Infections After High-Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplantation

4

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4.1   Introduction

High-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) is the standard treatment for some hematologic malignancies, especially multiple myeloma (MM), lymphoma (Hodgkin's and non-Hodgkin's), and acute myeloid leukemia (AML). Infection represents an important cause of morbidity after autologous HSCT, but its frequency and etiology depends on the presence of various risk factors.

The risk of infection in autologous HSCT recipients is the result of the interaction between the host, pathogens, and environmental exposure. Infections develop when an imbalance occurs between the weakened protective defense mechanisms of the host and the virulence factors of the offending pathogen. Table 4.1 presents a list of

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Table 4.1 Risk factors for infection after high-dose chemotherapy and autologous hematopoietic stem cell transplantation

Risk factor for infection	Risk category	
	Low	High
1. Pretransplant		
General condition including organ function		
Performance status	Good	Poor
Renal failure	No	Yes
Diabetes mellitus	No	Yes
Iron stores [1]	Normal or decreased	Increased
Age	Younger (<40 years)	Older (>65 years)
Smoking [1]	No	Yes
Underlying disease and its treatment		
Tumor burden	None	Large
Disease-related immunosuppression[a]	Absent	Present
Prior chemotherapy	None or minimal	Extensive
Receipt of purine analogues (fludarabine, cladribine, clofarabine) or monoclonal antibodies (rituximab, alemtuzumab)	No	Yes
Exposure to pathogens		
Prior history of infection[b]	No	Yes
Colonization with pathogens (bacteria, fungi)	No	Yes
Immunogenetics		
Deficiency of MBL [2, 3]	No	Yes
2. Pre-engraftment period		
Duration of neutropenia [1]	Short (<7 days)	Long (>10 days)
Stem cell source	Peripheral blood	Bone marrow
Quantity of stem cells infused[c]	>5 × 106/Kg CD34+ cells	<2 × 106/Kg CD34+ cells
Severity of oral and gastrointestinal mucositis	Absent or mild	Severe
Conditioning regimen	Less intensive	Intensive
Polymorphisms of genes associated with metabolism of chemotherapeutic agents (pharmacogenetics)	Absent	Present
Renal failure[d]	Absent	Present
Exposure to pathogens		
Nosocomial exposure to potential pathogens (water and airborne pathogens such as *Legionella*, *Aspergillus* spp. and other molds, resistant bacteria, respiratory viruses)	No	Yes
3. Post-engraftment		
T cell immune reconstitution	Fast	Delayed
Prior chemotherapy [4]	Minimal	Extensive

Table 4.1 (continued)

Risk factor for infection	Risk category	
	Low	High
CMV serostatus [5]	Negative	Positive
Need for additional chemotherapy to control the underlying disease[e]	No	Yes
In vitro manipulation of stem cells[c] [6, 7]	No	Yes
Exposure to pathogens		
Prior history of infection[b]	No	Yes
Community-acquired infections, especially respiratory viruses	No	Yes

MBL mannose-binding lectin, *TLR* Toll-like receptors, *CMV* cytomegalovirus

[a]Most common disease-related immunosuppression include: hypogammaglobulinemia (multiple myeloma, low-grade B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukemia), T-cell mediated immunodeficiency (Hodgkin's lymphoma and certain types of non-Hodgkin's lymphoma) and neutrophil dysfunction (acute myeloid leukemia with myelodysplasia)

[b]Infections with higher risk of recurrence after autologous hematopoietic stem cell transplantation include: mycobacteriosis (tuberculosis and others), aspergillosis, pneumocystosis, cytomegalovirus, herpes simplex and varicella-zoster virus, and toxoplasmosis and strongyloidiasis

[c]In vitro manipulation of stem cells decreases the content of CD34+ and T cells, increasing the duration of neutropenia in the early post-transplant period and delaying T cell immune reconstitution after transplant

[d]Renal failure increases the risk of severe mucositis in patients with multiple myeloma receiving melphalan-based conditioning regimens

[e]Need for additional chemotherapy in lymphoma and acute myeloid leukemia is usually related to relapse of the underlying disease, whereas in multiple myeloma additional chemotherapy is usually part of the treatment strategy

risk factors for infection in the different periods: pretransplant, early pre-engraftment, and post-engraftment period. Assessment of the risk of infection in each period and the identification of patients at higher risk of specific infections are critical to the appropriate management of infectious complications after autologous HSCT.

