# Infectious Complications and Multidrug-Resistant Bacteria in Patients With Hematopoietic Stem Cell Transplantation in the First 12 Months After Transplant

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ABSTRACT

Background. Hematopoietic stem cell transplantation (HSCT) has been used as treatment in different hematologic and solid malignancies. The aim of this study was to describe the frequency of infectious complications, microbiology, and outcome in patients undergoing HSCT in Mexico during the pre-engraftment period and the impact on mortality rates at 12 months.

Methods. We conducted a retrospective study of all hematologic malignancies that received HSCT from January 2009 and December 2014, at an oncology reference center.

Results. We included 210 patients: 144 autologous (69%) and 66 allogeneic HSCT (31%). There were 184 infections documented in 109 patients; incidence rate was 47.2 per 1000 neutropenia/days and 22.4 per 1000 hospitalization/days. The main infections reported were pneumonia (n = 40, 19%), bloodstream infections (n = 36, 17.1%), and central line–associated bloodstream infections (n = 28, 13.3%). There were 110 bacteria isolated, 31 were multidrug-resistant (26 were extended-spectrum beta-lactamase; *Escherichia coli*). There were 25 disseminated or complicated viral infections and 20 invasive fungal diseases. Fourteen patients died in the first 30 days (all related to the infectious process). In multivariate analysis leukemia, more than 2 chemotherapy regimens before transplant and pneumonia were related to 12-month mortality rates.

Conclusions. Even though infectious processes are frequent in patients with HSCT, multidrug-resistant bacteria were not as frequent as supposed; however, when these microorganisms are involved, mortality rate is increased. It is important to be alert that patients with pneumonia have a significantly increased mortality risk in the first year.

INFECTIOUS complications are a major threat for patients undergoing hematopoietic stem cell transplantation (HSCT), one of the main causes of morbidity and mortality in this population [1].

Patients with HSCT can develop infections through a wide range of pathogens: bacteria, fungi, viruses, and parasites. Neutropenia comprises the period of greatest risk for development of an infection during the first 30 days after transplantation [2–5]; however, the risk of infection is not limited to this period, it persists during 6 to 12 months after autologous HSCT and up to 24 months after allogeneic HSCT. Transplantation-related death was reported in 7% [6], but, in those who develop pneumonia or bloodstream infections (BSI), mortality rate could be as high as 30% to 40% [7,8].

In recent years reports have described a progressive increase in infections related to multidrug-resistant bacteria (MDRB), which are associated with augmented rate of treatment failure, prolonged length of hospitalization, and

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high morbidity and mortality rates [6]. Regular monitoring of the epidemiology of bacterial infections in each transplant unit, along with cautious prescription of antimicrobials, may decrease the emergence of resistant pathogens and their consequences [6].

The aim of this study was to describe the frequency of infectious complications, particularly by MDRB, and outcomes in patients undergoing HSCT at an oncology reference center.

## METHODS

The National Cancer Institute is a referral, teaching hospital located in Mexico City, Mexico, for adult patients with cancer, with 135 ward beds and 5 beds for HSCT. The study was approved by the Instituto Nacional de Cancerología Ethics Review Board ("Comité de Etica en Investigación," INCAN/CI/387/15). Consent was not obtained, but patient information was anonymous and de-identified before analysis.

We conducted a 5-year, retrospective, descriptive study of all patients with hematologic malignancies who received HSCT from January 1, 2009, to December 31, 2014. With the use of a standardized case-report form for all patients who underwent an HSCT, information including demographic data, comorbidities, hematologic diagnosis and therapy, days of neutropenia, type of HSCT (allogeneic or autologous), conditioning regimens, transfer to the intensive care unit, in-hospital deaths, and outcomes at 30 days and at 12 months were registered. All infections presented since the preengraftment period until the first 12 months were recorded.

Infectious prophylaxis for patients with allogeneic transplant was started the day after hospital admission with acyclovir (250 mg, 3 times daily) until day +35. On the day of infusion of hematopoietic progenitor cells (day 0), patients were started on oral ciprofloxacin (500 mg twice daily) and metronidazole (500 mg twice daily) until day +35, and fluconazole (100 mg once per day) and trimethoprim/sulfamethoxazole (800/160 mg twice daily) until day +100. Infectious prophylaxis for autologous transplantation begins on the day of the infusion (day 0) of hematopoietic progenitor cells with oral ciprofloxacin (500 mg twice daily) until severe neutropenia resolves and if not complicated by fever.

