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#### ORIGINAL ARTICLE

# Prospective surveillance of healthcare associated infections in a haematology-oncology department

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doi: 10.3396/IJIC.v15i1.002.19

#### Abstract

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In haematology-oncology, intensified procedures have been associated with higher risk of healthcare associated infections (HAIs). This study aimed to estimate the incidence and to identify risk factors of HAIs in a haematology-oncology unit in a Tunisian university hospital. We conducted a prospective study, during 6 months from March through September 2016 in the department of haematology-oncology in a tertiary teaching hospital in Tunisia. Patients, admitted for  $\geq$ 48 h, were followed until hospital discharge. The CDC criteria for site-specific infections were used to define HAIs. Bivariate and multivariate analyses were performed to identify risk factors of HAIs. A p value < 0.05 was considered as significant. A total of 150 patients were included in this study with mean age 23.12 ±18.36 years. The overall rate of HAIs was 32.6/100 patients with an incidence 15.7 per 1000 patient-days at risk. Nosocomial fever of unknown origin was the most frequent infection (42.9% of total HAI's). Independent risk factors for developing HAIs were male gender (OR[CI]95%= 4.60[1.43-14.61]; p=0.01), neutropenia (OR[CI]95%=10.20[2.26-45.72], p=0.002), aplasia inducing chemotherapy (OR[CI]95%=6.0 [1.07-33.19], p=0.004) and bone marrow aspiration and biopsy (OR[CI]95%=3.0 [1.10-8.03], p=0.03). In conclusion, our study highlights the burden of HAIs in this unit and the role of surveillance for specific HAIs and analyzing its risk factors. A comprehensive education program focused on evidence-based approaches for all healthcare workers should be implemented in this unit.

Keywords: healthcare associated infections, haematology, surveillance, risk factors, Tunisia.

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#### Background

Over the past few decades, major progress has been made in the curative treatment of haematological malignancies which has resulted in reduced overall mortality.<sup>1</sup> This improvement has allowed increasingly aggressive management in diagnostic and therapeutic procedures.<sup>2</sup> chemotherapy, bone marrow or peripheral blood stem cell transplantation. This could lead to severe and prolonged immunosuppression, increasing the risk of healthcare-associated infections (HAIs) and possibly worsening the prognosis.<sup>3</sup> HAIs are important adverse events in the disease history of patients with haematological malignancies, sometimes culminating in death; they are also responsible for longer hospital stay and increased healthcare costs.<sup>4</sup>

The occurrence of HAIs differs in different patient populations and different hospitals.<sup>2</sup> However, few studies have examined the incidence of HAIs in this patient population as most surveillance has focused only on bone marrow transplant patients or children.<sup>3</sup> In our tertiary teaching hospital, a HAIs surveillance program was implemented since 2000. In 2009, the incidence of serious adverse events including HAIs in medical departments was 13.7%.<sup>5</sup> Since 2016, a large prospective surveillance program was launched in several departments by the infection control department, and to our knowledge this is the first prospective study conducted in the haematology-oncology unit aiming specifically to evaluate HAIs.

The objectives of this study were:

- To assess HAIs incidence among patients with neoplastic diseases in a tertiary teaching hospital.
- To identify the common etiological pathogens for these infections.
- To identify the independent risk factors for these infections as a first step toward improving infection control policies in this unit.

# Methods

### Setting and patients

An observational prospective study, based on active surveillance for a period of 6 months from March through September 2016, was undertaken in the haematology-oncology unit of Farhat Hached teaching hospital of Sousse. This ward has a 28-bed capacity and has been recently renovated. All patients admitted to the unit were monitored for HAIs from admission until discharge from the unit; no active post-discharge surveillance was performed. All patients were screened daily by haematologists assisted by an infection control physician using a pretested and standardized survey record. Patients from day hospital were excluded.

