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Surveillance of Healthcare-Associated Infections Rates in Hematology-Oncology Patients

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Abstract

Background: Healthcare-associated infections (HAIs) consist of a major cause of morbidity and mortality among patients with hematologic malignancies, resulting in high length of stay and healthcare costs. The aim of this study was to assess the HAIs rates in adult hematology-oncology patients.

Patients and Methods: A prospective surveillance study was performed in a hematology-oncology unit in Athens, Greece. All patients who remained for ≥ 48 hours were studied. A standardized surveillance system based on the National Healthcare Safety Network of the Centers for Disease Control and Prevention was implemented.

Results: During 1,156 patient-days, 16 of 85 patients acquired 20 HAIs resulting in an overall rate of 18.8% of patients or 17.3 HAIs per 1,000 patient-days. FUO rate was 42.5 per 1,000 patient-days with neutropenia. Most of HAIs was laboratory confirmed (80%) than clinically documented (20%). Central line-associated bloodstream infection was the most commonly encountered type of infection, accounting for 25% of all HAIs, followed by soft tissue infections (20%). The rates of neutropenia, blood transfusion and presence of central venous catheter were significantly greater among patients with HAI, compared with patients without HAI ($p<0.05$). The crude mortality rate for patients with and without HAI was 12.5% and 2.9%, respectively ($p=0.234$).The mean length of stay was statistically longer for patients with HAI compared with patients without HAI (29.6 ± 28.5 vs. 9.8 ± 6.8 days, $p<0.001$). Gram-negative bacteria were the most prevalent pathogens (73.3%).

Conclusions: Our findings highlight the problem of HAIs in hematology-oncology patients and emphasize the importance of a comprehensive education program focused on evidence-based approaches for all healthcare workers and continuing active surveillance program, which will contribute to reducing the consequences of HAIs and improving patient safety.

Keywords: Healthcare-associated infections; Hematology-oncology; Surveillance; Neutropenia; Fever of unknown origin

Abbreviations HAIs-Healthcare-Associated Infections; FUO-Fever of Unknown Origin; NHSN-National Healthcare Safety Network; CDC-Centers for Disease Control and Prevention; MASCC Score-The Multinational Association for Supportive Care in Cancer risk index Score; SD-Standard Deviation; CLABSI-Central Line-Associated Bloodstream Infection; BSI-Blood Stream Infection; STI-Soft Tissue Infection; UTI-Urinary Tract Infection

Introduction

Despite advances in oncology care, infections remain a major cause of morbidity and mortality among patients with hematologic malignancies, resulting in high length of stay and healthcare costs [1-4]. The estimated incidence density of healthcare-associated infections (HAIs) ranges from 11 to 21.8 per 1,000 patients-days [5-7]. The attributable length of stay to HAIs has been found to vary from 6.8 to 11.5 days, the attributable mortality from 4.9% to 26.3%and the attributable cost from £6,324 (Canadian dollar) to £19,110 (US dollar) per oncology patient with HAI [8-13].

Increased risks for infection are attributed, in part, to immunosuppression caused by primary malignancy, neutropenia, disruption of mucosal barriers, splenectomy and functional asplenia, corticosteroids and other lymphotoxic agents and hematopoietic stem cell transplantation [14-17]. In addition, patients with hematologic malignancies may be leukopenic due to infiltration of the marrow with malignant cells or due to a dysfunctional marrow [1].