All patients who presented with fever (axillary temperature $\geq$38.3°C once or $\geq$38°C twice in 1 hour) and severe neutropenia ($<0.5 \times 10^9$ cells/L) underwent a thorough clinical examination and collection of blood cultures. Cultures of any other infection sites were performed as clinically indicated.

Bacteria were cultured with the use of standard microbiological methods. Antimicrobial susceptibility testing was performed by means of the BD Automated Phoenix and the Kirby-Bauer disk diffusion technique in the case of resistant strains (Clinical Laboratory Standards Institute, CLSI). Microorganisms were isolated and their susceptibility was recorded. MDRB was defined as acquired non-susceptibility to at least 1 agent in 3 or more antimicrobial categories. We included the following pathogens: methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin-resistant *Enterococcus faecium* (VRE); extended-spectrum beta-lactamase (ESBL) *Escherichia coli* and *Klebsiella* spp; *Pseudomonas aeruginosa*, *Acinetobacter* spp, and other Gram-negative bacteria [9].

Infections were classified as pneumonia, urinary tract infection, BSI, or central line–associated BSI (CLABSI) according to Centers for Disease Control classification, and complicated or disseminated viral infections (cytomegalovirus, herpes zoster, BK/JK virus, and others). Invasive fungal disease (IFD) was classified as follows: proven, by demonstration of fungal elements in diseased tissue; probable, with the required host-factor clinical features and with mycological evidence present; and possible, including cases with the appropriate host factors and with sufficient clinical evidence consistent with IFD but without mycological support [10].

### Statistical Analysis

Categorical variables were compared by use of the $\chi^2$ test or the Fisher exact test as appropriate. Continuous data were compared by means of the Mann-Whitney $U$ test or by the Student $t$ test, according to data distribution. Odds ratios with 95% confidence intervals were calculated. Overall survival rates were estimated by means of the Kaplan-Meier method with the use of the log-rank test. Variables with a value of $P < .1$ were included in the logistic regression analysis. Values of $P \leq .05$ were considered statistically significant. Data were analyzed with the use of STATA (version 12 statistical software) (Stata; College Station, Tex, United States).

## RESULTS

Two hundred ten patients received an HSCT during the study period: 144 autologous (69%) and 66 allogeneic (31%). The mean age of the whole group was 37.8 ± 14.4 years; 122 patients (58%) were male, 28 (13%) had received more than 2 chemotherapy regimens before transplant, and 195 patients (93%) had a myeloablative conditioning regimen. Other demographic and clinical characteristics are depicted in Table 1.

Two hundred two patients had severe neutropenia (96%), with median days of 7.5 (interquartile range, 6–9 days). Patients who had neutropenia for >7 days had more infections (60.5%) than did patients with neutropenia for $\leq$7 days (39.5%; $P = .001$).

There were 184 infections documented in 109 patients (51.9%), being more frequent in allogeneic (n = 55, 83%) versus autologous (n = 54, 37.5%) transplants ($P < .0001$). Incidence rate per 1000 neutropenia days was 47.2 and incidence rate per 1000 hospitalization days was 22.4.

The most frequent infection was pneumonia (n = 40, 19%), followed by BSI (n = 36, 17.1%), urinary tract infection (n = 30, 14.3%), and CLABSI (n = 28, 13.3%). The infections are described in Table 2.

There were 110 microorganisms isolated. Gram-negative bacteria were the most prevalent microorganisms (n = 71; 64.5%), whereas *Escherichia coli* (n = 52) was the most frequent Gram-negative bacteria isolated (n = 52, 47%). Gram-positive bacteria were identified in 39 cases (35.4%): *Staphylococcus epidermidis* was the most frequent (n = 13, 11.8%), all from CLABSI. There were 31 MDRB (28.2%) in 25 patients: 26 ESBL–*E coli*, 1 *P aeruginosa* MDR, 1 ESBL–*E cloacae*, 2 VRE, and 1 MRSA. There were significantly more MDR infections in allogeneic compared with autologous HSCT (n = 16, 24.2% versus n = 9, 6.2%, $P = .0002$).

Severe or refractory viral infections were documented in 25 cases (11.9%): 16 with zoster involving $\geq$2 dermatomes, 3 with molluscum contagiosum, 2 with cytomegalovirus,