

# Post-transplant Immune Recovery and the Implication for Infection Risk

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## 1. Introduction

During the process of stem cell transplant, the patient's own immune system disappears, usually on a permanent basis, so that all previous immunity and immune function are lost [1]. A new immune system is then re-grown from the new source of hematopoietic stem cells but it may take months to many years for this immune system to mature and protect the patient from numerous infectious processes. As a result, the patient remains quite susceptible to a whole variety of opportunistic infections. Over time, as the immune system matures, we expect that the risk of acquiring an opportunistic infection will diminish. However, a number of factors interfere with the normal maturation of the immune system in the patient undergoing stem cell transplants and this manuscript will highlight some of those problems which interfere with immune recovery.

The pace of immune recovery and the normal progression have been associated with periods of time when risks for certain infections are at their peak and then begin to diminish. This appears to be associated with the recovery of certain aspects of the immune system over others. Thus, the susceptibility to bacterial infections may be greatest early on after stem cell transplant and then will diminish over time. Likewise, the same may occur with the occurrence of fungal infections. For other infectious processes, the risk diminishes over a longer period of time and in fact may peak months after the actual stem cell transplant. Again, these factors will be briefly reviewed in this paper.

When a stem cell transplant is performed, it usually involves giving some sort of chemotherapy and/or radiation to eliminate the underlying hematopoietic and immunologic system making it possible for new stem cells to be accepted and then grow. The damage which is done by the preparative therapy also will unfor-

tunately have an impact on the overall susceptibility to infection.

## 2. Components of the Immune System

Ordinarily, the components of the immune system on which we focus usually are the white cells in the peripheral blood and lymphatic tissues. However, there are a number of other components of the immune system that help to protect us [2].

The skin and mucosal membranes are an important barrier to our immune system. It helps to maintain the integrity of the immune system keeping out most opportunistic infections. It is the breakdown of these tissues which early on can overwhelm the immune system completely and increase the susceptibility to a wide variety of opportunistic infections. Many of the components of the immune system are clustered along the mucosal surfaces since this in many situations is the initial barrier that has to be breached before an infectious agent gains access to the systemic circulation. In addition, there are numerous immune cells located in the subcutaneous tissues again, a barrier that needs to be crossed before many infectious agents reach the systemic circulation. Thus, the skin and the mucosal lining are important components of the immune system in terms of providing protection and an initial barrier to cross.

Our initial studies on the pace of lymphocyte recovery following transplant, particularly in patients who are at high risk for a delay in lymphocyte recovery, have demonstrated very nicely that it may take months to years before lymphocyte numbers actually reach normal levels and this also is reflected in the population of the various lymphocyte components that again may take months to years to reach normal levels. The actual level correlates very nicely with function so that as the cell numbers begin to increase, maturation of these

lymphocytes is also occurring [3,4].

Neutrophils usually are in short supply in the first several weeks after a stem cell transplant and then they slowly begin to increase to normal levels. There has been adequate demonstration over a long period of time that even with normal neutrophil numbers following the initial stem cell transplant, maturation of these neutrophils will take some time and that these neutrophils may not be entirely protective [5]. Migration of the neutrophils to sites of infection, for example, may be delayed for a period of time.

Migration of monocytes to tissues to become very specialized macrophages again will take variable periods of time and in some situations, that period of time is not well defined. Some patients remain at great risk of acquiring an overwhelming bacterial infection months to years after transplant and some of this is thought to be related to dysfunction of the reticuloendothelial system. It is not known whether this dysfunction is simply related to structural integrity disruption due to radiation or chemotherapy or whether it is related to inadequate population and proliferation of donor stem cell derived tissue macrophages. In either case, the reticuloendothelial system functions poorly or not at all and as a result, patients remain quite susceptible to overwhelming sepsis [6,7].

Platelet recovery has also been associated with risk of infection. Platelets are known to be involved in inflammatory processes that may actually be helpful in terms of adherence of immune mediated cells at sites of inflammation [8]. If the platelet count remains low for a period of time, risk of infection appears to be increased. Whether the lack of platelet recovery is reflective of slow recovery of the remaining portion of the hematopoietic and immune system or whether it relates to the lack of participation and help that platelets provide in the inflammatory process is unclear from any data currently available.