Furthermore, hematology patients are at risk of infection most serious complication, septic shock. The incidence of severe sepsis in patients with hematological malignancies is as high as 66 per 1000 population per year, with rates of 275 per 1000 population per year in patients with acute myeloid leukemia [18]. Mortality from severe sepsis is approximately 36%, with rates up to 45% in monocytic leukemia [18], and as high as 99% for patients requiring mechanical ventilation following hematopoietic stem cell transplantation [19]. Changes in the behavior of immune cells, including decreased apoptosis of lymphocytes or expansion of myeloid-derived suppressor cells, are associated with impaired anti-infective responses in hosts with

advanced malignant diseases [20]. Pathogens or microbial associated molecules cause tissue damage and inflammatory reactions. Organ dysfunction results from direct cytotoxic effects of inflammatory mediators and microbial toxins, dysregulation of circulation, oxygen transport and tissue oxygenation. Recruitment of inflammatory cells, endothelial damage and activation of endothelial cells leading to increased permeability of the vessel wall appear to be additional factors contributing to organ dysfunction [21-23]. Interstitial edema, capillary microembolization or microthrombi and loss of regulation of the microvascular blood flow lead to perfusion mismatch with a decrease in peripheral vascular resistance and myocardial depression caused by myocardial depressant factors, such as toxins, cytokines, metabolic defects of myocytes and down-regulation of beta-receptors [21-23]. Hematology patients with altered immunity may not mount the classical inflammatory response and so it is essential that clinicians are alert to the range of presentations of severe infection and have a low threshold for implementing treatment [24]. Therefore, diagnosis and management of sepsis according to guidelines could improve outcome of this patient population [21].

Given their vulnerable condition, great attention to infection prevention is warranted in the care of these patients. Data about clinically documented infections and fever of unknown origin (FUO) in this patient group are limited [6,7,25,26]. Comparing and benchmarking rates continues to be a challenge. Standardized definitions should be used to develop effective strategies to prevent and manage infectious complications in hematology-oncology patients. The primary objective of this study was to assess the incidence density of HAIs and FUO which will provide a basis to design a more effective, active surveillance program to case-finding, outbreak detection and identify opportunities for quality improvement of healthcare practices and modification of healthcare workers' habits and attitudes.

Patients and Methods

Patients and setting

A prospective surveillance study of HAIs and FUO was performed in a hematology-oncology unit in Athens, Greece, from August 2014 to December 2014. The hematology unit was a thirteen-bed unit with five 1-patient rooms and eight 2-patient rooms. The nurse to patient ratio was 1:8. There was a multidisciplinary infection control team with one infection control practitioner. The study protocol was approved by the institutional review board and patients' confidentiality was guaranteed.

Surveillance

All patients who remained in the hematology-oncology unit for ≥ 48 hours were studied and monitored for HAIs until discharge from the unit or death. A standardized surveillance system based on the National Healthcare Safety Network (NHSN) of the Centers for Disease Control and Prevention (CDC) was implemented [27]. Data were prospectively collected on an anonymous standardized survey record. All patients with HAI were identified daily from a specially trained nurse and were subsequently observed by an infectious diseases specialist who provided assistance if necessary. Patients' data included demographic characteristics, underlying hematologic malignancy, presence of central venous catheter or urinary catheter, catheter days, symptoms and signs of infection, laboratory findings, causative pathogens, antibiogram, antibiotics use, type and duration of administrated antibiotics, and presence of neutropenia (neutrophil count of 500/mm^3 or less). The Multinational Association for Supportive Care in Cancer risk index score (MASCC score) was calculated for febrile neutropenic patients. Patients with a score of ≥ 21 were regarded as low risk of complications, whereas patients with a score <21 were regarded as high risk [28].

The diagnosis of HAIs was based on CDC's/NHSN definitions of 2014 [27]. The diagnosis for FUO was based on the following definition: fever of at least 38˚C lasting more than 1 hour with onset 2 or more days after admission without 1. evidence of specific infection at any site, 2. isolation of specific microorganisms from body specimens, or 3. any apparent noninfectious cause for the fever (e.g., aggressive chemotherapy in a patient with a large tumor load, sickle cell crisis, drug fever, or transfusion-related fever within 6 hours after administration) [6].

We classified infections into two categories. Laboratory confirmed infections (infections that could be explained by microbiological confirmation) [26] and clinically documented infections (clinical symptoms or signs that may be due to infections with no culture taken or negative culture results) [7].

