Surveillance of Infectious Complications in Hemato-Oncological Patients

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ABSTRACT: **Background:** Monitoring the rate of infections in individual centers that treat patients with hematological malignancies is of major importance. However, there are no uniform guidelines for infection surveillance.

Objectives: To describe the epidemiology of bacterial and fungal infections in a single hematology ward and to compare methods for reporting surveillance and infection rates in other centers in Israel.

Methods: We conducted a prospective surveillance of all patients admitted to our hematology ward, applying standard definitions for invasive fungal infections and adapting definitions for non-fungal infections. Incidence rates were calculated using patients, admissions, hospital days and neutropenia days. We performed a search for other reported surveillance studies in Israel.

Results: We detected 79 infectious episodes among 159 patients admitted to the hematology ward during 1 year. Using neutropenia days as the denominator for calculation of incidence discriminated best between patients at high and low risk for infection. The incidence of invasive fungal infections was 7, 10 and 18 per 1000 neutropenia days, among all patients, those with acute leukemia and those with acute leukemia undergoing induction therapy, respectively. Only 10 reports from Israel were identified, 6 of which were prospective. Our data could not be compared to these reports because of the varying definitions and denominators used.

Conclusions: Hematology centers should monitor infection rates and report them in a uniform methodology.

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KEY WORDS: infections, bacteremia, fungi, leukemia, neutropenia

Infections constitute a major cause of morbidity and mortality among hematological cancer patients [1,2]. A special vulnerability to infections among these patients is due to the underlying disease, chemotherapy, graft-versus-host disease, intravenous catheters, surgical procedures and other exposure to the health-care environment. Sixty percent of febrile neutropenic patients are found to have a bacterial infection, while 20% develop bacteremia [3,4]. Bacterial infections predominate during the early neutropenic period, fungal infections usually occur later, while viral infections may occur throughout the neutropenic episode and mainly following hematopoietic stem cell transplantation [4].

In order to monitor the rate of infections in individual centers that treat patients with hematological malignancies, compare and benchmark infection rates, and assess the effects of interventions designed to decrease infection rates, common definitions for incidence rates of infections must be applied. This implies a common nominator, i.e., definitions for infections monitored, and a uniform denominator, i.e., number assessable. As for the first, definitions for invasive fungal infection have been established [5,6], although a need for a modification was recently noted [7]. Definitions for other microbiologically and clinically documented infections were proposed in 1990 for the design and conduct of trials in febrile neutropenia [8]. However, we are not aware of definitions for routine clinical surveillance of hospitalized patients in hemato-oncology wards. Regarding the denominator, a plethora of definitions can be used relying on patients (e.g., admissions number, chemotherapy course, the individual patient, etc.) or patient-days (e.g., neutropenia days, hospital days). Furthermore, subgroups of patients at risk (e.g., acute myeloid leukemia and acute lymphoblastic leukemia induction, allogeneic HSCT) must be defined uniformly.

We present the results of a 1 year prospective surveillance of infections in our ward, compare our results to reports from other Israeli hospitals, and identify the most appropriate methods to analyze and present infection rates in hematology units.

PATIENTS AND METHODS

The Hematology Ward (comprising the Hemato-oncology and Bone Marrow Transplant Units) at Davidoff Cancer Center was opened in March 2007 as a primary and tertiary care center for hemato-oncological and HSCT patients. From March 2007 to February 2008 the number of beds in the ward increased gradually to 15.

* The first two authors contributed equally to this study

HSCT = hematopoietic stem cell transplantation

Table 1. Baseline characteristics of 56 patients with 79 episodes

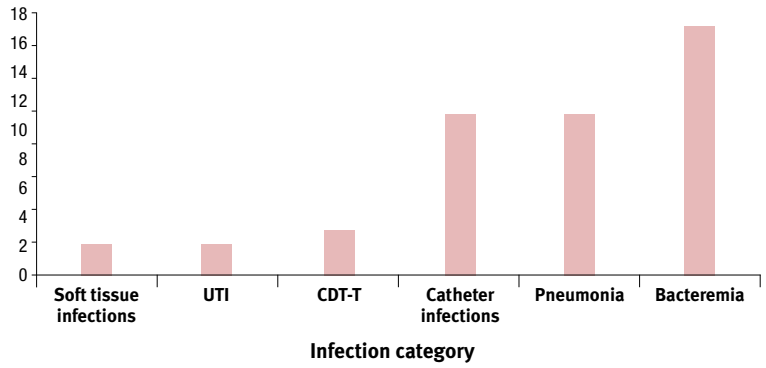
Age ± SD (yrs)		55 ± 16
Gender (M:F) (n)		33:23
Baseline disease (no. of episodes, %)		79 (100%)
	Lymphoma	37 (47%)
	AML	23 (29%)
	ALL	4 (5%)
	Multiple myeloma	9 (8%)
	Chronic leukemia	6 (8%)
HSCT (number of episodes)		
	Autologous	9
	Allogeneic	1
Neutropenia days (± SD)		8 ± 6
Profound neutropenia days (± SD)		4 ± 8
Median length of hospital stay (days)		6 (0–30)