## Data collection

The following data were collected:

- Patient characteristics: age, sex, weight, size, medical history life habits, previous hospitalizations' history, and immune status.
- Current hospitalization related data: date of admission and discharge, mode of admission, sector of admission (protective isolation or conventional hospitalization), reason for hospitalization, antibiotics prior to the admission, underlying disease, admission and discharge diagnosis, laboratory test results (routine blood tests), and mode of discharge. We defined neutropenia as absolute neutrophil count < 0.5 × 10<sup>9</sup>/L).<sup>6</sup>
- Invasive procedures used and their duration (intubation, urinary catheterization, peripheral or central venous catheterization, nasogastric tube, parenteral nutrition, implantable venous access port, bone marrow aspiration and biopsy, lumber puncture)
- HAI-related data for each suspected HAI: specific clinical data, documented signs and symptoms, and direct observation were used to identify possible HAIs. Source materials included medical records, temperature charts, information from nursing and medical staff, and results of microbiological testing. Once an HAI was confirmed, therapeutic interventions, and clinical course of the infectious episode were recorded.

Cultures from blood, urine, bronchial secretions, and from any other site with clinical suspicion of infection were performed based on the judgment of the treating physician. Bacteria were cultured using standard microbiological methods.

The Center for Disease Control and Prevention criteria (CDC) for site-specific infections were used as standard definitions for HAIs.<sup>7</sup> Infections that occurred less than 48 hours after admission, or those that were present or

incubating at the time of admission, were not regarded as nosocomial.

All suspected cases were discussed between haematologists and the infection control team. The aims of these meetings were first, to reach a consensus on type of HAI, and second to identify preventable nature or not of the infection, dysfunctional healthcare procedures, and to decide about corrective measures. Types of HAIs included in this particular study were mucocutaneous, pulmonary aspergillosis, bloodstream infections related to intravascular devices, pneumonia, primary bloodstream infections, urinary tract infections, gastrointestinal tract infections, bloodstream infections and nosocomial fever of unknown origin.

Nosocomial fever of unknown origin (FUO) was defined as fever of at least 38°C for more than 4 hours occurring on several occasions in a hospitalized patient in whom neither fever nor infection was present on admission and for which a cause cannot be determined after 3 days of investigation, including 2 days of cultures.<sup>8–10</sup> Nosocomial FUO was counted as a HAI according to Ibrahim KY *et al.* <sup>4</sup>

#### HAIs rate calculations

HAI rates measured during the surveillance period included the overall HAI attack rate (per 100 patients) and the incidence density rates of HAIs (number of HAI cases divided by 1,000 patient-days and multiplied by 1,000). Patient-days are the total number of days that patients are hospitalized during the selected time period .<sup>11</sup>

#### Statistical analysis

Statistical analysis of the pre-coded data was done using the Statistical Package for Social Science Program (SPSS, Version 10; IBM, Armonk NY). The first part of the analysis examined the entire cohort of patients. In this section, we described the overall population; categorical variables were expressed as count and percentage. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range. Also we calculated the overall HAI attack rate of HAIs in this unit and the incidence density of HAIs, as well as clinical and microbiological patterns of HAIs. The second section of results is the analytic part in which we compared outcomes between patients with HAIs and with those who did not develop HAIs. We used the chi-squared test for comparing mortality rates and the Student t-test for comparing length of hospital stay. The second objective of this part was to identify risk factors of HAIs. First we used bivariate analysis to identify potential factors associated with HAI's; the Student t-test was used for comparing quantitative variables, while the chi-squared test was used for qualitative variables. The significance level was set at a p<0.05. Variables identified as potential risk factors by the bivariate analysis with a p value < 0.2 were included in an unconditional logistic regression. Variables were introduced into the multivariate analysis in a stepwise manner to construct the final model. The condensed model was presented with crude odds ratio (OR) and 95% confidence interval (CI). The significance level was set at a p < 0.05

#### **Ethics statement**

The collected data remain strictly confidential. Our research protocol did not harm patients' health, safety, or privacy. This study was approved by our institution ethics committee.

#### Results

A total of 150 patients was included in the study. Patient characteristics are presented in Table I.

Among the 150 patients, 49 developed 58 HAIs. The overall HAI attack rate was 32.6/100 patients with an incidence of 15.7 per 1000 patient-days at risk. The majority of patients developed only one HAI, seven patients developed two HAIs, and one patient developed three HAIs. Concerning the patients' diagnosis, the highest incidence rate of HAIs was observed in patients with acute myeloid leukaemia (53.57/100 patients), followed by non-Hodgkin's lymphoma (35.71/100 patients), acute lymphoblastic leukaemia (28.75/100 patients), and Hodgkin's lymphoma (10.0/100 patients).

