Microbiological diagnosis in febrile neutropenia secondary to chemotherapy for hematologic malignancy

A cohort description

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Abstract

Objective: to describe the demographic, clinical, therapeutic and microbiological characteristics of patients with hematological malignancies undergoing chemotherapy who develop febrile neutropenia during treatment, as well as the mortality at discharge.

Methods: a retrospective cohort study of patients with hematologic neoplasms who developed febrile neutropenia and were seen at the Hospital Universitario San Vicente Fundación in Medellín.

Results: records of 110 episodes of febrile neutropenia were obtained. The mean age was 45 years. In 55.4%, a microbiological diagnosis was obtained; bacteremia was documented in 83.8% of these. The most common microorganisms were *K. pneumoniae* (30%) and *E. coli* (18%). Antibiotic resistance due to ESBLs or carbapenemases in *gram negative* bacilli was 33%. Death occurred in 17% of patients. Acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) were the most prevalent underlying diagnoses; the most prevalent clinical focus was bacteremia (24.5%).

Conclusion: in our case series, there are significant differences in the percentage of patients with bacteremia, as well as in global mortality, compared to the rest of the cohorts in the region. A new research study needs to be carried out to clarify the source of these differences. **(Acta Med Colomb 2020; 45. DOI: https://doi.org/10.36104/amc.2020.1386).**

Key words: *neutropenia, chemotherapy, microbiology.*

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Introduction

We are living in a time of remarkable progress in the treatment of cancer, and treatment advances have increased the survival rate. This progress is due essentially to the multimodal treatment approach, based on surgical management, radiation therapy, chemotherapy and the advent of targeted molecular therapy (1). Despite this, chemotherapy with cytotoxic agents continues to be the first line of treatment for blood cancers today (2). Of the various types of toxicity associated with its use, the most significant in terms of clinical repercussions and high prevalence are bone marrow and gastrointestinal toxicities (3-5). The combination of these two adverse effects significantly increases the risk of infection in those undergoing cytotoxic treatment, and thus mortality in this group.

Febrile neutropenia was first described in 1966; when this syndrome began, mortality reached up to 80% (6). Observational studies identified several important characteristics, namely that the main pathogens were gram negative, essentially *P. aeruginosa* (7). Towards 1980, with systemic prophylaxis along with the use of central venous catheters, the antimicrobial spectrum changed to a predominance of gram-positive microorganisms. It was also determined that blood cancers had a greater risk of presenting this complication (10-50% in patients with solid tumors versus 80% in hematology-oncology patients) (8). Finally, it was determined that rapid initiation of empirical antibiotic treatment (considering febrile neutropenia to be an infectious complication in 100% of cases) led to a reduction in mortality to values as low as 2.8% today (9). However, information regarding the epidemiology of bacterial infections is not static, nor can it be generalized to the whole world. Therefore, each region must periodically identify its own flora in order to implement the most rational diagnostic and therapeutic approach possible.

In Colombia, the most recent studies are from six years ago; their significant findings include microbiological identification in 35-45%, with a prevalence of *gram-negative* microorganisms (10,11). Keeping this aspect in mind, the present retrospective cohort was proposed with the main objective of determining the microbiological characteristics

of febrile neutropenia episodes in hospitalized patients with this diagnosis in an institution in the city of Medellín.

Materials and methods

An observational, descriptive, retrospective cohort study was performed on adult patients over the age of 18 with hematologic malignancies coded at discharge with ICD-10: C810-C960 codes (pertaining to malignant tumors of lymphatic tissue, hematopoietic organs and associated tissues), who received hospital treatment at the Hospital San Vicente Fundación in the city of Medellín between January 2013 and December 2016. Of these, the episodes (each hospitalization was considered to be a separate episode, regardless of whether the patient had already been included in the study due to a prior hospitalization) in which patients developed febrile neutropenia after chemotherapy were selected. Data was collected from the electronic medical records. The researchers did not participate in the care of these patients.

Population

The selected population had to have a histopathological diagnosis of hematologic malignancy and be undergoing chemotherapy. Febrile neutropenia cases were identified according to the fever and neutropenia definitions of the Infectious Diseases Society of America (IDSA) (12).

Fever: defined as any measurement ≥38.3°C or ≥38.0°C for at least one hour.

Neutropenia*:* a directly measured absolute polymorphonuclear neutrophil count <500 cells/mL.

