ARTICLE ORIGINAL

Prevalence surveillance of healthcare-associated infections at a Tunisian onco-hematology ward

Prévalence des infections associées aux soins en oncohématologie en Tunisie

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RÉSUMÉ

Prérequis : Les infections associées aux soins (IAS) sont redoutables chez les patients d'oncohématologie en raison de la forte morbi-mortalité qu'elle engendre et de leur surcoût.

But : Le but de notre étude était de déterminer la prévalence des IAS dans le service d'Hématologie du Centre National de Greffe de Moelle Osseuse (CNGMO) et d'étudier les facteurs de risque (FR) associés.

Méthodes : Nous avons mené six enquêtes répétées de prévalence ponctuelle tous les deux mois (Mai 2018- Avril 2019) au service d'Hématologie. Tous les patients hospitalisés les jours de l'enquête étaient inclus. L'étude d'association entre un éventuel FR et la survenue d'une IAS était estimée par le calcul de l'odds-ratio (OR) avec des intervalles de confiance (IC) à 95%. Les FR étaient évalués à l'aide d'un modèle de régression logistique.

Résultats : Dix-neuf patients parmi un total de 74 patients hospitalisés ont présenté un total de 19 IAS soit une prévalence de 25,7%. Aucune tendance significative à la baisse ou à la hausse de la prévalence n'a été constatée au cours de la période d'étude (p=0,3). L'infection respiratoire était la plus fréquente (57,9%) avec une prévalence de 14,9%. L'analyse multivariée révélait que l'IAS était significativement associée à la neutropénie (OR ajusté: 14; IC à 95%: 1,5-127; p=0,01) et à la durée de pose du cathéter veineux central (OR ajusté: 1,1; IC à 95%: 1-1,2 ; p=0,005).

Conclusion : Prévalence élevée des IAS au CNGMO avec un taux de mortalité élevé, nécessitant l'adoption des pratiques adéquates de contrôle des infections.

Mots clés : Infection associée aux soins, prévalence ponctuelle, oncohématologie.

SUMMARY

Introduction : Healthcare-associated infections (HAIs) are with high rates of mortality and an additional cost, in onco-hematology patients.

Aim : To assess the prevalence trends of HAIs in the onco-hematology ward of the Tunisian National Bone Marrow Transplant Center (NBMTC), and to determine the principal associated risk factors.

Methods: Six repeated point prevalence surveys were conducted, from May 2018 to March 2019, using a two months interval. All patients hospitalized in the day of the survey were included. Risk factors of HAIs were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). They were assessed using a logistic regression model.

Results: Nineteen patients out of a total of 74 patients have been diagnosed with 19 HAIs, representing a prevalence of 25.7%. No significant downward or upward trend of prevalence was revealed over time (p=0.3). The most common HAI was respiratory tract infection (57.9%) with a prevalence of 14.9%. Multiple logistic regression analysis revealed that HAI was significantly associated with neutropenia (Adjusted OR: 14; 95% CI: 1.5-127; p=0.01) and duration of central venous catheter (Adjusted OR: 1.1; 95% CI: 1-1.2; p=0.005).

Conclusion: High prevalence of HAIs in our center with a high rate of mortality, requiring identifying potential problems in infection control practices.

Key words: Healthcare-associated infection; point prevalence survey ; onco-hematology

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INTRODUCTION

Healthcare-associated infections (HAIs) rates depend on the severity of illness, the use of invasive devices and the type of care performed. In onco-hematology, after hematopoietic stem cell transplantation (HSCT), patients are at increased risk for acquiring potentially life-threatening HAI (1) which are associated with prolonged stays, increased healthcare costs and considerable morbidity and mortality in this population (1).

The estimation of the burden of HAIs and its trend over time, among onco-hematology patients, is lacking and poorly studied in Tunisia.

Repeated and regular point prevalence surveys (PPS) is a cost-effective surveillance method to evaluate the HAIs prevalence evolution over time.

