Hematopoietic stem-cell transplantation is associated with a profound immune deficiency manifested as an increased propensity to develop infections and probably also malignancies. Innate immunity, including epithelial barriers and phagocytes, typically recovers within weeks after grafting, and B-cell counts and CD8 T-cell counts recover within months. CD4 T-cell counts are low for years, and their recovery is particularly slow in older patients with poor thymic function. Therapies to improve immune function include vaccinations, immunoglobulins for recurrent infections, cytokines, and antigen-specific donor lymphocyte infusions.

Key words: hematopoietic stem-cell transplantation; allogeneic transplantation; autologous transplantation; immune system; lymphocytes; antibody formation.

After hematopoietic stem-cell transplantation, function is variably impaired in all arms of the immune system. With high-intensity conditioning there is a loss of recipient immune cells; however, recipient plasma cells may persist for months to years post-transplant. With low-intensity conditioning all types of recipient immune cells may persist. Many factors related to transplant may impact immune status, including underlying disease, prior chemoradiation therapy, transplant conditioning (chemotherapy, radiation and/or...
antilymphocyte antibodies), stem-cell source, graft manipulation including T-cell depletion, degree of human leukocyte antigen (HLA) matching, and serostatus for herpesviruses. Post-transplant factors such as graft-versus-host disease (GVHD), immunosuppressive drugs for GVHD prophylaxis/therapy, antimicrobial drugs or intravenous immunoglobulin for the prophylaxis of infections or donor lymphocyte infusions also affect immune function.

It is likely that the tempo of immune reconstitution is associated with clinical outcomes such as infection rates, survival or non-relapse mortality, based on retrospective studies which included relatively small numbers of patients (Table 1). However, a rigorous proof of the association is lacking. Larger, ideally prospective, studies are needed to eliminate publication bias (there is a tendency to publish studies which find the association but not the negative studies) and determine immune monitoring tests of prognostic value.

**INNATE IMMUNITY**

**Barrier immunity**

Within the respiratory, gastrointestinal and urogenital tracts and on the skin, intact epithelium provides a physical barrier preventing translocation of bacteria and infection.

---

<table>
<thead>
<tr>
<th>Immune test</th>
<th>Timing</th>
<th>Result</th>
<th>Outcome</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute lymphocyte count</td>
<td>Day 15</td>
<td>£500/µL</td>
<td>Improved OS, PFS (autotransplants)</td>
<td>Y</td>
</tr>
<tr>
<td>Absolute lymphocyte count</td>
<td>Day 30</td>
<td>&gt;300/µL</td>
<td>Increased OS, LFS, molecular remission and decreased NRM (CML patients)</td>
<td>Y</td>
</tr>
<tr>
<td>B-cell and monocyte counts</td>
<td>Day 80</td>
<td>Low (cut-off value not given)</td>
<td>Increased fungal infections (B cells) and viral infection (monocytes)</td>
<td>Y</td>
</tr>
<tr>
<td>CD4 T-cell counts</td>
<td>3 months</td>
<td>&lt;200 × 10^6/L CD4</td>
<td>Decreased OS</td>
<td>Y</td>
</tr>
<tr>
<td>CD8 T-cell and B-cell counts</td>
<td>6 months</td>
<td>Low (cut-off value not given)</td>
<td>Increased treatment failure (death, relapse or graft failure)</td>
<td>N</td>
</tr>
<tr>
<td>CMV peptide-specific CD8 T-cell counts</td>
<td>Every 2 weeks during days 0–65</td>
<td>&lt;7 cells/mL in all samples</td>
<td>Increased risk of recurrent or persistent CMV reactivation</td>
<td>Not specified</td>
</tr>
<tr>
<td>CMV-specific lymphoproliferation</td>
<td>4 months</td>
<td>Detectable proliferation</td>
<td>Decreased late CMV disease</td>
<td>N</td>
</tr>
<tr>
<td>NK-cell chimerism</td>
<td>First 100 days</td>
<td>Incomplete chimerism</td>
<td>Decreased RFS at 2 years</td>
<td>Y</td>
</tr>
</tbody>
</table>

