JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Mortality in patients with hematological malignancies, febrile neutropenia, and septic shock

Beda Islas-Muñoz[1], Patricia Volkow-Fernández[1], Jorge Silva-Zamora[1], Ana Ramírez-Ibarguen [2], Patricia Cornejo-Juárez[1]

[1] Infectious Diseases Department, Instituto Nacional de Cancerología (INCan), Alcaldía Tlalpan, 14000 Mexico City
[2] Hematology Department, Instituto Nacional de Cancerología (INCan), Alcaldía Tlalpan, 14000 Mexico City, Mexico

Abstract

Introduction: Patients with severe neutropenia who develop septic shock (SS) have high mortality. This study aimed to evaluate the risk factors and mortality of SS in patients with HM and febrile neutropenia.

Methodology: We included all patients with hematological malignancies (HM) who presented fever and severe neutropenia, admitted to an oncological tertiary care center in Mexico City for one year.

Results: Two hundred ninety-two episodes of fever and severe neutropenia were documented; 68 patients (23.2%) developed SS. Documented clinical infection was different between SS and non-SS patients (94.1% vs. 63.4%, $p < 0.001$); pneumonia was the most frequent infection (36.8% vs. 23.2%, $p = 0.02$). Also, in SS vs. non-SS, there were more positive cultures (69.1% vs. 38.4%, $p < 0.001$), higher frequency of Gram-negative bacteria (89.3% vs. 63.9%, $p < 0.001$), particularly *Escherichia coli* (68% vs. 44.2%) and *Klebsiella spp.* (23.4% vs. 15.1%). There were no differences when multidrug-resistant (MDR) microorganisms were compared. In the multivariate analysis, associated risk factors for SS were: prolonged neutropenia, a documented site of infection, and having received highly myelosuppressive chemotherapy. Risk factors for mortality at 30 days were: older patients, prolonged neutropenia, and SS.

Conclusions: Severe and prolonged neutropenia was associated with SS development and mortality at 30 days. ICU management should be offered to all critically ill patients with HM if long-term survival of the underlying malignancy is expected.

Key words: Neutropenia; hematological malignancies; septic shock; mortality.

J Infect Dev Ctries 2024; 18(2):235-242. doi:10.3855/jidc.17451

(Received 27 September 2022 – Accepted 05 June 2023)

Introduction

The development of intensive chemotherapy protocols has increased the cure rate of patients with cancer [1]. Nonetheless, many of these regimes are myelosuppressive; Patients receiving chemotherapy for solid tumors generally have rates of neutropenia of 5-10%, whereas patients with hematological malignancies (HM) have rates above 20%, and recipients of a bone marrow transplant reach a rate of between 70-100% [2]. The myelosuppression caused by these treatments enhances the incidence of infection, with severe and prolonged neutropenia being the most important cause of morbidity and mortality [1-3].

Over 50% of patients with neutropenic fever will produce sepsis syndrome, 20-30% will develop severe sepsis, and 5-10% will develop SS [2]. While in the general population, the mortality rate in sepsis remains ≥ 20%, in patients with HM and febrile neutropenia, mortality rates of 35% have been reported with severe sepsis, 47% with SS, and up to 85% with multiorgan failure [2,4].

This study aimed to evaluate the risk factors and mortality of SS in patients with HM and febrile neutropenia.

Methodology

All hospitalized patients with HM, fever, and severe neutropenia admitted between January 1st, 2019, and December 31st, 2019, were included in this study.

The following demographic and clinical data were recorded: age; gender; type of HM; cancer status (recent diagnosis, progression, relapse, or complete or partial remission); treatment with chemotherapy during the previous month; Hematopoietic Stem Cell Transplantation (HSCT); days with neutropenia; the number of previous hospitalizations related with febrile neutropenia; documented site of infection; pathogens isolated during hospitalization: Multidrug-Resistant (MDR) bacteria; Intensive Care Unit (ICU) admission;

SOFA (Sequential Organ Failure Assessment) score at ICU admission; the presence of organic failure, and clinical outcome at 48 hours, at 30 and 60 days.

Fever was defined as a single oral temperature of 38.3 °C measured from the oral or axillary route or a body temperature of > 38 °C persisting for one hour [5].

Severe neutropenia was defined as an absolute neutrophil count of ≤ 500 /mm^3.

Prolonged neutropenia was defined as a duration of neutropenia ≥ 7 days.

Fever without demonstrable microbiological, clinical, or laboratory evidence of infection was defined as Fever with No Source Documented (FNSD).

Chemotherapy schemes were classified as high, intermediate, or low-level according to the risk of developing neutropenia in grade 3 or grade 4. High level included schemes with expected severe neutropenia of > 90%; intermediate: schemes between 30-90%; and low level: risk for severe neutropenia of < 30% [6-10].

