Neutropenic patients and their infectious complications at a University Hospital

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Objective: *The aim of this study was to analyze the characteristics and infectious complications of neutropenic patients in a referral hospital.*

Methods: *A cross-sectional study was carried out between April and September 2008, which enrolled all neutropenic patients identified by daily blood counts in the Universidade Federal de Minas Gerais. Demographic data and information on infections were obtained from the Hospital Infection Control Committee. Statistical analysis was performed using the Statistical Package for Social Sciences.*

Results: *One hundred and sixteen patients were followed up during 129 hospitalizations. The patients had a mean age of 48.7 years old. Sixty-four (55.2%) patients were male and 25 (21.6%) died during the follow-up. In 97 (75.2%) of the hospitalizations, patients had episodes of febrile neutropenia. Patients classified as low-risk had a mortality rate of 16.2% (n = 12) vs. 39.1% (n = 9) among high-risk patients (p-value = 0.02). The death rate of the patients who had been submitted to hematopoietic stem cell transplantation was 13.5% (n = 5) vs. 26.7% (n = 16) among patients not submitted to transplantation (p-value = 0.13). Of the 155 infections diagnosed, 45.5% were defined as clinically documented. The etiological agent most frequently isolated was Escherichia coli and the main topography reported was bloodstream infections. The most used antimicrobial agents were cefepime, vancomycin and fluconazole. Approximately 24% of patients evolved with impaired renal function during hospitalization.*

Conclusion*: Most reported infections in neutropenic patients were defined as clinically documented, which shows the importance of suspicion in patients without specific signs and symptoms for early diagnosis and the need for the classification of risk for timely interventions.*

Keywords: *Neutropenia; Bacterial infections; Anti-bacterial agents; Renal insufficiency; Hospitals, university*

Introduction

Neutropenia is one of the most serious and common complications in oncological treatment. Patients under chemotherapy are susceptible to infections because therapy directly affects the production of neutrophils. Reductions in these cells predisposes the body to bacterial invasion and proliferation, and inhibits the appearance of any inflammatory response[1,2]. Over the last three decades the approach to febrile neutropenia has been based on the early and empirical use of antibiotics, a conduct that has proved to reduce mortality rates[1].

Recent research indicates that neutropenia is a prevalent complication in immunocompromised patients and is associated with high costs and high morbidity and mortality rates[1]. It is estimated that the incidence of hospitalization for neutropenia is 60,000 cases per year in the U.S. and that the average total cost of hospitalization is greater than US$ 20,000[2].

The description of infectious events in neutropenic patients is extremely important. Knowledge about these events in this population helps to reduce costs and to adapt published data to the reality of the institution, permits continuous improvement of the service offered and maximizes the benefits of treatment[3]. However, clinical manifestations of infections due to neutropenia may be mild, or even absent, a situation that complicates diagnosis, initial treatment and the follow-up of patients with febrile neutropenia [4,5].

This work aims to analyze the characteristics and complications related to infectious events in neutropenic patients treated at the Hospital das Clínicas of the Universidade Federal de Minas Gerais (HC-UFMG).

Methods

This cross-sectional study was carried out at the HC-UFMG between April and September 2008. All neutropenic patients admitted to the service identified by daily reviews of all the blood counts performed at the institution were included, except for Emergency Department patients.

Patients who presented neutrophil counts ≤ 500 cells/mm^3 or ≤ 1000 cells/mm^3 when there was a downward trend to 500 cells/mm^3 within two days were considered neutropenic. A neutrophil count of less than 100 cells/mm^3 was classified as severe neutropenia. Fever was

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defined as axillary temperature > 38.0°C or axillary temperature of 37.8°C that persisted for more than one hour[1,6].

Data were collected in respect to gender, the referring service of the patient, underlying diseases, previous transplantation, chemotherapy, presence and duration of fever, neutropenia with neutrophil count < 100 cells/mm^3, renal function (serum creatinine and creatinine clearance), presence of infection and microorganisms in cultures (blood, urine and catheter tip), antimicrobials used and clinical outcome (discharge or death).