Among the 58 HAIs, nosocomial FUO was the most frequent infection (42.9% of total HAIs), followed by mucocutaneous infections and pulmonary aspergillosis. Table II summarizes rates of specific infections.

| Variables                                    | Mean±SD n (%) |
|--|---------------|
| Age (Years)                                  | 23.1±18,3     |
| Gender                                       |               |
| Male   | 100(66.7)     |
| Female                                       | 50(33.3)      |
| Mode of admission                            |               |
| Scheduled admission                          | 107(72.3)     |
| Emergency                                    | 24(16.2)      |
| Transfer from another department or hospital | 17(11.4)      |
| Hospitalization sector                       |               |
| Protective isolation                         | 60(40.5)      |
| Conventional hospitalization                 | 80(59.5)      |
| Previous hospitalization                     |               |
| <3mois                                       | 108(72.5)     |
| 3-6mois                                      | 4(2.7)        |
| None   | 37(24.8)      |
| Haematological malignancies                  |               |
| Acute Myeloid leukaemia                      | 28(20.3)      |
| Acute Lymphoblastic Leukaemia                | 80(58.0)      |
| Non-Hodgkin's Lymphoma                       | 14(10.1)      |
| Hodgkin's Lymphoma                           | 10(7.2)       |
| Burkitt's Lymphoma                           | 2(1.4)        |
| Others                                       | 4(2.9)        |
| Underlying diseases                          |               |
| Diabetes                                     | 9 (6.0)       |
| Pulmonary aspergillosis                      | 5(3.3)        |
| Mucositis                                    | 11(7.4)       |
| Antibiotics at admission(±48h)               | 16(10.7)      |
| Neutropenia                                  | 79(53)        |
| Immunodeficiency                             | 26(10.1)      |
| Medication usage                             |               |
| Prolonged corticosteroids therapy            | 20(14.5)      |
| Recent corticosteroids therapy               | 57(38.0)      |
| Chemotherapy                                 | 132(88.0)     |
| Radiotherapy                                 | 2(1.3         |
| Immunosuppressive therapy                    | 2(1.3         |

| Table I. Patients characteristics at admission (continued) |                 |
|--|-----------------|
| Variables  | Mean±SD n (%)   |
| Exposure to invasive devices or procedures n (%)           |                 |
| Peripheral Venous Catheter                                 | 137(91.3)       |
| Central Venous Catheter                                    | 2(1.3)          |
| Implantable venous access port                             | 12(8)           |
| Mechanical Ventilation                                     | 5(3.3)          |
| Urinary Catheter   | 7(4.7)          |
| Lumber puncture  | 52(34.9)        |
| Bone marrow aspiration                                     | 64(43.0)        |
| Bone marrow biopsy   | 7(4.7)          |
| Routine blood test :Median [Q1-Q3]                         |                 |
| White blood cell (×109cells/L)                             | 5.8 [4.0-11.6]  |
| Platelets (×109cells/L)                                    | 162[74.5-233.0] |
| Haemoglobin (g/L)  | 11.2[10.1-12.6] |
| Neutrophil granulocyte (×109cells/L)                       | 3.2[1.7-6.0]    |
| Hospital Outcomes n (%)                                    |                 |
| Median hospital days [Mean±SD]                             | 20.9±18.2       |
| Mortality n (%)  | 14(9.3)         |
|  |                 |