Studies refer to allotransplants unless otherwise specified. OS, overall survival; PFS, progression-free survival; LFS, leukemia-free survival; NRM, non-relapse mortality; CML, chronic myeloid leukemia; RFS, relapse-free survival; CMV, cytomegalovirus; DLI, donor lymphocyte infusions.
Secretions like tears or saliva that contain antimicrobial molecules (including lysozyme) further facilitate this barrier function. Chemotherapy, radiation therapy and GVHD cause mucosal damage and skin damage. Mucosal damage is typically repaired within several weeks, except in the presence of GVHD which is associated with failure to return to baseline saliva production (Figure 1). Most patients have intravenous catheters in place during and after transplantation to facilitate blood draws, transfusions, and medication administration. These are a potential portal for infection by skin organisms such as staphylococci or _Candida_ species.

**Complement**

Complement proteins are produced in many tissues, including monocytes/macrophages, and in largest amounts in the liver. After bone-marrow transplant, complement levels are not generally deficient. Congenital deficiencies of complement factors that are asymptomatic in otherwise healthy individuals may become clinically manifest post-transplant. For example, coding mutations in the _MBL2_ gene for mannose-binding lectin, a molecule which binds carbohydrate moieties on infectious pathogens and opsonizes them either directly or through complement activation, increases the risk of major infection post-transplantation.

**Natural killer cells**

Natural killer (NK) cells play a role in antiviral immunity and graft-versus-leukemia (GVL) effect, and recipient NK cells may also be important in graft rejection. NK cells comprise the majority of lymphoid cells in the first 30 days after transplant, by which time they have reached normal levels and do not differ substantially between recipients of peripheral-blood and bone-marrow stem cells.

**Neutrophils**

During the period of neutropenia following myeloablative hematopoietic cell transplantation, fever and infection are common. Use of peripheral-blood stem cells has

---

**Figure 1.** Parotid salivary flow rate in two groups of patients after allogeneic (73%) or autologous stem-cell transplant with ($n=6$) and without ($n=9$) GVHD. Day 0 coincides with transplantation day. GVHD, graft-versus-host disease; BMT, bone-marrow transplantation. Reproduced from Chusau et al (1995, *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology & Endodotics* 79: 164–169) with permission.
decreased the median time to neutrophil recovery from approximately 16 to 12 days, and use of non-myeloablative regimens has further shortened the period of neutropenia. However, use of umbilical-cord blood is also becoming more common and is associated with prolongation of the neutropenic period to a median of 26–27 days. Although use of granulocyte-specific colony-stimulating factor (G-CSF) shortens the neutropenic period, its use is controversial as it may hamper CD4 T cell recovery and has not been demonstrated to increase overall survival.

Neutrophil function is often impaired in the early post-transplant period and in the presence of GVHD. Patients with pyogenic infections are more likely to have neutrophil function abnormalities.

**Antigen-presenting cells**

**Dendritic cells**

Dendritic cells are found in mucosal and lymphatic tissues. Their function is to present the HLA–peptide complex to T cells together with co-stimulatory molecules to stimulate antigen-specific immune responses or antigen-specific T-cell tolerance.

Langerhans cells are antigen-presenting cells in the skin which decrease immediately post-transplant and recover by 3–6 months; this can be delayed in the presence of GVHD. In the blood, counts of myeloid dendritic cells (DC1, expressing CD11c) become normal by 3 months post-transplant, whereas counts of plasmacytoid dendritic cells (DC2, expressing CD123) are low up to 1 year post-transplant. Follicular dendritic cells, important to support immunoglobulin class switching and somatic mutation, remain markedly decreased at 1 year which may contribute to the slow regeneration of germinal centers and memory B cells.

**Monocytes/macrophages**

Monocyte recovery after allogeneic transplant is rapid and occurs within approximately 1 month. Infused monocytes become undetectable by approximately 1 week post-transplant, probably due either to cell death or to transition into macrophage form (Storek, unpublished data). There have been conflicting reports of monocyte function being normal post-transplant or suppressed for up to 1 year, with evidence of decreased chemotaxis in pulmonary macrophages for 1 year after marrow transplantation.

