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ORIGINAL ARTICLE

Nosocomial pneumonia in patients with haematological malignancies

Lucía Martínez-Hernández[1,2], Diana Vilar-Compte[1], Patricia Cornejo-Juárez[1] and Patricia Volkow-Fernández[1]*

[1]Department of Infectology, Instituto Nacional de Cancerología; [2]Infectology Department, Hospital Español de México (current assignment), Mexico City, Mexico

Abstract

Introduction: *Nosocomial pneumonia (NP) in patients with hematological malignancies (HM) has an attributable mortality over 90%. There are few studies that report the incidence of nosocomial infections in patients with HM.* **Objective:** *To describe the epidemiology and clinical course of NP in a cohort of patients with hematologic malignancies.* **Material and methods:** *Single-center study of patients with leukemia, lymphoma or multiple myeloma diagnosed with NP, hospitalized between January 2011 and December 2012.* **Results:** *One-hundred and five NP were recorded: 51 leukemias (48%) and 45 lymphomas (43%); 50 (48%) were in relapse or progression. Median days for NP development were 13 days (IQ 6-20). Sixty percent of the patients had severe neutropenia. The most frequent symptom was fever 73 (70%). CT scan showed infiltrates in 100% of cases; 45 (43%) with findings suggestive of invasive fungal infection. Seven (7%) had confirmed invasive fungal infection, possible 9 (9%) and 45 (43%) probable. There were 99 cultures taken, 30 blood cultures (67% were positive) and 31 sputum (71% positive). Sixty percent of Gramnegative bacteria were multi-drug resistant and 50% of the Grampositive,* E. coli*, 19 (30%) was the most frequent isolated,* Aspergillus *spp. was the third, but the one with the highest associated mortality. Attributable mortality for pneumonia was 50% and 73% in patients that required mechanical ventilation (p = 0.001).* **Conclusions:** *We observed a high mortality rate in patients with HM and NP. Standardized diagnostic routes are needed for patients with HM with suspicion of pneumonia. Novel diagnostic techniques to enhance Aspergillus and respiratory viruses diagnosis should be introduced in this setting.* (Gac Med Mex. 2016;152:418-24)

Corresponding author: *Lucia Martínez Hernández, luciamh82@gmail.com*

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Introduction

During the last decade there have been great advances in the treatment of patients with hematologic malignancies (HM), which has resulted in an increase in overall survival. However, highly myelotoxic chemotherapy schemes expose patients to prolonged periods of neutropenia and to the risk of developing serious infectious complications with an increase in morbidity and mortality, days of hospital-stay and medical care costs[1].

In 40 to 60% of patients with febrile neutropenia the lung is affected, and pneumonia is the first cause of death. In 90% of patients with HM who die, pneumonia

Correspondence:
*Lucía Martínez Hernández
Departamento de Infectología
Instituto Nacional de Cancerología (INCan)
San Fernando, 22
Col. Sección XVI, Del. Tlalpan
C.P. 14080, Ciudad de México, México
E-mail: luciamh82@gmail.com

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is diagnosed, with this being an autopsy finding in 50%.

Risk factors for nosocomial pneumonia (NP) in patients with HM are: immunocompromise type and duration, underlying disease, comorbidities, previous treatment schemes, previous antibiotic use (prophylactic or therapeutic), use of corticosteroids or antacids and mucositis, in addition to environmental exposure to different pathogens. Interior remodeling works in hospitals, air conditioning systems lack of maintenance and absence of HEPA filters increase the risk[3,4].

There are few studies reporting the incidence of nosocomial infections in patients with HM, and available information generally originates from studies in pediatric patients undergoing hematopoietic stem cells transplantation (HSCT) or nosocomial influenza outbreaks[5,6].

In Mexico, 10,400 HM new cases were diagnosed in 2002; 80% required highly ablative chemotherapy. There are no reports on NP epidemiology, microbiology, clinical course or associated mortality in adult patients with HM.