Our aims was to assess the prevalence trends of HAIs in the onco-hematology ward of the Tunisian National Bone Marrow Transplant Center (NBMTC), and to determine the associated risk factors (RF).

METHODS

Patients

A punctual cross-sectional study (one day) was repeated every two months (May 2018-March 2019) in the adult hospital ward of the NBMTC. Six PPS of HAIs were conducted using a standardized methodology. All patients hospitalized on the day of the survey were included.

Patients were screened for multidrug-resistant bacteria by rectal swabs at admission and weekly thereafter until discharge. After that, patients received a selective digestive decontamination (SDD) using enteral colimycin, gentamicin and fungizone to eliminate Gram-negative rods and fungi.

Day of infusion of HSCT was considered day 0 for HSCT recipients.

Definitions

A HAI was defined as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s). There must be no evidence that the infection was present or incubating at the time of admission to the acute care setting (2). Once an infection is deemed to be HAI, the specific type of infection should be determined (3).

Specific types of HAIs considered were: Bacteremia, respiratory tract infection (RTI), urinary tract infection, fungemia and nosocomial fever from unknown origin (NFUO).

NFUO was defined as fever of at least 38ºC for more than four hours occurring in a hospitalized patient in whom neither fever nor infection was present on admission and for which an infectious cause cannot be determined after three days of investigation, including two days of cultures (4, 5).

Neutropenia was defined as a neutrophil count <500/ mm^3 (6).

We classified each identified site of HAI as microbiologically, clinically or both microbiologically and clinically documented.

Mortality was considered as due to HAIs if there was no other apparent cause of death.

Data collection

For each study, all included patients were surveyed on a single day by trained investigators. A standard form was used, collecting informations related to clinical characteristics (gender, age, underlying disease, HSCT, neutrophil counts, graft versus host disease (GVHD), presence of central venous catheter (CVC)), infection (type of infection, prior colonization with the same strain, treatment received and outcome) and microbiological data.

Microbiological study

In case of fever or other signs of infection and systematically in patients on corticosteroids, samples were obtained according to the presumed infection. Samples were analyzed according to the “Référentiel En Microbiologie Médicale” guidelines (7). Bacterial identification was based on morphologic, cultural and biochemical characteristics (Api systems, BioMérieux®). *C. albicans* was identified by its filamentation on human serum. Antimicrobial and antifungal susceptibilities testing were performed by the diffusion method on agar medium according to the European Committee on Antimicrobial Susceptibility Testing standards (8).

Statistical analysis

Means and extreme values or medians and Inter Quartile Range IQR (25%-75%) were calculated for quantitative variables.

Proportions were compared using chi square test. Means were compared using Student's t-test for quantitative variables which were normally distributed.

The Mann Whitney Test was used to compare the distribution of CVC duration, days on neutropenia and length of stay, between infected patients versus others.

Univariate and multivariate logistic regression analysis was performed to identify the RF for HAIs.

In the univariate logistic regression, RF were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Variables having a significance level of $p < 0.25$ level were added to the multivariate logistic regression model.

Backward step- wise selection strategy was used to obtain the final model.

A p value < 0.05 was considered as statistically significant.

RESULTS

Patient features

During the six prevalence surveys, 74 patients were included. The mean age was 37 years (SD=16.1 ; range : 5-66) and the sex-ratio was 1.2 (Table 1).

The median length of stay from admission to study day was 10 days (range: 0–82).

Infections

Nineteen patients out of 74 have been diagnosed with 19 HAIs, an overall prevalence of 25.7% (95% CI [16.2 – 36.5]) with no statistically significant difference by gender (27.5% male, 23.5% female, p=0.7).

No significant downward or upward trend of prevalence was revealed over time (Chi square test for linear trend; p=0.3).

The lower and the highest prevalence of HAI were recorded, respectively, in March 2019 (7.7 % (1/13)) and in September 2018 (45.5% (5/11)) with a statistically significant difference (p=0.04) (Figure 1).