Lastly, soluble immune factors also are slow to recover and appear to be very dependent on recovery of the cellular immune system. For example, normal production of immunoglobulin in some patients may be particularly delayed when there is delay in lymphocyte recovery [9]. There appears to be conflicting evidence as to whether or not these patients will benefit from immune globulin infusions since immune globulin infusions may modulate graft-vs-host disease [10].

### 3. Integrity of the Host

As mentioned previously, the integrity of the skin and the mucosal surfaces are important barriers to protect the patient following a stem cell transplant. A number of immune mediated factors line these surfaces to help protect the host from invasion with opportunistic infections. For example, lysozyme in tears and other secretions may actually be an important component of the immune system to help protect from invasion through those surfaces [1]. Fatty acids and other immune mediated cells within the skin may serve as a protective

barrier. The constant flushing of the urinary tract and rapid changes in the pH of the gut may also help alter the milieu for growth of opportunistic infections. Acquisition of sinus infections or infections through nasal passages appears to be an important way for fungus particularly to gain access to the systemic circulation. Whether this is related to structural integrity disruption of the mucosal lining from the preparative therapy or whether it's related to the lack of soluble factors and cells within the lining to protect the patient from fungal invasion is unclear. However, one can imagine that all of these factors are important components to help protect the patient from overwhelming infection.

Some preparative therapies appear to be much more disruptive to mucosal surfaces than others. Few if any studies have ever been done comparing one preparative therapy versus another in regards to the morbidity, number of hospital days, or mucosal surface disruption that may occur thereby potentially compromising recovery of the patient.

## 4. Environment

The environment in which the patient resides also has an implication on the post-transplant immune recovery. There are three aspects of this that clearly can be addressed at the current time.

### 4.1. Nosocomial Infection

It is clear that patients with compromised immune systems, particularly those undergoing stem cell transplants, are susceptible to acquiring infections while in the hospital [11]. Adequate barriers must be erected to maintain isolation of patients and in select situations, such as those with aplastic anemia, use of HEPA filtration appears to be warranted in terms of improving the overall outcome of the patients. Nosocomial infections in regards to acquiring particular viral or fungal infections have also been implicated in epidemics of particular diseases and impairment of long-term survival for stem cell transplant patients. Thus, patients with compromised immune systems who acquire a significant systemic infection may actually find their immune systems further compromised thereby delaying recovery or worsening the potential for recovery and increasing the possibility of a patient not surviving the transplant process.

### 4.2. Cytomegalovirus (CMV)

The incidence of CMV has been decreasing over time primarily related to the use of blood filtration techniques [12]. Before blood filtration was available, adequate screening of donors for those less likely to transmit CMV also helped to reduce the incidence of CMV. CMV is known to be an immune modulating virus and those who acquire CMV often have depressed immune systems for periods of time increasing the likelihood of acquiring other infectious processes. A number of pro-

phylactic medications are often given post-transplant to prevent the acquisition of CMV and likewise a number of invasive techniques have been utilized over a long period of time to try and identify those early on who may have acquired CMV infection.

4.3. Respiratory Syncytial Virus (RSV)

The respiratory tree and the upper airways appear to be mucosal surfaces particularly susceptible to early invasion and infection post-stem cell transplant. Infections in this area, particularly pulmonary infections, may be rather serious and require rapid intervention. Seasonal variations of risk do occur and the most important risk appears to be related to the acquisition of RSV. In many situations, this may be a nosocomial infection and thus great care needs to be exercised during certain seasons in regards to hospitalization and isolation of those with compromised immune systems. Again, acquisition of RSV may be associated with a decreased ability to handle other infectious processes.