Mortality has been reduced for cancer patients in most oncology centers; however, the frequency of hospital-acquired infections has increased[7]. In the National Cancer Institute (INCan – *Instituto Nacional de Cancerología),* a 9.4-fold increase in the rate of NP incidence was observed in patients with HM between 2000 and 2011. The purpose of this study was to know the epidemiology, evolution and outcomes of NP in Mexico's INCan patients.

Material and methods

The INCan is a hospital in Mexico City for adult patients with cancer. It has 135 beds available, 34 for hemato-oncology patients, one bone marrow transplantation unit with 3 total-isolation and 2 partial-isolation beds.

Annually, 130 cases of acute leukemia, 36 chronic leukemias, 250 lymphomas and 60 myeloma multiple cases are admitted. The hemato-oncology ward has no air conditioning system.

Patients with HM hospitalized from January 2010 through December 2012, with NP diagnosis established by the INCan Nosocomial Infections Control and Surveillance Board, were included. NP was defined as a pulmonary infection occurring 48 hours after hospital admission, according to the criteria established by the Centers for Disease Control (CDC) of the USA[8,9]. Patients admitted to the Bone Marrow Transplantation Unit were not included.

Statistical analysis

Qualitative variables were described as number and proportion, continuous variables as mean ± standard deviation or median (interquartile range [IQR] 25 and 75%), according to their distribution. The incidence ratio was estimated by the number of NP cases per 100 hospital discharges from the hemato-oncology ward, and the incidence rate was calculated as the number of NP cases per 1,000 patient-days of hospitalization at risk.

A univariate analysis was carried out according to the type of variable, using Student's t-test or Wilcoxon test for quantitative variables, and the chi-square test or Fisher exact test for nominal variables. Risk variables association with death was quantified using the odds ratio (OR) and 95% confidence intervals (CI). Variables with a p-value ≤ 0.15 were introduced in a conditional logistic regression model. A p-value ≤ 0.15 was considered statistically significant. Stata v. 12.0 was used for statistical analysis.

Results

One-hundred and five NP episodes were identified, with an incidence ratio of 4.34 per 100 discharges in 2011 and 4.5 in 2012, and a NP incidence of 5.2 per 1,000 patient-years in 2011 and 4.5 in 2012. No seasonal variations were documented.

Fifty-five subjects (52.4%) were male, and mean age was 40 years ± 18.5. The most frequent comorbidity was diabetes mellitus (DM) in 11 patients (11%). Most common admission diagnosis was acute leukemia in 48 patients (46%); 53 (50%) had never received treatment at the moment of the hospitalization where they developed NP. The reasons for admission were: chemotherapy administration in 38 (37.2%) and febrile neutropenia in 15 (14%). Most frequently used chemotherapy regimens were: Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, mesna and methotrexate) in 20 (19%) and IDAFLAG (fludarabine, high-dose cytarabine, idarubicin and granulocyte colony-stimulating factor) in 19 (18%). Table 1 shows baseline characteristics of the population.

Mean hospital-stay days prior to NP diagnosis was 13 days (IQR: 6-20); 63 (60%) patients had serious neutropenia (< 500 cells/mm^3) and fever, with a median of 6 (IQR: 0-9.5) days of neutropenia prior to the development of NP.

Median days for the development of NP after the last day of chemotherapy administration was 12 days (IQR:

Table 1. Population general characteristics (n = 105)

Variable		n (%)
Age, years ± SD		40 ± 18.5
Sex	Males	52
Hematological diagnosis	Non-Hodgkin lymphoma	37
	Acute lymphocytic leukemia	25
	Acute myelocytic leukemia	21
	Myeloma multiple	8
	Hodgkin lymphoma	4
	Chronic granulocytic leukemia	1
Disease status	Newly diagnosed	50
	Disease recurrence	48
	Disease progression	9
	Recovery	6
Chemotherapy period	Remission induction	52
	Second-line	19
	No chemotherapy	11
	Maintenance	9
	Third-line or beyond	5
Reason for admission	Chemotherapy administration	37
	Fever and neutropenia	14
	Respiratory failure	12
	Hemorrhage	8
	Water-electrolyte imbalance	6
Comorbidities	None	63
	Type 2 diabetes mellitus	11
	Systemic arterial hypertension	6
	HIV	3
	Prior cancer	4

4-23). In the previous month, 56 patients (54%) had been hospitalized and 46 (85%) had received antibiotics during previous hospitalization.