Patients were stratified according to the predictive model of the Multinational Association for Supportive Care in Cancer (MASCC)[7], which classifies the episode of febrile neutropenia as low-risk (score ≥ 21) or high-risk (when presenting score < 21).

Renal function was considered abnormal when creatinine increased by two times the baseline level, creatinine was above 2 mg/mL or creatinine clearance was less than 50 mL/min.

Data was obtained through an active daily evaluation of all neutropenic patients identified by blood count screening. Medical records were checked on a daily basis which allowed the identification of infections reported to the service, according to the Immunocompromised Host Society criteria[8] which classifies three categories of infection: fever of undetermined origin, microbiologically documented infection (with or without bacteremia) and clinically documented infection. Bloodstream infections associated with central venous catheter were assessed in accordance with the guidelines of the Infectious Diseases Society of America[9]: isolation of a microorganism with the same phenotypic profile in the blood culture and on the catheter tip or in the catheter blood flow. Patients were followed up throughout their hospitalization.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 13.0). Frequency distribution and percentage of categorical variables and mean, median, standard deviation (SD) for continuous variables were included in the analysis. Chi-square and t-test or Mann-Whitney tests were used for comparative analysis. The result was considered statistically significant when the p-value < 0.05.

The study was approved by the Ethics Committee of UFMG (ETIC 237/09).

Results

During the study period, 116 cases of neutropenia were identified in 129 admissions. Patients had a mean age of 48.7 years and SD of 17.42 (95% confidence interval: 43.5-49.9). Sixty-four (55.2%) of these patients were male and twenty-five (21.6%) died during the follow-up.

The highest number of episodes of neutropenia were observed in patients from the Hematology Service (48.1%), followed by patients from Hematopoietic Stem Cell Transplantation (HSCT - 32.8%), General Medicine (13.8%), Infectious and Parasitic Diseases (3.9%) and Solid Organ Transplantation Services (2.3%). The main baseline diseases of the 116 neutropenic patients (Table 1) were identified as neoplasms (70.7%), infectious diseases (8.6%), blood diseases, hematopoietic organs and certain immune disorders (7.8%). Seven patients were infected by the human immunodeficiency virus (HIV). One of these patients died and another had no infection diagnosed.

Table 1 - The baseline diagnosis of neutropenic patients

Baseline diagnoses	n	%
Neoplasms	82	70.7
Infectious and parasitic diseases	10	8.6
Blood diseases, hematopoietic organ diseases and immune disorders	9	7.8
Respiratory diseases	3	2.6
Diseases of the musculoskeletal system and connective tissue	3	2.6
Digestive tract diseases	2	1.7
Others	7	0.6
Total	116	100.0

Of the 116 neutropenia cases, 83 (71.6%) patients had been treated with chemotherapy and 40 (34.5%) patients had undergone HSCT. Of the 83 patients who had been treated by chemotherapy, 37 (44.6%) had been submitted to HSCT.

Of the 116 cases of neutropenia, 97 (75.2%) were considered episodes of febrile neutropenia and 90 (69.8%) of these episodes presented neutropenia with neutrophil counts of less than 100 cells/mm^3. The average duration of neutropenia was nine days (range: 1 - 53 days). There was no statistical difference on comparing the duration of neutropenia in HSCT patients compared to the duration in the other patients (p-value = 0.7).

Considering the 97 episodes of febrile neutropenia, the median duration of fever was five days (range: 1 - 26 days). The majority (n = 74; 76.3%) of reported neutropenia episodes were classified as low-risk with 23 (23.7%) being classified as high-risk, according to the model of MASCC[7].