5. Concomitant Use of Other Drugs/Graft-vs-Host Disease (GvHD)

A variety of drugs have been utilized over a long period of time as prophylaxis against the development of GvHD. Although patients undergoing autografting generally do not receive such medications, they too remain susceptible to a wide variety of opportunistic infections due to the delayed maturation of their own cells following an autograft [13]. However, in many situations, delay of the immune system and the increased susceptibility to opportunistic infections occurs more commonly in those receiving an allograft, particularly an allograft where the risk of serious GvHD is

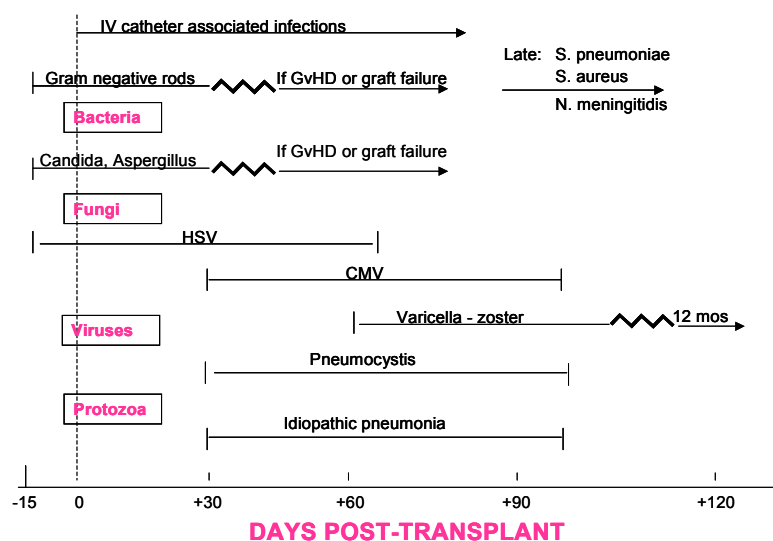
high [14]. These latter patients require increased use of prophylactic measures to suppress donor lymphocyte activity and increase the possibility of the patient's recovery without significant GvHD. Prednisone and other related steroids remain the mainstay of therapy for prevention and treatment and these drugs often not only result in a decreased number of lymphocytes, but may paralyze other components in the immune system in regards to recovery and activity.

Immune globulin for quite a number of years was given on a prophylactic basis to prevent the acquisition of CMV and other viral infections and yet there are data now to suggest that the long-term use of immune globulin in a prophylactic basis may result in immune modulation and actual decreased ability to handle certain infections [10]. Prophylactic use of certain antivirals may in select patients increase the possibility of renal compromise, which in itself may be an inhibitor to the immune system and recovery of normal immune function.

6. Periods of Risk

The periods of risk for acquiring infection have been well delineated and a diagram of this risk is in Figure 1. As can be seen, the initial risks appear to be primarily related to the acquisition of bacterial and fungal infections.

For the first several weeks following the stem cell transplant, neutrophil recovery will vary depending upon the cell dose, the type of graft which has been utilized, and the preparative therapy which has been given.<sup>(15, 16)</sup> For example, stem cell grafts that come from related closely matched donors tend to grow much more quickly and neutrophil recovery may be faster. Stem cell grafts that come from umbilical cord donors, where



Adapted from Clinics in Hematology by Lowell S. Young, Vol 13, No. 3, October 1984

Figure 1.

the cell dose may be particularly lower, due to the cell volume collected, may influence the pace of neutrophil recovery so that it may take more than three weeks for neutrophils to recover to a normal level. The delay in neutrophil recovery to an adequate level increases the susceptibility of the patient to bacterial and fungal infections [17].

It is easy to demonstrate in animals that the number of stem cells provided will decrease the susceptibility to a wide number of infections early after transplant. This is much more difficult to demonstrate in humans. However, it is relatively easy in pediatrics to obtain higher cell doses since most of the allogeneic donors are adults and many of the children are considerably

smaller compared to their adult donors. As a result, higher cell doses in children may result in a decreased number of infections which may be related to the improved survival often seen in younger patients undergoing similar types of preparative therapy and treatment [3]. However, there are adequate data already published that the volume of cord blood collected relates to the number of stem cells within the cord blood sample [15]. Use of cord blood samples with lower volume and therefore containing even fewer numbers of stem cells is associated with slower recovery, and decreased survival presumably related to a delay in the recovery of the immune system and an increased susceptibility to infection. This latter point is by implication since data are lacking to adequately prove this point.

