Applying the concept of healthcare-associated infections to hematology programs

Sami Chehata
Chiraz Grira
Patrick Legrand
Cécile Pautas
Sébastien Maury
Mathieu Kuentz
Jean Carlet
Catherine Cordonnier

Infection is a leading cause of mortality in hematology. Although data on nosocomial infections are available, little is known about events falling into the broader category of healthcare-associated infections. Our aim was to evaluate the incidence and causes of healthcare-associated infections in hematology patients, comparatively with nosocomial infections. Using predefined criteria, we classified 223 infectious episodes in 137 patients for their association with healthcare and nosocomial occurrence. Of the 223 infectious episodes, 204 (91%) were healthcare associated, 94/223 (42%) were also nosocomial, and 9% were community-acquired. Healthcare-associated infections should be preferred to nosocomial infections - which underestimates half of the healthcare-associated infections - as quality indicators for preventive programs.

Key words: infections in hematology patients, neutropenia, nosocomial infection.

Haematologica 2006; 91:1414-1417

From the Hematology Department (SC, CG, CP, SM, MK, CC) and Microbiology Laboratory (PL), Henri Mondor Teaching Hospital, AP-HP and Paris 12 University, 94000 Créteil; Intensive Care Unit, Saint-Joseph Hospital, Paris, France (JC).

Correspondence:
Catherine Cordonnier, MD, Service d'Hématologie, Hôpital Henri Mondor, 94000 Créteil. France.
E-mail: carlcord@club-internet.fr

Infection remains a major cause of morbidity and mortality in hematology patients.[1] Most of the previous reports on infections in hematology patients focused on the type and severity of infections rather than on their relationship with healthcare. A few studies have addressed nosocomial infections in hematology.[2-4] Many of the infections seen during the course of hematological diseases are related not to the hospital environment, but rather to the effects of treatments. Moreover, healthcare for hematology patients has shifted in recent years from the hospital ward to day-hospitals and home-care programs. As a result, many treatment-related infections occur outside the hospital. Therefore, although prevention of cross-transmission is crucial,[5] describing infections in hematology patients from the broader perspective of healthcare-associated infection (HAI)[6] is likely to be more helpful than the narrower nosocomial-infection approach, limited to the hospital stay. There is a grwoing consensus that the HAI approach should be used to develop broader preventive programs than those aimed at preventing nosocomial infections.[6-8] As part of the quality-control program in our department, we investigated the incidence and causes of HAI over a 6-month period and we evaluated the potential of the HAI rate as an indicator of quality of care. Thus, we looked beyond nosocomial infections to include all infections related to healthcare.

Design and Methods

Our department comprises 40 beds, including 18 laminar air-flow rooms for myeloablative stem cell transplant and acute leukemia patients. Stem cell transplant and acute leukemia patients are given non-absorbable antibacterials and oral polyens. Simple isolation measures including hand disinfection, and use of gowns are implemented for patients who are expected to be neutropenic for ≥10 days. Blood and urine cultures, and samples from accessible foci of infection, are taken from febrile patients. Patients with pneumonia are investigated by bronchoscopy, bronchoalveolar lavage, and protected aspiration. Microbiological studies of clinical specimens are performed as recommended by the French Society for Microbiology.[9] Intravascular catheter tips are cultured as described by Brun-Buisson *et al*.[10] All clinically significant bacteria are subjected to phenotype-based identification and to disc-diffusion susceptibility testing.

Patients with febrile neutropenia are treated with a β-lactam and a short course of an aminoglycoside. Patients still febrile after 4 days of antibacterial treatment receive intravenous polyens. We follow the recommendations of our infection control unit for isolation of patients infected or colonized by transmissible pathogens (e.g. resistant bacteria, *P. jirovecii*). We retrospectively assessed infectious episodes in consecutive patients admitted to our hematology department

between July 1- December 31, 2000. Infectious episodes were identified from medical charts. Two of us (SC and CC) classified each infectious episode, whether microbiologically documented or not, as a HAI, a nosocomial infection, or a community-acquired infection, based on the definitions below.