Patients whose medical record underreported clinical, microbiological and therapeutic variables, and those with known concomitant immunosuppression (HIV infection, known pulmonary or extrapulmonary tuberculosis, genetic diseases, poorly controlled diabetes mellitus, end-stage renal disease defined as a glomerular filtration rate lower than 15 (GFR <15) or on renal replacement therapy) were excluded.

The following definitions were used for infectious entities:

Bacteremia: bloodstream invasion proven by positive blood cultures. Divided into primary (if the only clinical and isolation site was the bloodstream) and secondary (if the initial infection was in another organ) (13).

Pneumonia: considered as such if radiological criteria for pneumonia were present, with or without symptoms (14).

Urinary infection: defined by a positive urine culture together with symptoms of upper or lower urinary tract infection (15).

Neutropenic colitis: defined as such based on the clinical evaluator´s concept or on radiological criteria, when available. (16, 17).

Cellulitis: this site was assumed if the physical exam described an erythematous, warm and painful area not explained by a noninfectious etiology (18).

Musculoskeletal infections: determined by radiological criteria or if the patient was taken to surgery and the surgical description recorded signs of inflammation and/or purulent secretion from muscles, tendons, joints or bones.

Data collection

Medical records contained in the database of the Hospital San Vicente Fundación servers (SAP® system) were reviewed by the researchers to collect data on the patients´ demographic, clinical, microbiological and therapeutic variables including age, sex (male or female), hematological diagnosis (according to the hematological malignancies classification published by the World Health Organization [WHO] in 2016), chemotherapy regimen, days elapsed since the last chemotherapy session at the onset of the febrile neutropenia episode, and condition at discharge (alive or dead). The following microbiological variables were considered: microorganism isolated (if there was an isolate), isolation site (by systems) and isolation method (cultures, molecular, antigens). In cases with more than one identified microorganism, all of them were recorded and they were considered to be polymicrobial infections. If the isolate was *S. aureus, methicillin resistance was recorded. Likewise,* vancomycin resistance was recorded *for Enterococcus spp,* along with the presence of broad spectrum betalactamases or carbapenemase for gram-negative bacilli.

The above data, including crude death rate at discharge, obtained in this study were verified by two researchers who independently evaluated the medical records.

Regarding bias control for the type of study, we recognize a possible information bias as it is likely that there was a more exhaustive search for the causal agent in the more seriously ill patients. There were no losses to follow up since outcomes were assessed up to discharge.

Statistical analysis

The quantitative variables will be expressed as mean and interquartile range (IQR). The qualitative variables will be presented as absolute frequencies and percentages. The data were collected on an Excel® 2010 program. The research protocol was approved by the Ethics Committee of the Hospital Universitario San Vicente Fundación.

Results

The identification numbers of 1,250 potentially eligible episodes were obtained and 1,140 were excluded, mainly due to a lack of neutropenia (n=496) or febrile neutropenia (n=315) (Figure 1).

Of the 110 episodes included, 50.9% (n=55) of the patients were male, with a mean age of 45 years, IQR 33 (Q1 26-Q3 55). The main hematological diagnoses were acute lymphocytic leukemia (n=29, 26.3%), acute myeloid leukemia (n=29, 26.3%) and lymphomas (n=27, 24.5%) (Table 1). The main chemotherapy regimens received

were, in order from greater to lower frequency, CALBG (cyclophosphamide, daunorubicin, vincristine, prednisolone, pegaspargase) (n=19, 17.27%), 7 + 3 regimen (cytarabine, idarubicin) (n=11, 10%) and R-CHOP (prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) (n=10, 9.09%) (Table 2). An average number of days elapsed from the last chemotherapy session to a neutropenia diagnosis was established at nine (range 3-33 days), differentiated according to the main malignancy groups: acute myeloid leukemia: nine days: acute lymphocytic leukemia: nine days; lymphomas: nine days, and plasma cell neoplasms: 10 days. The crude inpatient mortality was 17% (n=19). With regard to clinical diagnoses, 25.8% (n=28) had no suspected site, 24.5% (n=27) had primary bacteremia and 19% (n=21) had pneumonia (Table 3).

A microbiological diagnosis was achieved in 55.4% (n=61) of the episodes, blood being the most frequent isolation source, with positive blood cultures in 83% (n=51). Of these bacteremias, 53% were primary (n=27) and 47% (n=24) were secondary (Table 4). The remaining microbiological isolation sites were the genitourinary system in 11% (n=7), abdominal cavity and gastrointestinal tract in 8.1% (n=5) (two intra-abdominal abscesses with a sample obtained by percutaneous aspiration, and three isolates from fecal matter), and skin and soft tissues and respiratory tract, with one patient each (fungal infections in both cases).