Twelve patients (11.4%) had received antimicrobial prophylaxis: 6 with amoxicillin/clavulanate and 6 with ciprofloxacin; 17 patients (16.2%) received acyclovir and 29 (27.6%) fluconazole as prophylaxis.

Figure 1 shows the prevalence of signs and symptoms at the moment of the NP diagnosis, according to the presence or not of serious neutropenia. The most common symptom was fever in 73 (70%) patients, with no difference in patients with or without serious neutropenia (39 [37%] vs. 61 [58%], respectively, p = 0.15).

All patients were taken a chest X-ray: 48 (46%) had lobar consolidation, 28 (26%), interstitial infiltrate, 21 (19%), multiple-foci pneumonia, 10 (93.3%), pleural effusion and in 23 (21%) no abnormalities were observed. Ninety-nine patients (93.3%) had a CT-scan practiced, all with abnormal findings: 39 (37.1%) had lobar consolidation and 21 (20%), pulmonary nodules. In 45 subjects (43%), there were findings consistent with fungal infection, with bilateral nodules in 28 patients (62%) being the most common finding (Fig. 2).

Some type of culture was obtained from 65 (66%) patients (n = 99) at the moment NP was suspected. Figure 3 shows the number and type of microbiological studies practiced. Of 45 blood cultures, 30 (67%) developed some microorganism: 13 (44%), gram-positive cocci (GPC) and 17 (56%), gram-negative bacilli (GNB).

Of the blood-isolated GPCs, 6 (46%) were *Staphylococcus aureus,* out of which 50% were methicillin-resistant (MRSA); 7 (54%), *Enterococcus faecium,* with 30% being vancomycin-resistant (VRE). Among the GNB isolates, *Escherichia coli* was identified in 13 (76%), out of which 68% were extended-spectrum beta-lactamase (ESBL)-producing organisms; 2 (12%) *Pseudomonas aeruginosa,* both multi-drug resistant (MDR), with carbapenem resistance and sensitive only to colistin and tigecycline; and 2 (12%), *Klebsiella* spp, with 1 of them (50%) being ESBL-producer.

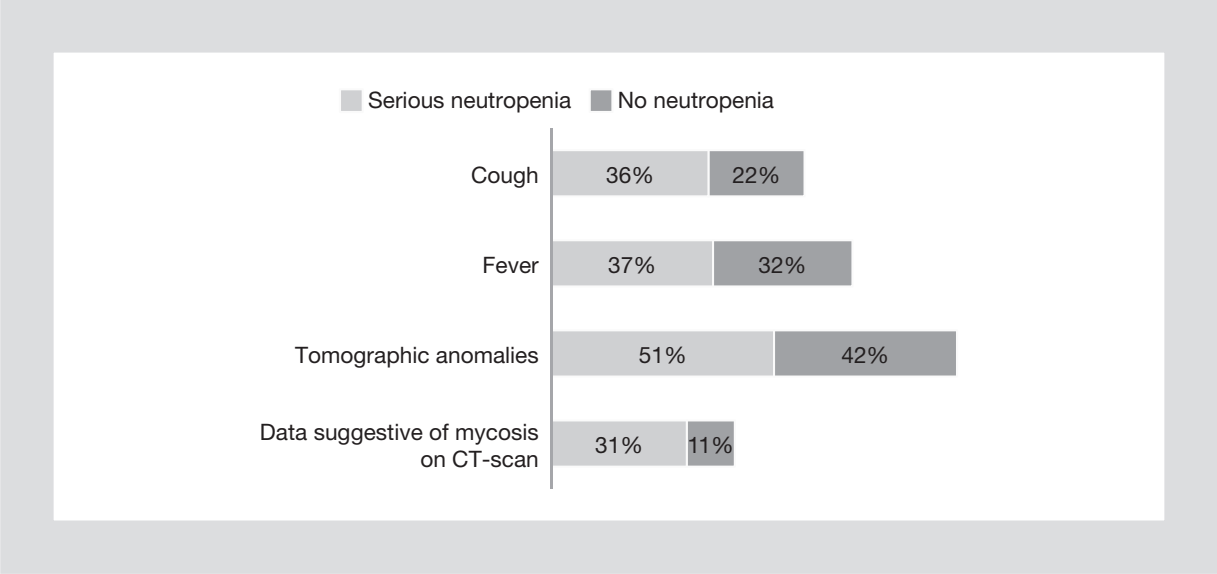

Figure 1. *Signs and symptoms at diagnosis, according to the presence of neutropenia (n = 105).*