Definitions

Bacteremia was defined as ≥1 positive blood culture for organisms other than coagulase-negative *Staphylococcus*, *Micrococcus*, *Corynebacterium* (other than group JK), and *Bacillus spp.*, for which two positive blood cultures were required. Catheter related-infection was defined as sepsis associated with tunnel infection or thrombophlebitis with or without microbiological documentation or as sepsis with a catheter culture yielding ≥10^3 cfu/mL by quantitative culture techniques. International definitions were used to define sepsis, severe sepsis, and septic shock,[11] bacterial pneumonia,[12] proven or probable invasive fungal infections[13] and cytomegalovirus infections and disease.[14] Neutropenia was defined as a polymorphonuclear count ≤500/mm^3. Febrile neutropenia episodes were classified as fever of unknown origin, clinically, or microbiologically documented infection. Infections that occurred in the hospital or at home were classified as HAI if they were related to treatment procedures and/or to treatment-related immune deficiency and/or to nursing care received within 1 month before the onset of symptoms. In doubtful cases, when the immunodeficiency related to the disease might have promoted the development of infection (e.g., hypogammaglobulinemia in chronic lymphocytic leukemia), the episode was classified as a HAI if specific treatment for the disease was ongoing. Examples of this situation included febrile neutropenia subsequent to chemotherapy, herpes virus reactivation in patients seropositive for the virus, toxoplasmosis reactivation, proven and probable invasive fungal infections, and infections within 6 months after transplantation or later when immunosuppressive treatment was continued after this date. Infections in patients presenting with a previously undiagnosed hematologic disease who had not undergone invasive procedures or received treatments were not classified in the HAI group. Infections other than aspergillosis were classified as nosocomial if they occurred ≥48 h after admission in a patient who was free of evidence of infection at admission.[15] Aspergillosis was classified as nosocomial when the symptoms started at least 7 days after admission, as the incubation period is probably longer for molds than for bacteria. Nosocomial infections were also HAI, and some HAI were also nosocomial infections. Infections that failed to meet the criteria for HAI were classified as community-acquired.

Resistant (potentially hospital-acquired) strains were strains that met any of the following criteria: *Staphylococcus spp.* resistant to nafcillin, enterobacteriaceae resistant to third generation cephalosporin, or *P. aeruginosa* resistant to ceftazidime or carbapenem.

Table 1. Main clinical characteristics of the patients at onset of the infectious episodes (n=137).

	Stem-cell transplant patients (n=59)	*Non stem-cell transplant patients (n=78)*	*Total (n=137)*
Age			
< 35	13	8	21
35-55	29	23	52
>55	17	47	64
Sex			
Men	31	38	69
Women	28	40	68
Underlying disease			
Acute leukemia	21	18	39
Myelodysplasia	4	9	13
Myeloproliferative disorder	2	11	13
Lymphoma	28	29	57
Others	4	11	15
Disease state			
At diagnosis	0	11	11
First line therapy	27	34	61
≥Second-line therapy	25	19	44
End-stage disease	7	14	21

Results and Discussion

During the 6-month study period, 204 patients had 438 admissions; 223 infectious episodes occurred in 137 (137/204, 67%) patients during 184 (184/438, 43%) hospital stays (Table 1). Of the 223 infectious episodes, 176 (79%) occurred during periods of neutropenia. The median age of the patients was 52 years (range, 17-85). Of the 223 infectious episodes, 72 (32.3%) were microbiologically documented: of these, 42 were bacterial infections, 20 viral, 9 fungal, and 1 was due to toxoplasmosis (Table 2). Gram-positive bacteria accounted for 25 (60%) of the 42 bacterial infections. Of the 176 infectious episodes during periods of neutropenia, 98 (55.5%) were manifested as fever of unknown origin, 26 (15%) were clinically documented infections, and 52 (29.5%) were microbiologically documented. Of the 223 episodes, 204 (91.4%) were HAI, including 94 (42%) that were also nosocomial, and 19 (9%) were community-acquired. Most of the bacterial and fungal episodes (32/51), and none of the viral episodes were nosocomial. The proportions of HAI, nosocomial infections, and community-acquired infections were not significantly different in non-transplant and transplant subgroups of patients (Table 3). Of the 42 microbiologically documented bacterial infections, 20 (47.6%) were

Table 2. Clinical entities and causative pathogens in the 223 consecutive infectious episodes.

Clinical entity/ Pathogen	*Bacterial**	*Fungal and Toxoplasmosis*	*Viral*	*Not documented*	*Total*
Sepsis, severe sepsis, or shock	27 *Staphylococcus sp.* 15 Other documented: 11	*C albicans:*1		105	133
Pneumonia	4 Documented:3	*Aspergillus sp.*:3 *C guillermondi:* 1 *P jiroveci*: 1	RSV:2	28	39
Cystitis	4 Documented:4	*C. albicans:*2		2	8
Catheter-related Infection	5 Documented:2			2	7
CNS‡ infection		Toxoplasma:1		1	2
Gut infection	2		CMV: 3		5
Mucocutaneous infection			HSV: 7 VZV: 5	6	18
Other		Zygomycete: 1	CMV: 2 EBV: 1	7	11
Total (%)	42 (19%)	10 (4%)	20 (9%)	151 (68%)	223

**The main strains are cited. For small groups, only the number of microiologically documented episodes are cited. For the details on the bacterial strains, see the Results section. CNS: central nervous system; RSV: respiratory syncytial virus; CMV: cytomegalovirus; HSV: herpes simplex virus; VZV: varicella-zoster virus; EBV: Epstein-Barr virus.*

Table 3. Proportion of healthcare-associated infections (HAI), nosocomial infections, and community-acquired infections in each category of infection.