The main microorganisms were *K. pneumoniae* in 30% of isolates (n=20) (19 bacteremias and one urinary tract infection), *E. coli* in 18.4% of isolates (n=12) (eight bacteremias, two gastrointestinal tract isolates from intra-abdominal abscess aspiration, and two urinary tract infections), and *S. aureus* with bacteremia in eight of the isolates (12%).

There were documented fungal isolates in four episodes. Invasive candidiasis was diagnosed in three; two had evidence of *Candida tropicalis* fungemia and the third had evidence of hepatosplenic candidiasis with microbiological isolation from the culture of deep cutaneous mycosis obtained by biopsy. There was only one definitive diagnosis of invasive aspergillosis, isolated from the culture of a nasal septum biopsy (considered to be a respiratory tract isolate) (Figure 2). Seven probable episodes of invasive pulmonary aspergillosis were documented, detected by antigenemia for aspergillus and a compatible tomography.

The percentage of polymicrobial infection was 12% (n=11); 100% were isolated from blood and had at least one gram-negative bacillus, with *K. pneumoniae* predominating in 81.8% of the cases (n=9). In 54% of these episodes (n=6), probable invasive pulmonary aspergillosis was diagnosed (all of these had *K. pneumoniae* as a concomitant agent; one had an ESBL pattern, one had carbapenemase production and the rest were wild).

With regard to the resistance pattern (Table 5), 23.8% of the gram-negative bacilli had ESBL (n=10), of which 60% (n=6) had received antibiotics within the previous 30 days (33.3% had received quinolones and 66.6% beta-lactams). In addition, 9.5% (n=4) of the isolates with gram-negative

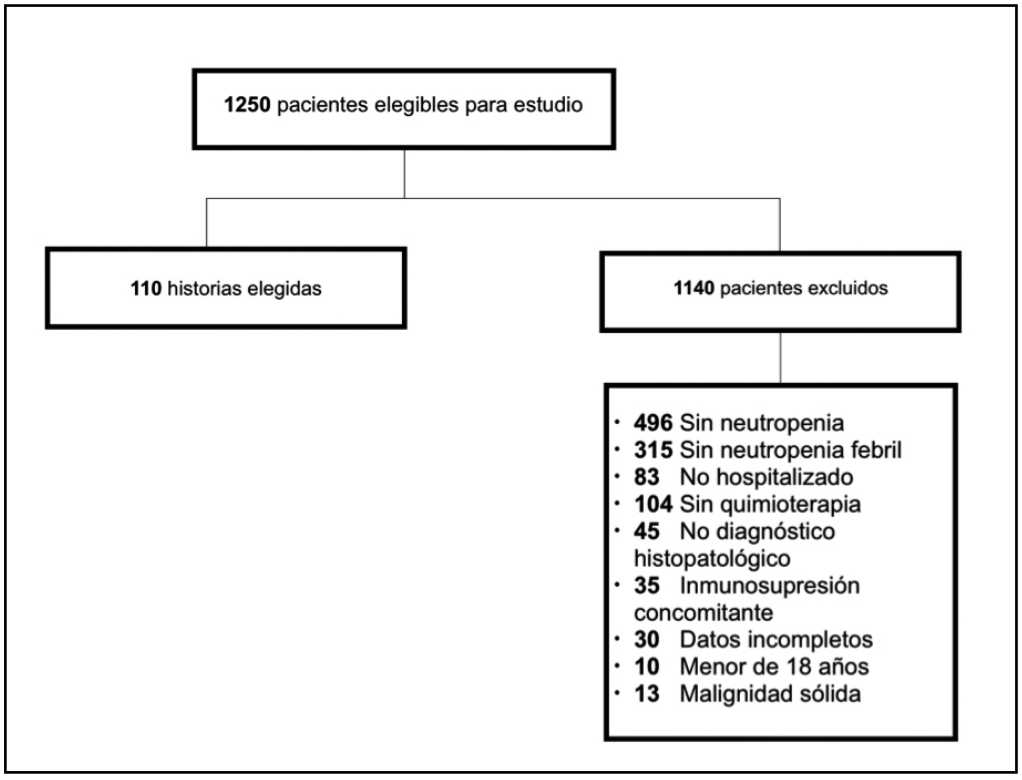

Figure 1. *Flow chart showing the inclusion and exclusion of study participants.*

bacilli had carbapenemase production. Of these, 100% (n=4) had been exposed to antibiotic treatment within the previous 30 days (100% carbapenems: 75% piperacillin/tazobactam and 25% quinolones).