After the initial recovery of neutrophils and potential decrease in the risk for subsequent bacterial infection, the risk of fungal infection continues for a period of time based on the use of medications to prevent or treat GvHD. Medications that continue to suppress the immune system interfere with the pace of neutrophil maturation and also paralyze other components of the immune system increasing the possibility of acquiring a fungal infection. However, as time progresses and a patient becomes more tolerant to the donor graft, medications to suppress the immune system and prevent GvHD are decreased and therefore the risk of acquiring a fungal infection also is decreased [1].

However, as time progresses, the risk of acquiring a viral infection continues to increase. The reason for this increased susceptibility is not particularly clear. Often it has been related to discharge from the hospital and exposure of the patient to others increasing the possibility of acquiring a viral infection from other individuals.

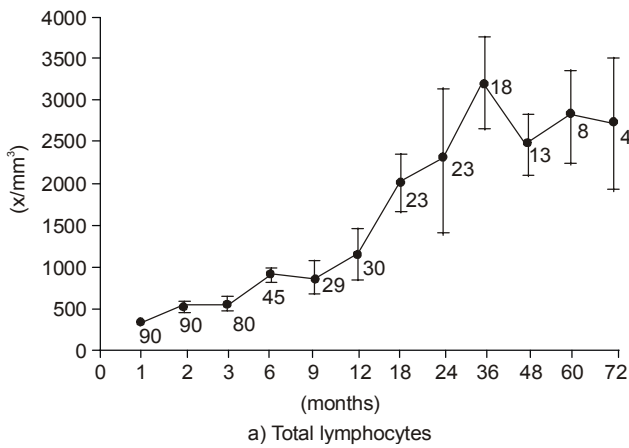


Figure 2.

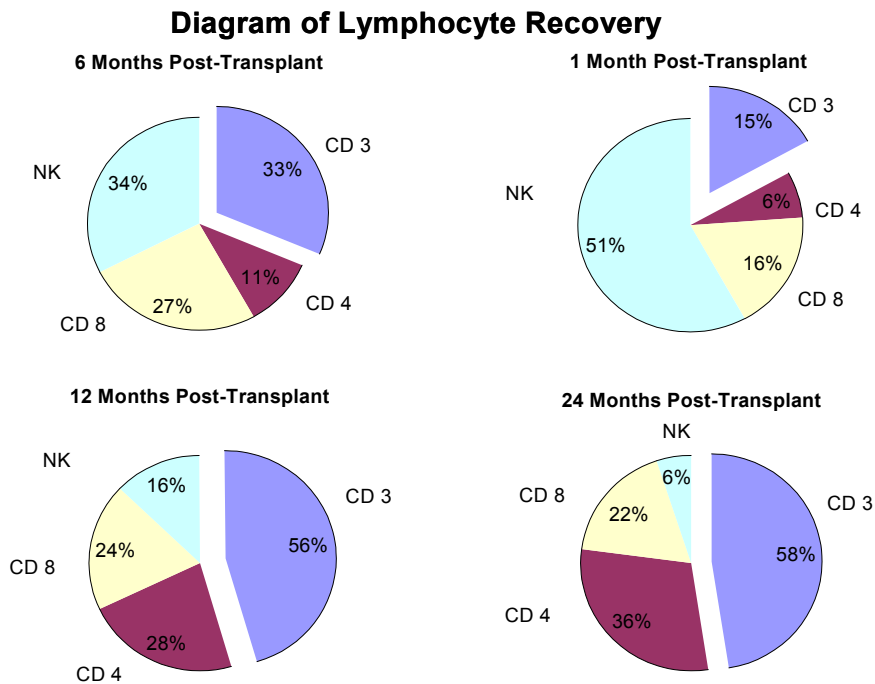


Figure 3.