Isolated bacteria were classified as susceptible, multidrug resistant, extensively-drug resistant, and pan-drug resistant according to published criteria [29].

HAIs rate calculations

HAIs rate measured during the surveillance period included the incidence density rates of HAIs (number of HAI cases divided by 1,000 patient-days and multiplied by 1,000 or number of CLABSI cases divided by 1,000 central line-days and multiplied by 1,000).

Device utilization ratios have been calculated by dividing the total number of device-days by the total number of patient-days. Device-days are the total number of days of exposure to each device (central catheter or urinary catheter) for all of the patients during the selected time period. Patient-days are the total number of days that patients are hospitalized during the selected time period.

Cost calculations

Costs that were taken into account were the hospital-based costs per patient. We distinguished diagnostic costs, costs of hospital stay and antibiotic costs for the treatment of each patient. Diagnostic costs taken into account were radiologic imaging, laboratory studies and microbiological investigations. We reported costs in Euros for the year 2014.

Statistical analysis

Continuous variables were described as mean and standard deviation and discrete variables as number and percentage. Continuous variables were compared using Student's t-test for normally distributed variables and Mann-Whitney U-test for non-normally distributed variables. The x^2 statistic or Fisher's Exact Test was used to compare categorical variables. All P values of <0.05 were considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics, version 22.

Results

Over the study period, 85 patients were hospitalized for a total of 1,156 days. Characteristics of patients with and without HAI are summarized in Table 1. The rates of neutropenia, blood transfusion

and presence of central venous catheter were significantly greater among patients with HAI, compared with patients without HAI ($p<0.05$). The mean length of stay was statistically longer for patients with HAI compared with patients without HAI (29.6 ± 28.5 vs. 9.8 ± 6.8 days, $p<0.001$). The crude mortality rate for patients with and without HAI was 12.5% and 2.9%respectively, yielding an overall crude excess mortality rate of 9.6% (relative risk, 4.7; 95% CI, 0.6-36.9; p=0.234) (Table 1).

	HAI		P Value
	Yes	No	
Variables	**N=16**	**N=69**	
At admission			
Age (Mean ± SD)	72.6 ± 9.6	73.2 ± 11.9	0.436
Sex			
Male	13 (81.2%)	48 (69.6%)	0.379
Female	3 (18.8%)	21 (30.4%)	
Hematological disease			
Multiple myeloma	4 (25%)	16 (23.2%)	0.703
Non- Hodgkin's lymphoma	3 (18.7%)	15 (21.7%)	0.632
Chronic lymphoid leukemia	3 (18.7%)	12 (17.4%)	0.736
Myelodysplastic syndrome	2 (12.5%)	12 (17.4%)	0.367
Hodgkin disease	2 (12.5%)	11 (15.9%)	0.456
Acute myeloid leukemia	1 (6.2%)	3 (4.3%)	0.231
Acute lymphoid leukemia	1 (6.2%)	1 (1.4%)	0.371
During hospitalization			
Neutropenia (neutrophils <500/mm^3)	9 (56.2%)	5 (7.2%)	<0.001
Blood transfusion	14 (87.5%)	21 (30.4%)	0.004
Central venous catheter	8 (50%)	3 (4.3%)	<0.001
Port catheter	2 (12.5%)	7 (10.1%)	1
Urinary catheter	2 (12.5%)	6 (8.6%)	1
Deaths	2 (12.5%)	2 (2.9%)	0.234
Length of stay, days (Mean ± SD)	29.6 ± 28.5	9.8 ± 6.8	<0.001
Length of neutropenia, days (Mean ± SD)	8 ± 7.6	3.5 ± 3.7	0.135
SD-Standard deviation			

Table 1: Characteristics of patients with and without HAI during the study period.

Characteristics of patients with neutropenia are summarized in Table 2. The mean length of stay was 32.2 ± 32.8 days and the mean length of days with neutropenia was 6.7 ± 6.9 days. The incidence of HAIs was 42.8% and the incidence of FUO was 28.6%. Of the 9 episodes of febrile neutropenia, 6 (66.7%) were cases of MASCC score <21. Of the 6 patients with MASCC score <21, 5 (83.3%) developed HAI.