Table 1. Hospitalized patients and transplant characteristics

Clinical features	Number of hospitalized patients (%)	Number of infected patients (%)
Total of patients	74 (100)	19
Hematological disease		
Acute myeloblastic leukemia	15 (20.3)	4 (26.7)
Acute lymphoblastic leukemia	10 (13.5)	3 (30)
Mixed phenotype acute leukemia	2 (2.7)	0 (0)
Chronic myeloblastic leukemia	2 (2.7)	0 (0)
Aplastic anemia	5 (6.8)	3 (60)
Lymphoma	13 (17.5)	3 (23.1)
Myeloma	19 (25.7)	5 (26.3)
Myelodysplastic syndrome	5 (6.8)	0 (0)
Mycosis fungoides	2 (2.7)	1 (50)
Fanconi anemia	1 (1.3)	0 (0)
Treatment		
Allograft	39 (52.7%)	10 (25.6)
Autograft	29 (39.2%)	9 (31)
No HSCT	6 (8.1%)	0 (0)

HSCT: hematopoietic stem cell transplantation

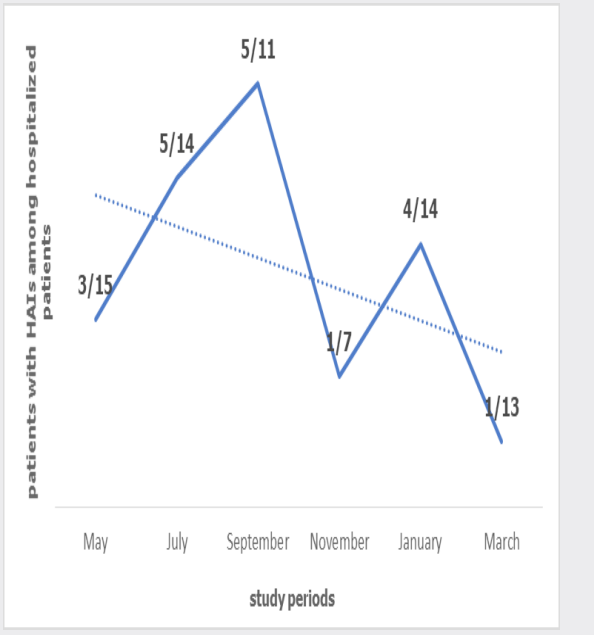

Figure 1. Temporal trends of health-care associated infections during the study period

No significant differences were detected when comparing prevalence between each two successive surveys.

The highest prevalence rate was observed in surveys conducted in summer with no statistically significant seasonal variations (23.8% in winter (November 2018 and January 2019), 14.3% in spring (May 2018 and March 2019), 40 % in summer (July and September 2018); p=0.09). All infected patients had received HSCT.

The prevalence of HAIs was higher in autografts (9/29, 31%) than in allografts (10/39, 25.6%).

Seven HAIs out of 19 occurred within 100 days post graft (range: -10 to 2537 days). Proportionally, RTI was the most common site (57.9%; n=11) with a prevalence of 14.9% (95% CI: 6.8-23), followed by bacteremia (10.5%; n=2), cutaneous infection (10.5%; n=2) and fungemia (5.3%; n=1). NFUO was reported in 15.8% (n=3) of cases.

Bacteremia was related to catheter in one of two cases.

Fever was the major sign, present in 15 cases. It was the only reported symptom in seven of 15 cases. Among the 19 HAIs, nine infections were clinically documented (47.4%) (cutaneous infection (n=2) and RTI (n=7), two (10.5%) were microbiologically documented (bacteremia (n=1) and fungemia (n=1), and five (26.3%) were both clinically and microbiologically documented (RTI (n=4) and bacteremia (n=1)). The median duration of hospital stay until developing a HAI was 14 days (IQR: 4-37).

