

# Immune Deficits in Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Recipients

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**Abstract** Immune deficits account for the high frequency of life threatening bacterial, viral, and fungal opportunistic infections seen in allogeneic HSCT recipients. Despite advances in infectious disease management, the integrity of host defenses remains the mainstay of defense. The intensity of the preparative regimen, degree of HLA matching, source of stem cells (marrow, blood, or cord), extent of T-cell depletion, and immunosuppressive therapy are some of the factors that impact the kinetics, characteristics, and quality of immune reconstitution. Graft-versus-host disease and its prophylaxis or treatment produce a host environment that is particularly vulnerable to infections. Mucosal disruption and prolonged severe neutropenia usually confine their impact to the early course of transplant. After initial engraftment, HSCT recipients remain at great risk for opportunistic infections and this is related to prolonged and severe T-lymphocyte dysfunction of a complex multifactorial nature. B cell dysfunction is less problematic clinically, but includes deficiencies of immunoglobulin subclasses and impaired ability to mount a vaccine response. Advances in understanding of these

immune deficits have resulted in successful strategies including revaccination, growth factors, thymic protection, and adoptive cellular therapy with antigen-specific cells.

**Keywords** Hematopoietic stem cell transplantation · Infection · Immune reconstitution · Allogeneic

## Introduction

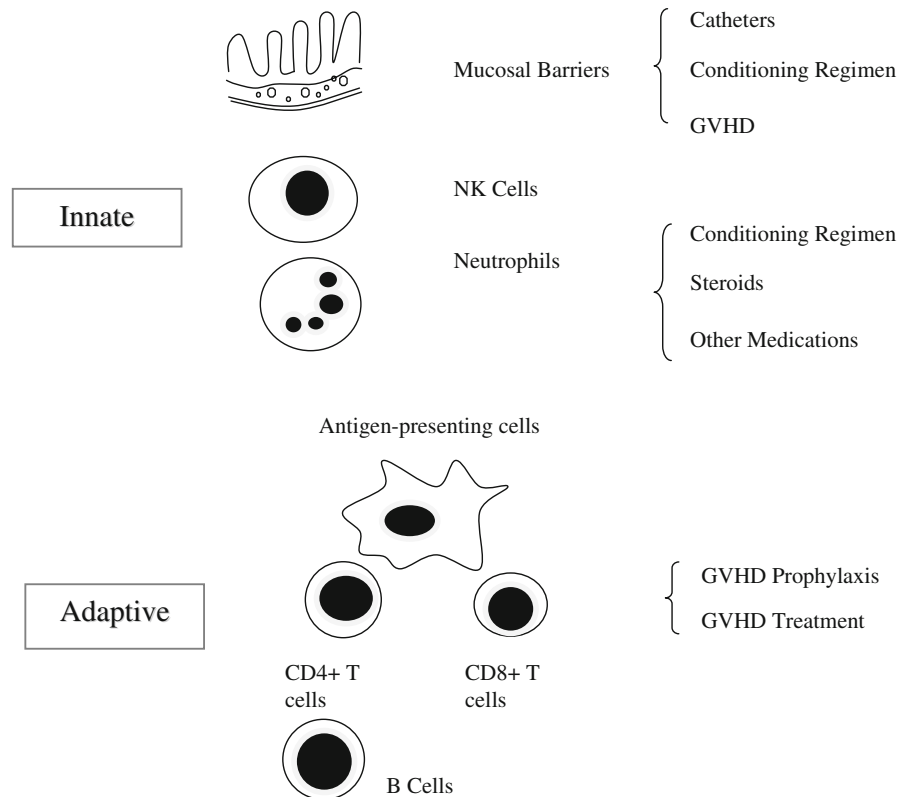
Multiple factors contribute to the severe and sustained immunocompromised status of the allogeneic hematopoietic stem cell transplant (HSCT) recipient (Fig. 1). The preparative (conditioning) regimen of chemotherapy and/or radiation (for the treatment of underlying disease and to permit engraftment) eradicates the recipient's lymphoid tissue and variably disrupts mucosal barriers. The recipient's immune system is then restored from the extremely limited number of donor immune precursors present in the graft. The occurrence of acute or chronic graft-versus-host disease (GVHD) and its prevention/treatment induce further immunologic compromise. Finally, prolonged debility and adverse effects of a complicated pharmaceutical regimen are liable to exacerbate the situation. Allogeneic HSCT recipients may receive months to years of prophylactic antimicrobial medications and endure severe lifestyle

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**Fig. 1** Transplant factors affecting innate and adaptive immunity



restrictions in order to avoid succumbing to an opportunistic infection.