Pathogens/ Relation to healthcare	*Bacteria*	*Fungi/ Toxoplasma*	*Virus*	*Not microbiologically documented*	*Total (% of all episodes)*
Nosocomial HAI	14/9	3/3	0/0	25/37	42 (32%)/ 49 (53.2%)
Non-nosocomial HAI	15/4	1/3	6/12	51/21	73 (55.7%)/ 40 (43.4%)
Community -acquired infections	0/0	0/0	1/1	15/2	16 (12.3%)/ 3 (3.4%)
Total	29/13	4/6	7/13	91/60	131/92

For each category, the first number is the number of episodes in non-transplant patients and the second number is the number of episodes in stem cell transplant recipients.

due to resistant – potentially hospital-acquired – strains which contributed 16 (69.5%) of the 23 microbiologically documented nosocomial infections versus 4 (21%) of the 19 microbiologically documented non-nosocomial HAIs ($p<0.005$). The 19 community-acquired infections included two respiratory syncytial virus infections and 17 non-microbiologically documented infections. Of the 223 episodes of infection, seven (3.6%) were considered to be directly responsible for death: aspergillosis: (n=1); toxoplasmosis: (n=1); severe sepsis: (n=3); pneumonia: (n=2).

Our study shows that 91% of infectious episodes in hematology patients are healthcare-associated, whereas only 41% are nosocomial. This suggests that HAI rates may be more logical quality-of-care indicators than nosocomial infection rates in this population since they would capture more events, and events of complementary nature. In recent years, the management of hematology patients has shifted in large part from hospital wards to day-hospitals, homecare programs, and nursing homes, in an effort to improve quality of life and avoid unnecessary admissions. Therefore, rates of events that occur during inpatient management no longer adequately reflect rates of treatment-related complications.[6]

Hematology wards use simple environmental measures recommended for preventing nosocomial infections, i.e., hand washing and isolation of patients who are infected or colonized by hospital strains, and sometimes air-filtered rooms for specific populations. Despite these measures, infection remains the leading cause of death after allogeneic stem cell transplantation,[16] and outbreaks can be a major stumbling block for transplant programs.[17] The definition of HAI is not agreed on.[8] This is why we chose broad criteria for defining HAI for this first study. In a previous study,[18] HAI were defined as infections occurring within the first 48 hours after admission of patients having a recent history of contact with the healthcare system. However, this definition disregards the fact that nosocomial infections are also HAI. In addition, for some infections the preventive strategy is identical in or out of the hospital; for instance, good intravenous line management reduces the risk of catheter-related infections, regardless of the patient's living arrangements. Developing effective preventive measures at home is as important as prevention in the hospital for those patients who alternate between home care and hospital care.

Very limited data are available in the literature on the incidence of HAI versus nosocomial infections in immunocompromised patients, and they focus on specific infections. For example, in a study of aspergillosis in immunocompromised patients, Pegues *et al.*[19] showed that only 25% of 72 cases were nosocomial, whereas 62.5% were community-acquired and 12.5% of indeterminate origin.

The concept of HAI shifts the focus from in-hospital infections to all potentially preventable infections. However, evaluating the preventability of HAI constitutes an enormous challenge for hematologists. A systematic review showed that at least 20% of all nosocomial infections were probably preventable.[7] In theory, all the infections in our population could have been prevented. However, some infections are so rare that they

should be considered to be unpredictable events related to treatments whose benefits exceed the risks. Moreover, for common infections such as cytomegalovirus infection after allogeneic stem cell transplantation, prevention may not be the best option given that a pre-emptive strategy produces similar survival rates. Thus, preventable infections should be defined clearly by the medical community, with frequent updates according to evidence-based data and to the benefit/risk of preventive strategies. The concern that nosocomial infections, as currently defined, may not be appropriate quality indicators, in particular for benchmarking, is shared by physicians in other specialties, such as intensivists and epidemiologists.[8] It is likely that combining quality indicators to both structures, processes of care, and outcomes, could be the best way to assess quality of care in the hospitals.[20] The main limitation of our study was that we did not collect data on episodes which occurred in outpatients and did not lead to admission. These episodes may have been healthcare-associated, leading us to underestimate the incidence of HAI. However, underestimating HAI results in overestimating the relative contribution of nosocomial infections and therefore does not detract from our finding that nosocomial infections fail to reflect the burden from infection. Moreover, the impact of the lack of outpatient data on our results was probably limited, since most of our patients live closely and contact us directly to obtain admission in the event of a fever or infection.