During the follow-up, infections were diagnosed in 155 of all neutropenia episodes. According to the Immunocompromised Host Society[7] classification, of 155 infections, 72 (45.5%) were defined as clinically documented, 44 (28.4%) were infections of unknown origin and 39 (25.2%) were microbiologically documented, 32 of which were associated to bacteremia and seven were not (five cases of local infections of vascular catheters and two cases of urinary tract infections). Characterizations of infectious events according to demographic and clinical data are shown in Table 2.

Table 2 - Frequency of infectious events in neutropenic patients according to demographic and clinical data

	n	%
Gender		
Male	98	(63.2)
Female	57	(36.8)
Neutrophil count		
≥ 100/mm^3	124	(80.0)
< 100/mm^3	31	(20.0)
Hematopoietic stem cell transplantation		
Yes	71	(45.8)
No	84	(54.2)
Febrile neutropenia		
Yes	97	(62.6)
No	58	(37.4)
Creatinine clearance		
> 50 mL/min	136	(87.7)
< 50 mL/min	19	(12.3)

Among the 71 bloodstream infection cases, 34 (47.9%) were reported as catheter-associated infections (clinical signs of infection in patients using catheters without any other identified focus) and five (7.0%) as bloodstream infections associated with central venous catheters (CVC).

Of the 39 microbiologically documented cases of infection, the majority was gram-negative with *Escherichia coli* in 11 (28.2%) cases and *Pseudomonas aeruginosa* in seven (17.9%) cases. Bacteria were isolated in most of the gram-positive cases: *Staphylococcus epidermidis* (6 cases - 15.4%) and *Staphylococcus aureus* (5 cases - 12.8%) (Table 3).

Table 3 - Distribution of microorganisms isolated in neutropenic patients with episodes of infection

	n	%
Gram-negative (61.5%)		
Escherichia coli	11	28.2
Pseudomonas aeruginosa	7	17.9
Klebsiella pneumoniae	4	10.3
Acinetobacter baumannii	1	2.6
Stenotrophomonas maltophilia	1	2.6
Gram-positive (38.5%)		
Staphylococcus epidermidis	6	15.4
Staphylococcus aureus	5	12.8
Corynebcterium sp	1	2.6
Enterococcus faecium	1	2.6
Enterococcus sp	1	2.6
Streptococcus sp	1	2.6
Total	39	100.0

Seven cases (17.5%) involved resistant microorganisms according to standards based on the antimicrobial susceptibility profile of the institution, which follows the recommendations of the National Committee for Clinical Laboratory Standards[10]. Three (20.0%) of the 15 gram-positive cases and four (16.7%) of the 24 gram-negative cases were considered resistant. Furthermore, two (5.0%) were defined as having a beta-lactamase producing extended spectrum.

Considering the episodes of febrile neutropenia, of the 74 patients classified as low-risk by the MASCC predictive model[7], 16.2% (n = 12) died during the follow-up. There was a significantly higher mortality (p-value = 0.02) among patients classified as high-risk (39.1%, n = 9). Mortality was also evaluated in the 97 episodes of febrile neutropenia comparing patients submitted to HSCT and those not. Of the 37 patients who underwent HSCT, 13.5% (n = 5) died during the follow-up. The mortality of 60 febrile neutropenic patients who were not submitted to HSCT was 26.7% (n = 16). There was no statistical difference between these two groups (p-value = 0.13).

Treated infection was diagnosed in a median of 23 days after admission (range: 1 - 135 days) and a median of eight days after the laboratory definition of neutropenia (range: 0 - 92 days). Patients took antimicrobial agents for a median of eight days (range: 0 - 63 days). Patients took a median of five antimicrobial agents (range: 1 - 19 antimicrobial agents); the main antimicrobial agents used are listed in Table 4.