In the cases in which *S. aureus* was isolated, 25% were methicillin resistant. None of these patients had had prior exposure to antibiotics (Table 6).

None of the previously mentioned patients was on trimethoprim sulphamethoxazole, fluconazole or ciprofloxacin prophylaxis.

Discussion

This cohort of patients undergoing chemotherapy for blood cancer who developed febrile neutropenia requiring hospitalization was similar in size to others previously reported in Colombia and Latin America. The mean age at presentation was 45 years, and the male:female ratio was 1:1, in line with studies carried out in Colombia (11), Chile (19) and Cuba (20). With regard to the underlying cancer diagnosis, most of the regional cohorts were based on patients with both solid tumor and hematologic malignancies. In order to have a more homogenous population, this study was based solely on a population of hematologic cancer patients, as was the study carried out at Hospital Pablo Tobón Uribe in Medellín, Colombia (11). A comparison of these

Table 1. *Hematological diagnosis prior to the episode of febrile neutropenia in 110 episodes*..

Hematological diagnosis	Number of cases (n)	Percentage (%)
Acute B cell lymphoblastic leukemia	29	26.36
Acute myeloid leukemia	29	26.36
Acute promyelocytic leukemia	8	7.27
Diffuse large B cell lymphoma	8	7.27
Multiple myeloma	6	5.45
Chronic lymphocytic leukemia	4	3.64
Follicular lymphoma	4	3.64
Classical Hodgkin lymphoma	4	3.64
T-cell acute lymphocytic leukemia	3	2.73
Burkitt lymphoma	3	2.73
T-cell lymphoma	3	2.73
Chronic myeloid leukemia	2	1.82
Grey zone B lymphoma	2	1.82
Mantle cell lymphoma	1	0.91
T-cell lymphoma	1	0.91
Mixed cellularity Hodgkin lymphoma	1	0.91
Cd4c plasmacytoid dendritic cell neoplasm	1	0.91
Hairy cell leukemia	1	0.91

Table 2. *Chemotherapy regimen administered prior to the febrile neutropenia episode*.

Chemotherapy Regimen *	Number of cases (n)	Percentage (%)
CALGB	19	17.27
7+3	11	10
R-CHOP	10	9.09
HYPERCVAD	8	7.27
GRAALL 2003	7	6.36
ABVD	2	1.82
HIDAC	2	1.82
R-EPOCH	2	1.82
FLAG.IDA	1	0.91
ICE	1	0.91
R-BENDAMUSTINE	1	0.91
FRALLE	0	0
PETHEMA	0	0
CODOX M	0	0
OTHERS	46	41.82

*CALGB (daunorubicin, vincristine, prednisolone, pegaspargase, cyclophosphamide); 7+3 (cytarabine, idarubicin); R-CHOP (prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab); HYPERCVAD (cycle A: cyclophosphamide, vincristine, doxorubicin, dexamethasone cycle B: methotrexate + cytarabine); GRAALL 2003 (prephase prednisolone, methotrexate; vincristine, prednisolone, daunorubicin, asparaginase, cyclophosphamide); ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); HIDAC (high dose cytarabine); R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin); FLAG.IDA (fludarabine, cytarabine, G-CSF, idarubicin); ICE (ifosfamide, carboplatin, etoposide); R-BENDAMUSTINE (bendamustine-rituximab); FRALLE (prednisone, vincristine, daunorubicin, asparaginase); PETHEMA (idarubicin, all-trans retinoic acid); CODOX-M (cyclophosphamide, vincristine, doxorubicin, high dose methotrexate).

Table 3. *Clinical diagnosis at febrile neutropenia diagnosis*.

Clinical diagnosis	Number of cases (n)	Percentage (%)
Primary bacteremia	27	24.5
Pneumonia	21	19
Neutropenic colitis	17	15.4
Cellulitis	9	8.1
Urinary tract infection	6	5.4
Musculoskeletal system	2	1.8
Without clinical diagnosis or isolate	28	25.8

Table 4. ***Clinical site in secondary bacteremias***.