Neutropenia days – defined as days with neutrophil count ‹ 0.5x 109/L

Profound neutropenia is defined as ‹ 0.1x 109/L

Length of hospital stay is defined as the number of hospitalization days in the month prior to the beginning of the episode

Figure 1. Specific categories of clinically and microbiologically documented episodes



CDT-D = *Clostridium difficile* toxin-associated diarrhea, UTI = urinary tract infection

In our ward, antibacterial prophylaxis with ciprofloxacin is administered to patients with AML and ALL for induction and consolidation and to patients undergoing allogeneic HSCT and autologous HSCT, from the onset of neutropenia until its resolution or the development of febrile neutropenia [9]. Antifungal prophylaxis with fluconazole is administered to patients undergoing allo-HSCT [10]. The empirical antibiotic regimen for febrile neutropenia includes piperacillin-tazobactam monotherapy, with or without vancomycin. Empirical antifungal therapy, voriconazole, is administered following 5–7 days of fever persistence, with the addition of broad-spectrum antibiotic treatment when neutropenia is not expected to resolve within the next 2–3 days. During induction or salvage treatment for leukemia and allogeneic bone marrow transplantation, patients are hospitalized in single high efficiency particulate air-filtered positive air pressure rooms. Complications following chemotherapy, including infections, are treated mostly in the hematology ward. Galactomannan testing in blood and the cytomegalovirus antigenemia assay are performed in-house, while polymerase chain reaction tests for viruses, bacteria and fungi are sent to external laboratories. Microbiology and radiology were performed as clinically indicated. No routine surveillance or screening was performed, except for CMV antigenemia following allogeneic HSCT.

We attempted to monitor infections developing in our ward (hospital-acquired infections) and infectious complications resulting from neutropenia and necessitating hospitalization in the hematology ward. Thus, we included all consecutive patients admitted to the hemato-oncology and bone marrow transplantation units between March 2007 and February 2008. Daily surveillance was performed as part of the clinical management by the resident on duty. We defined an infectious episode according to one of the following: a) fever occurring after more than 48 hours of hospitalization in the hematology ward, b) fever occurring in newly admitted patients for whom chemotherapy or high dose corticosteroids was administered within the previous 30 days, or c) fever occurring in newly admitted patients with a neutrophil count < 0.5 x 10^9/L.

Patients could be included in the surveillance more than once for different episodes of infection. Data were collected prospectively using a uniform case report form and entered into an electronic database.

DEFINITIONS

We used consensus definitions to classify infections [8]. Briefly, the following major classes were defined:

- Clinically documented infections: clinical symptoms or signs that may be due to infections with no culture taken or negative culture results
- Microbiologically documented infections other than bacteremia
- Bacteremia
- Fungal infections, defined according to previously published criteria [5,6]
- Fever of unknown origin

Lacking definitions of specific diagnoses for the CDI and MDI in the neutropenic host (e.g., pneumonia, catheter-related infection, etc.), we adapted those used for nosocomial infections [11].

AML = acute myeloid leukemia
ALL = acute lymphoblastic leukemia
CMV=cytomegalovirus

CDI = clinically documented infections
MDI = microbiologically documented infections

The unit of analysis was the infectious episode. To assess incidence, we used the number of patients, admissions, hospital days and neutropenia days. Neutropenia was defined as < 0.5x 10^9/L. We subgrouped all patients with acute leukemia (both AML and ALL), patients with induction AL, allo-HSCT, auto-HSCT, and other patients.

SURVEILLANCE REPORTING IN ISRAEL

In order to assess the current methods used in Israel for surveillance, we performed a search in the Pubmed database for other Israeli surveillance studies, regarding type of pathogen or infection. We used the search term: "(surveillance OR incidence OR prevalence OR rate) AND (infection OR infection* OR fungal OR bacteremia) AND Israel* AND (hematology OR leukemia OR bone marrow OR stem cell)".