Table 4 - Antimicrobial agents used to treat neutropenic patients

Antimicrobial agent	n	%
Cephalosporins (cefepime and ceftazidime)	132	19.9
Antifungal (fluconazole, amphotericin B, voriconazole)	127	19.1
Gycopeptide (vancomycin and teicoplanin)	96	14.5
Carbapenems (imipenem and meropenem)	64	9.6
Sulfamethoxazole-Trimethoprim	62	9.3
Acyclovir	56	8.4
Amikacin	40	6.0
Metronidazole	27	4.1
Other	60	9.0
Total	664	100

In respect to renal function, patients experienced creatinine clearance above 50 mL/min on admission in 107 hospitalizations with 81 (75.7%) of these cases showing no change in renal function during the follow-up. The renal function changed in 26 (24.3%) of these cases during hospitalization, according to the following criteria:

- two-fold increases in creatinine baseline levels: in 17 (65.4%) hospitalizations
- creatinine above 2 mg/mL: in ten (38.5%) hospitalizations
- creatinine clearance less than to 50 mL/min: in 11 (42.3%) hospitalizations

More than one criterion was observed in each patient with impaired renal function. The median time to renal dysfunction was 25.9 days (range: 9 - 66 days) with a median of 24 and SD of 13.7 days.

Discussion

HC-UFMG is one of the main referral centers for hematology in the State of Minas Gerais, which explains the large number of patients originating from other hematology services and those who had been submitted to bone marrow transplantation (80.6%).

The death rate found (21.6%) was higher than that described by some studies. A prospective multicenter study showed mortality rates of 15% among high-risk patients and only 1% in the low-risk group[11]. In another study, mortality was similar to that found by the authors of this study, with a rate of 21.5%, but this rose to 55% when the patient had bacteremia or fungemia[4].

The large number of oncological patients may have influenced the high mortality rate in this study. According to the literature[12], patients treated with chemotherapy are at an increased risk of infection compared to patients who develop neutropenia secondary to viral infection, bone marrow aplasia or who have congenital neutropenia because bacterial translocation may occur with disruption of the mucosal integrity. However, when comparing patients submitted to HSCT and other patients in this study, there was no statistical difference in the outcomes during the study period.

The median duration of neutropenia was nine days (range: 1 - 53 days). Fever was present in 75.2% (n = 97) of the patients which reaffirms the importance of this sign in the care of neutropenic patients. These patients often present fever as the only sign of infection[13,14].

In Brazil, the most commonly used risk classification of patients with febrile neutropenia episodes was developed by Klastersky et al. (MASCC)[7]. A low-risk score predicts a risk of less than 5% of serious complications during an episode of febrile neutropenia and very low mortality (less than 1%). In this study, most patients (76.3% of the total) were low-risk but the mortality rate (16.2%) was higher than that described in the literature. The mortality was also greater for the high-risk group than that found in a study by Klastersky[15] (39.1% vs. 14.0%).

Few studies aimed to report infections in neutropenic or immunosuppressed patients. The literature acknowledges and accepts the limitations of using established criteria for reporting these infections when applied to this group of patients[16]. Members of the Cleveland Clinic Department of Infectious Diseases have changed internal surveillance definitions for leukemia and bone marrow transplantation patients. In this service, bloodstream infections of neutropenic patients with mucositis acquired in the hospital due to *Streptococcus viridans* are not considered catheter-related blood infections. The application of the modified definition showed significant changes in bloodstream infection rates associated to catheters[17].

Dix et al.[18] reported infections related to CVC in patients with hematologic malignancies and found that one quarter had complications related to catheter placement. Additionally, they identified the insertion site, underlying diseases and CVC duration as risk factors. Elishoov et al.[19] studied bone marrow transplant patients and emphasized the need of daily cultures to identify infections. In this group of patients, 50% had infections identified by the National Healthcare Safety Network criteria and over 30% had infections related to CVC. The results of these studies suggest that the proposed criteria may not be ideal when the population comprises neutropenic patients.

In the literature[4,14,20] it is well established that, in many cases, febrile neutropenia patients have bacteremia without any specific focus (up to 14.3 episodes per 100 neutropenia cases)[21]. Of the 155 episodes of infection, 72 (45.5%) were only diagnosed clinically. The importance of the clinical examination is reaffirmed by other authors including Billote et al.[4], whose work shows that the diagnosis of infection in neutropenic patients is clinical in 72% of cases.