Variables	N=14 (%)
Age (Mean ± SD)	69.5 ± 9.5
Sex	
Male	10 (71.4%)
Female	4 (28.6%)
Severe neutropenia (neutrophils <100/mm^3)	12 (85.7%)
Length of stay, days (Mean ± SD)	32.2 ± 32.8
Length of neutropenia, days (Mean ± SD)	6.7 ± 6.9
Febrile neutropenia	9 (64.3%)
MASCC score ≥ 21	3 (33.3%)
MASCC score <21	6 (66.7%)
HAI	6 (42.8%)
FUO	4 (28.6%)
Deaths	1 (7.1%)
SD-Standard deviation; HAIs-Healthcare-associated infections; FUO-Fever of Unknown Origin	

Table 2: Characteristics of patients with neutropenia.

HAIs rates are described in Table 3. During the study, 16 of 85 patients acquired 20 HAIs resulting in an overall rate of 18.8% of patients or 17.3 HAIs per 1000 patient-days (95% CI, 17.0-17.5). FUO rate was 42.5 per 1000 patient-days with neutropenia <500/mm^3 (95% CI, 41.1-43.8).

HAIs	N=20 (%)	Incidence rate per 100 patients	Incidence density rate per 1,000 patient-days
Laboratory confirmed HAIs	16 (80)	18.8	13.8
CLABSI	5 (25)	5.8	15.2*
STI	4 (20)	4.7	3.4
BSI	3 (15)	3.5	2.6
Pneumonia	3 (15)	3.5	2.6
UTI	1 (5)	1.2	0.9
Clinically documented HAIs	4 (20)	4.7	3.4
Pneumonia	4 (20)	4.7	3.4
Overall	20 (100)	23.5	17.3
HAIs-Healthcare-associated infections; CLABSI-Central Line-Associated Bloodstream Infection; BSI-Blood Stream Infection; STI-Soft Tissue Infection; UTI-Urinary Tract Infection; *1,000 central line days			

Table 3: Healthcare-associated infections rates.

Most of HAIs was laboratory confirmed (80%) than clinically documented (20%). Central line-associated bloodstream infection (CLABSI) was the only detected device-associated HAI (15.2 per 1000 days with central line, 95% CI, 14.7-15.6) (Table 3). The device utilization ratio was 28.3% for central lines and 11.5% for urinary catheters. The incidence density rate of HAIs was higher during days with neutropenia (63.8 per 1,000 days with neutropenia, 95% CI, 12.75-114.9) compared with days without neutropenia (12.1 per 1,000 patient-days, 95% CI, 5.77-18.45, relative risk, 4.5, p=0.02).

Infection site	Isolated pathogens	Undetermined	Total
Pneumonia	*Klebsiella pneumoniae*: 2	4	7
	Pseudomonas aeruginosa: 1*		
CLABSI	*Klebsiella pneumoniae*: 2	-	5
	Staphylococcus epidermidis: 2		
	Staphylococcus aureus: 1		
STI	*Pseudomonas aeruginosa*: 3	1	4
BSI	*Escherichia coli*: 1	-	3
	Pseudomonas aeruginosa: 1		
	Staphylococcus epidermidis: 1		
UTI	*Escherichia coli*:1*	-	1
Total	15	5	20

CLABSI-Central Line-Associated Bloodstream Infection; STI-Soft Tissue Infection; BSI- Bloodstream Infection; UTI-Urinary Tract Infection; *Multidrug resistant

Table 4: Distribution of pathogens by site of infection.

The distribution of pathogens by site of infection varies (Table 4). Overall, 73.3% of isolated pathogens were Gram-negative bacteria. *Pseudomonas aeruginosa* was the most common isolated pathogen (33.3%), followed by *Klebsiella pneumoniae* (26.7%) and *Staphylococcus epidermidis* (20%).The majority of isolated pathogens (86.7%) were susceptible to most antibiotics and 13.3% were classified as multidrug resistant.