# Table II. Characteristics of 58 HAIs: site of infection, infection rate, and isolated pathogens

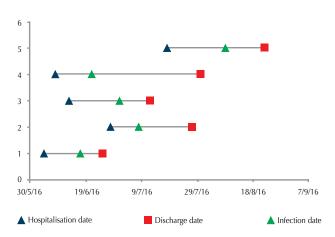
| Site of Infection  | No. (% of total HAI's)<br>N=58 | Specific incidences<br>(/100 exposed patient) | Isolated Pathogens (n)  |
|--|--------------------------------|---|---|
| Nosocomial Fever of unknown origin                             | 21(42.9)                       | 26.58   | -   |
| Mucocutaneous<br>infections                                    | 8(16.3)                        | 5.33  | Geotrichum capitatum (2)<br>Proteus mirabilis (1)<br>Escherichia coli (1)   |
| Pulmonary aspergillosis  | 7(14.3)                        | 4.66  | Aspergillosis Antigen (2)   |
| Bloodstream infections<br>related to intravascular<br>devices. | 6(12.2)                        | 4.10  | Klebsiella pneumoniae (1)   |
| Pneumonia  | 6(12.2)                        | 4.00  | -   |
| Gastro-intestinal system infections                            | 5(10.2)                        | 3.33  | Geotrichum capitatum (2)<br>Candida albicans (1)  |
| Primary Bloodstream infections                                 | 4(8.2)                         | 2.66  | Geotrichum capitatum (1)<br>Enterobacter cloacae (1)<br>Klebsiella pneumoniae (1)<br>Streptococcus pneumoniae (1) |
| Urinary tract infections                                       | 1(2)                           | 14.28   | -   |

Only 24.1% of infections were laboratory documented (Table II). *Geotrichum capitatum* and *Gram-negative bacteria* were the most isolated pathogens (41.66% each) followed by *Streptococcus pneumoniae* (8.3%) and *Candida albicans* (8.3%).

Concerning cases of Geotrichum capitatum, a total of 5 infections caused by this germ were recorded during June and the first week of July 2016: 2 mucocutaneous infections, 2 gastrointestinal infections, and 1 primary bloodstream infection. In 3 cases, HAIs were associated with neutropenia, and in 2 cases patients died. Characteristics of these 5 cases are shown in Table III. Microbiological confirmation was performed by oral swabbing in mucocutaneous and gastrointestinal cases and by blood culture in primary bloodstream infection. Figure 1 shows an overlap between cases hospitalizations periods and suggests the same origin of this germ. After discussion of these cases we performed several samplings, including sampling of food which was prepared by a subcontracting company. Food samples were negative and we did not identify the source of this outbreak. No other cases were observed after this outbreak.

Concerning outcomes of HAIs, there was no significant difference in mortality rates between patients with HAIs and with those without HAIs (12.2% versus





7.9%, p=0.57). In contrast, mean length of stay was significantly longer among patients with HAIs than others (31.8±17.9 days versus 15.5±15.9 days, p<10<sup>-3</sup>) On bivariate analysis, factors significantly associated with HAIs were admission from emergency (p=0.03), duration of neutropenia (p=0.035), recent corticosteroid therapy (p=0.02), chemotherapy (p=0.038), acute myeloid leukaemia (p=0.009), aplasia inducing chemotherapy (p<10-3), lumbar puncture (p=0.02), bone marrow aspiration and biopsy (p=10-3), neutropenia (p<10-3), and duration of neutropenia (p=0.019). Although not reaching statistical significance, male gender was associated with HAIs (p=0.2).

| lable III. | Utiltiaia |                |  | ucs of cases with firsts        |  |                                  |       |
|------------|-----------|----------------|--|---------------------------------|--|----------------------------------|-------|
| Case N°    | Gender    | Age<br>(years) | Neutrophil<br>granulocyte<br>at admission<br>(Cells/mm3) | Hematological<br>diagnosis      | Type of HAI                                | Treatment                        | Death |
| 1          | Male      | 34             | 1640   | Acute Lymphoblastic<br>Leukemia | Gastro-<br>intestinal system<br>infections | Amphotericin B                   | Yes   |
| 2          | Female    | 46             | 152  | Acute Lymphoblastic<br>Leukemia | Mucocutaneous infections                   | Amphotericin B                   | No    |
| 3          | Female    | 32             | 112  | Acute Lymphoblastic<br>Leukemia | Primary<br>Bloodstream<br>infections       | Voriconazole +<br>Amphotericin B | Yes   |
| 4          | Female    | 62             | 0  | Acute Lymphoblastic<br>Leukemia | Gastro-<br>intestinal system<br>infections | Voriconazole +<br>Amphotericin B | No    |
| 5          | Male      | 41             | 1225   | Acute Lymphoblastic<br>Leukemia | Mucocutaneous infections                   | Amphotericin B                   | No    |

#### Table III. General and clinical Characteristics of cases with HAIs

Table IV shows that after logistic regression, independent risk factors for developing HAIs were male gender (OR [CI]<sub>95%</sub> 4.60 [1.43-14.61]; p=0.01), neutropenia (OR[CI]<sub>95%</sub> 10.20[2.26-45.72],p=0.002), aplasia inducing chemotherapy (OR[CI] 6.0 [1.07-33.19], p=0.004) and bone marrow aspiration and biopsy (OR[CI]<sub>95%</sub> 3.0 [1.10-8.03], p=0.03).