Sepsis was defined as a life-threatening condition caused by a dysregulated host response to infection, resulting in organ dysfunction. SS was defined as persistent hemodynamic instability (systolic blood pressure < 90 mmHg or a reduction in systolic blood pressure > 40 mmHg from baseline), despite adequate fluid resuscitation (30 mL/kg of crystalloid) with at least two systemic inflammatory response-syndrome criteria [11].

The primary focus of infection was classified as one of the following: bloodstream infection [Mucosal Barrier Injury-Laboratory Confirmed (MBI-LCBI); secondary bacteremia or Central-Line Associated Bloodstream Infection (CLABSI)], pneumonia, urinary tract, neurologic, skin or soft tissue, gastrointestinal, perianal, upper respiratory, bone, arthritis, endocarditis, or other infections were documented. Microorganisms isolated or documented with stains, PCR, or surrogate tests were divided into Gram-negative, Gram-positive, fungal, viral, or parasitic. MDR bacteria included the following: Methicillin-Resistant *Staphylococcus aureus* (MRSA); Vancomycin-Resistant Enterococcus (VRE); Extended-Spectrum Beta-Lactamase (ESBL)-producing or Carbapenem-Resistant (CR). *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., and other Gram-negative bacteria

Table 1. Clinical characteristics related with the infectious process comparing patients with and without septic shock.

Characteristic	Total (*n* = 292), (%)	Septic shock (n = 68), (%)	Non-septic shock (n = 224), (%)	*p* value
Age (years)[a]	43 ± 30	41 ± 17	42 ± 18	0.877
Gender – Masculine	169 (57.9)	36 (52.9)	133 (59.45)	0.346
Hematologic malignancy				
Non-Hodgkin lymphoma	129 (44.2)	31 (45.6)	98 (43.8)	0.789
Acute lymphoblastic leukemia	68 (23.3)	11 (16.2)	57 (25.4)	0.113
Acute myeloid leukemia	62 (21.2)	17 (25)	45 (20.1)	0.358
MM/Plasmacytoma	18 (6.1)	6 (8.8)	12 (5.4)	0.385
Myelodisplastic syndrome	5 (1.7)	2 (2.9)	3 (1.3)	1
Hodgkin lymphoma	4 (1.4)	0	4 (1.8)	n/a
Other[b]	6 (2.4)	2 (2.9)	3 (1.3)	0.330
Stage				
Recent diagnosis	167 (57.2)	29 (42.6)	138 (61.6)	0.005
Progression	59 (20.2)	20 (29.4)	39 (17.4)	0.03
Relapse	58 (19.9)	18 (26.5)	40 (17.9)	0.118
Complete remission	8 (2.7)	1 (1.5)	7 (3.1)	0.686
Chemotherapy within last 30 days	265 (90.8)	61 (89.7)	204 (91.1)	0.811
Myelosupression related to CT				
Low	127 (47.9)	22 (32.4)	105 (46.9)	0.03
Medium	112 (42.3)	31 (45.6)	81 (36.2)	0.161
High	26 (9.8)	8 (11.8)	18 (8)	0.338
Days from CT to neutropenia[a]	10.1 ± 7.8	7.9 ± 6.4	10.7 ± 8.1	0.003
Days of neutropenia[c]	7 (4,15)	7 (5, 18)	7 (4, 14)	0.142
HSCT[d]	7 (2.4)	2 (2.9)	5 (2.2)	0.666
Hospital stay (days)[c]	8 (5,16)	9 (7,17)	8 (5, 16)	0.168
Previous episodes of neutropenia[c]	1 (0, 2)	1 (0, 3)	1 (0, 2)	0.876
Not recovered from neutropenia	54 (18.5)	23 (33.8)	31 (13.8)	< 0.001
ICU admission	29 (9.9)	28 (41.2)	1 (0.5)	< 0.001
ICU stay[c] **(days)**	2 (1-6)	3 (1-7)	2 (0-9)	0.714
Renal failure	36 (12.3)	27 (39.7)	9 (4)	< 0.001
Liver failure	14 (4.8)	7 (10.3)	7 (3.1)	0.02
Respiratory failure	26 (8.9)	21(30.9)	5 (2.2)	< 0.001
Hematologic failure	265 (90.8)	63 (92.6)	202 (90.2)	0.808
Vasopressor requirement	62 (21.2)	59 (86.8)	3 (1.3)	< 0.001

[a]Mean ± Standard Deviation (SD). [b]Other: Chronic myeloid leukemia; chronic lymphoid leukemia; chronic granulocytic leukemia, and hypereosinophilic syndrome. [c]Median (InterQuartile Range). [d]HSCT: Hematopoietic Stem Cell Transplantation; CT: Chemotherapy.

were considered MDR if they showed resistance to fluoroquinolones, cephalosporins, and carbapenems.