Post-transplant immune deficits occur in overlapping phases. In the pre-engraftment phase of initial hospitalization, neutropenia and mucosal disruption predispose to bacterial infections. However, the most important deficit is the prolonged quantitative and qualitative impairment of T lymphocytes, predisposing to viral, fungal, or protozoal infection.  $T_H$  lymphocytes have a central role to ensure the coordination and synergy of other immune components including dendritic cells, macrophages, CD8 lymphocytes, and B-lymphocytes in orchestrating a specific, amplified response against intruding antigens. Impaired antibody production from B-lymphocytes increase susceptibility to common encapsulated organisms and loss of response to vaccines.

Donor-derived T-cell reconstitution occurring variably over months to years plays a central role in allogeneic transplantation by mediating an effective malignancy effect (the graft-versus-malignancy effect), prevents and controls opportunistic infections, and is the principle effector of acute GVHD.

The thymus plays a critical role in T-cell reconstitution and is adversely affected by older recipient age, radiation-based conditioning and GVHD. Early reconstitution occurs from the homeostatic expansion of donor-derived mature post-thymic T cells already present in the graft [1, 2]. In patients who receive significantly T-cell depleted grafts, NK cells play an early role in reconstitution. Thymic recovery takes place over a period that is usually about 1 year for children and even longer for adults. Eventually, circulating lymphocytes are produced from naïve prethymic cells derived by differentiation of donor hematopoietic stem cells. The breadth of the T-cell repertoire is reduced by heavy T-cell depletion and improved by the extent of thymic recovery.

The degree of immune deficiency is variable and reflects the complex interplay of controllable as well as uncontrollable factors such as recipient age (impacts thymic reserve), prior donor immunity [relevant for cytomegalovirus (CMV)], graft source (progenitor cell and lymphocyte counts), graft manipulation (such as ex vivo T-cell depletion), use of anti-T-cell antibodies (in vivo T-cell depletion), the

intensity of conditioning regimen and infectious disease burden at the time of transplant.

GVHD is associated with the highest risk of opportunistic infection; interfering with T-cell immune reconstitution by three distinct mechanisms: thymic epithelium injury, reduction in the number of circulating T cells, and increased expression of *Fas* or *FasL* causing activation-induced apoptosis of donor T cells. Although neutropenia following the conditioning regimen remains an important risk factor for opportunistic fungal infections, most cases of invasive fungal infection in allogeneic HSCT recipients occur *after* neutrophil recovery during the second or third month after transplantation, during GVHD [3, 4]. GVHD is an independent risk factor for CMV, varicella-zoster virus (VZV), and adenovirus infection [5–7]. High-dose steroid administration increases the likelihood of a rising CMV viral load by 10-fold despite ganciclovir therapy [8]. Pneumococcal infections are significantly increased in HSCT recipients with chronic GVHD [9].

### Epidemiology of Infections After Allogeneic HSCT

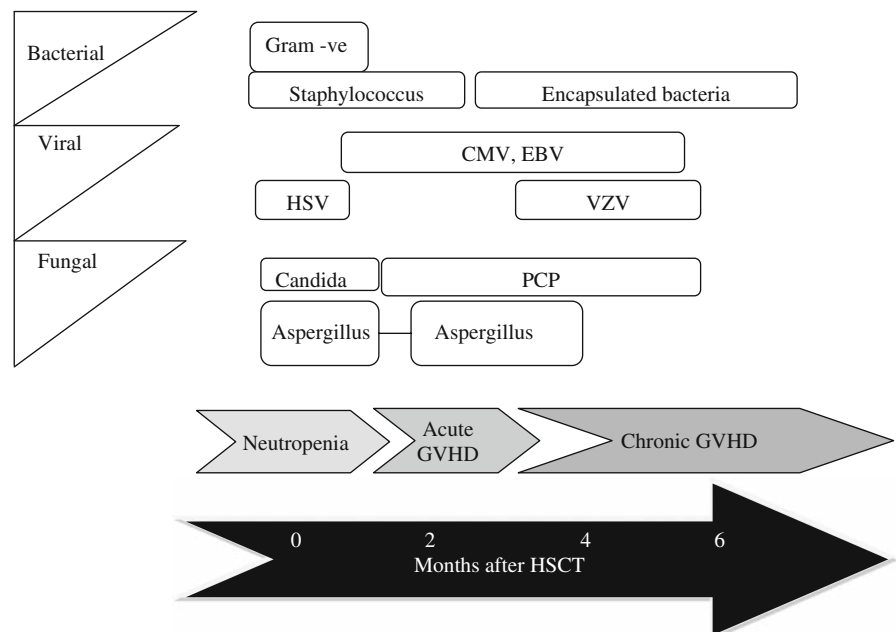
The timeline of infections after HSCT is summarized in Fig. 2 and their cumulative incidence in Fig. 3.