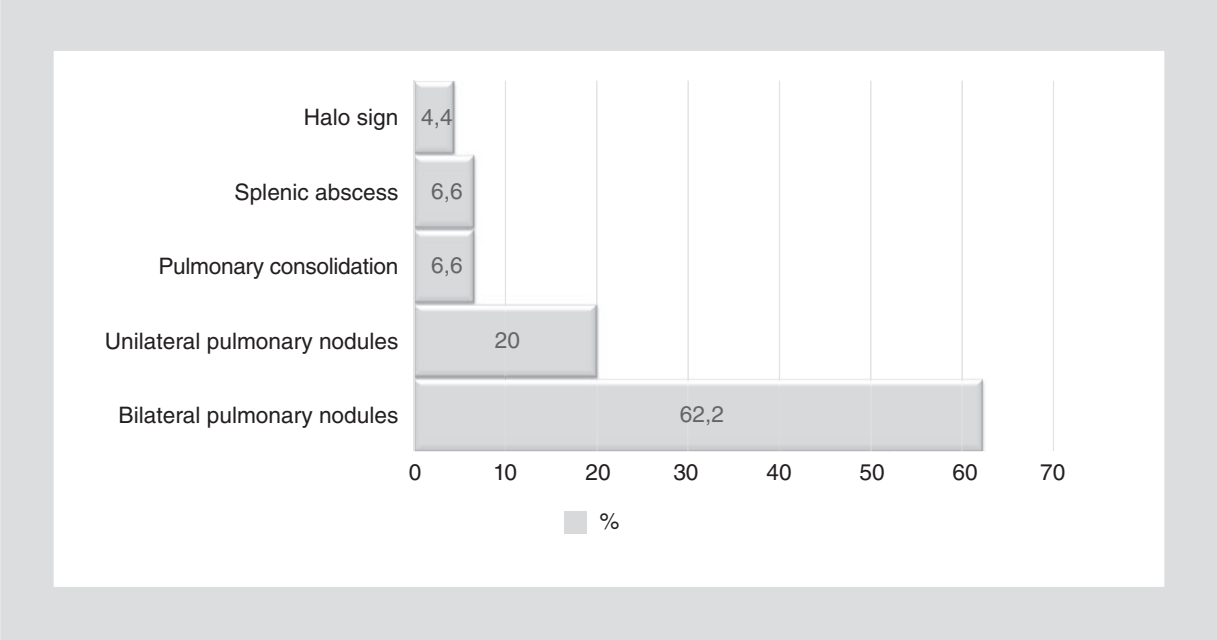

Figure 2. *Tomographic abnormalities suggestive of mycosis (n = 45).*

Fifty-one sputum cultures (48.6%) were performed: 37 (71%) developed some pathogen germ. Six GPCs (16%), all *Staphylococcus aureus* were MRSA. Twenty-four (64%) GNB isolates: 9 (37%) *Acinetobacter baumanii,* 68% of these MDR, only sensitive to colistin; 6 (25%) *Escherichia coli,* 33% ESBL-producer; 6 (25%) *Klebsiella pneumoniae,* 50% ESBL, and 4 (13%) *Pseudomonas aeruginosa,* with all of them being MDR. Seven *Aspergillus* spp (20%) were isolated.

Bronchoalveolar lavage (BAL) was carried out in 9 patients: 4 samples (55.5%) showed no growth, *S. aureus* was isolated in 2 (22%), *P. aeruginosa* in 2 (22%), and *E. fecalis* in 1 (11%).