The total cost of HAIs (43,676.8 €) and FUO (10,427.9 €) was 54,104.7 €. The higher mean cost was consumed for UTI (2,832.1€) and CLABSI (2,448.9 ± 1,362.1 €) (See Table 5). Sixty two per cent (62.4%) of total HAIs and FUO cost was associated with hospitalization stay (33,776.8 €) and 26% with antibiotic usage (14,076.6 €) (Figure 1).

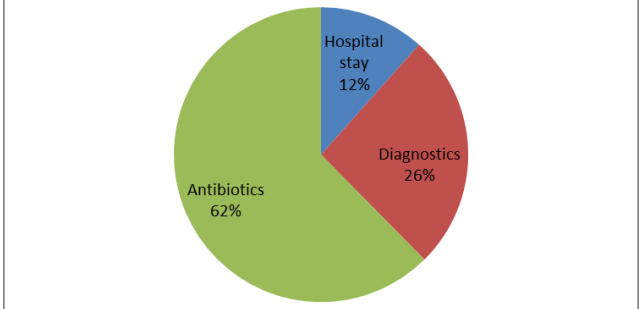

Figure 1: Distribution of costs in patients with HAI and FUO.

Infection site	Cost category, € (Mean ± SD)			
	Diagnostics	Antibiotics	Hospital stay	Total costs
Pneumonia	240.1 ± 139.8	674.1 ± 935.9	913.8 ± 694.7	1,828 ± 1,391.1
CLABSI	190.7 ± 140.4	686.2 ± 876.1	1,572 ± 1,181.4	2,448.9 ± 1,362.1
STI	302.7 ± 149	729.3 ± 809.1	1,180 ± 395.9	2,212.1 ± 912.2
BSI	199.4 ± 223.8	98.8 ± 75.2	2,020 ± 1,381.7	2,318.3 ± 1,334.5
UTI	464.9 (NA*)	827.2 (NA*)	1,540 (NA*)	2,832.1 (NA*)
All HAIs	245.4 ± 153.2	609.5 ± 769.4	1,328.8 ± 912.9	2,183.8 ± 1,187.8
FUO	335.5 ± 271.3	471.3 ± 343.4	1800 ± 1600.9	2606.9 ± 2192.4

SD-Standard deviation; CLABSI-Central Line-Associated Bloodstream Infection; STI-Soft Tissue Infection; BSI-Bloodstream Infection; UTI-Urinary Tract Infection; HAI-Healthcare-Associated Infection; FUO-Febrile of Unknown Origin; *Non applicable due to small number of cases

Table 5: Mean medical costs per HAI and FUO.

Discussion

The Centers for Disease Control (CDC) Study of the Efficacy of Nosocomial Infection Control (SENIC) Project have shown that an integrated infection control program, with HAIs surveillance as its cornerstone, can reduce the incidence of HAIs by 30%, yielding economic benefits [30].

The current study showed that HAIs are a significant problem in the Greek hematology-oncology patients studied (17.3 HAIs per 1000 patient-days, 95% CI, 17.0-17.5), especially during neutropenia (63.8 HAIs per 1,000 patient-days with neutropenia, 95% CI, 12.75-114.9).

In our study, HAIs density rate is considerably higher than the rates reported in a previous study (11 HAIs per 1000 patient-days) from Germany [6] and Israel [7] (12.7 HAIs per 1000 patient-days). However, our results are much lower than those reported in a Greek study [5] (21.8 per 1000 patient-days). It is difficult to make comparison among facilities because of differences in the reporting of infections, patient population, length of stay, and lack of CDC's/NHSN standard definitions of HAIs [6,26,31-33].