### Bacterial

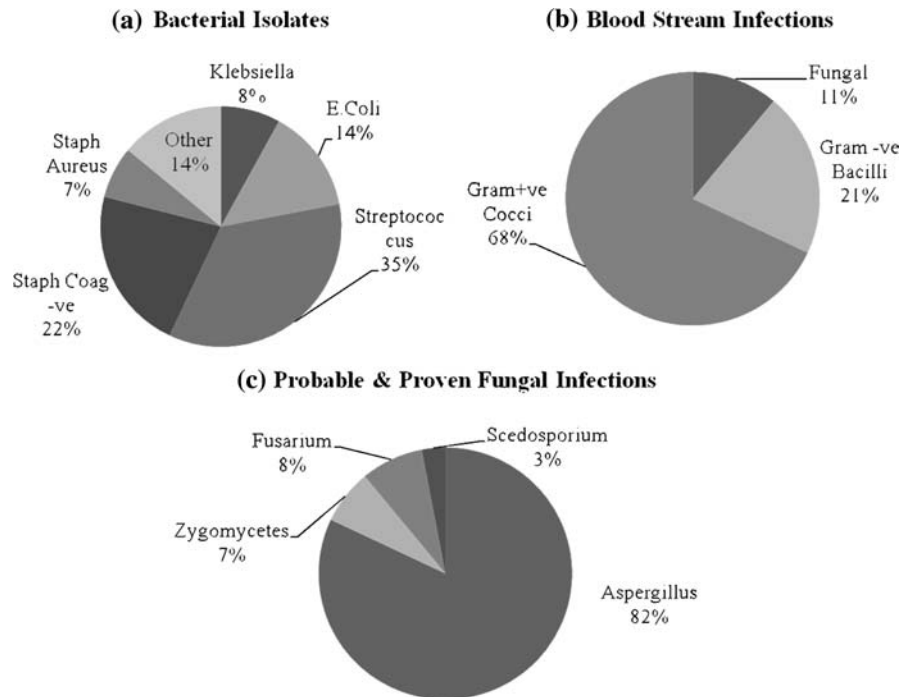
The majority of infections during the neutropenic phase after HSCT are bacterial. Microbial contamination of the graft occurs at a low frequency (1.2%) and is most often due to *Staphylococcus epidermidis* [10]. Post-HSCT bacteremia is more frequent as illustrated by a single institution Brazilian study where among 411 HSCT recipients, fever occurred in 333, and 91 developed bacteremia (118 isolates): 47% gram-positive, 37% gram-negative, and 16% caused by gram-positive plus gram-negative bacteria. *Pseudomonas aeruginosa* (22%), *Klebsiella pneumoniae* (19%), and *Escherichia coli* (17%) accounted for the majority of gram-negative isolates, and 37% were multi-drug resistant [11].

Over the years bloodstream bacterial isolates have shifted from gram-negative to gram-positive, reflecting ubiquitous use of indwelling central venous catheters, with *Staphylococcus epidermidis* responsible for the majority. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum-beta-lactamase (ESBL) organisms, and resistant *Clostridium difficile* reflect ongoing challenges. Patients colonized with VRE are twice as likely to die by day 100 after transplant compared to non-colonized

**Fig. 2** Timeline of infections after HSCT [93]



**Fig. 3** Infections after HSCT [94–96]



patients, possibly reflecting cumulative therapy-related debility [12].