Statistical analysis

Descriptive analysis was performed for continuous and categorical variables. Continuous variables were analyzed using independent samples with the Student-t test or the Mann–Whitney *U* test samples for the corresponding parametric or non-parametric variables. The Chi-square test or the Fisher exact test was employed as appropriate for categorical variables. Variables with $p < 0.1$ were included in multivariate

Table 2. Clinical characteristics related to the infectious diseases process, microorganisms identified, and site of infection.

Characteristic	Total (*n* = 292), (%)	Septic shock (*n* = 68), (%)	Non-septic shock (*n* = 224), (%)	*p* value
Documented clinical infection	207 (70.9)	64 (94.1)	142 (63.4)	< 0.001
One site of infection	153 (52.4)	44 (64.7)	109 (48.7)	0.02
Two sites of infection	44 (15.1)	13 (19.1)	31 (13.8)	0.286
Three sites of infection	10 (3.4)	6 (8.8)	4 (1.8)	0.01
Site of clinical infection				
Lung	77 (26.4)	25 (36.8)	53 (23.2)	0.026
MBI-LCBI[a]	59 (20.2)	19 (27.9)	40 (17.9)	0.069
Gastrointestinal	38 (13)	15 (22)	23 (10.3)	0.01
Urinary	29 (9.9)	10 (14.7)	19 (8.5)	0.163
Skin and soft tissue	26 (8.9)	6 (8.8)	20 (8.9)	1
Secondary BSI[b]	13 (4.5)	8 (11.8)	5 (2.2)	0.002
CLABSI[c]	9 (3.1)	4 (5.9)	5 (2.2)	0.220
Other[d]	20 (6.8)	2 (2.9)	18 (8)	0.178
Microbiologically confirmed	133 (45.5)	47 (69.1)	86 (38.4)	< 0.001
Total number of isolates	154 (52.7)	58 (85.3)	96 (42.9)	< 0.001
One	115 (39.4)	39 (57.4)	76 (33.9)	0.001
Two	18 (6.2)	8 (11.8)	10 (4.5)	0.04
Three	1 (0.3)	1 (1.5)	0	n/a
Gram-negative bacteria	98 (33.6)	43 (63.2)	55 (24.6)	< 0.001
Escherichia coli[e]	70 (23.9)	32 (47.1)	38 (17)	< 0.001
Susceptible	45 (64.3)	26 (81.3)	19 (50)	0.01
ESBL[f]	22 (31.4)	5 (15.6)	17 (44.7)	0.001
CR[g]	3 (4.3)	1 (3.1)	2 (5.3)	1
Klebsiella spp.[e]	23 (7.8)	11 (16.2)	12 (5.4)	0.008
Susceptible	16 (69.6)	9 (81.8)	7 (58.3)	0.221
ESBL[f]	4 (17.4)	2 (18.2)	2 (16.7)	0.923
CR[g]	3 (13)	0	3 (25)	n/a
Pseudomonas aeruginosa[e]	9 (3.1)	4 (5.9)	5 (2.2)	0.219
Susceptible	9 (100)	4 (100)	4 (80)	n/a
CR[g]	0	0	1 (20)	n/a
Enterobacter spp.	2 (0.7)	0	2 (0.9)	n/a
Stenotrophomonas maltophilia	4 (1.4)	1 (1.5)	3 (1.3)	1
Serratia marcescens	2 (0.7)	1 (1.5)	1 (4.5)	0.412
Other Gram-negative	9 (3.1)	3 (4.4)	6 (2.7)	0.439
Gram-positive bacteria	30 (10.3)	9 (13.2)	21 (9.4)	0.365
CoNS[h]	11 (3.8)	2 (2.9)	9 (4)	1
MRSA[i]	4 (1.4)	0	4 (1.8)	n/a
Enterococcus faecium	6 (2.1)	3 (4.4)	3 (1.3)	0.141
E. faecalis	1 (0.3)	1 (1.5)	0	n/a
Streptococcus spp.	6 (2.1)	1 (1.5)	5 (2.2)	1
Clostridioides difficile	6 (2.1)	2 (2.9)	4 (1.8)	0.626
Fungi	9 (3.1)	5 (7.4)	4 (1.8)	0.034
Candida albicans	3 (1)	1 (1.5)	2 (0.9)	0.550
Candida spp.	2 (0.7)	1 (1.5)	1 (0.5)	0.412
Aspergillus spp.	3 (1)	0	3 (1.3)	n/a
Trichosporum spp.	1 (0.3)	0	1 (0.5)	n/a
Influenza	12 (4.1)	1 (1.5)	11 (4.9)	0.306
Herpes zoster	4 (1.4)	0	4 (1.8)	n/a
Mycobacterium tuberculosis	1 (0.3)	1 (1.5)	0	n/a
Multidrug resistant bacteria	31 (10.6)	11 (16.2)	20 (8.9)	0.174
FNSD[j]	89 (30.5)	4 (5.9)	85 (37.9)	< 0.001
Mortality at 48 hours	13 (4.4)	10 (14.7)	3 (1.3)	< 0.001
Mortality at 30-days	44 (15.1)	28 (41.1)	16 (7.1)	< 0.001
Mortality at 60-days	61 (20.9)	34 (50)	27 (12.1)	< 0.001