However, some viral infections are known to propagate very slowly and it has been suggested that the slow growth of certain viruses accounts for the delayed appearance of a particular viral infection. However, this point is not well understood. In addition, there are some patients who are particularly susceptible to the development of Epstein Barr virus-induced lymphoproliferative disorders and these appear to increase the frequency during the first 3-6 months post-transplant. They particularly occur in those who have had significant immune suppression associated with a transplant, such as those who receive T-lymphocyte depleted grafts using a variety of methods to deplete the lymphocytes from the donor inoculum [10,17,18]. Some of those patients who develop EBV-induced lymphoproliferative disorders are cured with current cellular or monoclonal antibody therapy and never have a recurrence of the disease. Questions arise as to what happens to the virus and whether it is completely eliminated or whether it becomes dormant. The mechanism for this is unclear. Likewise, there are no studies to date to indicate why such patients no longer are susceptible despite the fact that they may still require the use of immune suppressive drugs to prevent or control GvHD.

Lastly, as has been suggested, there are some patients who remain very susceptible to overwhelming bacterial sepsis due to reticuloendothelial dysfunction. The risk period for this dysfunction is not well understood and some patients are on antibiotic prophylaxis for years. The hope is that we will better define the period of risk over the next 10 years and we'll have a better picture as to the recovery of all aspects of the immune system to know how long that risk remains for acquiring such infections.

## 7. Pace of Recovery

The best example that we have of the pace of lymphocyte recovery are the studies which we published from a large number of children undergoing T-lymphocyte depleted marrow transplants from haploidentical or unrelated donors. As can be seen in Figures 2 and 3, there is a marked delay in the recovery of total lymphocyte numbers as well as the recovery of certain lymphocyte subclasses. Some of this delay is secondary to the use of a T-lymphocyte depleted graft thereby increasing the duration of time before lymphocytes are repopulated [20,21]. Some relates to the high risk nature of these transplants and the fact that these children were much more susceptible to the development of serious GvHD or were under treatment for serious GvHD. GvHD is an immuno depleting disease as is the treatment and as a result, this will delay the recovery of normal lymphocytes and therefore normal lymphocyte function. However, a number of children had minimal-to-no GvHD and their recovery patterns suggest just a delay in the normal growth and maturation of the immune system particularly in those receiving T-lymphocyte depleted grafts [20]. However, similar data appear for those who receive grafts from perfectly matched sibling donors

thereby suggesting that there is an obligate period for normal lymphocyte growth and maturation [21,22].

Data have also been reported in regards to neutrophil recovery and that there is an obligate period of time following transplant before neutrophil numbers are increased to normal and before neutrophil function reaches normal levels. There is a suggestion that the use of certain immune modulators may actually expedite the improvement in lymphocyte numbers but whether this decreases the risk of infection remains unclear.

The pace of neutrophil recovery appears to be affected significantly by the use of neutrophil-growth factors, such as GM-CSF and G-CSF. However, it remains unclear as to whether or not the use of these growth factors significantly decrease the risk of acquiring a serious infection and therefore increase the chances of long-term survival. Controlled studies on the use of such growth factors have not adequately demonstrated an improvement in survival that can be traced to a decreased incidence of infections related to an improvement in neutrophil numbers. As mentioned previously, the pace of immune recovery may also be related to acquisition of other infections, particularly in regards to viral infections which may suppress normal lymphopoiesis and hemopoiesis.

## 8. Immunizations and Immune Adjuvants

A number of recommendations have been made in regards to immunization of hosts post-transplant and when this should be done. Immunizations may help to protect these patients from acquiring a wide variety of infections as well as meeting the requirements that these individuals, particularly children, will have to meet in order to return to school and normal childhood activities. Since little of the donor's immunity is passed through to the recipient in an allograft situation, it therefore remains important to re-immunize these patients in order to regain normal immunity to childhood illnesses such as rubeola, rubella and polio. Attempts have been made to immunize the donors to see whether or not such immunity may be passed through to the recipient, but this has not a procedure or process that has been well studied or applied. There have been certain allergic tendencies which have been passed from donor to new host suggesting that some donor immunity may actually survive the transplant process and will be exhibited in the new host. However, under normal circumstances, one does not count on any immunity from the donor coming through in the allograft [1].