With the exhaustion of donor and recipient B-cells after their normal life span, impaired antibody production against encapsulated respiratory bacteria, particularly *Haemophilus influenzae* type B (HIB) and *Streptococcus pneumoniae*, causes late infections [13]. These infections, including pneumonia, sepsis, and meningitis, occur at a median of 9–15 months post-allogeneic HSCT and are often associated with the immune dysregulation induced by chronic GVHD [9, 14, 15].

#### Fungal

Fungal infections complicate about 11% of all patients undergoing HSCT. More than 80% of all invasive fungal infections are caused by *Candida* spp. and *Aspergillus* spp. commonly during therapy for GVHD [16]. Predisposing factors include the duration and severity of neutropenia, mucositis, GVHD and therapies to treat it (steroids and other immunosuppressive therapies), central catheters, and CD4 lymphopenia. Invasive pulmonary aspergillosis is the most common form of fungal infection and *Aspergillus fumigatus* is the most common cause of

community acquired pneumonia among HSCT patients with chronic GVHD [17]. Non-fumigatus *aspergillus* have been increasingly isolated from these severely immunocompromised patients as well as other molds such as *Zygomycetes* spp., *Fusarium* spp., *Pseudallescheria* spp., *Trichosporum* spp., and *Scedosporium* spp. [3]. Other fungal pathogens are relatively rare species such as *Pseudoallescheria boydii*, *Blastoschizomyces capitatus*, *Malassezia furfur*, and *Mucormycosis*.

*Pneumocystis jirovecii*, formerly *carinii*, pneumonia (PCP) poses a life-threatening risk of pneumonia to transplant patients. Long-term trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis virtually eliminates the risk of infection. Early and late PCP has been described. In the pre-prophylaxis era, between 1976 and 1991, of 1,454 BMT patients at the University of Minnesota, PCP occurred in 19 patients; 18 of whom had not received PCP prophylaxis [18].

Advances in antifungal prophylaxis, imaging technology and serum galactomannan, and (1,3)- $\beta$ -D-Glucan PCR assays have increased diagnostic yield of fungal infections compared to conventional biopsies or tissue cultures. Strategies that incorporate these advances into clinical management of these

complex patients are evolving and the epidemiology of fungal infections is likely to change [19].

## Viral

Viral infections and reactivation are a frequent and life-threatening complication, emphasizing the central role of T-lymphocyte dysfunction. The herpes viruses, which produce latent infections, capable of immune evasion by down-regulating MHC Class I expression, and require constant T-cell immune surveillance for control, are the commonest pathogens. These include CMV, VZV, Epstein–Barr virus (EBV), and herpes simplex virus (HSV).

CMV used to be a major cause of mortality, approaching 25%, in recipients of allogeneic stem cell transplantation [20, 21]. The ability to clear CMV is related to donor T-cell immunity, with a clear relationship to the absolute number of CMV tetramer-specific T cells in the graft [22]. In the allogeneic HSCT setting, CMV has greater tropism for the lungs and GI tract than the brain or retina. Reactivation can be detected in circulating white cells before the development of organ disease. With the advent of effective antivirals, the epidemiology of CMV has changed dramatically. A strategy of using CMV safe blood products, regular screening for reactivation and either prophylactic or preemptive therapy at the first sign of reactivation has greatly reduced the incidence of breakthrough CMV organ disease and mortality to about 5% [23, 24]. Despite these advances, CMV seropositive patients continue to have higher mortality than patient–donor pairs who are both CMV seronegative. Reasons include: antiviral toxicities, ganciclovir-induced neutropenia, and ganciclovir-mediated immunosuppression [25]. Consequently, there is considerable scope for improvement in the therapeutic strategies for CMV. Given the critical immunological deficit exposed by CMV, immune reconstitution against CMV has been a fundamental model for understanding T-lymphocyte recovery post-transplant and predicting the long-term success of the transplant [26]. Absolute CD4+ and CD8+ counts less than  $100 \times 10^9/l$  and  $50 \times 10^9/l$ , respectively; bone marrow as the source of stem cells; and high-dose steroid use all predict delayed recovery of functional CMV-specific T-cell immunity at 3 months after transplantation [27].