Five pulmonary biopsies were performed: 3 (60%) had no growth; MRSA was identified in one (20%) and, in the other (20%), *S epidermidis.*

Antifungal treatment with amphotericin B deoxycholate was administered to 55 patients and, during their evolution, 39 (55.5%) received voriconazole. Of these, 45 (81%) had tomographic alterations suggestive of fungal infection. Fifteen serum galactomannan tests were performed; 9 (60%) had positive results (> 0.5 IU).

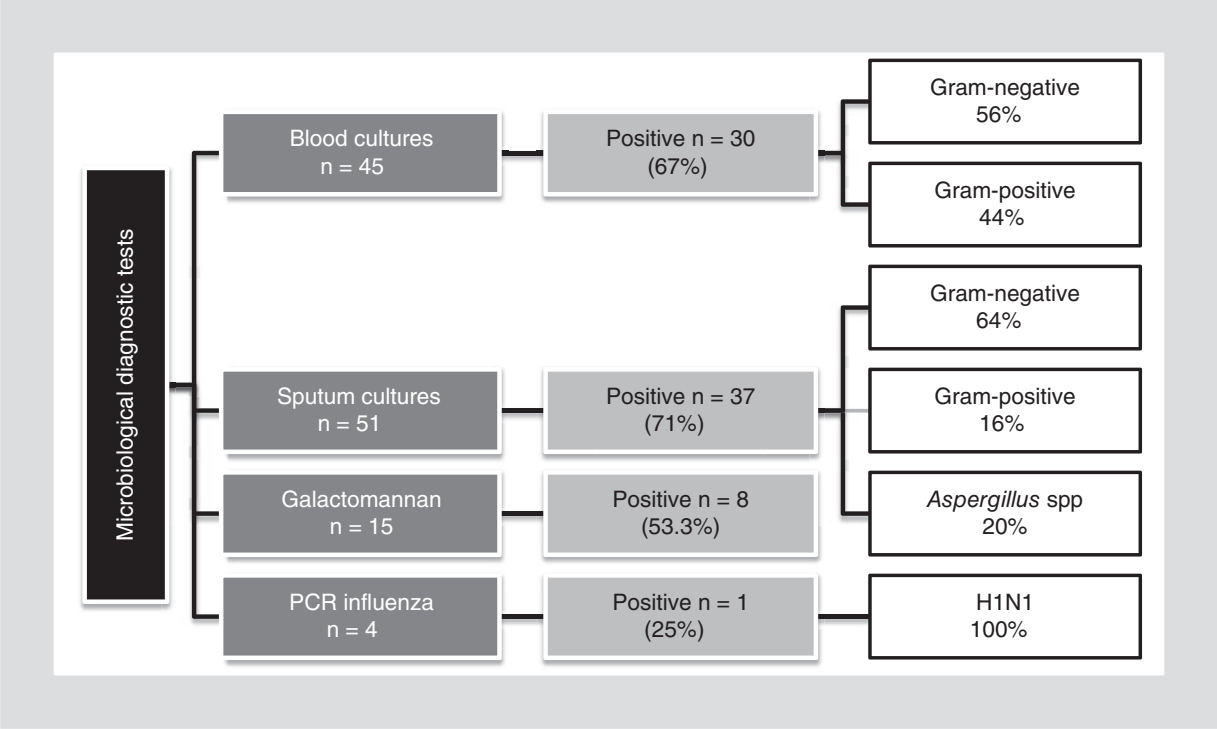

Figure 3. *Microbiological tests in 105 patients with hematological malignancies and nosocomial pneumonia.*

Five (60%) of the patients who had sputum-isolated *Aspergillus* spp had tomographic anomalies suggestive of mycosis. Six (80%) of the patients who had *Aspergillus* spp isolated had another microbiological isolate, which in all cases was a GNB.

Mean hospital-stay after NP was 20 days (± 19), for a total of 35 (± 23) days. Forty-two patients (40%) required mechanical ventilation (MV), 44 (42%) vasoactive amines and 31 (28.6%) had to be transferred to the intensive care unit (ICU); of the latter, 21 subjects (67%) died (p = 0.01), as well as 31 (73%) of those who required MV (p = 0.001) and 6 (80%) of those who had sputum-isolated *Aspergillus* spp (p = 0.05). Of the patients with endotracheal tube, 27 were transferred to the ICU (4 ± 8 days on average); mean intubation days was 4 (± 8), 38 subjects (90%) required vasosuppressant support and 31 patients (73%) died as a direct consequence of the infection, with an in-hospital-stay average of 36 (± 24) days.