An important and difficult element of risk assessment in autologous HSCT recipients is to quantify the risk associated with the status of the underlying disease and prior therapies. For example, a patient with MM who undergoes a first autologous HSCT after having received a short course of induction therapy with dexamethasone plus thalidomide and whose disease is under control is at lower risk for certain infections compared with a patient with the same underlying disease, but who is receiving a third or fourth autologous HSCT in the setting of relapse after multiple treatment lines.

4.2   Risk for and Epidemiology of Infection

Immunodeficiency is the key risk factor for infection in autologous HSCT recipients. It is a result of interplay between the underlying disease and its therapy and may involve breakdowns in skin and mucous membrane barriers, qualitative and

Table 4.2 Immunodeficiency in autologous hematopoietic cell transplantation

	Disruption of skin and mucous membranes	Hypogamma-globulinemia	T-cell mediated immunodeficiency	Neutropenia and neutrophil dysfunction
Immunodeficiency associated with untreated underlying disease				
Acute lymphoid leukemia	+	+	+++	++
Acute myeloid leukemia	+	+	+	+++
Hodgkin's lymphoma	+	−/+	+++	−/+
Non-Hodgkin's lymphoma	+	−/+	+/+++	−/+
Multiple myeloma	−	+++	−/+	+
Immunodeficiency associated with the conditioning regimen				
Corticosteroids	+	−	+++	+
Cytotoxic chemotherapy	−/+++[a]	+/++	+/+++[a]	−/+++[a]
Monoclonal antibodies	−	+/++	+/+++	+/++
Use of catheters	+++	−	−	−

(−) no, (+) mild, (++) moderate, (+++) severe
[a]Severity of mucositis and neutropenia depend on the intensity of the conditioning regimen; duration of neutropenia also depends on the stem cell dose infused and the in vitro manipulation of the stem cell product

quantitative defects in various arms of the immune system including innate immunity (neutropenia, neutrophil dysfunction), impaired production of immunoglobulins, and defective cell-mediated immunity (CMI). While autologous HSCT recipients have deficits in various arms of the immune system, the nature of the pathogens causing infection is frequently determined by the immunodeficiency that is predominant at a given time (Tables 4.2 and 4.3).

Pretransplant variables that significantly impact the risk for major infection include host factors such as poor performance status and older age, comorbidities such as diabetes and renal failure [8], iron overload [1], smoking [1], and high tumor burden. In addition, the risk and pattern of infection after autologous HSCT are strongly influenced by the intensity of prior treatment for the underlying disease and the type of treatment. For example, patients who received purine analogues and monoclonal antibodies are at increased risk for specific infections post-transplant [9, 10]. Finally, some genetic polymorphisms in genes linked to the innate immunity are associated with an increased risk of infection. In a series of 113 autologous HSCT for multiple myeloma, patients homozygous for wild-type mannose-binding lectin (MBL) 2 were at lower risk to develop septicemia compared with patients carrying the variant MBL2 [2]. In another study, MBL deficiency was associated with higher risk of bacterial infections [3].

Table 4.3 Frequent pathogens causing infection according to immunodeficiency

	Disruption of skin and mucous membranes	Hypogamma-globulinemia	T-cell mediated immunode-ficiency	Neutropenia and neutrophil dysfunction
Bacteria				
Gram-positive cocci				
Coagulase-negative staphylococci	+++	−	−	++
Staphylococcus aureus	+++	−	−	++
Viridans streptococci	+++	−	−	++
Enterococci	++	−	−	++
Streptococcus pneumoniae	−	+++	−	−
Gram-positive bacilli				
Bacillus spp.	++	−	+	++
Corynebacterium jeikeium	++	−	+	++
Listeria monocytogenes	−	−	+++	−
Gram-negative bacilli				
Enterobacteriaceae[a]	++	−	−	+++
Pseudomonas aeruginosa	++	−	−	+++
Other nonfermentative bacteria[b]	++	−	−	+++
Salmonella spp.	+	+	++	+
Legionella spp.	−	++	++	−
Anaerobes				
Clostridium difficile	++	−	−	++
Clostridium septicum	++	−	−	++
Fungi				
Yeasts				
Candida spp.[c], mucosal disease	+	−	+++	−
Candida spp.[c], invasive disease	++	−	−	+++
Cryptococcus neoformans[a]	−	−	+++	−
Trichosporon spp.	++	−	+	++
Molds (mainly *Aspergillus* spp.)[d]	−	−	++	+++
Other				
Pneumocystis jirovecii	−	−	+++	−
Viruses				