EBV reactivation may result in post-transplant lymphoproliferative disorder (PTLD) or Hodgkin's lymphoma late (median 4.2 years) after HSCT. Estimates of the overall incidence of EBV reactivation and EBV PTLD range between 1 and 3%, but can be much greater in patients in the context of T-cell depleted transplants [28–30]. Since there is no effective antiviral agent, successful treatment requires rapid immunosuppression taper, antilymphoma agents such as rituximab or adoptive cellular immunotherapy.

VZV infection is seen equally frequently in both autologous and allogeneic HSCT [31]. In both groups, patients recover cytotoxic T cells that recognize and lyse autologous target cells expressing VZV proteins in about a year [32]. The rate of visceral dissemination of VZV increased to 71% when the absolute lymphocyte count declined to  $<100$  cells/ $\mu$ l [33].

HSV reactivation occurs during the early, pre-engraftment, neutropenic phase of HSCT [34]. Prophylaxis with acyclovir has dropped the incidence below 5% [35]. T lymphocytes are responsible for disseminated HSV disease since agammaglobulinemic patients handle HSV infection well and antibody formation does not prevent reactivation [36].

Polyoma viruses such as BK- or JC-associated hemorrhagic cystitis is an emerging infectious entity in HSCT recipients [37–39]. Arenaviruses such as adenovirus are also being recognized more frequently with pediatric and adult haploidentical transplants, use of anti-T-cell antibodies such as Campath or total body irradiation (TBI) having been identified as risk factors [39–43].

## Immune Deficits in Specific Transplant Scenarios

### Autologous Transplantation

Understanding the nature of immune deficits in *autologous* HSCT, which are uncomplicated by GVHD or by immunosuppression, is useful in providing a comparative conceptual framework to understand the deficits in *allogeneic* stem cell transplantation. Autologous HSCT patients develop immune deficits predominantly related to intense chemotherapy inducing transient severe neutropenia and mucosal disruption followed by a short period (6–12 months) of impairment of the adaptive immune

response before homeostatic lymphocyte expansion occurs from the graft.

A brief impairment in the qualitative and quantitative recovery of CD4+ T cells seems to be the major deficit noted early after autologous HSCT [44]. Recovery of CD4+ T-cell function in the first year post-autologous HSCT is usually from surviving memory cells (CD45RO+ CD4+) and thus *thymus-independent* [45]. Only about one-third of the T-cell recovery occurs from naïve T cells (CD4+ CD45RA+ CD62L+) from *thymus-dependent* regenerative mechanisms, usually in patients <50 years of age [2]. Age-related thymic degeneration appears to be a contributor as the CD4 recovery is less impaired in children. The rate of opportunistic infections has an inverse relationship with CD4+ T-cell recovery. Patients who sustain CD4+ counts below 100/μl have decreased survival [46].

Whereas the deficiency in the different subclasses of CD4+ cells (helper, naïve, and memory) are apparent at 1 year after autologous transplant, B cell and antibody pools recover to adequate levels by 3 months [44]. Relatively rapid recovery of CD8+ T cells due to clonal expansion of CD8+ CD57+, and CD8+ CD28– cells results in inversion of the CD4/CD8 ratio [47]. Delayed CD4+ recovery in this population predisposes to opportunistic infections such as *Pneumocystis carinii* or *jirovecii* (PCP) even 6 months after autologous HSCT [48]. In lymphoma patients undergoing autologous HSCT, after 4–10 years, the proportion of patients with protective antibody titers against poliomyelitis and diphtheria was reduced. Responses to pneumococcal vaccination, considered to be a *T-cell-independent* vaccine, showed that levels of serum antibodies against different pneumococcal serotypes were lower in the patients than in the controls prior to vaccination. Unlike controls, only one-third of patients achieved protective levels of antibodies after a single revaccination with 23-valent pneumococcal vaccine as compared to 94% of healthy controls. Secondary booster responses after one vaccination with T-cell-dependent vaccines (tetanus, diphtheria, and polio) were reduced [49].