**ADAPTIVE IMMUNITY**

**T-lymphocyte number and function**

T-lymphocyte function is essential for cell-mediated immunity protective against fungal, viral, and protozoan infections, and for control of B-lymphocyte responses to encapsulated bacteria. The number of mature T cells infused during transplantation is 1 to 1.5 log higher when allogeneic stem cells are obtained from blood than marrow. Cord blood contains fewer T cells than a typical adult marrow graft, and has a high naive:memory/effector T-cell ratio.

CD8 cell counts recover rapidly (by 3 months post-transplant) and are often normal or supranormal at 1 year; this is possibly related to expansion of herpesvirus-specific CD8 T cells. However, CD4 T-cell numbers recover slowly with subsequent
reversal of the normal CD4:CD8 ratio (Figure 2). CD4⁺ T-cell counts are <200 cells/μL during the first 3 months after bone-marrow transplant and slowly rise to 300 cells/μL by 1 year and 450 cells/μL at 5 years; at 20–30 years post-transplant they are normal. This recovery is faster in children.

The number of T cells infused with the graft significantly influences T-cell counts after transplant. T-cell-depleted transplants display decreased T-cell counts and a more limited repertoire of T cells, and there appears to be a correlation between the number of CD4 cells in the graft and the number of CD4 circulating cells after engraftment. Recipients of blood stem cells have higher T-cell counts than recipients of marrow. This is clinically significant, as the blood-stem-cell recipients have fewer post-engraftment infections. However, blood-stem-cell recipients also appear to have a higher incidence of chronic GVHD. Post-transplant T cells can originate

Figure 2. Recovery of leukocyte subsets. All horizontal axes display days post-transplant. Patient medians (diamonds) and 25th–75th percentiles (error bars) are shown. Normal medians are indicated by the dashed horizontal lines (neutrophils not available). The thick horizontal lines denote the normal 5th and 95th percentiles (neutrophils 2.5th and 97.5th percentiles). Pretransplant studies are arbitrarily shown as day −50 studies. Reproduced from Storek et al (2004, Clinical Immunology 113: 285–298) with permission.
either from grafted T cells or from grafted stem cells that have differentiated into T cells in the host thymus.54,55

GVHD decreases the number of CD4 T cells probably by inhibiting thymic output or altering thymic stroma, or as a result of the effects of immunosuppressive drug treatment; in contrast, CD8-cell recovery is faster in patients with GVHD or CMV seropositivity and commonly numbers transiently overshoot to above normal levels.56,57

**CD4 T lymphocytes**

Phenotypically, post-transplant CD4 cells suggest a prominence of antigen-primed cells rather than the high numbers of naive cells seen in early lymphoid ontogeny at birth (Figure 3).58 Transplant recipient CD4 T cells are larger in size than normal adult or neonatal CD4 T cells.59 There is more frequent expression of CD11a, CD29, CD45RO, and HLA-DR than in normal adults and less frequent expression of CD28, CD45RA, CD62L; this pattern is directly opposite from that in newborns compared to normal adults.60–64 Circulating T-cell diversity is initially sparse, with over-representation of some clones and decreased numbers of clones; as T cells are generated de novo, the diversity of T cells gradually improves late post-transplant.65

In children, retrospective analysis of T- and B-cell reconstitution after autologous transplantation revealed normalization of T-lymphocyte numbers and lymphoproliferation in response to phytohemagglutinin (PHA) or alloantigen in two thirds of patients.
by 6 months after transplant. The production of stem-cell-derived CD4 T cells de novo is prominent in children, who have a more rapid rise in CD4 counts than adults. Adults can have a prolonged (>5-year) time to recovery of CD4 count and probably repopulate the CD4 population largely from donor lymphocytes rather than de novo from stem cells. This may be partly due to reduced thymic function for support of donor hematopoietic stem cells with increasing age (Figure 4).

**CD8** T lymphocytes

The rapidly increasing CD8 T cells early post-transplant consist largely of memory/effector cells with slow recovery of naïve or TREC CD8 T cells. The phenotype of recovering CD8 cells suggests increased antigen-primed cells rather than naïve cells. A large percentage of CD8 T cells are CD28−/CD57+, a phenotype that has been ascribed to suppressive, anergic, or terminally differentiated cells.