(continued)

Table 4.3 (continued)

	Disruption of skin and mucous membranes	Hypogamma-globulinemia	T-cell mediated immunode-ficiency	Neutropenia and neutrophil dysfunction
Herpes simplex	++	−	+++	++
Varicella-zoster	−	−	+++	−
Cytomegalovirus	−	−	+++	−
Epstein-Barr virus	−	+	+++	−
Respiratory viruses[e]	+	+	++	−
Hepatitis A, B and C	−	+	+	−
Parvovirus B 19	−	++	++	−
Parasites				
Strongyloides stercoralis	−	−	++	−
Toxoplasma gondii	−	−	++	−
Cryptosporidium parvum	−	+	++	−
Mycobacteria				
Mycobacterium tuberculosis	−	−	+++	−
Rapid growing mycobacteria	++	−	+	−
Mycobacterium avium complex	−	−	+++	−

(−) no, (+) occasional, (++) frequent, (+++) very frequent
[a]Most frequent: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp;
[b]Most frequent: *Acinetobacter* spp., *Stenotrophomonas maltophilia*;
[c]Most frequent: *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*;
[d]Most frequent: *A. fumigatus* (~90 %), *A. flavus*, *A. terreus*, *A. niger*;
[e]Most frequent: Respiratory syncytial virus, metapneumovirus, influenza A and B, parainfluenza 1–3, adenovirus, rhinovirus, coronavirus

4.2.1   Pre-Engraftment Period

The main risk factors for infection in the pre-engraftment period are neutropenia, oral and gastrointestinal mucositis, and the presence of central venous catheters. In general, infection occurs more frequently with longer periods of neutropenia [1], and a decrease in the rates of bacteremia has been observed with the utilization of peripheral blood, instead of marrow, as the source of stem cells [11]. In addition, severe mucositis is associated with increasing risk for infection [6, 12], and indwelling venous catheters, present in virtually all ASCT recipients during the early period, may predispose to certain bloodstream infections [13].

The majority of bacterial infections during neutropenia are caused by Gram-positive organisms; *Staphylococci* (coagulase-negative and *S. aureus*), viridans *Streptococci* and the *Enterococci*; Gram-negative bacteria including the Enterobacteriaceae *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp., and the nonfermentative bacteria *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas maltophilia* [14, 15]. In addition, patients with severe mucositis

are at increased risk to develop bloodstream infections caused by anaerobes [16], alpha-hemolytic streptococci [17, 18], *Stenotrophomonas maltophilia* [19], vancomycin-resistant enterococci [20], and *Candida* spp [21, 22].

Considerable shifts in the spectrum of bacterial infections have occurred over time as a result of antimicrobial prophylaxis therapy with more severely mucotoxic drugs [23] and the widespread use of intravascular catheters. Until the late 1980s, Gram-positive and Gram-negative organisms were equally distributed as causes of bloodstream infections. The introduction of quinolone prophylaxis was associated with a significant reduction in Gram-negative infections [24] but at the cost of an increase in infections caused by Gram-positive bacteria. A reemergence of bacteremia by resistant Gram-negative organisms has been recently observed [25–27] including quinolone-resistant Enterobacteriaceae [28], extended-spectrum c-lactamase (ESBL)-producing bacteria (Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter* spp., others) [29], multidrug-resistant *P. aeruginosa*, and others [30]. Infections by resistant Gram-positive organisms have also been noted with vancomycin-resistant enterococci (VRE) and nosocomial and community-acquired methicillin-resistant *S. aureus* (MRSA) [31, 32]. A more serious problem in neutropenic patients with leukemia is the marked increase in *Clostridium difficile* colitis [33, 34]. In a retrospective study in 242 autologous HSCT recipients, 157 developed diarrhea between 1 week before and 30 days after HSCT, and 135 were tested for *C. difficile* toxin A. A diagnosis of *C. difficile-* associated diarrhea (CDAD) was made in 21 subjects (15.5 %) and occurred both before (4 patients) and after (17 patients) transplant. Patients receiving mobilization with paclitaxel and growth factor were at lower risk for CDAD compared with patients mobilized with growth factors with or without cyclophosphamide. Receipt of vancomycin or cephalosporins were risk factors for CDAD [35].