#### Discussion

The primary objective of this prospective study was to determine the incidence of HAIs in a haematologyoncology department and to identify their risk factors. We showed that HAIs are a significant problem in the haematology-oncology ward of our hospital.

#### Table IV. Risk factors of HAIs in hematology-oncology department

|  | Bivariate analysis |            | Multivariate analysis |       |
|--|--------------------|------------|-----------------------|-------|
|  | OR [95% CI]        | <b>P</b> * | OR [95% CI]           | Р*    |
| Male gender  | 1.64 [0.75-3.39]   | 0.21       | 4.60 [1.43-14.61]     | 0.01  |
| Age  | 1.01 [0.99-1.03]   | 0.24       |                       |       |
| Sector of hospitalization<br>(Conventional /Protective<br>isolation) | 1.53 [0.78-3.14]   | 0.22       | -                     | -     |
| Mode of admission<br>(emergency/scheduled<br>admission)              | 0.37 [0.15-0.92]   | 0.03       | -                     | -     |
| Prior hospitalization  | 0.54 [0.25-1.16]   | 0.11       | -                     | -     |
| History of pulmonary<br>aspergillosis                                | 1.41 [0.22-8.6]    | 0.72       | -                     | -     |
| History of diabetes  | 1.70 [0.43-6.66]   | 0.43       | -                     | -     |
| Acute Myeloid leukemia   | 2.98 [1.28-6.92]   | 0.009      | -                     | -     |
| Acute Lymphoblastic<br>Leukemia                                      | 0.68 [0.344-1.35]  | 0.27       | -                     | -     |
| Neutropenia (neutrophils<br><500/mm³)                                | 12.74 [4.94-32.8]  | 10-3       | 10.20 [2.26-45.72]    | 0.002 |
| Duration of neutropenia  | 1.05 [1.004-1.113] | 0.035      | -                     | -     |
| Antibiotherapy at<br>admission (±48hours)                            | 1.70 [59-4.88]     | 0.31       | -                     |       |
| Recent corticosteroids<br>therapy                                    | 2.24 [1.11-4.5]    | 0.02       | -                     | -     |
| Chemotherapy   | 4.40 [0.97-20.07]  | 0.038      | -                     | -     |
| Duration of<br>chemotherapy  | 1.01 [0.99-1.028]  | 0.28       | -                     |       |
| Aplasia inducing<br>chemotherapy                                     | 24.15 [5.5-106.13] | 10-3       | 6.0 [1.07-33.19]      | 0.04  |
| Lumber puncture  | 2.28 [1.12-4.65]   | 0.02       | -                     | -     |
| Bone marrow aspiration<br>and biopsy                                 | 3.28 [1.6-6.7]     | 10-3       | 3.0 [1.10-8.03]       | 0.03  |
| Implantable venous<br>access port                                    | 0.65 [0.1-2.5]     | 0.55       | -                     | -     |
| *P<0.05 is considered significant                                    | t                  |            |                       |       |

The overall HAI attack rate of HAIs in this unit was 32.6/100 patients with an incidence 15.7 per 1000 patient-days at risk. A higher incidence was reported in several studies. A prospective surveillance study performed in a haematology-oncology unit in Athens, Greece,<sup>12</sup> revealed an incidence of 17.3 HAIs per 1,000 patient-days. Also, in a 6-year prospective surveillance in a French haematology department, the HAIs attack rate was 31.4 per 100 patients with an incidence of 18.2 per 1000 patient-days at risk.<sup>6</sup> This rate reached 21.52 per patient-days in a recent Chinese study.<sup>13</sup> However, lower incidences (4.7 per 100 patients) were reported in a Mexican study.<sup>1</sup> Several factors may contribute to these differences in estimating HAIs incidence in haematology-oncology departments, including the sample size, the length of study, the inclusion criteria, the data collection methods as well as the definition of HAIs in the studied population. Moreover, the infection control and healthcare care practices, the type of ICU and the country income level may affect the rate of HAIs in different studies.