Recovery of virus-specific CD8 T cells appears important for preventing severe infections due to herpesviruses. In 14 patients who developed CMV antigenemia, Gratama et al measured CMV peptide-specific CD8 T cells; they were usually normal or supranormal in the ten patients who did not develop CMV disease and were virtually undetectable in the four patients who developed CMV disease.

**B lymphocytes/humoral immunity**

B-cell counts are low in the 2 months post-transplant and may be undetectable; they subsequently rise, and by approximately 1–2 years after transplant may be higher than

![Figure 4](https://example.com/image.png)

**Figure 4.** Naïve (CD45RA high) CD4 T-cell count at 1 year after bone-marrow transplantation (BMT) is inversely correlated with patient age at transplant, suggesting diminished ability of CD4 T-cell production de novo (from stem cells) with increasing age (Spearman rank correlation coefficient -0.68, P < 0.001). Allograft (n = 33) and autograft (n = 7) recipients were studied. Reproduced from Storek et al (1995, Bone Marrow Transplantation 16: 413–425) with permission.
in healthy individuals.\textsuperscript{46,72} The recovery may occur earlier in cord-blood transplants than in BMT.\textsuperscript{73} Donor B cells are present in approximately 18-fold greater numbers in peripheral-blood stem cells than marrow stem cells, and a faster rate of B-cell recovery in the first 3 months in recipients of allogeneic peripheral-blood stem cells may be due to higher numbers of B cells transferred in the graft.\textsuperscript{21} By 3 months post-transplant, marrow recipients have equal or higher numbers of B cells than peripheral-blood HCT recipients (Figure 5).\textsuperscript{21,40}

Plasma cells are chemoradioresistant, and therefore recipient antibody production is present immediately post-transplant (Figure 6).\textsuperscript{74} Levels of IgG do not differ initially between recipients of peripheral-blood and bone-marrow stem cells, but after 90 days they may be slightly higher in bone-marrow recipients.\textsuperscript{52} B-cell immunity becomes primarily donor in origin within several months after allotransplant; post-transplant B cells are derived from grafted B cells and transplanted stem cells, with the latter most likely predominating. Because of the persistence of recipient plasma cells, which are not destroyed by conditioning but may be destroyed by GVHD, recipient-type immunoglobulins may be detectable for years.\textsuperscript{75}

Recapitulation of normal lymphoid ontogeny occurs during reconstitution of B lymphocytes. A relatively rapid initial rise in naive B cells is followed by a slow recovery of memory B cells.\textsuperscript{76} Germinal centers may be non-existent for approximately 1 year post-transplant.\textsuperscript{35} The phenotype of the B cells post-transplant is similar to that of neonatal cells, with a lower percentage expressing CD25 and CD26L, and a higher number expressing CD1c, CD38, CD5, membrane IgM and IgD than in normal

Figure 5. Circulating B-cell counts after bone-marrow transplantation (BMT) (left) and in normal ontogeny (right). In early ontogeny, there is a rapid rise leading to supranormal counts at 0 and 4 years of age, followed by a decline. After BMT, the trend is similar, although the initial rise is less steep, particularly in allograft recipients with significant GVHD (grade II–IV acute or extensive chronic GVHD). Reproduced from Storek and Witherspoon (2004, in Atkinson K et al, eds Clinical Bone Marrow and Blood Stem Cell Transplantation, Cambridge University Press, 3rd edition, pp. 194–226) with permission.
adults. Memory (somatically mutated) B cells are low for at least 1 year post-transplant. Serum isotypes develop in the order they develop in childhood, with normalization of IgM, IgG1 and IgG3 followed by IgG2, IgG4 and IgA by approximately 2 years as memory B cells regenerate. However, the extent of heterogeneity in tetanus-specific antibodies may remain abnormal.

Adoptive transfer of antigen-specific humoral immunity occurs through infusion of antigen-specific B cells, T cells, or perhaps pre-plasma cells. The production of the antigen-specific antibodies is typically detectable only if the antigen is present in the recipient peri- and post-transplant. After allogeneic transplant, antibody-mediated immune disorders have been transferred from donor to recipient, including IgE-mediated allergic disease, Hashimoto’s thyroiditis, immune thrombocytopenia, and other disorders.

