auto-HCT recipients with listeriosis. There was no difference in mortality between early listeriosis and late listeriosis. Three of 75 controls (4%) died within 3 months of their inclusion date. One of 38 patients (3%), who survived listeriosis, had residual neuropathy (cranial nerve VII).

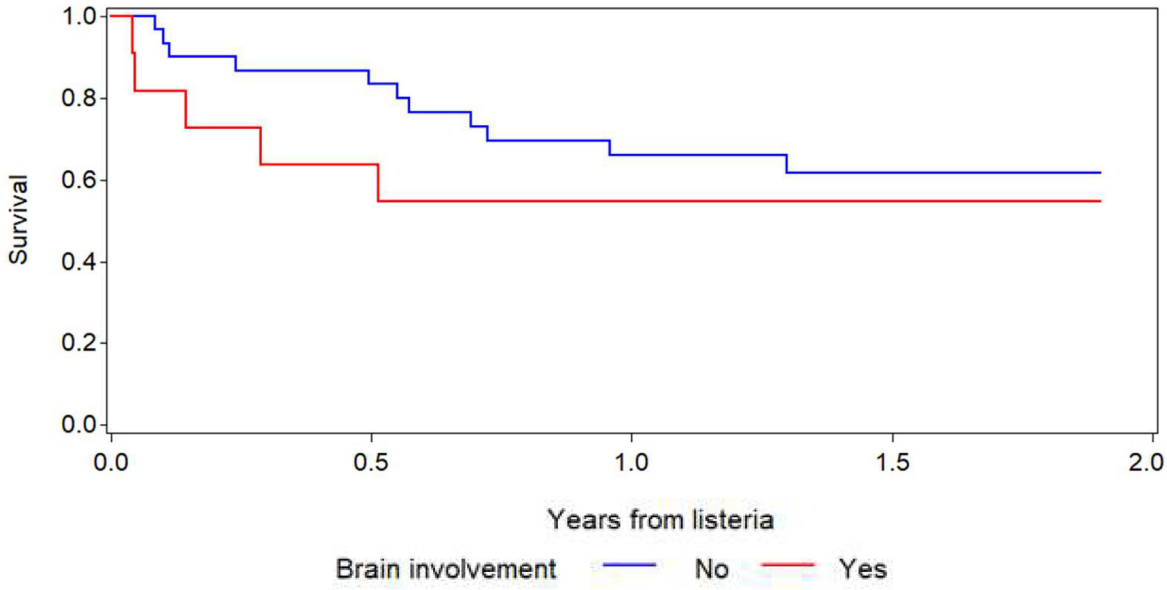
Comparison of Cases and Controls

Seventy-four control subjects were included. Comparison of cases and controls showed that fewer controls had more than one HCT, fewer were being treated with gastric acid suppressive drugs, immunosuppressive medications, and specifically steroids or tacrolimus, and were taking 2 or more immunosuppressive medications; and fewer had severe lymphocytopenia, low plasma immunoglobulin, or chronic and extensive GVHD and were not in complete remission, whereas while more controls received T cell-depleted grafts and cyclosporin (Table 1). Recent viral infections were significantly less frequent among the controls. Multivariate analysis showed that receipt of more than 1 HCT and development of severe lymphocytopenia were significantly less frequent among the controls (Table 3).

DISCUSSION

In this multinational retrospective study, we evaluated clinical, imaging, laboratory, treatment, and outcome data on 41 patients with invasive listeriosis following HCT. To the best of our knowledge, this is the most extensive study undertaken to date on listeriosis in this patient population and the only study to identify risk factors for listeriosis through a case-control analysis. The estimated incidence of listeriosis in our study was much higher than .52 cases per 100,000 population reported in 2022 by the European Centre of Disease Prevention and Control [16], with the notification rates for listeriosis (with 2770 cases) in 2022 the highest in more than 10 years.

The majority of cases were reported during the later study years, possibly because of the number of HCTs performed, both total and in specific patient populations, or reporting and documentation bias, or differences in post-HCT survival. Since 1993, 7 case series including a total of 27 patients have been published, the most recent series in 2006 [5–11]. Supplementary Table S3 compares these reported cases and ours. The median time of listeriosis presentation was 6.2 months (IQR, 1.6 to 19.3 months) after HCT in our study, compared to 2.2 months (IQR, 1.1 to .9 months) in the previously reported series. This difference may be related to underreporting of



Neurolisteriosis	OS (95% C.I.)		
	3-months	1-year	2-year
No	87 (68-95)	66 (46-80)	62 (41-77)
Yes	73 (37-90)	55 (23-78)	55 (23-78)
P value	0.3	0.3	

Figure 2. Survival in patients with and without neurolisteriosis.