Table 2. Use of different denominators for infection surveillance reporting

			Bacterial episodes		Fungal infections	
	Optional denominators	**All febrile episodes**	**MDI**	**Bacteremia**	**All IFI**	**Proven + probable IFI**
No. of episodes in all patients		79	8	17	5	3
	100 admissions (n=356)	22	2	4.80	1.4	0.8
	100 patients (n=159)	50	5	11	3	2
	1000 hospital days (n=3546)	22	2	5	1	1
	1000 neutropenia days (n=778)	100	10	22	7	4
No. of episodes in AL		27	0	5	4	2
	100 AL admissions (n=61)	44	0	8	6.5	3.3
	100 AL patients (n=24)	NA	0	21	17	8
	For 1000 hospital days (n=1011)	27	0	5	4	2
	For 1000 neutropenic days (n=392)	69	0	13	10	5
No. of episodes in induction of AL		14	0	2	4	2
	100 inductions for AL admissions (n=21)	66	0	10	19	10
	100 inductions for AL patients (n=21)	66	0	10	19	10
	1000 hospital days (n=475)	29	0	4	8	4
	1000 neutropenic days (n=221)	63	0	9	18	9

AL = acute leukemia, MDI = micobiological documented infections, IFI = invasive fungal infections

RESULTS

Throughout the study period, there were 356 admissions of 159 adult patients with a total duration of 3546 hospital days and 778 neutropenia days. There were 79 infectious episodes that fulfilled inclusion criteria: 15 CDI, 8 MDI, 17 bacteremias, 5 fungal episodes and 34 episodes of fever of unknown origin. Patient characteristics are summarized in Table 1.

NON-FUNGAL EPISODES

Figure 1 depicts the specific diagnoses included under MDI and CDI. When bacteremia was present the episode was counted as bacteremia only. Of the 17 episodes of bloodstream infection, there were 7 episodes (41%) of Gram-positive bacteremia and 10 (59%) of Gram-negative bacteremia. The most frequently isolated pathogens were *Escherichia coli* (33%), followed by *Staphylococcus aureus* (*22%*) and *Pseudomona aeruginosa* (11%).

Overall, there were 10 episodes of non-bacteremic MDI per 1000 neutropenia days versus 22 episodes of bacteremia/1000 neutropenia days. There was no difference in the incidence of bacteremic and non-bacteremic episodes when admissions, patients and hospitals days were used as denominators [Table 2]. Among the patients with AL there were no cases of non-bacteremic MDI. The incidence of bacteremic episodes was 21% among all patients with AL versus 10% among patients undergoing induction treatment. Per 1000 neutropenia days the rates were 13 and 9, respectively.

FUNGAL INFECTIONS

We documented five episodes of fungal infections. Of these, three were probable or documented IFI . The median number of days with neutropenia below 0.5 x 10^9/ L and 0.1 x 10^9/L prior to the onset of the infectious episode was 16 (4–28) and 10 (3–22), respectively. Two episodes occurred among patients with acute leukemia during induction therapy: a documented *Aspergillus terreus* invasive fungal sinusitis and brain lesion and a probable disseminated fungal infection, most probably due to *Candida* spp. The third patient with myelodysplastic syndrome had a proven *Candida tropicalis* IFI with fungemia.

The incidence among all admissions was 1.4%. Among admitted patients with AL the incidence was 6.5% and during the induction period the incidence was 19% [Table 2]. Respective rates per 1000 neutropenia days were 7, 10 and 18.

SURVEILLANCE REPORTING IN ISRAEL

The search terms yielded 131 studies, of which 10 were considered relevant [Table 3] [12-21]. Six studies were prospective

AL = acute leukemia
Allo-HSCT = allogeneic HSCT
auto-HSCT = autologous HSCT

IFI = invasive fungal infection

Table 3. A summary of other infections surveillance reports from Israel

Reference	Type of study	Population	Infection category	Nominator	Denominator	Rate	Inpatient/ outpatient
Paul 2007 [19]	Retrospective	All admitted patients with febrile neutropenia	Bacteremia	Episodes of bacteremia	None	NA	Inpatient
Oren 2006 [17]	Prospective	AL+HSCT patients who received anti-fungal prophylaxis	IFI	Patients with IFI	All patients admitted	11%	NA
Adler 2006 [12]	Prospective	Patients in hemato-oncology ward	Catheter infections	Episodes of catheter infections	1000 catheter Days	2.264	Inpatient
Greenberg 2005 [20]	Prospective	All admitted patients with febrile neutropenia	Bacteremia	Patients with bacteremia	Admitted patients with febrile neutropenia	37%	Inpatient
Oren 2001 [16]	Retrospective	AL patients in a general ward without air filtration	IFI	Patients with IFI	All patients admitted	43%	Inpatient
Elishoov 1998 [13]	Prospective	HSCT patients	Catheter-related infections	Patients with catheter-related infections	All patients admitted	33%	Inpatient
Roguin 1996 [18]	Retrospective	AL patients	Infection rate	Episodes of certain and probable infection	All febrile neutropenia episodes	31%	Inpatient
Engelhard 1996 [14]	Prospective	HSCT patients	CONS-related CVC infection	Patients with CONS infection or colonization	All patients admitted	15%	Inpatient
Lossos 1995 [15]	Prospective	HSCT	CDI+MDI-Pneumonia	Patients with pneumonia	All patients admitted and follow-up available after discharge	15%	Inpatient and outpatient
Shpilberg 1991 [21]	Retrospective	All admitted patients with AL	IFI	Patients with IFI	All admitted patients with AL	14%	Inpatient

