I11 Epidemiology and risk factors for serious infections in the stem cell transplant setting

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Infection is a main cause of death after stem cell transplantation, especially after allogeneic transplant. Since the routine practice of preemptive or prophylactic therapies for CMV infection, mould infections are the main concern of the transplant community. The occurrence of infectious complications roughly follows the different phases of immune reconstitution which are highly influenced, after allogeneic transplant, by graft-versus-host disease (GVHD). The increasing use of reduced-intensity conditioning regimens for allogeneic transplant has reduced the incidence of early bacterial infections, but also modified the timing of fungal and viral infections. We will review here the epidemiology and main risk factors of the infectious complications observed in the stem cell transplant setting.

Keywords: Stem cell transplant; Infection; Invasive fungal infections; Viral infections.

Stem cell transplantation offers a unique model of gradual immune reconstitution, and illustrates the relationship between the type of immune deficiency and infection by special pathogens perfectly. Despite major progress for the early diagnosis of infections and for prophylaxis and treatment of these complications, infection remains a main provider of non-relapse death after SCT, and much remains to be done to significantly reduce this risk.

The description of the different phases of immune reconstitution after the classical, myelo-ablative approach for SCT has been the subject of a large literature describing how the donor – in case of allogeneic SCT – or the recipient – after autologous SCT – -cells are able to proliferate, mature and differentiate until they are capable of attaining the full functions of immune cells. However, one knows that for allogeneic SCT recipients with severe graft-versus-host disease, normal immune function may never be reached for most patients. The recent development of non-myeloablative conditioning regimens for allogeneic SCT leads us to revise some of our management strategies.

Main phases of immune reconstitution and corresponding infections after allogeneic SCT: After allogeneic myeloablative SCT, it is usually considered that the sequence of infections may be classified into three periods:

1. The first is the conditioning period and the aplastic phase until neutrophil recovery from the donated marrow. This phase is characterized by neutropenia and thrombocytopenia, and the infectious complications of SCT patients are not very different at this time from those encountered in other profoundly neutropenic patients such as acute leukaemia patients. This aplastic phase is also at risk of invasive fungal infection. However, it is clearly known from the literature that most of the *Aspergillus* infections do not occur during the initial neutropenic phase, but later.
2. The second phase corresponds to the period from initial marrow engraftment to at least the third or fourth month, and is characterized by cell-mediated immune deficiency with decreased number and function of specific and non-specific cytotoxic cells. CMV infection, which is mainly due to reactivation, was the most disquieting problem in this setting until improved therapy and the routine practice of early diagnosis through PCR or antigenaemia and of preemptive therapy, which finally decreased the mortality due to CMV disease. Other viral diseases, less frequent than CMV, have been described during this phase, especially those due to adenovirus, enteric and respiratory viruses. The occurrence and severity of GVHD is the main factor delaying immune recovery and favouring infections. Although most investigations have focused on lymphocytic reconstitution, it is known that these patients also have phagocytic deficiencies of both neutrophils and macrophages, responsible for defects in bactericidal and fungicidal activities that may sometimes last for more than one year.
3. The third phase, beginning after the fourth month, is considered to be the late post-transplantation period. Here again, the immune reconstitution is mainly influenced by the presence and severity of chronic GVHD. Most patients have immunoglobulin deficiency, particularly of IgG2, which is responsible for a decrease in the response to polysaccharide antigens. In such cases, they are threatened with encapsulated bacteria (e.g. *S. pneumoniae* and *H. influenzae*), which should be especially considered in cases of pneumonia occurring after three months and treated urgently. In the absence of chronic GVHD,

this deficiency will often be transient and will resolve over time. In other cases, it may persist indefinitely. However, even in these cases, active immunization may be beneficial, especially with conjugate vaccines.

Each time a new approach in SCT is undertaken, new infectious complications can be observed. Mismatched transplants, for example, or phenoidentical transplants, are followed by more severe and protracted immune deficiency, and the best prophylactic and therapeutic approaches to these patients for infection have not been yet determined, since the characterization of the immune reconstitution in these patients is currently poorly understood.