Great variability exists, between and within countries, in the etiology of bacterial infections and their susceptibility profiles [36], and an intimate knowledge of the local epidemiology remains critical in applying strategies of prophylaxis, empiric antibiotic therapy, and treatment of established infection. In a study of bacteremias in 519 HSCT recipients from a single institution, Gram-positive and Gram-negative bacteria accounted for 62 and 38 % of bacteremias, respectively [26]. The rates of bacteremias decreased over the 7-year study period, but were particularly more pronounced for Gram-positive bacteria, with a drop in the ratio of Gram-positive to Gram-negative organisms from 2.7 to 1.3.

In a prospective survey of 411 HSCT in 13 Brazilian centers, 91 patients developed bacteremia in the early post-transplant period: 47 % were caused by Gram-positive, 37 % due to Gram-negative, and 16 % were due to both Gram-positive and Gram-negative bacteria. *Pseudomonas aeruginosa* (22 %), *K. pneumoniae* (19 %) and *E. coli* (17 %) were the most frequent bacteria among Gram-negative; among Gram-positive bacteria, coagulase-negative staphylococci (50 %) and *S. aureus* (23 %) accounted for the majority of infections. Multi-drug-resistant (MDR) Gram-negative bacteria were isolated in 22 % of bacteremias (5 % of all transplants), and receipt of third-generation cephalosporins was an independent risk factor for infection due to MDR bacteria [37].

During the early post-transplant period, gastrointestinal mucositis and neutropenia predispose to the occurrence of invasive candidiasis, and unless patients are receiving

fluconazole prophylaxis, this is the leading invasive fungal infection in this period. With the introduction of fluconazole prophylaxis, the incidence of candidiasis decreased dramatically, with a shift in species distribution; fewer infections due to *C. albicans* and *C. tropicalis*, but increased infections caused by *C. glabrata* and *C. krusei* [38]. This may be illustrated by three epidemiologic studies. A prospective study of 16,200 HSCTs (autologous and allogeneic) in 23 centers in the USA (Transnet database) reported 217 cases of invasive candidiasis (1.3 %). *C. glabrata* was the most frequent species, accounting for 32 % of cases. Invasive candidiasis was diagnosed within 30 days after autologous HSCT in 66 % of cases, and within 4 months in 74 % of cases [39]. In a retrospective study involving 11 centers in Italy, only 16 cases of invasive candidiasis were reported among 1979 autologous HSCTs (0.8 %). Eight of the 16 cases were caused by *C. glabrata* ($n=5$) or *C. krusei* ($n=3$) [40].

Invasive aspergillosis occurs typically in patients with profound (<100 neutrophils/mm^3) and prolonged (>10–15 days) neutropenia. Because the duration of neutropenia after autologous HSCT is shorter, the incidence of invasive aspergillosis is low. However, patients with concomitant severe CMI deficiency are at risk. This group is represented by patients with lymphoma previously treated with purine analogues [41] and heavily pretreated myeloma patients [42]. We recently analyzed a cohort of 113 patients with multiple myeloma who developed invasive aspergillosis (data not published). Sixty-three episodes occurred after autologous HSCT, at a median of 16 days after transplant. In 29 of the 63 episodes (46 %), invasive aspergillosis occurred in the pre-engraftment period. Most patients had relapsed myeloma, had been heavily pretreated, and had received high doses of corticosteroids (median cumulative dose in the last 60 days of 1,380 mg patients, prednisone equivalent).

In the Transnet database, a total of 80 cases of invasive aspergillosis were diagnosed in 9534 autologous HSCT recipients (0.8 %). Forty cases were diagnosed within 30 days after transplant [39]. In the Italian retrospective study, seven cases were diagnosed in 1979 autologous HSCT recipients (0.3 %) [40]. Except for candidiasis and aspergillosis, other invasive fungal infections are rare.

Viral infections in the early post-transplant period are limited to reactivation of herpes simplex virus (HSV) and respiratory viral infections (Influenza A and B, parainfluenza 1–3, respiratory syncytial virus [RSV], metapneumovirus, and adenovirus). In the absence of prophylaxis (acyclovir or valacyclovir), most autologous HSCT recipients will develop reactivation of HSV, manifested as oral ulcers [43, 44]. The occurrence of symptomatic HSV disease is particularly frequent in patients with severe oral mucositis [45]. Although in most cases the disease is self-limited, causing pain and discomfort, it may evolve to pneumonia as a result of aspiration of the oral secretions with the virus [46].