As far as HAI types are concerned, nosocomial FUO was the most frequent HAI in our study and all cases were neutropenic. It is in agreement with several other studies which reported a high incidence of nosocomial FUO reaching up to 50% in hematology/oncology.14-16 Viral infections may be among the pathogens responsible for FUO in these patients, but we did not screen for viruses because of lack of resources. The high rate of these infections can be explained by several factors: due to the severity and high mortality of infections in this population of patients, prompt empiric therapy is necessary. Therefore, for many febrile episodes, the infectious etiology cannot be established before antimicrobial therapy is initiated. Moreover, diagnosis of infections in neutropenic patients often is impeded, because of the diminished inflammatory response and often muted clinical signs.<sup>9</sup>

We did observe different HAI attack rates among patients with haematologic malignancies originating from different lineages. The highest attack rate was observed in acute myeloid leukemia indicating variability in each patient's vulnerability to nosocomial infections. This result was in line with those found in literature. <sup>3,13,17,18</sup> The differences in the immunological

and biological mechanisms of the myeloid neoplasm lineages may affect the vulnerability to HAI. In myeloid neoplasms, differentiation and maturation of myeloid stem cells (neutrophils, macrophages, and megakaryocytes) is impaired.<sup>19</sup> In lymphoid neoplasms, fewer mature T/NK and B-cells, and a reduced adaptive immune-response are usually observed, however the innate system remains relatively intact to protect against HAIs.<sup>13</sup>

HAIs were mostly clinically documented in our study; this is in line with some other studies.<sup>12,20,21</sup> This could be explained by the fact that doctors prefer early empirical therapy over microbiological confirmation of infections.<sup>15</sup> However, appropriate antibiotic therapy should be preceded by laboratory confirmation of pathogens and according to antibiogram.

During this surveillance, we recorded an unusual increase in positive cases of fungal infections caused by Geotrichum capitatum (5 HAIs) during June and the first week of July 2016. Infections caused by Geotrichum capitatum are uncommon, and have been exclusively reported in immunocompromised patients.<sup>22</sup> They mainly present as septicaemia with occasionally secondary localization.<sup>23</sup> Unfortunately, after investigation, we did not find a source of this germ. Gram negative bacteria were isolated in 41.66% of cases, The predominance of these organisms was frequently reported in similar populations;<sup>4,24</sup> this might be due to the use of less cytotoxic chemotherapy that includes less severe mucositis and less profound neutropenia or the failure to perform routine prophylaxis against Gram-negative bacteria.

Independent risk factors for developing HAIs were male gender, neutropenia, aplasia inducing chemotherapy and bone marrow aspiration and biopsy. Gender differences are a known contributory factor in the susceptibility to infection.<sup>25</sup> Different bacterial species may elicit opposite responses among the sexes. Males usually generate a more aggressive inflammatory immune response to microbial stimuli with a higher mortality rate whereas females showed more protective immune and humoral responses.<sup>26</sup> Clinically, male gender was shown as an independent risk factor for the development of nosocomial bloodstream infection.<sup>24</sup>

Neutropenia was revealed as a risk factor of HAIs in our study, this goes hand in hand with Hui Liu et al. 13 and Biswal et al. 17 who found that neutropenia increases risk of nosocomial infections in haematology ward. Previous studies have demonstrated that neutropenia usually occurs during the first course of induction chemotherapy<sup>17</sup> and this increases the risk of infections among patients undertaking induction chemotherapy. Severity of infection in patients with haematological malignancies is related directly to the degree and duration of neutropenia.<sup>27</sup> Neutrophils are the first line of defence against bacteria and fungi. Lack of circulating neutrophils has a detrimental effect on the integrity of the normal human skin and mucosa, which are at great risk of invasive infection due to the colonizing bacteria, viruses and fungi as neutropenia impairs the phagocytic activity of the neutrophils.<sup>17</sup> This supports the role of neutropenia as a risk factor predisposing to HAIs and necessitates more careful management with strict application of infection control measures for this group of patients.<sup>14</sup>