It has been well demonstrated with transplants for acute myeloid leukemia that the use of interferon as an immune adjuvant may improve long-term survival. The assumption is that this improves long-term survival by decreasing the risk of acquiring certain opportunistic infections. It may also decrease the risk of relapse either by direct cytotoxic effects against leukemic cells or alternatively, by stimulating the immune system to deal with any residual leukemic cells [23]. However, the risk of recurrence for those with acute myeloid

leukemias in remission following stem cell transplants is relatively small compared with other malignancies and as a result, it becomes somewhat difficult to evaluate the effect of interferon in this situation.

A number of other immune adjuvants are under development or trial and may help to accelerate maturation of the immune system thereby decreasing the risk of acquiring an opportunistic infection. It is this risk which unfortunately impacts on long-term survival for many patients undergoing transplant, whether an autograft or allograft. In addition, with the increasing use of umbilical cord blood as a source of stem cells, it is well recognized that the number of stem cells provided with cord blood is relatively small compared with other sources of stem cells and as a result, lymphocyte recovery and recovery of other components of the immune system appears to be delayed and therefore there is an increased risk to the patient of acquiring an infection.

The question arises with some patients as to whether or not they actually ever acquire a normal immune system [1]. This actually is a question that has not been well studied over a long period of time. It's certainly possible when looking after patients long-term after stem cell transplants to have a sense that many of them have continued problems with minor infectious illnesses suggesting that perhaps they do not have complete recovery of their immune system [24-26].

The use of cellular adjuvants has been well documented to treat certain infectious problems which develop post-transplant, long before there is normal maturation of stem cell derived immune cells. For example, cellular therapy has been well applied to the treatment of EBV lymphoproliferative disorders and other significant viral infections. Donor lymphocytes have been selected for cytotoxic activity against EBV and CMV and these cells have been propagated in vitro and cryopreserved for subsequent use when such opportunistic infections occur. These cells have been useful in regards to treating such infections. Whether or not these cells should be harvested and grown from all donors and be given prophylactically post-transplant to decrease the risk of acquiring such infections is unknown. However, the process is cumbersome and expensive and there may not be the resources available for such widespread application of these cellular techniques. Prophylactic use of lymphocytes or other cellular components post-transplant have been tried and insufficient information is available to know how helpful or useful these techniques may be.

## 9. Conclusion

In certain stem cell transplant situations, the risk of acquiring an infection is the major impediment to long-term survival [25]. Efforts to speed up or enhance the recovery of cell numbers and function will certainly diminish this risk and may have a significant impact on long-term survival. However, this latter point remains untested to some extent.

An interesting study appeared many years ago in regards to techniques to T-lymphocyte deplete donor marrow. When comparing two groups of adults with similar diseases and of similar ages undergoing transplant for similar diseases, those who received donor stem cells which had been T-cell depleted had a significantly decreased risk of acquiring GvHD and an increased risk of acquiring an opportunistic infection thereby impairing long-term survival. Those who did not receive T-lymphocyte depleted marrow had a decreased risk of acquiring opportunistic infection and an increased risk of relapsing from their underlying disease, presumably related to the fact that these patients live long enough for their underlying malignancy to recur. Survival was therefore similar in both groups [27]. Thus, efforts to improve or enhance the outcomes in one aspect of transplantation may alter the risks with other variables post-transplant thereby negating the potential beneficial effect on long-term survival. Clearly, well controlled studies are needed in order to determine the effects of immune adjuvants and other efforts to accelerate immune recovery in regards to decreasing the risk of infection. A variety of practices have developed over a long period of time, which some believe have helped to enhance hematopoietic and immunologic recovery, and decrease the risk of infection [8]. However, many of these practices are of unknown benefit and, in the case of prophylactic immune globulin, may actually be detrimental. The field of stem cell transplant certainly is ripe for studies looking at efforts to not only prevent the acquisition of infections and better treat those which occur, but also to enhance recovery of cellular function, ultimately decreasing the risk of acquiring opportunistic infections.

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