[a]MBI-LCBI: Mucosal-Barrier Injury-Laboratory Confirmed Bloodstream Infection. [b]BSI: Bloodstream Infection. [c]CLABSI: Central line-associated bloodstream infection. [d]Neurologic, upper respiratory tract infection, bone, cholangitis, abscess, perianal. [e]The percentages of susceptibility and resistance of each bacterium were obtained from the total of each one. [f]ESBL: Extended-Spectrum Beta-Lactamase. [g]CR: Carbapenem resistant. [h]CoNS: Coagulase-Negative Staphylococcus. [i]MRSA: Methicillin-Resistant *Staphylococcus aureus*. [j]FNSD: Fever with No Source Documented.

regression analyses. Odds Ratios (OR) with 95% Confidence Intervals (95% CI) were calculated. *p* values of ≤ 0.05 were considered statistically significant. Data was analyzed employing STATA (ver. 14) statistical software. This study was approved by the Institution's Ethics Committee (Rev/135/20).

Results

During the study period, 1248 patients with an HM disease were hospitalized. Two hundred ninety-two episodes of fever and severe neutropenia were documented; 68 patients (23.2%) developed SS during the neutropenic episode. Patients' mean age was 43 ± 30 years, and 169 (57.9%) were male. The most frequent malignancies associated with febrile neutropenia were non-Hodgkin lymphoma (*n* = 129; 44.2%), acute lymphoblastic leukemia (*n* = 68; 23.3%), and myeloblastic acute leukemia (*n* = 62; 21.2%). Progression or relapse occurred in 38 (55.9%) patients with SS, compared with 79 (35.3%) with non-SS (*p* = 0.02). Seven (2.4%) patients had HSCT; all were allogeneic. Two hundred sixty-five patients (90.8%) had received chemotherapy during the previous 30 days, with a mean time of 10.1 ± 7.8 days from chemotherapy to neutropenia development. The median duration of neutropenia was seven days (IQR 4-15 days). Prolonged neutropenia was more frequent in patients with SS (33.8%) than in non-SS (13.8%, *p* < 0.001)

Some fewer patients have received a low-risk myelosuppressive chemotherapy scheme in non-SS (46.9%) compared with SS (32.4%, *p* = 0.03). ICU admission, renal failure, and respiratory failure were more frequent in patients with SS than in non-SS. Other clinical data are presented in Table 1.

There were 207 (70.9%) clinical focus of infection documented; 54 (18.5%) patients had ≥ 2 infection sites. A documented clinical site was more frequent in patients with SS than in non-SS (94.1% vs. 63.4%, *p* < 0.001). Pneumonia was the most common infection site (n = 77, 26.4%), followed by MBI-LCBI (n = 59, 20.2%) and gastrointestinal (n = 38, 13%). Data are shown in Table 2.

The microbiological source was reported in 133 episodes (45.5%): 47 (69.1%) in the SS patients and 86 (38.4%) in the non-SS group (*p* < 0.001). Gram-negative bacteria were the most common pathogens identified in 98 isolates, more common in patients with SS vs. non-SS (63.2% vs. 24.6%, respectively, *p* < 0.001). *Escherichia coli* was the main microorganism isolated, also more frequent in SS vs. non-SS patients (47.1% vs. 17%, *p* < 0.001). Gram-positive bacteria comprised the second most frequent group identified (n = 30), without differences between both groups (13.2% vs. 9.4%, *p* = 0.365). MDR bacteria were documented in 36 cultures without differences in the groups. Fungi were identified in 9 patients (3.1%), being more frequent in SS (7.4%) vs. non-SS (1.8%, *p* = 0.03). In 89 (30.5%) patients, there were no clinical or microbiological foci identified; these were classified as FNSD (5.9% in SS and 37.9% in non-SS; *p* < 0.001) (Table 2).

As expected, mortality at 48 hours was higher in patients who developed SS (14.7%) compared with those who did not (1.3%; *p* < 0.001); this difference was maintained at 30 days (41.1% vs. 7.1%; *p* < 0.001); and at 60-days (50% vs. 12.1%, *p* < 0.001). Survival at 30 days is depicted in Figure 1.

In univariate analysis, the risk factors associated with developing SS were: intermediate/high-risk level

Table 3. Univariate and multivariate analysis for septic shock.