4.2.2   Post-engraftment Period

Although the frequency and mortality of infection after engraftment are much lower than in the early pre-engraftment period, infection is a significant cause of morbidity and an important cause of non-relapse mortality. In a retrospective

analysis of 1,482 autologous HSCT, 32 % of non-relapse deaths occurring after day +100 post-transplant were caused by infectious complications. Sepsis and pneumonia were the most frequent infections, and viral and fungal disease were rare causes of death [47].

The risk for infection in the post-engraftment period is a function of the dynamics of immune reconstitution. Factors that delay immune reconstitution following ASCT are related to the underlying disease and/or to the stem cell product (Table 4.1). The most important factors influencing the speed of immune reconstitution are the immune status before HSCT and the need for additional immunosuppressive treatment. Heavily pretreated patients who exhibit severe immunodeficiency before HSCT are at greater risk of infectious complications. Likewise, additional chemotherapy after HSCT greatly increases the risk of infection. This is true for patients with MM, who receive consolidation and maintenance after HSCT.

The occurrence of neutropenia increases the risk for infection after engraftment. In a study, receipt of rituximab was an independent risk factor for delayed onset neutropenia [9]. Receipt of rituximab pretransplant has also been associated with an increased risk for CMV reactivation post-transplant [10].

In vitro manipulation of stem cells is usually associated with depletion of T cells from the harvest and results in delayed immune reconstitution and an increased risk for fungal, viral, and protozoal infections [48–52]. The influence of in vitro manipulation of stem cells on the risk of infection may be illustrated by a study of 148 patients, which reported that high T-cell content in the graft was associated with a lower incidence of varicella-zoster virus (VZV) reactivation [6] and another study of autologous HSCT for autoimmune disease. A 64 % CMV reactivation was observed with in vitro CD34 selection [7]. However, in a study in patients with lymphoma, MM and breast cancer, the incidence and causes of infection were not different among patients receiving unmanipulated or CD34 selected peripheral blood stem cells [53].

The frequency and etiology of infections occurring after engraftment were assessed in 244 autologous HSCT recipients with non-Hodgkin's lymphoma ($n=207$), Hodgkin's lymphoma ($n=27$), and MM ($n=43$). Infection occurred in 64 patients (26 %). The most frequent infections were VZV disease (56 %) and bronchopneumonia (25 %). By multivariate analysis, receipt of fludarabine was the only variable associated with infection [4]. In another study in 127 patients with breast cancer, among 99 patients with prolonged follow up, 32 (32 %) developed infection in the first year posttransplant. Upper respiratory infection ($n=11$) and dermatomal VZV disease ($n=9$) were the most frequent infections. Bacteremia occurred in only two patients [54].

Cytomegalovirus (CMV) reactivation is frequent in the late post-transplant period. In a retrospective study, 16 of 41 febrile episodes in CMV seropositive patients were associated with CMV reactivation. CMV infection was the sole cause of fever [55]. In a prospective study in 171 autologous HSCT recipients, weekly CMV antigenemia was performed from engraftment until day +60 post-transplant. Forty of 102 (39 %) CMV seropositive patients presented CMV reactivation at a median of 32 days after transplant. The majority of patients ($n=30$) were asymptomatic. Fever ($n=5$) and enteritis ($n=5$) were the clinical manifestations in the remaining patients [5].

In addition to VZV and CMV, respiratory viral infections are frequent in autologous HSCT recipients and may contribute to significant morbidity, especially in patients with lymphopenia [56].

Less frequent infections in the post-transplant period include hepatitis B and C [57], toxoplasmosis [58], tuberculosis [59, 60] and pneumocystosis, [61] and, in certain areas of the globe, Chagas disease [62].

4.3   Summary

Infection represents an important cause of morbidity after autologous HSCT. Infection results from an imbalance between host defenses and the pathogen, and the risk vary according to the phase of HSCT. Pretransplant variables that significantly impact the risk for major infection include host factors, genetic predisposition, comorbid conditions, tumor burden and the type, and duration and intensity of prior chemo- or radiotherapy. After HSCT and before engraftment, significant risk factors include neutropenia, mucositis, and central venous catheters. In the post-engraftment period, the risk of infection depends on the dynamics of the immune reconstitution that follows HSCT. Assessment of the risk of infection in each period and the identification of patients at higher risk of specific infections are critical to the appropriate management of infectious complications after autologous HSCT.

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