Among the other infections documented in this study, 28.4% were of undetermined origin and 25.2% were microbiologically documented. Moreover, the number of febrile episodes without specific signs and symptoms, defined as infections with undetermined origin, presents a rate of 60% in the literature[5].

Although most infections in neutropenic patients are only clinically documented, the bloodstream is the primary site of infection in this group[6,21,22]. In this study, the blood culture was shown to be the specimen with the highest frequency for the isolation of microorganisms (80.0%).

The number of infections confirmed through laboratory analysis was lower than the rate described by Link et al.[23] who identified the involved microorganisms in one third of patients in the early stages of infection and in 20% to 30% of patients with advanced infection. As the etiological infectious agent is not defined in most neutropenic patients, guidelines recommend empirical treatment[6,21].

The etiology of the infection in febrile neutropenia patients varies according to a number of factors such as type of prophylactic antibiotic therapy used, sensitivity of the microorganism, the chemotherapy regimen used for the patient, the patient's risk classification, hospitalization time and even the local climate[6,22].

The microorganisms isolated in this study are similar to the trend reported in the literature with increases of gram-negative bacilli over recent years (annual increases of 3.4%)[24]. The bacterium *E. coli* was the most prevalent (28.5%) in microbiologically documented infections in this study, followed by *P. aeruginosa* (17.9%) and *Klebsiella pneumoniae* (10.3%). Gram-negative bacilli corresponded to 61.6% of the microorganisms isolated. These three main gram-negative bacilli were reported in another Brazilian study[25] which reported a higher percentage of *P. aeruginosa* (22%).

Of the gram-positive bacteria, the most commonly isolated were *S. epidermidis* and *S. aureus*. These microorganisms are described as common etiologic agents of infection in this population with the increases in the prevalence of these agents in the 1980s and 90s being favored by the use of invasive devices[6,22], frequently used in interventions and patient support. In Brazil, there are reports of a higher percentage of gram-positive infections isolated in microbiologically documented cases with the rate reaching 47% of the 91 febrile neutropenia cases described by Oliveira et al.[25].

The rate of isolated microorganisms considered resistant in this study (17.5%) was lower than that reported in the literature with 15.4% of gram-negative and 23.0% of gram-positive bacilli. Some studies showed that more than 50% of *S. aureus* were resistant to methicillin and demonstrated that the rate of vancomycin-resistant enterococcal infections was greater than or equal to 30%[26,27]. In a Brazilian study, it was observed that 37% of gram-negative infections in patients submitted to HSCT were considered multidrug resistant (MDR) [25].

The most commonly used antimicrobial agents were cephalosporins (ceftazidime and cefepime), antifungal medications (fluconazole, amphotericin B and voriconazole) and glycopeptides (vancomycin and teicoplanin). The antimicrobial agents used are recommended in febrile neutropenia guidelines. Antibiotics are often used in combination for empirical coverage in treatment[6,27].

Another important aspect is the nephrotoxicity of antibiotics which are often used in combination. In the study by Farber and Moellering[28], 5% of patients who received vancomycin developed renal failure. This percentage rose to 35% in patients who used vancomycin associated with aminoglycosides. Luber et al.[29] found mild to moderate nephrotoxicity in 50% of patients with 8% developing severe renal failure that was reversible with the discontinuation of the drug. In this study, 24.3% of patients had altered renal function during hospitalization. A two-fold increase in the baseline creatinine level was the method that most frequently detected changes in renal function.

Conclusion

Most patients had severe neutropenia, which is associated with the high mortality rate found, especially in the high-risk group.

Most infections in neutropenic patients were defined as clinically documented. This study highlights the importance of suspicion for early diagnosis due to the nonspecific signs and symptoms and the need of risk classification for timely interventions.

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