#### Matched Allogeneic HSCT (T-cell Replete)

In recipients transplanted with unmodified bone marrow from human leukocyte antigen (HLA) identical

sibling, the number of peripheral blood CD4 cells and production of IgG recover over at least 7–9 months following HSCT in the absence of GVHD [50]. Even after apparent recovery in numbers, qualitative defects in T-cell signal transduction and reduced TNF- $\alpha$  production by CD8 cells have been shown to occur after HSCT [51, 52]. Sustained antibody production will resume only once adequate T-lymphocyte function is achieved [53]. Chronic GVHD blunts the development of new CD4+ T lymphocytes [54].

#### Non-myeloablative Allogeneic HSCT

Non-myeloablative conditioning uses reduced conditioning intensity that is sufficient for allowing engraftment without ablating the recipient's hematopoietic system; initial immunohematopoietic recovery is recipient in origin (mixed chimerism) gradually transitioning to complete donor chimerism [55]. Mucosal and marrow toxicity are reduced, along with the risk of early infection.

Non-myeloablative HSCTs do not reduce the incidence of CMV infection or reactivation [56]. Indeed, anti-T-cell antibodies such as Campath or antithymocyte globulin (ATG), commonly used to supplement chemotherapy in these transplants, increase the risk for CMV infection by up to 75% [57, 58]. Nevertheless, in patients with history of prior chronic infection, non-myeloablative HSCT may be more desirable to avoid debility associated with a myeloablative approach. Such patients may benefit from the reduced depth and duration of neutropenia associated with a non-myeloablative approach [59].

#### T-cell Depleted Transplant

Given the relative absence of perfectly matched donors (typically sibling), there is a growing reliance on mismatched donors including haploidentical and umbilical cord blood (UCB) transplants. Mismatched transplants typically require higher intensity conditioning and a greater degree of immunosuppression or T-cell depletion to achieve engraftment, with consequent adverse impact on infection risk.

Several centers routinely manipulate the stem cell graft by removing lymphocytes (ex vivo depletion) to reduce GVHD. A similar functional outcome can be achieved by anti-T-cell antibody preparations such as

Campath or ATG; these antibodies circulate for several weeks, further depleting the lymphoid cells (in vivo). Most T-cell depletion techniques are repertoire non-selective; that is they do not discriminate between lymphocytes that are allogeneic (destined to produce GVHD) versus those mediating other functions of the repertoire (such as anti-microbial or anti-malignancy). In contrast, “selective depletion” is an investigational approach to immune repertoire manipulation that selectively eliminates alloreactive T cells while preserving the rest of the repertoire against malignancy and microbial pathogens. For the purposes of this discussion, T-cell depletion (TCD) will refer to non-selective approaches.

Ex vivo TCD can result in 3 to 4 log (that is 99.9–99.99%) CD3+ depletion [60] and repertoire reconstitution is markedly delayed [61]. Viral and fungal infections are greatly increased. EBV infections and PTLD increase exponentially with T-cell depletion especially with use of anti-CD3 monoclonal antibody, but less so when balanced loss of B and T cells occurs [28]. In mice following T-cell depleted allogeneic HSCT, production of TH<sub>2</sub> type cytokines, IL-4 and IL-10 is increased while TH<sub>1</sub> type cytokines IL-2, IFN- $\gamma$  and TNF- $\alpha$  are impaired, predisposing to lethal fungal infections [62]. Adenoviral and other respiratory viruses infections including human parainfluenzae virus (HPIV) are increased [41, 63]. In a large study of 404 recipients of unrelated donor transplantation, patients were randomized to receive one of two GVHD prophylaxis strategies, marrow T-cell depletion (TCD), or standard immunosuppression therapy. Bacterial infections accounted for 1/3 of serious infections in each treatment arm. A significantly higher incidence of severe CMV and life-threatening or fatal *aspergillus* infections was observed in the patients receiving TCD (CMV, 28% vs. 17%; aspergillosis, 16% vs. 7%) [64].

#### Haploidentical Allogeneic HSCT (TCD)

Partially mismatched or haploidentical transplants may provide a transplant option to patients who do not have a fully-matched related donor [65]. Exhaustive T-cell depletion and high CD34+ doses remove the risk of graft rejection and GVHD leaving slow immune reconstitution as the major concern in haploidentical HSCT. Life threatening fungal and

viral infections are frequent [66, 67]. In the Perugia experience with 104 haploidentical transplants for acute leukemia, 27 patients died of infection (17 viral, five fungal, and five bacterial) [66]. Avoiding post-transplant G-CSF, which polarizes incoming donor lymphocytes to a Th2 phenotype, has led to a reduction in infections [68]. In one study of 63 pediatric haploidentical transplants, the cumulative incidence of lethal viral infections was 16% at day 180 and adenovirus-associated mortality was 8.5% [42]. An unusually high incidence of acyclovir- and foscarnet-resistant HSV infection has also been observed [69].