There was a significant upward trend in prevalence of HAI with different levels of neutropenia severity. More the neutropenia numeration was severe more the proportion of HAIs increased (Chi square trending test, p=0.02).

In patients with neutropenia, days on neutropenia was not significantly associated with HAI (Mann Whitney test, p=0.15). GVHD was not significantly associated with HAI (17.6% vs. 26.9%; p=0.7).

Using the univariate logistic regression, significant RF for HAIs (with p<0.05) were: neutropenia (OR: 2.8 ; 95% CI: 1.3-5.9 ; p=0.007), severity levels of neutropenia (Chi square trending test, p=0.02), administration of granulocyte colony-stimulating factor (G-CSF) (OR: 3.4 ; 95% CI: 1.3-9.4 ; p=0.006), duration of CVC insertion (p=0.003, Mann Whitney test), duration of length of stay (from admission to survey day) (p=0.02)) and length of stay >12 days before starting the survey (p=0.05) (Table 2).

Table 2. Risk factors associated with occurrence of HAI as a result of univariate logistic regression analysis

	Infected patients N (% HAI)	OR	95% IC	p
Age >60	Yes 3 (33.3) No 16 (24.6)	1.35	0.5-3.7	0.7
Sex	Male 11 (27.5) Female 8 (23.5)	1.2	0.5-2.6	0.7
Previous hospitalization within 3 months prior to admission	Yes 9 (26.5) No 101 (25)	1.05	0.5-2.3	0.9
HSCT	Yes 19 (31.7) No 0 (0.0)	-	-	0.2
Community acquired infection history	Yes 5 (27.8) No 14 (25)	1.1	0.5-2.6	1
GCSF	Yes 15 (39.5) No 4 (11.4)	3.4	1.3-9.4	0.006
Conditioning for HSCT	Yes 19 (27.9) No 0 (0)	-	-	0.3
SDD	Yes 11 (35.5) No 8 (18.6)	1.9	0.9-8.8	0.1
Neutropenia	Yes 10 (47.6) No 9 (17)	2.8	1.3-5.9	0.007
Level of neutropenia				
No neutropenia	9 (17)	ref	ref	0.02
PNN 100-500	3 (37.5)	2.9	0.6-14.5	0.18
PNN<100	7 (53.8)	5.7	1.5-21.0	0.009
Length of stay until survey day>12 days	Yes 12 (37.5) No 7 (17.5)	2.14	1-4.8	0.05
Mucositis grade>=3	Yes 8 (34.8) No 11 (21.6)	1.6	0.7-3.5	0.2
CVC	Yes 12 (27.3) No 7 (23.3)	1.2	0.5-2.6	0.7
PVC	Yes 8 (22.9) No 11 (28.2)	0.8	0.4-1.8	0.6
Urinary catheter	Yes 2 (67) No 17 (24)	2.8	1.1-6.8	0.16
GVHD	Yes 3 (17.6) No 7 (26.9)	0.7	0.2-2.2	0.7
Number of devices				
1	16 (24.2)	1.5	0.6-4.2	0.4
2	3 (37.5)			
Length of stay until survey				
Median [IQR]				
HAI(+)	18 [9-39]	1.1	1-1.1	0.02
HAI(-)	8 [4-20]			
Days on neutropenia in neutropenic patients				
Median [IQR]	11 [4-30]		0.9-1	0.15
HAI(+)	16 [14-28]			
HAI(-)		1		
CVC Duration				
Median [IQR]				
HAI(+)	31 [17-40]	1.1	1-1.2	0.003
HAI(-)	14 [10-20]			

HSCT : hematopoietic stem cell transplantation, G-CSF: granulocyte colony-stimulating factor, SDD: selective digestive decontamination, CVC: central venous catheter, GVHD: graft versus host disease, PVC: peripheral venous catheter.

Explanatory variables entered for the multivariate logistic regression were G-CSF (p=0.006), mucositis grade>=3 (p=0.22), DDS (p=0.1), urinary catheter (p=0.16), duration of CVC insertion (p=0.003), neutropenia (p=0.007) and length of stay >12 days before starting the survey (p=0.05).