**NON-MYELOABLATIVE TRANSPLANTATION**

Non-myeloablative transplants use non-intensive chemoradiation, relying on graft anti-neoplastic activity to treat the underlying disease. Some non-myeloablative conditioning regimens include anti-T-cell antibodies. Non-myeloablative transplants are increasingly used in patients with comorbidities or increased age in an attempt to reduce treatment-related mortality, and result in decreased damage to mucosal and dermal barriers.
In comparison to myeloablative transplantation, reduced-intensity conditioning has been associated with shorter duration of severe neutropenia.\textsuperscript{84}

No randomized prospective trials evaluate immune reconstitution in myeloablative and non-myeloablative transplantation. Several studies with inherent selection bias have compared immune reconstitution in series of patients with non-myeloablative transplants to historical cohorts with myeloablative transplants.\textsuperscript{45} Significant clinical infections continue to occur with opportunistic organisms, at a frequency comparable to those with myeloablative transplants.\textsuperscript{45,85} However, if anti-T-cell antibodies are not used, early post-transplant infections appear less frequent after non-myeloablative transplants. In one study, CMV-specific T-helper cells were higher in non-myeloablative transplants up to day 90, which corresponded with lower rates of CMV infection before but not after 90 days. This is likely due to the contribution of recipient anti-CMV T cells early post-transplant.\textsuperscript{86}

Certain non-myeloablative conditioning regimens containing anti-T-cell antibodies cause significant loss of T-cell function and demonstrate increased rates of CMV infection. A study of 101 patients given non-myeloablative conditioning, including Campath-1H, reported a very high incidence of CMV reactivation in 85\% of patients with a CMV-positive donor or recipient at a median of 27 days despite a low incidence of grade III–IV GVHD.\textsuperscript{87} Median time to CD4\(^+\) cell count \(>200/\mu\text{L}\) was prolonged to 9 months. Use of a conditioning regimen based on antithymocyte globulin (ATG) was associated with a 65\% incidence of CMV reactivation compared to historical reactivation rates of approximately 40\%.\textsuperscript{88,89} These studies demonstrate the impact of lymphodepletion on post-transplant immunity.

**THERAPIES**

**Pathogen avoidance**

During the neutropenic period regular hand-washing, isolation of hospitalized patients with resistant organisms to prevent spread, and the use of high-efficiency particulate air (HEPA) filters on hospital units as well as avoidance of ill contacts are important in avoiding infection.\textsuperscript{90,91} A diet avoiding unwashed fruits and vegetables, uncooked meats and unpasteurized dairy products may prevent exposure to environmental and food-borne pathogens; the impact on infection rates of strict adherence to a sterile diet is not well studied.\textsuperscript{92} Avoiding mold exposures e.g. at construction sites may decrease aspergillus infections.\textsuperscript{93} CMV-negative and/or leukapheresed blood products prevent CMV infections in CMV-negative patients.\textsuperscript{79} Guidelines have been published regarding prophylaxis and treatment of specific infections during the peritransplant period.\textsuperscript{94}

**Barrier immunity**

Currently, the routine use of gut decontamination is not recommended in the transplant period.\textsuperscript{94} Optimal skin care with regular inspections for loss of skin integrity, maintenance of good oral hygiene, including rinses and brushing with ultrasoft toothbrushes, and strict catheter care are important to prevent infections from barrier compromise.

Keratinocyte growth factor (KGF) was recently approved by the FDA to prevent severe mucositis associated with myeloablative conditioning after a prospective randomized placebo-controlled trial of palifermin found decreased incidence of grade
3–4 mucositis from 98% to 63%, and the median time of mucositis decreased from 9 to 6 days. Other KGF compounds are undergoing clinical trials. The increasing use of non-myeloablative conditioning regimens has also decreased the incidence of severe mucositis in patients being given allogeneic transplants. KGF promotes epithelial cell proliferation and differentiation in many tissues, including thymus; in mice it enhances thymopoiesis, accelerates thymic recovery following chemoradiation, increases peripheral T-cell numbers post-BMT, and may decrease damage from GVHD. Further human studies are required.