#### Umbilical Cord Blood HSCT

UCB combines “off-the-shelf” availability along with greater tolerance for HLA mismatch compared to traditional graft sources (marrow or peripheral blood), resulting in a reduced frequency of GVHD. Immune reconstitution is greatly impaired and infectious mortality is the primary cause of death in UCB transplant. Two features contribute to the infectious complications of cord blood transplants compared with traditional graft sources: the relative paucity of hematopoietic progenitors (1/10 as many CD34+ cells as recipients of allogeneic marrow) and the low numbers and immaturity of cord lymphocytes.

The initial post-transplant period is complicated by prolonged neutropenia related to low hematopoietic progenitor counts; the median time to absolute neutrophil count  $\geq 500/\mu\text{l}$  is 26–27 days in UCB transplant versus 18 days for marrow [70, 71].

For several months, until recovery of the thymus supports de novo T-cell generation, protective antiviral immunity depends on the activity of post-thymic T cells infused within UCB grafts. However, UCB T lymphocytes are not only antigen inexperienced (naïve) but are functionally tolerized to protect pregnancy. UCB T cells need to undergo in vivo priming, Th1/Tc1 maturation, and peripheral expansion before they can provide immunologic protection [72]. Patients remain at greater risk for fungal and viral infections until thymic recovery [40].

Results of UCB transplant have not been as promising in older recipients, probably related to the importance of the thymus for long term immune reconstitution. A prospective study of T-cell immune recovery after UCB transplant in adults reported

prolonged and profound T-cell lymphopenia and compensatory expansion of B and natural killer (NK) cells. In addition, there was impaired functional recovery to CMV and superantigens. The severe thymopoietic failure was characterized by a relative paucity of CCR7<sup>+</sup> naive and central memory cells and late memory T-cell skewing [73]. T lymphocytes of *recipient* origin may contribute to the recovery of specific immune response toward viruses and fungi in UCB transplantation in children [74]. T-regulatory cells found in UCB grafts are more potent suppressors than their adult counterparts [75]. Human transitional B lymphocytes (CD19<sup>+</sup> CD24<sup>+</sup> CD38<sup>+</sup>), intermediates in B-cell development, represent around 4% of B cells in healthy adult peripheral blood. In contrast, they are abundant in cord blood (near 50% of B cells) although their proportion progressively declines during infancy [76].

### Strategies for Enhancing Immune Regeneration

Since T-cell deficits are the fundamental defect after allogeneic HSCT, there is a considerable body of research that has focused on replenishing this critical aspect of the immune arsenal. These include supplementing T lymphocytes, promoting lymphocyte growth and revaccination.

In the simplest form of lymphocyte supplementation, unselected donor lymphocyte infusions can induce regression of EBV-associated PTLD [77]. Adoptive cellular immunotherapy utilizing *ex vivo* expanded microbe-specific lymphocytes offer the promise of infection control without inciting GVHD. Donor CD8 class I MHC-restricted CMV-specific cytotoxic T lymphocytes (cloned and expanded in the presence of CMV antigens plus IL-2) have been shown to control CMV infection [78, 79]. Rapid generation of enriched, CD4<sup>+</sup> and CD8<sup>+</sup> CMV-specific T cells is now possible [80]. The approach has been extended to EBV and aspergillus [81]. Selective supplementation of virus-specific T cells is feasible, can be planned in advance, and protective in T-cell depleted transplants [82].

Administration of keratinocyte growth factor (KGF), approved to reduce chemotherapy-associated mucositis, enhances mucosal regrowth and may indirectly prevent infection [83]. KGF has been shown to improve thymus-dependent immune reconstitution by

protecting thymic epithelium from effects of GVHD and irradiation [84].