Characteristic	Univariate			Multivariate	
	Non-shock (*n* = 224), (%)	Septic shock (*n* = 68), (%)	*p* value	OR (95% CI)	*p*-value
Age < 60 years	180 (80.4)	55 (80.9)	0.923	-	-
Age ≥ 60 years	44 (19.6)	13 (19.1)	0.923	-	-
Low level chemotherapy[a]	105 (51.4)	22 (36.1)	0.034	1	0.017
Intermediate-high chemotherapy	99 (48.6)	39 (63.9)	0.034	3 (1.21 – 7.848)	0.017
Recent diagnosis, partial or complete remission	158 (70.5)	34 (50)	0.001	1	0.068
Progression or relapse	66 (29.5)	34 (50)	0.001	2.3 (0.9 – 5.5)	0.068
Severe neutropenia < 10 days	144 (64.3)	38 (55.9)	0.210	-	-
Severe neutropenia ≥ 10 days	80 (35.7)	30 (44.1)	0.210	-	-
0–2 previous febrile neutropenia episodes	166 (74.1)	40 (58.8)	0.015	1	0.441
> 2 previous febrile neutropenia episodes	58 (25.9)	28 (41.2)	0.015	1.43 (0.57 – 3.56)	0.441
Non-documented site of infection	82 (36.6)	4 (5.9)	< 0.001	1	0.001
Documented site of infection	142 (63.4)	64 (94.1)	< 0.001	7.04 (2.28 – 21.67)	0.001
Non-Gram-negative bacteria isolated[b]	31 (36.1)	5 (10.6)	0.001	1	0.01
Gram-negative isolated	55 (63.9)	42 (84.4)	0001	4.44 (1-37-14.35)	0.01
Non-bloodstream infection	176 (78.6)	40 (58.8)	0.001	1	0.058
Bloodstream infection	48 (21.4)	28 (41.2)	0.001	1.95 (0.97- 3.92)	0.058

[a]Analysis was performed in 265 patients who received chemotherapy (61 with septic shock and 204 without shock). [b]Analysis was performed in 133 patients with microbiology documented infection (47 with septic shock and 86 without shock).

chemotherapy, HM in progression or relapse, more than two previous febrile neutropenia episodes, documented infection, BSI, and Gram-negative bacteria isolated. The multivariate analysis associated intermediate/high-risk level chemotherapy and documented infection (Table 3).

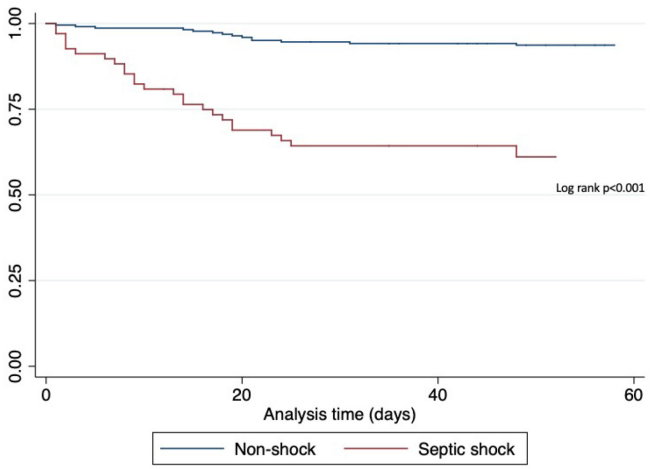
The risk factors for 30-day mortality found in the univariate analysis were HM in progression or relapse, infection site documented, and SS. In the multivariate analysis, only the presence of SS was associated (Table 4).

Discussion

In this study, we included all episodes of febrile neutropenia in patients with HM hospitalized for one year, analyzing clinical and infectious characteristics in those who developed SS compared with those who did not.

We documented SS in 23.3%, higher than reported by other authors (range, 3.2% - 13.4%) [12]. Nevertheless, in the study by Guarana and cols., the authors included up to 40% with Hodgkin lymphoma, multiple myeloma, and other diagnoses, who usually receive intermediate or low-level myelosuppressive chemotherapy schemes, and only 54% with acute leukemia and Non-Hodgkin Lymphoma (NHL), which are those with more intensive chemotherapies. Our study included 88% of patients with NHL or acute leukemias having received high or intermediate myelosuppressive chemotherapy schemes associated with SS.

Figure 1. Kaplan–Meier survival curve. Mortality at 30 days in patients with septic shock compared with non-shock.



Despite what has been reported in the literature that myeloid leukemia is more frequent than lymphoblastic leukemia, we attend, on average, twice of lymphoblastic leukemia cases at our center than acute myeloid leukemia. In 2022, we attended 53 lymphoblastic leukemia and 25 myeloid leukemia cases. However, the chemotherapy administered to the patients in our study was at high risk of immunosuppression in both leukemias (ALL 85.7% and AML 63%).

Clinical foci were documented in 70.7%, and microbiological foci in 45.5% of the events. These data are higher than those reported in other countries, where clinical documentation of the primary infection site has

Table 4. Univariate and multivariate analysis for mortality at 30-day.