AL = acute leukemia, HSCT = hematopoietic stem cell transplantation, CONS = coagulase-negative Staphylococcus, CVC = central venous catheter, IFI = invasive fungal infections

surveillances. Seven studies reported on the incidence of bacterial infections (three studies reported catheter-related infections, two reported incidence of bacteremia, one reported total infection incidence and one reported the incidence of pneumonia). Three studies reported IFI incidence. The nominator was defined as patients in seven studies and as episodes in three studies. The denominator was defined as all patients in five studies, all patients with febrile neutropenia in two studies, all episodes in two studies and total catheter days in one study assessing catheter-related infections.

DISCUSSION

We present the initial results of an infection surveillance program in a hematology ward and discuss the appropriate methodology for surveillance and reporting of infection incidence in this setting. The use of neutropenia days as the denominator for the reporting of infection incidence rates in our cohort best indicated the distinction between the incidence of the more severe infections (i.e., bacteremia) and other infections, as well as the difference in the incidence rates of infections among patients at highest risk (i.e., AL) versus those at a lower risk. Infection rates were markedly different among hemato-oncological patients at varying risks for infection. We lacked standardized case definitions for clinically and microbiologically documented infections among neutropenic patients, addressing the fact that many of the so-called clinically documented episodes are non-infectious in origin (e.g., diarrhea and mucositis). We noted that a large percentage of the microbiologically documented infections in our patients were related or associated with central venous catheters, although we lacked the appropriate denominator to describe the incidence of catheter-related infection, i.e., catheter days.

We assessed the reported data on infections in hemato-oncology and bone marrow transplant units in Israel. We could not compare our results with other centers, largely due to lack of data and the wide variability in reporting of infections in the few existing studies. In two studies that assessed IFIs and used the number of AL admitted patients, infection rates were comparable – 11% [21] and 14% [19]. However, as previously noted, the appropriate comparison should stratify patients' risk for IFI using the number of neutropenic days in patients experiencing a prolonged neutropenia. Furthermore, several studies were retrospective; retrospective surveillance might lack standardized case definitions and might miss cases without microbiological confirmation that were not documented appropriately.

The literature search, although restricted to Israeli hospitals, exemplifies the problem of non-standardized surveillance reporting. Currently, it is difficult to compare between centers and to benchmark the performance of individual centers with regard to the incidence of infections in hematology wards. Furthermore, non-standardized methods prohibit adequate follow-up of trends within individual centers and the assessment of changes in interventions routinely implemented to prevent or manage infections. Examples include catheter management

techniques, prophylaxis, window sealing, hand hygiene methods, and empirical antibiotic and antifungal treatments.

Our study is limited by the small number of infectious episodes given the short surveillance time and does not allow us to discuss the data. We rather used the data to highlight the importance of surveillance and to assess the appropriate methodology. We did not monitor infections occurring among patients treated in the outpatient and day-care units of our department or those that were diagnosed in other departments. The in-patient and ambulatory services of hemato-oncology and bone marrow transplant units should probably be included in surveillance projects as some infections may be diagnosed post-discharge or, vice versa, could be acquired in the ambulatory service but diagnosed in the ward. Specific monitoring of catheter-related infections will be revised for our future surveillance program. Following this 1 year analysis, we added antifungal prophylaxis using fluconazole for patients with AML and ALL undergoing induction and salvage therapy to the routine departmental guidelines.

Based on our limited experience and that of other centers in Israel we conclude the following. Individual hematology wards should monitor infection rates and report them in a uniform methodology, using accepted criteria for reporting of various infections. Uniform definitions are needed for clinically documented infections and non-bacteremic microbiologically documented infections. Focused surveillance is needed for catheter-related infections, recording the number of catheter days and types of catheters used. Finally, the number of admissions, hospital days and neutropenia days should be recorded. The last is probably the most discriminative denominator and needs to be actively recorded, since it is not automatically available in administrative databases. Reporting of infections by neutropenia days will appropriately represent the cohort at risk. Furthermore, IFIs and other severe infections should be reported separately for high risk patients, such as those experiencing a prolonged neutropenia or those with AL in induction or allo-HSCT. International groups formulating guidelines on the management of hemato-oncological patients should include the component of infection surveillance [22].

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