Clinical diagnosis	Number of cases (n)	Percentage (%)
Neutropenic colitis	10	41
Pneumonia	6	25
Cellulitis	4	16
Urinary tract infection	3	12.5
Musculoskeletal	1	4.1

two studies showed differences in the underlying cancer conditions of these cohorts; the main cancer diagnosis in the other study was acute myeloid leukemia, while in our study there was an equal prevalence of acute lymphocytic leukemia and acute myeloid leukemia (each with 26.3%), with promyelocytic leukemia and diffuse B cell lymphoma in third and fourth place, respectively (7.2% in each case). The most frequent chemotherapy in the other study was HiDAC, followed by Hyper-CVAD; in our study it was CALGB (17.2%) followed by 7+3 (10%). While these differences represent different risks for febrile neutropenia, since both studies only included patients who already had it, we do not feel that the differences affect the results. With regard to the clinical diagnoses in these patients, most patients in our cohort did not have a suspected clinical site of infection, as was true for the Hospital Pablo Tobón cohort, although in different proportions (25.4 vs. 63.5%). A relevant fact is that the mortality in our study was 17%, a seven percentage point difference from most cohorts in this region (11, 19, 20), indicating the need to explore other conditions to clarify the source of this difference.

The microbiological findings showed that in 55.4% of the febrile neutropenia episodes which occurred between January 2013 and December 2016, a microbiological agent responsible for this clinical picture was isolated; regionally, microbiological diagnoses range from 41 to 66% of cases (21). The two clinical foci with the greatest contribution to microbiological isolation were urinary tract infection (11%) and bacteremias (83%), which differs significantly from most local, regional and global studies where bacteremia only contributes 20-30% of the findings (12). The sites presumed to be the source of the infection leading to bacteremia are the gastrointestinal tract, respiratory tract, genitourinary tract and skin (10), which coincides with our findings.

With regard to the microbiological agents, it is relevant to point out that, until 1980, most isolates in these patients were *gram negative* (with *P. aeuruginosa being especially relevant). After that date, the microbiological profile turned towards gram positive organisms (especially coagulase negative organisms), which is probably explained by the use of central venous catheters and antibiotics with a gram-negative focus. Since the beginning of the current century, a microbiological change has once again occurred, which is reflected in the other national cohorts, with a predominance of gram-negative bacilli (10, 11). Thus, the agents with the greatest number of isolates in these cohorts were E.coli and K. pneumoniae. In our study, the germ distribution between gram-negative bacteria, gram-positive bacteria and fungi was* 68.8, 21.3 and 8.1%, respectively. The microorganism with the largest number of isolates was *K. pneumoniae. The presence of coinfection with gram-negative bacilli and fungi is striking, specifically Aspergillus* with *K. pneumoniae;* although it is a small sample, this finding is not negligible.

Regarding antibiotic resistance, the prevalence of extended spectrum betalactamase in regional studies ranges from 7 to 26% (10, 11); in our hospital, it was 23%. In these