Characteristic	Univariate			Multivariate	
	Alive (*n* = 248), (%)	Dead (*n* = 44), (%)	*p-value*	OR (95% CI)	*p*-value
Male	141 (56.9)	28 (63.6)	0.401	-	-
Female	107 (43.1)	16 (36.3)	0.401	-	-
Hematological malignancy non-acute leukemia	138 (55.6)	23 (52.3)	0.678	-	-
Acute leukemia	110 (44.4)	21 (47.7)	0.678	-	-
Recent diagnosis, partial or complete remission	169 (68.2)	23 (52.3)	0.04	1	0.361
Progression or relapse	79 (31.9)	21 (47.7)	0.04	1.4 (0.68-2.88)	0.361
Severe neutropenia < 10 days	158 (63.7)	24 (54.5)	0.247	-	-
Severe neutropenia ≥ 10 days	90 (36.3)	20 (45.5)	0.247	-	-
< 2 days of previous neutropenia	138 (55.6)	30 (68.2)	0.121	-	-
≥ 2 days of previous episodes	110 (44.4)	14 (31.8)	0.121	-	-
Non-septic shock	208 (83.9)	16 (36.4)	< 0.001	1	< 0.001
Septic shock	40 (16.1)	28 (63.6)	< 0.001	6.9 (3.27-14.4)	< 0.001
No infection site documented	82 (33.1)	4 (9.1)	0.001	2.58 (0.83-7.96)	0.098
Infection documented	166 (66.9)	40 (90.9)	0.001	2.58 (0.83-7.96)	0.098
Non-Bloodstream infection	185 (74.6)	31 (70.5)	0.563	-	-
Bloodstream infection	63 (25.4)	13 (29.5)	0.563	-	-
Non-Gram-negative bacteria isolated[a]	32 (29.9)	4 (15.4)	0.217	-	-
Gram-negative isolated	75 (70.1)	22 (84.6)	0.217	-	-
Non-MDR bacteria	68 (75.6)	16 (61.5)	0.216	-	-
MDR bacteria	22 (24.4)	10 (38.5)	0.216	-	-

[a]Analysis was performed from 133 patients with microbiology documented infection (107 alive and 26 dead). [b]MDR: Multidrug resistant bacteria, were calculated from 114 bacteria isolated (85 non-MDR and 31 MDR).

been reported in 56.5%, and microbiological diagnosis identified in 30% [3].

Gastrointestinal endogenous flora that contains Enterobacteriaceae can cause bacteremia in patients with neutropenia due to the injury of mucosal barriers secondary to chemotherapy, thus bacterial translocation [13]. Bacteremia can be documented in nearly 25% of febrile neutropenic episodes [2,14]. In this study, BSI was documented in 27.7%, with a higher frequency in patients with SS.

Our study's bacterial isolates pattern is similar to other countries, where Gram-negative bacteria are the most common [3]. We have previously reported that *E. coli* has been the most prevalent pathogen over the last decade [15-17]. In this study, *E. coli* was also the predominant pathogen (24%), followed by *Klebsiella* spp (8.2%) and *P. aeruginosa* (3.1%). Although BSI due to Gram-negative bacilli had been associated with three-fold higher mortality in patients with HM and bacteremia [2], we did not find an impact on 30-day mortality in patients with these pathogens.

The rate of Methicillin-resistant coagulase-negative Staphylococci (CoNS) reported in patients with cancer is over 50% in European centers, while *S. aureus* is far less common (5%) [22]. We documented CoNS in 8.3% and *S. aureus* in 4.5%.

MDR bacterial infections have been associated with an independent predictor of mortality [2,18,19]. Some reports have shown MDR bacteria in 23.5% of patients with SS and 34.6% of non-SS patients [20]. In another study of patients with neutropenia and septic shock, 12.9% had ESBL-bacteria [21]. We described MDR bacteria in 10.9% of the microbiologic isolates, being ESBL producers the primary pathogens (24.8%), without differences between SS and non-SS patients and an impact on mortality.

Fungi were documented in only 3.1% of the whole sample. This low prevalence is related to the difficulty in isolating these microorganisms; most fungal episodes are classified as possible or probable and were not included in this series unless confirmed by histopathology or culture.

Mortality rates in patients with neutropenia without SS have been reported as around 15%, while mortality rates among patients with febrile neutropenia and SS are between 25% to 43% [19,23-25]. In contrast, in some reports of patients with acute leukemia, mortality can reach between 60 and 68% [26]. In our study, 30-day mortality was 15.1% in the whole sample, with 7.1% for non-SS and 41.2% for patients with SS.

The risk factors found in this study for developing SS were having received intermediate or high myelosuppressive chemotherapy, a documented clinical or microbiological infection, and Gram-negative isolation. Other studies have reported these, particularly the presence of Gram-negative bacteria [19]. We found the only risk factor associated with 30-day mortality was septic shock. It differed from other studies, associated with older age, comorbidities, SS, severe prolonged neutropenia, bacteremia, isolation of resistant microorganisms, localized infection focus, and type of underlying malignancy [3,4].