This study revealed that the clinically documented HAI's rate was 20%, phenomenon that could be explained by the fact that doctors prefer early empirical therapy over microbiological confirmation of infections [6]. The implementation of a protocol for invasive diagnoses in patients with clinical signs and the laboratory confirmation of pathogens according to antibiogram are indispensable for appropriate antibiotic therapy [34].

To our knowledge, this is the first prospective surveillance study of HAIs in Greece that includes FUO as a separate clinical entity. The density rate of FUO (42.5 per 1000 patient-days with neutropenia) was higher than the rate reported by previous studies in Germany [6] (15.4 per 1000 patient-days with neutropenia) and Brazil [28] (39.8 per 1000 patient-days with neutropenia). However, our results are comparable to those from Israel [7] (43.7 per 1000 patient-days with neutropenia). Previous authors recommend that FUO be included as an important and frequent clinical entity in surveillance for HAIs in hematology-oncology patients. Without its inclusion, studies results would be less comparable, underestimating the real condition in this population [6].

According to CDC/NHSN report CLABSI rates and central line utilization ratios should be examined together, so that preventive measures can be targeted appropriately [35,36]. In our study central line utilization ratio (28.3%) was almost identical to those reported in the NHSN report for the year 2013 (26.7%). In contrast, our observation of higher CLABSI rate compared with NHSN report [36] (15.2 infections versus 1.7 infections per 1000 central line-days, respectively) may be attributed to the minimal compliance with hand hygiene (62.8%) and central line maintenance care bundle (58.3%) (Data not shown) [37]. A combination of central line bundle adoption, compliance monitoring and performance feedback is the key to reducing CLABSI rates and improving patient safety [38-42].

On the other hand, the higher pneumonia rate (6.0 infections per 1000 patient-days) compared with those reported by other studies in Greece [5](3.0 per 1000 patient-days), France [43] (3.3 per 1000 patient-days) and Germany [6] (3.7 per 1000 patient-days) may reflect the fact that 71.4% of patients with pneumonia had used respiratory therapy devices such as nebulizers (Data not shown). CDC's guidelines for preventing healthcare-associated pneumonia should be a priority in studied population [44].

In our study there was a predominance of Gram-negative bacteria among hematology-oncology patients with HAIs, as has been reported in other studies [12,26,45]. 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 [46-49].

Finally, it is noteworthy that this is the first study that attempted to estimate the nosocomial cost of HCAIs in hematology-oncology patients in Greece. The cost of HCAIs is an important factor for economic analysis. We specifically focused on the costs of treating the patient with HAI from a hospital perspective, without taking into account the economic consequences of HAIs from a societal point of view. Mean nosocomial cost of HCAIs in oncology patients is reported in the range of USD 6,324 to 19,110 from different countries [9-11]. In this study, the mean nosocomial cost was found as 2,183.8 ± 1,187.8€, which was lower than findings elsewhere. It is difficult to make comparisons because of wide variability among studies including small sample size and varying healthcare costs for comparable services internationally and between regions in countries. In the current study, the lower mean nosocomial cost per HAI may reflect the other cost categories that we did not take into account, such as drugs, other healthcare materials and other interventions [50,51].

The strength of our study was the cohort design. Potential sources of bias were the same as those related to any voluntary surveillance system. Furthermore, diagnoses could be misclassified. However, the use of a common protocol with standard definitions of HAIs provided by the CDC's NHSN and the prospective data collection limit the possibility of systematic bias having affected our clinical outcomes. The study also had several potential limitations. First, our study did not include enough patients for detailed estimates of clinical outcomes for HAIs to be computed. Second, the study was performed only in one hematology-oncology unit in Athens, and the results should not be generalized to other settings. 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.

Our study confirms the problem of HAIs in hematology-oncology patients, in particular during the neutropenia period. The high rates of device-associated infections and FUO highlight the importance of establishing an active modified surveillance program, developing a comprehensive education program focused on evidence-based approaches for all healthcare workers, which will contribute to reducing the burden of HAIs and improve quality of care and safety in Greek hematology-oncology patients.

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