Table 3
Comparison of Listeriosis Cases and Controls (Multivariate Analysis)

Variable	OR	95% CI	*P* Value
Most recent HCT			
First	1.00		
Second or more	5.84	1.10-30.82	.038
Severe lymphopenia			
No	1.00		
Yes	7.54	1.50-37.83	.014

There was no difference between the 2 groups in antibiotic exposure to cotrimoxazole, fluoroquinolones, or penicillins at the time of diagnosis/inclusion.

cases that occurred later after HCT; or due to increased survival of patients after HCT over the years [17], with more patients who remain immunocompromised and at risk for listeriosis.

We compared the manifestations of listeriosis in our cohort of HCT recipients with those described in a national prospective observational cohort study, MONALISA, that summarizes data from 818 patients reported within a routine surveillance in France [15]. The main clinical presentation in our study was fever (95%) and diarrhea (20%), the latter more frequent in auto-HCT patients (45%). These rates are close to those reported in the MONALISA study (89% and 18%, respectively). The incidence of septic shock was

higher in our population (10% versus 1%, respectively). This may indicate the more severe course of listeriosis in HCT patients, although the comparison is hindered by the significantly smaller number of patients in our study.

The rate of neurolisteriosis was slightly lower in our study (27%) compared to the HCT case series (41%) and the MONALISA study (32%). Nuchal rigidity (18%) and impaired consciousness—classical signs of meningitis—were less common in our study than previously reported in patients with neurolisteriosis (18% and 55% versus 65% to 73% and 85%, respectively). None of our patients experienced seizures, compared with 5% to 18% in the other studies [4,14,15]. One-third of our neurolisteriosis patients presented with nonspecific findings, including fever and 1 of headache/vomiting/chills/septic shock. This is similar to a study from The Netherlands, in which the classic triad of fever, neck stiffness, and altered mental status was present in only 13 of 30 patients (43%) with *Listeria* meningitis [4]. Comparison of our CSF findings with those from the MONALISA study revealed lower protein levels (median, 1432 mg/L [IQR, 1220 to 1807 mg/L) versus 2100 mg/L [IQR, 1400 to 3200 mg/L]) and lower WBC count in the CSF (median, 172 cells/mm^3 [IQR, 91 to 623 cells/mm^3] versus 457 cells/mm^3 [IQR, 174 to 1117 cells/mm^3]). *Listeria* was identified on Gram stain in less than one-half of the patients in our cohort, supporting the addition of empirical anti-*Listeria* coverage for all immunocompromised patients with meningitis/encephalitis regardless of Gram stain analysis results [18].

Interestingly, our findings differ from previously published data on HCT recipients (Supplementary Table S3) that showed a lower rate of encephalitis and higher protein levels, WBC counts, and glucose levels in the CSF. The lymphocyte/neutrophil ratio in our study was variable, but neutrophils predominated, with a median ratio of 79%, close to the 65% reported in the MONALISA study. CNS imaging was normal in one-half of the patients in our study, similar to the 40% rate in the published data for HCT recipients but considerably higher than the MONALISA's 13% [19]. The absence of classical signs of meningitis/encephalitis, with relatively low protein and CSF WBC numbers and normal CNS imaging in our cohort can be attributed to the diminished inflammatory response in immunocompromised patients. Current guidelines recommend high-dose antibiotics for 3 weeks in patients with neurolisteriosis [2,18], with 2 weeks sufficient for patients without meningitis/encephalitis [20].

Our data demonstrate that meningoencephalitis cannot be excluded in HCT patients with *Listeria* bacteremia based on clinical signs or imaging findings. CSF analysis can exclude CNS involvement, and if not provided, a 3-week course of high-dose antibiotics capable of penetrating the CNS should be considered. Interestingly, the addition of aminoglycosides, which is frequently considered in patients with neurolisteriosis [18], was relatively uncommon in our study.

The risk factors for listeriosis identified by our case-control analysis were severe lymphocytopenia and non-first HCT. The number of patients in previously published reports was too small for a risk factor analysis. Only a small proportion of our patients were neutropenic, and one-half were severely lymphocytopenic, underscoring the role of T cell immunity against listeriosis. Two additional factors were found to be significantly associated with listeriosis in the univariate analysis but not in the multivariate analysis, likely owing to a small sample size: a higher rate of chronic GVHD among cases, supporting the importance of T cell immunity, and a higher rate of previous use of gastric acid-suppressive medications, which that could predispose to infection, given that *Listeria* is acquired through the gastrointestinal tract. Thus, the risks and benefits for gastric acid-suppressive medications should be assessed in each patient.