Some limitations of this study include that it was retrospective and it was performed at a single institution. Although antimicrobial prophylaxis for neutropenic patients is not recommended at our center, some hematologists still use it, and it could impact antimicrobial resistance and clinical outcomes. However, we did not have access to this information on the electronic record, and we cannot describe this information. However, one of the main study strengths is that our hospital is one of Mexico's most critical oncological centers; therefore, these results could be extrapolated to those of similar hospitals in our country.

Conclusions

Mortality in patients with febrile neutropenia and SS was similar to those reported in other countries. Severe and prolonged neutropenia was the risk factor associated with SS development and mortality at 30 days. ICU management should be offered to all critically ill patients with HM if long-term survival may be compatible with the prognosis of the underlying malignancy.

Acknowledgements

Authors would like to thank the Infectious Diseases and Critical Care specialists' team that attended the patients during the study period.

Authors' contributions

Beda Islas-Muñoz performed the database and writing of the manuscript; Patricia Volkow-Fernández contributed to the analysis of the results; Jorge Silva-Zamora contributed to the review and writing of the discussion; Ana F. Ramírez-Ibarguen contributed to the review and writing of the discussion; Patricia Cornejo-Juárez performed the statistical analysis and writing of the manuscript.

References

1. Calik-S, Ari A, Bilgir O, Cetintepe T, Yis R, Sonmez U, Tosun S (2018) The relationship between mortality and microbiological parameters in febrile neutropenic patients with hematological malignancies. Saudi Med J 39: 878-885. doi: 10.15537/smj.2018.9.22824.