There were a total of 53 (52%) deceases as a direct consequence of NP.

In the multivariate analysis, the following variables were found to be associated with mortality: MV (OR: 4.6; 95% CI: 1.2-16; p = 0.01), LDH higher than 250 IU at admission (OR: 3.3; 95% CI: 1.2-9.4; p = 0.01) and having received a second chemotherapy line (OR: 2.7; 95% CI: 1.0-7.2; p = 0.05).

Discussion

NP is a complication with high mortality in patients with HM, usually associated with serious neutropenia. The pathogenesis of this condition includes the contribution of chemotherapy-related damage to the lung[10-12]. There are few reports on the incidence, risk factors and outcomes in patients with NP and HM. There are no validated diagnostic or therapeutic algorithms, since pathogen flora epidemiology can vary from one country to another, by regions and by type of hospital[5]. This is why, although our study has many limitations, such as being retrospective, single-center and in a period of time when there was limited access to diagnostic methods with higher yield for fungal infections, such as serum galactomannan, it provides valuable information, since it is about national experience in a center with high concentration of patients with HMs.

NP incidence has been reported in studies to be 9.7 per 1,000 patient-days in rooms without positive-pressure equipment. In this study, the incidence was 5.2 and 4.5 per 1,000 patient days in 2011 and 2012, respectively[13]. In our setting, there are so far no positive-pressure rooms available.

Most patients had acute leukemia diagnoses; nearly half were receiving a second line of treatment and were admitted to the hospital for highly myelotoxic chemotherapy

administration (hyper-CVAD or IDAFLAG). Both schemes produce deep and prolonged neutropenia episodes (longer than 10 days).

One of the main problems in patients with HM and NP is the difficulty to identify causative agents, which may underestimate the incidence of certain pathogens as the cause of these infections, especially viruses[14].

The onset of pneumonia can be subtle, and patients often only exhibit neutropenia-associated fever without respiratory or systemic inflammatory response signs or symptoms. Signs observed on plain chest X-ray can range from overt focal consolidation to minimal anomalies, or even no changes may be observed, as it happened in 21% of patients in this series. Infiltrates can rapidly progress to diffuse or multifocal changes consistent with respiratory distress syndrome, hence the need to repeat the X-ray in unstable patients[15].

High-resolution CT of the lungs is a fundamental diagnostic tool in the immunosuppressed patient with suspected lower respiratory tract infection; it has a high negative-predictive value and enables identifying lesions susceptible to be biopsied; even by guided puncture[16].

In this study, CT was abnormal in all patients on whom it was practiced, and was the most commonly used tool to establish the presumptive diagnosis of invasive pulmonary aspergillosis (IPA). It has been described that, at early stages of the disease, CT is able to show pulmonary infiltrates in up to 50% of patients with normal chest X-ray, thus helping to determine if there is the need for further studies such as bronchoscopy or pulmonary biopsy[17].

In patients with HM and fever, an early diagnostic and therapeutic route has to be established in order to obtain a favorable patient result[18]. It is essential obtaining blood and sputum cultures in case of suspected NP prior to the start of antibiotics. In this series, only 66% of patients had any microbiological-approach test, only in 42% were there blood cultures obtained, and sputum cultures only in 49%. The most frequently germs found were GNB. But something that is really noteworthy is the elevated prevalence of multi-resistant strains in the different clinical isolates. In a study of the University of Texas that included 3,451 patients, the infectious etiology was documented only in 27% of episodes[19]. In this series, blood and sputum cultures diagnostic yield was 60%, a value that is higher than those reported in the literature.