We do not have a clear explanation of the higher rate of T cell depletion in controls compared to cases in the univariate analysis. This difference likely can be explained by the lower rate of GVHD in patients with in vitro T cell depletion and, subsequently, less post-HCT immune suppression. Interestingly, there was no significant difference between cases and controls in terms of cotrimoxazole exposure.

Comparison of the outcome of listeriosis with that in the published literature reveals interesting differences. Sequelae occurred in only 1 patient in our cohort (facial nerve paralysis), compared with 79 of 181 surviving patients with neurolisteriosis (44%) in the MONALISA study [15], who suffered persistent impairment (altered consciousness or focal signs). One-month and 3-month mortality in our study was lower than previously reported in HCT patients (5% versus 19% and 17% versus 30%, respectively), although mortality in patients with neurolisteriosis was the same (27%) (Supplementary Table S3). The higher reported mortality could be due to the shorter interval between HCT and listeriosis in the published cases. We did not find any difference in mortality between early

and late listeriosis, however. In our study, mortality was numerically higher in patients with neurolisteriosis compared to those without, but this difference did not reach significance, probably because of low patient numbers. In the MONALISA study, the mortality in cases with neurolisteriosis was 30%, similar to our study; however, different from our data, the mortality was higher in cases with bacteremia without neurolisteriosis (45%).

Comparisons between listeriosis cases in allo-HCT recipients and auto-HCT recipients revealed some differences that probably can be related to the differences in immune recovery, although the numbers are too small to allow for statistical conclusions. Listeriosis occurred earlier after auto-HCT compared to allo-HCT (median, 2.4 months versus 10.1 months). All mortality was among allo-HCT recipients; there were no deaths in the auto-HCT recipients with listeriosis.

Our study has several limitations. First, as a retrospective analysis, data were obtained from the medical records, and some data were missing. Second, because of the small number of cases, we could not identify risk factors for mortality due to listeriosis. Third, the relatively small patient numbers limit comparisons of our data to data from larger studies in a heterogenous patient populations and can influence risk factor analysis. Adding more controls likely could improve the analysis of risk factors for listeriosis. Fourth, the post-HCT follow up protocol varied across centers. Follow-up may have been limited in some patients, and thus some cases of listeriosis, especially those that were mild or occurred late (>6 months) after HCT, could have been missed or unreported, and risk factors for late listeriosis could not be assessed. Even in EU epidemiology reports, the milder forms of listeriosis causing gastrointestinal symptoms usually are not diagnosed and notified. The EU surveillance of listeriosis focuses on severe, invasive forms of the disease [16].

CONCLUSION

The importance of the study is that collaboration between EBMT centers enabled comprehensive description of 41 listeriosis cases, the largest cohort published in the last 30 years. Listeriosis can cause severe disease, leading to septic shock, meningoencephalitis, and mortality. Similar to other infections, listeriosis can be more severe in HCT recipients compared to general population, while symptoms of listeriosis may vary and overlap with other clinical conditions. It should be mentioned that some empirical protocols in HCT recipients (eg, cefepime) do not cover *Listeria*. We show that neurolisteriosis can present without the classical picture of meningoencephalitis but with nonspecific signs and symptoms and normal imaging findings. CSF findings are characterized by relatively low WBC count and protein levels, and a predominance of neutrophils. Lymphocytopenia and other than first HCT are associated with an increased risk of listeriosis. Cotrimoxazole was not shown to be protective against listeriosis; thus, it is important to consider listeriosis in patients with a compatible clinical picture, such as meningoencephalitis, even in patients receiving cotrimoxazole prophylaxis.

A shift from primary inpatient to outpatient management of HCT recipients exposes them to an increased risk of listeriosis, as control of dietary intake is more difficult to manage, and dietary indiscretions are more likely. This is supported by the fact that most of our cases were community-acquired. The incubation period for bacteremic listeriosis varies from 12 to 29 days, and thus the true rate of community-acquired listeriosis can be even higher than the reported 68.3% (28 of 41) [21,22]. Prevention of listeriosis, including dietary restrictions, is extremely important in these vulnerable patients, regardless of cotrimoxazole prophylaxis.

ACKNOWLEDGMENTS

Financial disclosure: Nothing to declare.

Conflict of interest statement: There are no conflicts of interest to report.

Data sharing statement: The datasets generated and/or analyzed in this study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtct.2024.04.008.