RF associated with occurrence of HAI as a result of multivariate logistic regression analysis (Final model) were: neutropenia (Adjusted OR: 14; 95% CI: 1.5 - 127; p=0.01) and duration of CVC insertion (Adjusted OR: 1.1; 95% CI: 1-1.2; p=0.005).

Antibiotic use

The first-line antibiotherapy was based on a monotherapy in four cases and a dual-therapy or more in 15 cases. Time to start it ranged from one to two days. The most commonly prescribed antibiotic was imipenem (n=10), mainly in combination with amikacin (n=5). This first-line antibiotherapy was appropriate in 13 cases.

A second-line antibiotherapy was indicated in eight of cases because of antimicrobial resistance (n=3), persistence of fever or worsening of symptomatology (n=4) or toxic complications (n=1). Ciprofloxacin and imipenem were prescribed in three and two cases, respectively.

In-hospital mortality

HAIs evolved into sepsis in three patients. A septic shock occured in two cases. Mortality was related to HAIs in two cases (2/19). Dead patients had as underlying hematologic malignancies myeloma and mycosis fungoides. One of them had a severe neutropenia at the time of HAI and the other experienced a delay of two days to start an adequate antibiotherapy. Death occurred after *P. aeruginosa* RTI complicated with septic shock. *P. aeruginosa* was a pan drug-resistant strain in one case.

Microbiological testing results

The microorganisms (n=7) isolated were *P. aeruginosa* (n=3), *C. albicans* (n=2), *M. morganii* (n=1) and *G. haemolysans* (n=1).

Four RTI (n=11) were microbiologically documented, caused by *P. aeruginosa* in two cases, *G. haemolysans and C. albicans* in the other two cases.

For bacteremia (n=2), *P. aeruginosa* and *M. morganii* were the incriminated pathogens.

C. albicans was the fungus isolated in the case of fungemia.

Two strains of *P. aeruginosa* were resistant to piperacillin-tazobactam, ceftazidime, amikacin, ciprofloxacin and colistin and one of them was resistant to imipenem.

G. haemolysans was resistant to amoxicillin, cefotaxime and erythromycin and susceptible to glycopetides, pristinamycin, and gentamicin (low-level resistance).

DISCUSSION

HAIs are important adverse events in the disease history of HSCT recipients.

Considered among the first study of HAIs in onco-haematology patients using standardized protocols and adjusted consensus definitions, our study confirms that these patients are at an increased risk to develop specific HAIs.

We noticed a high prevalence of HAIs in our center (25.7%). Similar results were reported in a French (31.4%) (9) and a German (29.4%) (1) prospective studies in onco-hematology.

No significant downward or upward trend of prevalence was revealed over time (Chi square test for linear trend; p=0.3). Many robust safety measures, including a comprehensive HAI prevention strategy such as isolation of contaminated patients, and personnel discipline according to the guidelines can reduce the prevalence of HAIs (10).

The highest prevalence rate was observed in surveys conducted in summer season (p=0.09) (40%) with no statistically significant seasonal variations. The reduced number of staff could explain this during these two periods (summer holidays, the back to school) that could affect the quality of care.

HAIs were more common in patients with acute leukemia (36.8%). Indeed, this hematological disease is associated with deep and prolonged immunodeficiency, leading to an increased susceptibility to infections.

The prevalence of HAIs was higher in autografts (31%) than in allografts (25.6%), contrary to what was noticed in literature (11, 12). In fact, infection was more frequent

in patients who received allogenic HSCT because of the highly immunosuppressive condition that induces allograft such long lasting neutropenia and GVHD (11).