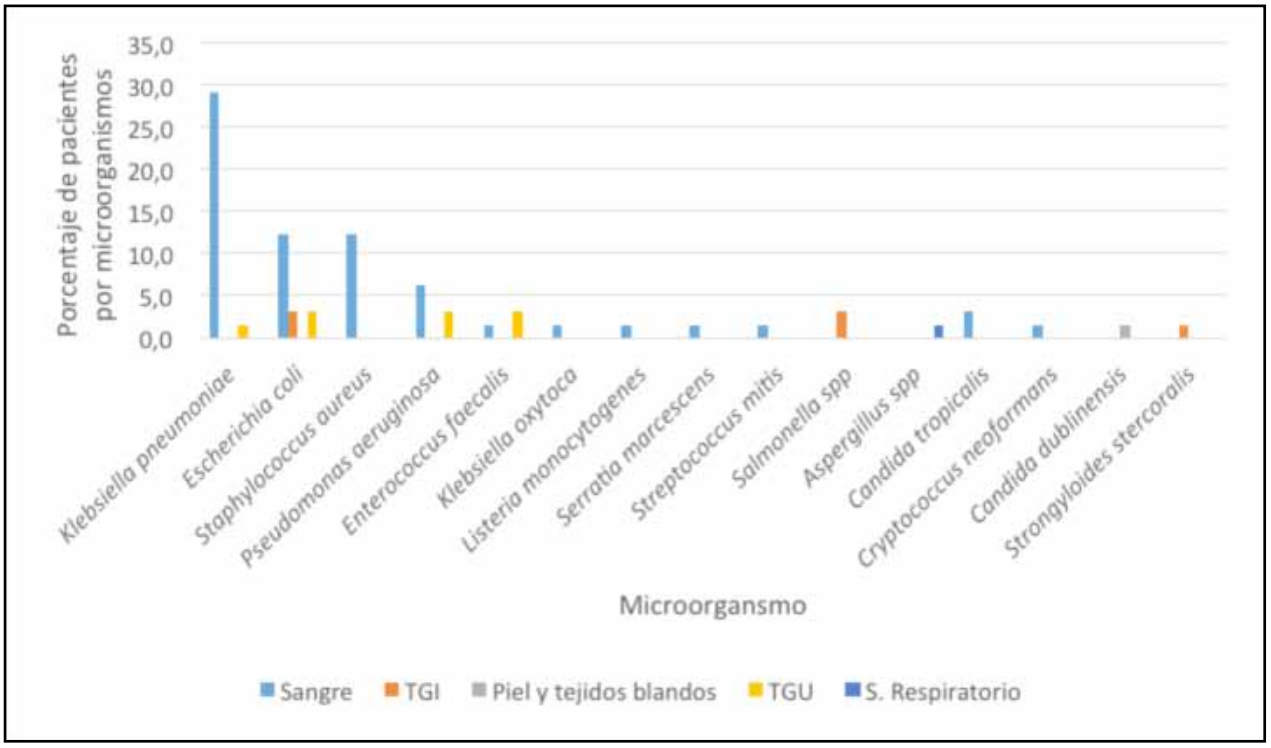

Figure 2. Microbiological identification and isolation sites in patients with febrile neutropenia. (GIT: gastrointestinal tract; GUT: genitourinary tract).

Table 5. *Antimicrobial resistance profiles in gram-negative microorganisms.*

Microorganism (n)	Extended spectrum beta lactamases (n)	Carbapenemase (n)
E. coli (12)	2	0
K.oxytoca (1)	0	0
K. pneumoniae (20)	7	4
P. aeruginosa (6)	1	0
Salmonella spp (2)	0	0
S. marcescens (1)	0	0

Table 6. *Antimicrobial resistance profiles in gram-positive microorganisms..*

Microorganism (n)	Methicillin resistance	Vancomycin resistance
S. aureus (8)	2	0

same studies, *S. aureus* methicillin resistance was 25%, just as it was in our study.

One of the limitations of this study is its retrospective nature, with the information bias that this tends to entail. However, given that the findings which are markedly different from previous studies, specifically the number of patients with documented bacteremia, were obtained from objective records (that is, laboratory results) and that blood cultures are recommended by the febrile neutropenia treatment guidelines (12), we consider that this bias may not have influenced the results. We recognize that not having information regarding the duration of the neutropenia, and thus not being able to differentiate between the population with or without prolonged neutropenia, is a significant limitation for interpreting the number of non-pyogenic isolates. However, other published studies that do differentiate have similar proportions, which indicates that we are probably within the same range of patients with prolonged neutropenia (22). In addition, given the high percentage of patients with documented bacteremia, it would have been desirable to differentiate between primary versus catheter-related bacteremia, which would require maintaining the same operative system for sample processing. Likewise, given the high mortality, it would have been convenient to have recorded the risk of death when febrile neutropenia was diagnosed (for example, using the MASCC scale). However, since these patients were high risk by virtue of being hematologic patients requiring hospitalization, we did not consider this point during project inception.

With regard to its strengths, we highlight the sample size which was similar to most of the regionally published cohorts, as well as the source of the data being a quaternary level hospital where febrile neutropenia can be thoroughly studied and managed due to the availability of resources. In addition, homogenous data sources were used, and the also homogenous population characteristics (all having hematologic malignancies) with the majority of confounding factors excluded (for example, HIV diagnosis and uncontrolled diabetes mellitus) lead us to believe that the population´s susceptibility to infections and the isolated microorganisms are all closely related to the cancer process and chemotherapy administered.

We believe that this study contributes to knowledge of the microbiological aspects of patients with febrile neutropenia. In essence, we found very similar characteristics to those documented in the rest of the publications. However, the elevated prevalence of bacteremia and high mortality should be highlighted. We consider that these warrant a new study to determine the differences leading to these findings, probably through a comparative study of the demographic and clinical characteristics which have not been explored to date (for example, the presence of chills, among others). Given the study´s methods and the previously mentioned limitations, direct clinical recommendations cannot be given. Nonetheless, it does encourage new research areas which will permit a better approach to these patients (22).

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