REFERENCES

1. Radoshevich L, Cossart P. *Listeria monocytogenes*: towards a complete picture of its physiology and pathogenesis. *Nat Rev Microbiol*. 2018;16:32–46. https://doi.org/10.1038/nrmicro.2017.126.
2. Koopmans MM, Brouwer MC, Vázquez-Boland JA, van de Beek D. Human listeriosis. *Clin Microbiol Rev*. 2023;36 e0006019. https://doi.org/10.1128/cmr.00060-19.
3. van Veen KE, Brouwer MC, van der Ende A, van de Beek D. Bacterial meningitis in hematopoietic stem cell transplant recipients: a population-based prospective study. *Bone Marrow Transplant*. 2016;51:1490–1495. https://doi.org/10.1038/bmt.2016.181.
4. Brouwer MC, Dvd Beek, Heckenberg SG, Spanjaard L, Jd Gans. Community-acquired *Listeria monocytogenes* meningitis in adults. *Clin Infect Dis*. 2006;43:1233–1238. https://doi.org/10.1086/508462.

5. Chang J, Powles R, Mehta J, Paton N, Treleaven J, Jameson B. Listeriosis in bone marrow transplant recipients: incidence, clinical features, and treatment. *Clin Infect Dis*. 1995;21:1289–1290. https://doi.org/10.1093/clinids/21.5.1289.
6. Girmenia C, Iori AP, Bernasconi S, et al. Listeriosis in recipients of allogeneic bone marrow transplants from unrelated donors. *Eur J Clin Microbiol Infect Dis*. 2000;19:711–714. https://doi.org/10.1007/s100960000343.
7. Safdar A, Papadopoulous EB, Armstrong D. Listeriosis in recipients of allogeneic blood and marrow transplantation: thirteen year review of disease characteristics, treatment outcomes and a new association with human cytomegalovirus infection. *Bone Marrow Transplant*. 2002;29:913–916. https://doi.org/10.1038/sj.bmt.1703562.
8. Long SG, Leyland MJ, Milligan DW. *Listeria* meningitis after bone marrow transplantation. *Bone Marrow Transplant*. 1993;12:537–539.
9. Martino R, López R, Pericas R, Badell I, Sureda A, Brunet S. Listeriosis in bone marrow transplant recipient. *Clin Infect Dis*. 1996;23:419–420. https://doi.org/10.1093/clinids/23.2.419.
10. Nolla-Salas J, Almela M, Coll P, Gasser I. Listeriosis in bone marrow transplant recipients. *Bone Marrow Transplant*. 1997;19:956–958.
11. Radice C, Muñoz V, Castellares C, et al. *Listeria monocytogenes* meningitis in two allogeneic hematopoietic stem cell transplant recipients. *Leuk Lymphoma*. 2006;47:1701–1703. https://doi.org/10.1080/10428190600648135.
12. European Society for Blood and Marrow Transplantation. MED-AB Forms Manual: A guide to the completion of the EBMT HSCT Med-AB forms). Available at: https://www.ebmt.org/sites/default/files/2018-03/MED-AB%20Forms%20Manual.pdf. Accessed June 1, 2023.
13. Knutsen AP. IgG subclass deficiency. Available at: https://www.uptodate.com/contents/igg-subclass-deficiency. 2023. Accessed February 1, 2024.
14. Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with *Listeria monocytogenes*: 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine (Baltimore)*. 1998;77:313–336. https://doi.org/10.1097/00005792-199809000-00002.
15. Charlier C, Perrodeau E, Leclercq A, et al. Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. *Lancet Infect Dis*. 2017;17:510–519. https://doi.org/10.1016/S1473-3099(16)30521-7.
16. European Centre for Disease Prevention and Control. Listeriosis - Annual Epidemiological Report for 2022. 2024. Available at: https://www.ecdc.europa.eu/en/publications-data/listeriosis-annual-epidemiological-report-2022. Accessed April 7, 2024.
17. Styczyński J, Tridello G, Koster L, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplant*. 2020;55:126–136. https://doi.org/10.1038/s41409-019-0624-z.
18. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect*. 2016;22 (suppl 3):S37–S62. https://doi.org/10.1016/j.cmi.2016.01.007.
19. Charlier C, Poirée S, Delavaud C, et al. Imaging of human neurolisteriosis: a prospective study of 71 cases. *Clin Infect Dis*. 2018;67:1419–1426. https://doi.org/10.1093/cid/ciy449.
20. Lorber B. Listeriosis. *Clin Infect Dis*. 1997;24:1–9. https://doi.org/10.1093/clinids/24.1.1.
21. Angelo KM, Jackson KA, Wong KK, Hoekstra RM, Jackson BR. Assessment of the incubation period for invasive listeriosis. *Clin Infect Dis*. 2016;63:1487–1489. https://doi.org/10.1093/cid/ciw569.
22. Goulet V, King LA, Vaillant V, de Valk H. What is the incubation period for listeriosis? *BMC Infect Dis*. 2013;13:11. https://doi.org/10.1186/1471-2334-13-11.