In our study, only neutropenia and duration of CVC insertion were significant RF for HAIs in multivariate logistic regression analysis. The most frequently reported RF for HAIs, in patients with or without hematological malignancies, were neutropenia and prolonged length of stay and duration of CVC insertion (1, 9, 10, 13, 14). Indeed, authors support the role of neutropenia as a RF that predisposes to HAIs and necessitates more careful management with strict application of infection control measures for this population (5). Besides, a significant proportion of infected patients (9/19) didn't have neutropenia at the time of diagnosis, that's why a regular monitoring shouldn't be limited to this period.

Duration of length of stay (from admission to survey day) and length of stay >12 days before starting the survey were found to be significant RF for HAIs in the univariate but not in the multivariate logistic regression analysis. Several studies have investigated the association between hospital stay and outbreak of HAIs. Prolonged hospital stay is consistently one of the most important RF for the acquisition of HAI (13).

In our study, contrary to what has been reported in the literature (1, 10, 11, 13, 14), non-statistically significant associations were identified between HAI and HSCT, mucositis grade ≥ 3 or acute GVHD grade ≥ 3.

RTI was the most frequent HAI site (11/19). This complication is the most commonly acquired infection in the immunosuppressed host (14, 15). In fact, acute GVHD increases the risk of this infection (15).

Among the 19 HAIs, nine were clinically documented (47.4%). In a Greek study, the clinically documented HAIs rate was 20%. This rate could be explained by an early administration of empirical therapy before microbiological confirmation of infections (16).

In our study, clinical or microbiological evidence of HAIs was obtained in 16/19 HAIs (84.2%). In Germany, clinical, microbiological or clinical and microbiological documentation was obtained only in about 50% of cases in neutropenic patients (17) . A concrete application of a protocol for diagnosis in symptomatic patients and the microbiological confirmation according to the antibiogram are crucial for an appropriate antibiotic therapy (18).

We found NFUO in three cases. Several studies reported a high incidence of NFUO (5, 19). Viral infections might be among the pathogens responsible for NFUO in our patients, but we did not screen for viruses because of lack of resources. In addition, we may underestimate bacterial and fungal pathogens because of empiric antifungal agents and antibiotics.

Fever was the most common manifestation (15/19). Because of neutropenia, patients have a low capacity to produce an inflammatory infiltrate, which makes the clinical presentation poor and limited to fever (15).

For all HAIs, first-line treatment was appropriate in 13 cases. Imipenem was the most prescribed antibiotic (n=10), mainly in combination with amikacin (n=5). Imipenem is highly prescribed in onco-hematology and it continues to have crucial place in the empirical as well as the targeted treatment of severe infections. Some authors recommend imipenem as effective therapy in healthcare-acquired pneumonia and febrile neutropenia (20).

Mortality was attributable to HAIs in two of cases in our study. In the literature, it ranged from 10% to 16% (21).

In the two cases, death occurred after *P. aeruginosa* RTI complicated with septic shock. In fact, in this population, *P. aeruginosa* represents one of the most severe healthcare-associated pathogens (22). RF of mortality, reported in the literature and found in our patients, were inadequate initial antibiotic treatment, deep and prolonged neutropenia and type of pathogen (23).

During the study period, the ratio Gram negative/Gram positive bacteria was 4/1 with predominance of *P. aeruginosa* strains. *P. aeruginosa* is the most frequently species responsible for HAIs (24) because of its high propensity to become multi-resistant and even pandrug-resistant to antibiotic therapy.

In our study *C. albicans* was isolated in two cases. Indeed, in patients with hematological malignancies, mucosal damage and deep neutropenia are the most important RF for the occurrence of invasive *Candida* infections (25).

To the best of our knowledge, trends in HAIs prevalence in onco-hematology have been poorly investigated in Tunisia. However, a punctual cross-sectional study over a larger period time including more patients is needed to determine the prognosis factors for HAIs.

CONCLUSION

Our study revealed a high prevalence of HAIs, mainly RTI, with a considerable rate of attribuable mortality so the implementation of a specific surveillance protocol for HAIs in immunocompromised population is crucial.

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