We found that aplasia inducing chemotherapy was a risk factor of HAIs. It is well established that chemotherapy is very likely to weaken the immune system as chemotherapeutic drugs can cause damage to the bone marrow, and they lead to the interference to the production of sufficient red blood cells, white blood cells, and platelets. Hence, chemotherapy is associated with more HAIs.<sup>18</sup> One study showed that the first course of induction chemotherapy is the stage when HAIs are most likely to occur.<sup>17</sup> Induction chemotherapy consists of a combination of myelosuppressive drugs and results in neutropenia in the majority of patients. As a consequence of severe leukaemia, a severe thrombocytopenia can be observed. Knowing the vital role in inflammation and immune response of platelets, the first course of chemotherapy is a predisposing factor for infections. Subsequently, as patients progress through the chemotherapy regimen, platelets counts increase, and their risks of developing HAIs decrease.<sup>18</sup>

Bone marrow aspiration and biopsy increased risk of HAIs in our sample. In patients with haematological disease, bone marrow aspiration is an important diagnostic tool.<sup>28</sup> Although some hazards are recognized, in general, bone marrow aspiration and biopsy are thought to be safe procedures.

Infection is uncommon and generally less serious than haemorrhage. This access act as a foreign body, causing inflammation at the insertion site, resulting in decreasing of local anti-infection defence due to neutropenia and defective neutrophil function, allowing infections established from small inoculants. Secondly, haemorrhage is a common complication of bone marrow biopsy, in some cases, a haematoma can develop which becomes infected. Patients exposed to bone marrow biopsy in our sample have been probably exposed to an infected haematoma. This adverse event caused by bone marrow biopsy might be counted as a cutaneous infection in our study or even a nosocomial fever of unknown origin. In literature, a prospective study conducted on patients receiving intensive induction chemotherapy in a haematology ward found that bone marrow aspiration and biopsy were associated to higher risk of HAIs.<sup>17</sup> Excluding this study, literature reports that the most frequent adverse event of bone marrow aspiration is haemorrhage.<sup>28,29</sup> Considering this fact, our result should be interpreted with caution; severity of illnesses, biological patterns and patients' outcomes could amplify the risk of HAIs in patients who were exposed to bone marrow aspiration.

#### Strengths and limitations

The strength of our study includes the prospective inclusion of consecutive patients using standardized case definitions. Moreover, the true incidence was assessed because all patients were followed until their discharge. We also analyzed both intrinsic and extrinsic factors associated with HAI, which can help to reduce their incidence as well as to develop surveillance programs.

There are a few limitations in our study: first, the short study period and scarce episodes of HAIs observed; second, no post-discharge surveillance was undertaken, which could have led to underestimation of the incidence because infections with long incubation periods could have been missed; and third, this study was a single-centre study, with all of the recruited patients from a university teaching hospital, thus the generalisability of our findings to other medical settings cannot be assumed.

The issue of considering the fever of unknown origin as HAI in patients with cancer is controversial in literature. Fever can be the only sign of infection within these patients in 36% of cases.<sup>8</sup> Furthermore, viral or fungal infections cannot be identified in our laboratory; even bacteriological infections can be missed due to use of broad spectrum antibiotics. On the other hand, some of these cases might not have been due to infection. Fever can be attributed to cancer itself or to the treatment (e.g. chemotherapy, radiotherapy, immunosuppressive therapy) without infection.

Finally, we used logistic regression to identify the relevant factors associated with HAIs, but this analytical method did not take into account of the possibility of changes in these factors over time. This potential drawback could be resolved by using other statistical methods, such as a proportional hazards model which considers the risks of event change over time. Despite those limitations, our findings provide health care workers with information about the burden of HAIs that will facilitate informed decisions and the implementation of evidence-based preventive strategies.

#### Conclusion

Our study highlights the burden of HAIs in our haematology-oncology department and the role of surveillance for specific HAIs and analyzing its risk factors. A comprehensive education program focused on evidence-based approaches for all healthcare workers should be implemented in this unit. Moreover, adequate cleaning of the environment; precaution measures during construction works; monitoring of air and water for moulds; instructions for patients, and visitors; and special preparation of nutrition, should be more effective. Continuing active surveillance program is crucial to reduce the consequences of HAIs, to improve patient safety and to evaluate effectiveness of these prevention measures.

#### **Competing interests:**

The authors declare that they have no competing interests.

#### Acknowledgement

We would like to appreciate and thank all those who have helped us during our research work.

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