Main phases of immune reconstitution and corresponding infections after autologous SCT: In standard settings, the overall prognosis of autologous SCT is less threatened by infectious problems than by relapse of the underlying disease. The almost universal use of peripheral blood instead of bone marrow stem cells has considerably reduced the duration of the initial neutropenic phase, from 20–24 days, to 8–12 days. Consequently, although bacterial, and even fungal infections, are still potential problems during the initial phase of transplant, the infectious mortality of autologous SCT is usually lower than 2–4%. Most of the initial infectious complications are due to streptococci – especially after total body irradiation, Gram-negative bacteria, and very rare candida infections. Aspergillosis is extremely rare, and probably more related to previous risk factors due to multiple previous treatment lines, rather than to autologous transplant per se. After the neutropenic phase, the immune reconstitution is highly variable according to the underlying disease, conditioning regimen, and CD34 selection. Patients transplanted with CD34+ selected grafts have an increased risk of *Aspergillus* [1] and viral [2] infection. Herpes virus infections, mainly due to herpes simplex, or later to varicella zoster virus, are common after autologous SCT. CMV reactivation is frequent but is very rarely complicated with CMV disease, so that systematic screening is not required in the absence of symptoms [3].

Invasive fungal infections: The allogeneic SCT population remains the population with the higher risk of invasive fungal infection, regardless of the type of transplant or donor-recipient HLA disparity. After allogeneic SCT, reported invasive aspergillus incidence varies from 0–20%, with a higher incidence in older patients and those receiving unrelated or mismatched grafts [4]. Most cases are now observed after recovery from neutropenia, during the second or third month post-transplant, at the time of acute GVHD.

The one-year cumulative incidence of aspergillosis was shown to have increased from 1992 to 1998 at the the Fred Hutchinson Cancer Research Center in Seattle, WA, USA. [4]. Multiple etiologies may be hypothesized to explain this increase:

1. Better survival from the early complications of transplantation.
2. Changes in the transplant approach, such the increasing use of cord blood – usually associated with prolonged neutropenia – or peripheral stem cell transplants, which provide a higher risk of GVHD than bone marrow transplantation.
3. Changes in the approach to treating cytomegalovirus, with a larger use of prophylactic ganciclovir with a consequent higher risk of neutropenia.

In clinical studies, the main risk factors for invasive aspergillosis after allogeneic SCT are age > 40 years, underlying diseases other than chronic myeloid leukemia in chronic phase or hematologic malignancy in first remission, and graft from an unrelated or HLA-mismatched donor [4]. However, even if this is difficult to analyze in clinical studies, SCT recipients have cumulative risk factors that have been shown to be related to the risk of *Aspergillus* infection in immunocompromised hosts: neutropenia, rupture of anatomical barriers, defects in respiratory epithelial cells, monocytic and macrophage functional deficiencies, and – more recently – deficient Th-1 response to *Aspergillus* [5].

Additionally, new immunosuppressive therapies may further increase the risk from GVHD. The use of infliximab, a humanized monoclonal anti-TNF-α antibody used to treat steroid-resistant GVHD, has been reported to be associated with an increased risk of mould, and especially of *Aspergillus,* infections in SCT recipients with severe GVHD [6].

Another issue specific to SCT patients when compared to other immunocompromised hosts is their past history, and especially previous neutropenic chemotherapy-induced phases. Consequently, some of them have prior *Aspergillus* infections when referred for transplant. Previous episodes of invasive fungal infection is a major risk factor for the recurrence of fungal infection after transplant, especially as soon as the patient is neutropenic [7]. This risk of recurrence of aspergillosis in such cases is higher when patients have received less than one month of antifungal therapy, and when resolution of radiographic abnormalities has not been achieved before transplant [7]. To date, secondary prophylaxis has been recommended for these patients, but the optimal choice is unknown