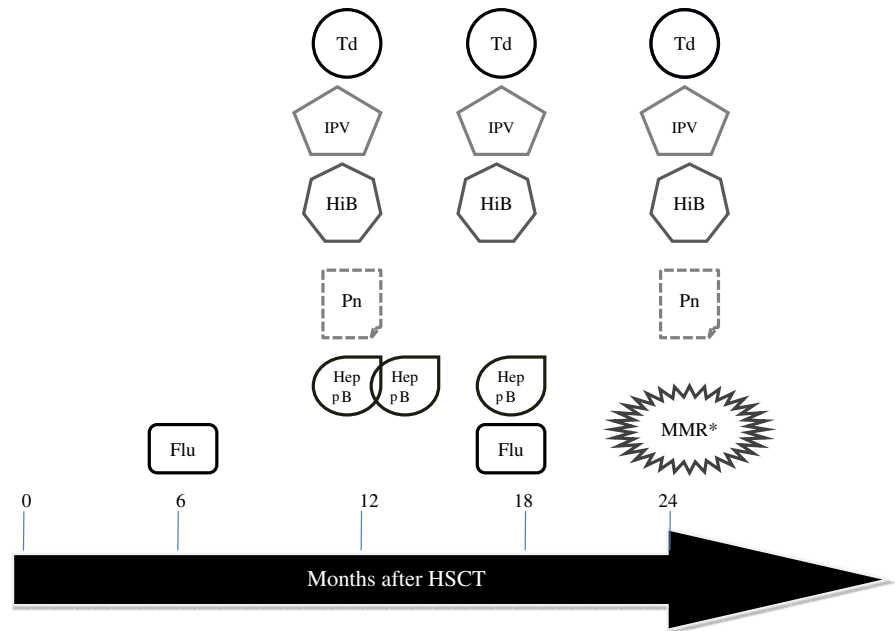
Thymic epithelium is a source of IL-7, a growth factor involved in production and maintenance of T cells. Administration of IL-7 can improve qualitative and quantitative aspects of T-cell function [83, 85, 86]. T-cell survival may be enhanced by the administration of synthetic oligo-deoxynucleotides containing unmethylated cytosine–guanine motifs [87].

Revaccination of allogeneic HSCT recipients is a simple and effective strategy to reverse the loss of the vaccine response. Antibody titers to vaccine-preventable diseases (e.g., tetanus, poliovirus, measles, mumps, rubella, and encapsulated bacteria) decline 1–4 years after allogeneic HSCT if the recipient is not revaccinated. Recipient response can be enhanced by vaccination of the donor before HSCT [88, 89] but this is usually avoided. Since the immune response is blunted post-transplant, safety and timing are critical issues. Center for Disease Control (CDC) guidelines (Fig. 4) recommend starting revaccination at least 6 months after cessation of immunosuppressive therapy [90]. Active chronic GVHD can induce immune dysregulation and live viral vaccines, such as measles, mumps, and rubella are best avoided. Lifelong annual (inactive) influenza vaccination is recommended for all HSCT recipients and family contacts. Chemoprophylaxis with oseltamivir should be considered during outbreaks. Heat killed fungal vaccines remain a work in progress [91, 92].

### Future Considerations

Understanding immune deficits allows development of strategies to counter them. Improving initial neutrophil recovery by judicious use of myeloid growth factors and by selecting grafts with higher progenitor counts are particularly useful in UCB transplant. Future graft manipulation will use selective rather than non-selective repertoire manipulation. Mucosal disruption may be minimized by reduced intensity conditioning regimens and KGF. Advances in central catheters and their care reduce blood stream infections. Pilot studies have already demonstrated the feasibility of adoptive cellular immunotherapy for CMV and EBV infections that take advantage of thymic independent homeostatic T-cell expansion in a lymphopenic host. Recognition of an important role for the thymus in T-lymphocyte education has led to

**Fig. 4** Summary of vaccinations after HSCT. *Flu* inactivated influenza (annually), *HepB* Hepatitis B, *Hib* *H. influenza* type B, *IPV* inactivated polio, *MMR* measles–mumps–rubella (\*in absence of GVHD and immunosuppressives), *Pn* 23-valent pneumococcal vaccine, *Td* tetanus–diphtheria toxoid



strategies focused on thymic epithelium regeneration with growth factors such as KGF and the use of cytokines such as IL-7 assist in thymic dependent T-cell recovery.

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