Granulopoietic cytokines and antibiotic prophylaxis

Granulocyte colony stimulating factor (G-CSF) shortens the neutropenic period for autologous and allogeneic transplantation; however, conflicting evidence exists regarding whether it shortens duration of hospital stay. It has not been shown to provide a survival benefit in allogeneic transplant. Routine use of antibiotic prophylaxis during the neutropenic period remains controversial; antibiotics decrease bacteremia rates but have not impacted overall survival, and concerns remains regarding emergence of resistant organisms. Acyclovir prophylaxis of herpes simplex virus is recommended, but is controversial for varicella zoster virus. Despite the lack of randomized trials, prophylaxis of Pneumocystis pneumonia with trimethoprim/sulfamethoxazole and pneumococcal prophylaxis with penicillin or trimethoprim/sulfamethoxazole in patients with chronic GVHD are recommended.

Vaccination

Vaccination of transplant recipients at more than 6–12 months post-transplant effectively enhances antibody levels to pathogens. The optimal vaccination strategy could be pretransplant vaccination of both donor and recipient (Figure 7). Current EBMT guidelines recommend only post-transplant vaccination for pneumococcus, Haemophilus influenzae type B, tetanus and diphtheria toxoids, and hepatitis B. Hepatitis B vaccination may be considered early if the patient is positive for anti-HBs before SCT, and should be considered pretransplant if feasible when the donor is HbsAg-positive and the recipient is negative. Annual influenza vaccines for patients, families and transplant unit staff should start 4–6 months post-transplant. Live vaccines against bacteria should generally be avoided in patients and immediate family members. Measles, mumps and varicella zoster virus live vaccines could be used in autotransplant patients or allogeneic recipients without GVHD or ongoing immune suppression at 24 months, and rubella in women who have pregnancy potential at 24 months.

Immune globulin

Intravenous immune globulin (IVIG) prophylaxis after allogeneic transplant was investigated in a prospective randomized controlled trial of 250 patients given IVIG monthly or no IVIG and followed for events during days 100–365 after marrow transplant. There was a slightly higher incidence of local infections the first year post-transplant (during the administration of IVIG/placebo) in control patients (0.44 versus 0.24, P < 0.07), but no difference in bacteremias, overall survival, obstructive airway disease, or chronic GVHD. Long-term endogenous humoral recovery was delayed in patients receiving IVIG, with control patients suffering fewer infections during the second post-transplant
year (incidence 0.12 versus 0.19, \( P = 0.03 \)), and lower IgG1 and IgA levels at day 730 in patients who received IVIG prophylaxis than in control patients (Figure 8). IVIG is not currently recommended for routine prophylaxis of infections or GVHD.

The role of specific immunoglobulins for prophylaxis of certain infections may be warranted: i.e., CMV hyperimmune globulin for active CMV disease, or post-exposure prophylaxis with specific antibodies to varicella zoster.107 These roles are not well studied.

T-cell infusion

Investigations are ongoing regarding therapeutic use of antigen-specific donor T lymphocytes to treat infections. Infusion of autologous or donor-derived T cells specific for Epstein-Barr virus (EBV) has decreased EBV titers in blood and treated post-transplant lymphoproliferative disorders.110,111 Use of this modality is being investigated in adenovirus, CMV and aspergillosis.112,113 However, this is costly and is useful only in the absence of extensive GVHD as immunosuppressive therapy also suppresses the infused pathogen-specific T cells.

Stimulation of T-cell expansion or improving thymopoiesis

Cytokines stimulating T-cell expansion — for example IL-7 — should be explored as prophylaxis of infections and malignancy relapse in the autologous setting.114,115 In the allogeneic setting, there may be a significant risk of GVHD.116 Theoretically, a better approach would be to stimulate thymopoiesis rather than T-cell expansion, as thymopoiesis (but not T-cell expansion) can improve T-cell repertoire. Improved thymopoiesis should also improve immunity against endogenous pathogens such as herpesviruses,117 as the thymus does not delete cells against endogenous pathogens. However, only weak ‘thymopoietins’ exist (e.g. growth hormone/insulin-like growth factor-1, Flt3 ligand, KGF). Engineering of an artificial thymus has been unsuccessful.