Over the last decade, multi-resistant pathogens have acquired importance as nosocomial-infection agents in patients with HM. The use of broad-spectrum antibiotics associated with empirical treatment of fever and neutropenia episodes has led to multi-resistant pathogen selection, especially in hospital environments, which today constitutes a public health problem[13]. Extensive use of broad-spectrum antibiotics against GNB, as well as prolonged use of indwelling catheters, has driven to an increase in infections by gram-positive microorganisms since the decade of the 90's[20]. A significant increase has been reported in the incidence of pathogens such as MRSA and VRE in several centers[21].

In our series, 60% of GNBs were resistant (68% blood-isolated and 33% sputum-isolated *E. coli* were ESBL-producing strains), 68% of *A. baumanii* isolates and 100% of *P. aeruginosa* isolates were MDR. With regard to GPC, 30% of *E. faecium* were VRE and 50% of *S. aureus* were MRSA.

At the INCan, 64% of *E. coli* isolated in blood of patients with HM has been reported to be ESBL-producing, with a growing trend since the first isolate in 2005. The main risk factor identified in this series was previous exposure to cephalosporins[22].

In this group of patients, 20% of sputum cultures had *Aspergillus* spp development, a lower percentage that that reported in other series, where up to 57% of patients with leukemia and NP had *Aspergillus* spp isolates[23]. Sputum cultures have low diagnostic efficacy, since 70% of sputum cultures from patients with IPA are reported to be negative[24]. On the other hand, all patients with sputum-isolated *Aspergillus* spp had positive galactomannan determination, with 100% diagnostic efficacy. Serum galactomannan sensitivity has been reported to be 70% and specificity 89% for IPA[25]; a recent study reported 100% sensitivity of galactomannan in BAL[26]. It should be noted that this test was not available during the first year of this study.

A high percentage of patients (n = 48, 51%) had thrombocytopenia, which hindered the use of invasive procedures. In total, 3 BALs and 5 pulmonary biopsies, 3 of them CT-guided, were performed; in all cases, these procedures contributed to etiologic diagnosis.

According to the EORTC/MSG revised criteria for the diagnosis of invasive fungal infections[27], 7 fungal infections (7%) were proven, 9 (8.5%) were probable and 45 (43%) were possible. Diagnostic approach with new molecular techniques such as PCR, serum galactomannan or BAL was generally suboptimal due to lack of availability; this explains why we had so little IPA proven cases (n = 7.7%).

It is well known that patients with infection early signs, if antimicrobial treatment is inadequate within the first 48 hours, have higher mortality rates even if

change for an adequate treatment is made based on microbiological data[5]. In this series, patients who received a treatment adequate to microbiological isolates had 40% less mortality (p = 0.01). A total of 27 patients (29%) had to be transferred to the ICU owing to infectious complications; 67% of them died. Shuster et al. also reported an elevated mortality of 80% in patients who required ICU attention[28].

In this series, NP-associated mortality was 50%. In a study of 65 patients, NP-related mortality risk factors were identified to be: underlying neoplasm, confirmed invasive aspergillosis, the need to use vasoactive amines and invasive MV. The presence of 3 factors is predictive of a fatal outcome[29]. In this series, the risk factor mostly associated with death was the use of MV (OR: 4.6; 95% CI: 1.2-16; p = 0.01). Multiple studies wave attempted to determine the best strategies for the prevention of bacterial, fungal and viral pneumonias in hematologic patients without any strategy being found demonstrating efficacy; therefore, as long as specific preventive measures are not available, efforts should be focused on being able to establish an early diagnosis. For this, clinical suspicion and a diagnostic approach are required in patients with fever and/or neutropenia, as already recognized risk factors, even if respiratory symptoms are not present. The diagnostic approach or route we propose includes obtaining blood and sputum cultures and performing a chest high-resolution CT scan. In patients with new pulmonary infiltrates, bronchoscopy with BAL should be performed, with cultures for pyogens, mycobacteria and fungi, and histopathological study.

We propose CT to be carried out when NP is suspected in all patients with HM owing to its high diagnostic value for IPA. We also consider that galactomannan serum antigen should be determined once-weekly in hospitalized patients in whom a prolonged neutropenia period is expected and in patients with nodular pulmonary lesion on CT; if the patient's conditions allow it, a biopsy of the lesion should be taken.

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