Nosocomial infection rates underestimate the burden caused by infections associated with diagnostic procedures and treatments used in hematology. All infections, regardless of their place of occurrence, are relevant to the quality of care in hematology programs. Hematologists must determine which infections are amenable to prevention and develop prevention programs for hematology wards. Infectious complications are likely to remain an important issue in therapeutic choices, and thus, looking prospectively at healthcare-associated infections might be of great importance.

SC and CG collected the clinical data; PL collected the microbiological data; CP, SM and MK participated in the design of the study; JC and CC designed the study, analysed the data, and wrote the manuscript. All authors have approved the paper.

Potential conflicts of interest: no conflicts.

The authors thank Dr. Antoinette Wolf for her careful reading of the manuscript.

Manuscript received April 11, 2006. Accepted July 13, 2006.

References

1. Leather HL, Wingard JR. Infections following hematopoietic stem cell transplantation. Infect Dis Clin North Am 2001;15:483-520.
2. Marena C, Zecca M, Careini ML, Bruschi A, Bassi ML, Olivieri P, et al. Incidence and risk factors for nosocomial infections among hematopoietic stem cell transplantation recipients, with impact on procedure-related mortality. Infect Control Hosp Infect 2001; 22:510-7.
3. Dettenkofer M, Ebner W, Bertz H, Babikir R, Finke J, Frank U, et al. Surveillance of nosocomial infections in adult recipients of allogeneic and autologous bone marrow and peripheral blood stem cell transplantation. Bone Marrow Transplant 2003;31:795-801.
4. Dettenkofer M, Wenzler-Röttele S, Babikir R, Bertz H, Ebner W, Meyer E, et al. Surveillance of nosocomial sepsis and pneumonia in patients with a bone marrow or peripheral blood stem cell transplant: A multicenter project. Hospital Infection Surveillance System for Patients with Hematologic/Oncologic Malignancies Study Group. Clin Infect Dis 2005;40: 926-31.
5. Jarvis WR. Controlling healthcare-associated infections: the role of infection control and antimicrobial use practices. Semin Pediatr Infect Dis 2004;15:30-40.
6. Pittet D. Infection control and quality health care in the new millenium. Am J Infect Control 2005;33:258-67.
7. Harbath S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Inf 2003;54:258-66.
8. Tokars JI, Richards C, Andrus M, Klevens M, Curtis A, Horan T, et al. The changing face of suveillance for health care-associated infections. Clin Infect Dis 2004;39:1347-52.
9. Soussy C, Cluzel R, Courvalin P. Definition and determination of in vitro antibiotic susceptibility breakpoints for bacteria in France. Eur J Clin Microbiol Infect Dis 1994;13:238-46
10. Brun-Buisson C, Rausse A, Legrand P. Semiquantitative culture of catheter tips. J Clin Microbiol 1987;25:1343-4.
11. Muckart DJJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions of the systemic inflammatory response syndrome (SIRS) and allied disorders in relation to critically injured patients. Crit Care Med 1997;25:1789-95.
12. Pham LH, Brun-Buisson C, Legrand P, Rauss A, Verra F, Brochard L,et al. Diagnosis of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 1991;143:1055-61.
13. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, Denning DW, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases.Clin Infect Dis 2002;34:7-14.
14. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002;34:1094-7.
15. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC Definitions for nosocomial infections. Am J Infect Control 1988;16:128-40.
16. Cordonnier C, Chevret S, Legrand M, Rafi H, Dhedin N, Lehmann B, et al. Should immunoglobulin therapy be used in allogeneic stem cell transplantation? A randomized, double-blind, dose effect, placebo controlled, multicenter trial. GREFIG Study Group. Ann Intern Med 2003;139:8-18.
17. McCann S, Byrne JL, Rovira M, Shaw P, Ribaud P, Sica S, et al. Outbreaks of infectious diseases in stem cell transplant units: a silent cause of death for patients and transplant programmes. Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant 2004;33:519-29.
18. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791-7
19. Pegues CF, Daar ES, Murthy AR. The epidemiology of invasive pulmonary aspergillosis at a large teaching hospital. Infect Control Hosp Epidemiol 2001;22:370-4.
20. Weinstein RA, Siegel JD, Brennan PJ. Infection-Control report cards: securing patient safety. N Engl J Med 2005;353: 225-7.