Figure 7. Median IgG levels for *Haemophilus influenzae* vaccination are significantly higher in the group with recipients vaccinated on days −1, 50 and 365 and donors vaccinated on day −20, compared to recipients vaccinated on days −1, 50 and 365 with donors unvaccinated pre-transplant (DNR\(_{-1,50,365}\)) or the recipients vaccinated only on day 365 with donors unvaccinated pretransplant (DNR\(_{365}\)). Reproduced from Storek et al (2004, Bone Marrow Transplantation 33: 337–346) with permission.
Immune reconstitution following allogeneic transplant involves all aspects of innate and adaptive immunity. Breakdown of barrier immunity due to chemoradiation or GVHD is repaired, and donor cells rapidly replace phagocytes. With myeloablative transplants, there is rapid reconstitution of B lymphocytes and CD8 T lymphocytes over months, with recapitulation of B-cell ontogeny, but CD8 T cells adopt a phenotype consistent with antigen-primed rather than naïve cells. CD4 T-lymphocyte recovery is of predominantly antigen-primed cell phenotype and is delayed over years, in part due to reduced thymic function, especially in the presence of GVHD and older recipient age. Immune reconstitution in reduced-intensity transplants is variable depending on conditioning and extent of T-cell depletion.

Infection prevention in the peri-transplant and post-transplant periods is improved by supportive measures including hand-washing, use of HEPA filters, avoidance of ill contacts and high-risk situations for exposure to aspergillus. Currently, the use of prophylactic gut decontamination is controversial and not routinely recommended. Prophylaxis of pneumocystis and pneumococcal infections is recommended, herpes simplex virus prophylaxis is recommended, and varicella zoster virus prophylaxis is
controversial. Vaccination strategies are being developed and may ideally involve vaccination of donor and recipient pre-transplant. IVIG is not routinely used for prophylaxis but may have a role in recurrent infections with hypogammaglobulinemia. The therapeutic use of antigen-specific T lymphocytes is being developed, and the role of keratinocyte growth factor and possibly cytokine therapy to prevent infectious complications is a topic for ongoing study.

**Practice points**

- after stem cell transplantation, both innate and adaptive immunity are impaired, requiring a low threshold of suspicion for infection
- supportive care including hand-washing, HEPA filtration, avoidance of infectious contacts, oral hygiene, skin and catheter care is likely to be important for prevention of infection
- intravenous immune globulin should not be routinely used to prevent infections following stem-cell transplantation
- vaccination post-transplant and prophylactic antibiotics for appropriate pathogens should be administered according to published guidelines
- infusions of T lymphocytes specific for certain pathogens may be useful after transplantation of severely T-cell-depleted grafts

**Research agenda**

- detail the mechanisms of immune response regulation in immune reconstitution, including by regulatory T cells
- identify methods to separate T lymphocytes that cause GVHD from T lymphocytes protecting against infections and malignancies
- explore methods to minimize barrier disruption while providing effective antineoplastic therapy
- identify genetic defects of donor immunity that are prevalent yet typically asymptomatic in healthy donors but manifest as increased propensity to develop infections after transplantation (defects similar to that of the MBL2 gene);(18) subsequently explore whether choosing donors without the defect(s) leads to improved post-transplant outcomes
- develop immunogenic vaccines against infections frequently occurring in transplant recipients
- engineer pathogen-specific T cells resistant to immunosuppressive therapy
- continue searching for ways to improve thymopoiesis

**REFERENCES**


43. Szabolcs P, Park KD, Reese M et al. Coexistent naive phenotype and higher cycling rate of cord blood T cells as compared to adult peripheral blood. Experimental Hematology 2003; 31(8): 708–714.


54. Storek J, Dawson MA & Maloney DG. Correlation between the numbers of naive T cells infused with blood stem cell allografts and the counts of naive T cells after transplantation. *Bioogy of Blood and Marrow Transplantation* 2003; 9(12): 781—784.