2. Thursky-KA, Worth-LJ (2015) Can mortality of cancer patients with fever and neutropenia be improved? Curr Opin Infect Dis 28: 505-513. doi: 10.1097/QCO.0000000000000202.
3. Ghosh I, Raina V, Kumar L, Sharma A, Bakhshi S, Thulkar S, Kapil A (2012) Profile of infections and outcome in high-risk febrile neutropenia: experience from a tertiary care cancer center in India. Med Oncol 29: 1354-1360. doi: 10.1007/s12032-011-9858-3.
4. Wang YG, Zhou JC, Wu KS (2018) High 28-day mortality in critically ill patients with sepsis and concomitant active cancer. J Int Med Res 46: 5030-5039. doi: 10.1177/0300060518789040.
5. Kochanek M, Schalk E, von Bergwelt-Baildon M, Beutel G, Buchheidt D, Hentrich M, Henze L, Kiehl M, Liebregts T, von Lilienfeld-Toal M, Classen A, Mellinghoff S, Penack O, Piepel C, Böll B (2019) Management of sepsis in neutropenic cancer patients: 2018 Guidelines from the Infectious Diseases Working Party (AGIHO) and Intensive Care Working Party (iCHOP) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol 98: 1051-1069. doi: 10.1007/s00277-019-03622-0.
6. Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, Green MR, Gottlieb A, Peterson BA (1992) Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327: 1478-1484. doi: 10.1056/NEJM199211193272102.
7. Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R (2003) Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 21: 16-19. doi: 10.1200/JCO.2003.03.139.
8. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, Kaiser U, Weidmann E, Dürk H, Ballo H, Stauch M, Roller F, Barth J, Hoelzer D, Hinke A, Brugger W; Study group indolent Lymphomas (StiL); Study group indolent Lymphomas (StiL) (2013) Bendamustine plus Rituximab versus CHOP plus Rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 381: 1203-1210. doi: 10.1016/S0140-6736(12)61763-2.
9. Mead GM, Sydes MR, Walewski J, Grigg A, Hatton CS, Pescosta N, Guarnaccia C, Lewis MS, McKendrick J, Stenning SP, Wright D, UKLG LY06 collaborators (2002) An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 13: 1264-1274. doi: 10.1093/annonc/mdf353.
10. Bartlett NL, Wilson WH, Jung SH, Hsi ED, Maurer MJ, Pederson LD, Polley MC, Pitcher BN, Cheson BD, Kahl BS, Friedberg JW, Staudt LM, Wagner-Johnston ND, Blum KA, Abramson JS, Reddy NM, Winter JN, Chang JE, Gopal AK, Chadburn A, Mathew S, Fisher RI, Richards KL, Schöder H, Zelenetz AD, Leonard JP (2019) Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. J Clin Oncol 37: 1790-1799. doi: 10.1200/JCO.18.01994.
11. Dugar S, Choudhary C, Duggal A (2020) Sepsis and septic shock: guideline-based management. Cleve Clin J Med 87: 53-64. doi: 10.3949/ccjm.87a.18143.
12. Guarana M, Nucci M, Nouér SA (2019) Shock and Early death in hematologic patients with febrile neutropenia. Antimicrob Agents Chemother 63: e01250-e012519. doi: 10.1128/AAC.01250-19.
13. van Vliet MJ, Harmsen HJ, de Bont ES, Tissing WJ (2010) The role of intestinal microbiota in the development and severity of chemotherapy-induced mucositis. PLoS Pathog 6: 5 e1000879. doi: 10.1371/journal.ppat.1000879.
14. Marín M, Gudiol C, Ardanuy C, García-Vidal C, Calvo M, Arnan M, Carratalà J (2014) Bloodstream infections in neutropenic patients with cancer: differences between patients with haematological malignancies and solid tumours. J Infect 69: 417-423. doi: 10.1016/j.jinf.2014.05.018.
15. Islas-Muñoz B, Volkow-Fernández P, Ibañez-Gutiérrez C, Villamar-Ramírez A, Vilar-Compte D, Cornejo-Juárez P (2018) Bloodstream infections in cancer patients. Risk factors associated with mortality. Int J Infect Dis 71: 59-64. doi: 10.1016/j.ijid.2018.03.022.
16. Hernáiz-Leonardo JC, Golzarri MF, Cornejo-Juárez P, Volkow P, Velázquez C, Ostrosky-Frid M, Vilar-Compte D (2017) Microbiology of surgical site infections in patients with cancer: a 7-year review. Am J Infect Control 45: 761-766. doi: 10.1016/j.ajic.2017.02.023.
17. Cornejo-Juárez P, Vilar-Compte D, García-Horton A, López-Velázquez M, Ñamendys-Silva S, Volkow-Fernández P (2016) Hospital-acquired infections at an oncological intensive care cancer unit: differences between solid and hematological cancer patients. BMC Infect Dis 16: 274. doi: 10.1186/s12879-016-1592-1.
18. Micozzi A, Gentile G, Minotti C, Cartoni C, Capria S, Ballarò D, Santilli S, Pacetti E, Grammatico S, Bucaneve G, Foà R (2017) Carbapenem-resistant Klebsiella pneumoniae in high-risk haematological patients: factors favouring spread, risk factors and outcome of carbapenem-resistant Klebsiella pneumoniae bacteremias. BMC Infect Dis: 17: 203. doi: 10.1186/s12879-017-2297-9.
19. Tumbarello M, Micozzi A, De Rosa FG (2015) Multidrug-resistant bacteria and bloodstream infections in onco-hematological patients. J Chemother 27: 250-252. doi: 10.1179/1973947814Y.0000000216.
20. Rosa RG, Goldani LZ (2014) Aetiology of bacteraemia as a risk factor for septic shock at the onset of febrile neutropaenia in adult cancer patients. Biomed Res Int: 561020. doi: 10.1155/2014/561020.
21. Kim YJ, Jung SM, Kang J, Ryoo SM, Sohn CH, Seo DW, Lim KS, Huh JW, Kim SH, Kim WY (2019) Risk factors for extended-spectrum beta-lactamase-producing Enterobacteriaceae infection causing septic shock in cancer patients with chemotherapy-induced febrile neutropenia. Intern Emerg Med 14: 433-440. doi: 10.1007/s11739-018-02015-x.
22. Gustinetti G, Mikulska M (2016) Bloodstream infections in neutropenic cancer patients: a practical update. Virulence 7: 280-297. doi: 10.1080/21505594.2016.1156821.
23. Legrand M, Max A, Peigne V, Mariotte E, Canet E, Debrumetz A, Lemiale V, Seguin A, Darmon M, Schlemmer B, Azoulay E (2012) Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 40: 43-9. doi: 10.1097/CCM.0b013e31822b50c2.
24. Bow EJ (2013) Infection in neutropenic patients with cancer. Crit Care Clin 29: 411-441. doi: 10.1016/j.ccc.2013.03.002.
25. Vincent JL, Jones G, David S, Olariu E, Cadwell KK(2019) Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Crit Care 23: 196. doi: 10.1186/s13054-019-2478-6.

26. Park HY, Suh GY, Jeon K, Koh WJ, Chung MP, Kim H, Kwon OJ, Kim K, Jang JH, Jung CW, Kang E, Kim MJ (2008) Outcome and prognostic factors of patients with acute leukemia admitted to the intensive care unit for septic shock. Leuk Lymphoma 49: 1929-1934. doi: 10.1080/10428190802353609.

Corresponding author
Dr. Patricia Cornejo-Juarez
Instituto Nacional de Cancerología (INCan),
Av. San Fernando No. 22, Col. Sección XVI,
Alcaldía Tlalpan, 14000
Ciudad de México (CDMX)
México. City, Mexico.
Tel: (+52) 555628-0447, ext. 12110
Email: patcornejo@yahoo.com

Conflict of interests: No conflict of interests is declared.