Title

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Immune Dysregulation and Pathobiology Working Group Report

Journal

Transplantation and Cellular Therapy, 23(6)

ISSN

2666-6375

Authors

Gea-Banacloche, Juan
Komanduri, Krishna V
Carpenter, Paul
et al.

Publication Date

2017-06-01

DOI

10.1016/j.bbmt.2016.10.001

Peer reviewed

HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2017 June ; 23(6): 870–881. doi:10.1016/j.bbmt.2016.10.001.

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Immune Dysregulation and Pathobiology Working Group Report

Juan Gea-Banacloche, MD,
Head, Infectious Diseases Unit Experimental Transplantation and Immunology Branch, NCI

Krishna Komanduri, MD,
Professor of Medicine and Microbiology & Immunology; Director, Sylvester Adult Stem Cell Transplant Program, University of Miami

Paul Carpenter, MD,
Member, Fred Hutchinson Cancer Research Center, Clinical Research Division, Professor, University of Washington School of Medicine Pediatrics

Sophie Paczesny, MD, PhD,
Associate Professor, Indiana University School of Medicine

Stefanie Sarantopoulos, MD, PhD,
Associate Professor of Medicine, Assistant Professor of Immunology, Duke Cancer Institute

Jo-Anne Young, MD,
Professor of Medicine, Division of Infectious Diseases and International Medicine, University of Minnesota

Nahed El Kassar, MD, PhD,
Medical officer NHLBI

Robert Q. Le, MD, PhD,
FDA Center for Biologics Evaluation and Research

Kirk Schultz, MD,
Director, Pediatric Oncology Research, CIHR/Wyeth Clinical Research Chair in Transplantation, Associate Professor of Pediatrics, BC Children's Hospital, The University of British Columbia

Linda M. Griffith, MD,
NIAID Autoimmunity and Mucosal Immunology Branch

Bipin Savani, MD, and
Professor of Medicine, Director, Long Term Transplant Clinic, Vanderbilt University Medical Center

Correspondence to: Juan Gea-Banacloche.

Disclosures: The opinions expressed here are those of the authors and do not represent the official position of the NIH or the United States Government.

John R. Wingard
Associate Director for Clinical Research, University of Florida Health Cancer Center, Director, Bone Marrow Transplant Program, Division of Hematology/Oncology, University of Florida College of Medicine

Abstract

Immune reconstitution following hematopoietic stem cell transplantation (HCT) beyond one year is not completely understood. Many transplant recipients who are free of graft versus host disease (GVHD) and not receiving any immunosuppression more than a year after transplant seem to be able to mount appropriate immune responses to common pathogens and respond adequately to immunizations. However, two large registry studies over the last two decades seem to indicate that infection is a significant cause of late mortality in some patients, even in the absence of concomitant GVHD. Research on this topic is particularly challenging for several reasons. First, there are not enough long term follow-up clinics able to measure even basic immune parameters late after HCT. Second, the correlation between laboratory measurements of immune function and infections is not well known. Third, accurate documentation of infectious episodes is notoriously difficult. Finally, it is unclear what measures can be implemented to improve the immune response in a clinically relevant way. A combination of long-term multicenter prospective studies that collect detailed infectious data and store samples as well as a national or multi-national registry of clinically significant infections (e.g., vaccine-preventable severe infections, opportunistic infections) could begin to address our knowledge gaps. Obtaining samples for laboratory evaluation of the immune system should be both calendar driven and eventdriven. Attention to detail and standardization of practices regarding prophylaxis, diagnosis and definitions of infections would be of paramount importance to obtain clean, reliable data. Laboratory studies should specifically address the neogenesis, maturation and exhaustion of the adaptive immune system and in particular how these are influenced by persistent alloreactivity, inflammation and viral infection. Ideally, some of these long-term prospective studies would collect information on long-term changes in the gut microbiome and their influence on immunity. Regarding enhancement of immune function, prospective measurement of the response to vaccines late after HCT in a variety of clinical settings should be undertaken to better understand the benefit as well as the limitations of immunizations. The role of intravenous immunoglobulin is still not well defined, and studies to address it should be encouraged.

Keywords

immune reconstitution; late infections; immunization; intravenous immunoglobulin

Introduction

The National Institutes of Health Blood and Marrow Transplantation Late Effects Initiative, comprised of pediatric and adult HCT health care providers, administrators, researchers, advocates and survivors across federal and non-federal groups and sponsored by the National Cancer Institute and National Heart, Lung and Blood Institute, aims to identify knowledge gaps, develop practice recommendations and formulate important research questions to improve transplant survivor monitoring and management (cite commentary).

The Immune Dysfunction and Pathobiology Working Group, established as one of 6 working groups within this initiative, convened in September 2015 with the goal of providing recommendations for immune function and infection control in the field of HCT survivorship. The working group focused on identifying trends in late infections, describing immune reconstitution in the lab and reviewing interventions to improve immune function in HCT survivorship studies. These findings and recommendations for research were presented at a public meeting in June 2016, including over 150 participants with expertise across HCT survivorship. The findings were revised based on audience comments and are presented here.

A major goal after allogeneic hematopoietic stem cell transplantation (HCT) is to achieve optimal immune reconstitution, which we define operationally (in the case of allogeneic HCT) as: *the restoration of functional pathogen-specific immunity and establishment of anticancer immunity in the absence of immune dysregulation* (e.g., GVHD and/or HCT-associated autoimmunity). Late after transplant (i.e., > 1 year) variable degrees of of immune recovery are observed in different patients, and the data are limited.

This paper will review what is currently known about immune function late after HCT, identify knowledge gaps and propose research priorities to fill those gaps, with an emphasis on what is arguably the most important function of the immune system: protection against infection.

Section 1. Late infections after Hematopoietic Stem Cell Transplantation (HCT)

Historically, infection is one of the 3 leading causes of death after HCT (along with relapse and graft versus host disease (GVHD)) [1]. Most infections occur during the first year and different types of infectious syndromes predominate at various times [2, 3]. Multiple factors influence the pace of immune recovery and the risk for and type of infectious complications. These factors include patient age, underlying disease, antecedent immunosuppressive state, prior infections, conditioning regimen, type of donor, degree of match, stem cell source, immunosuppressive regimen used to prevent GVHD, anti-infective practice, the occurrence of post-transplant GVHD and viral infections, and use of certain post-transplant therapies to prevent disease relapse that alter immune recovery [4–8] (Table 1).

By one year, immune reconstitution is well underway for many HCT recipients [15]. However, some immunologic deficits are detectable in many patients using sensitive immunologic assays at 1–2 years, and even beyond 10 years [16, 17]. Patients with GVHD or CMV infection or recipients of HLA mismatched donors frequently have delayed, incomplete, or dysregulated immune reconstitution. Chronic GVHD is associated with multiple deficits in different arms of immunity and many types of protective responses are dysregulated [1819–21]. Late infections are common complications and causes of death in patients with persistently active GVHD [22]. Functional asplenia has been reported to predispose to rapidly developing sepsis from *S. pneumoniae*, that can lead to mortality among GVHD patients [20]. Older studies suggested the use of unrelated donors (with or without GVHD) was also associated with an increase in late infections [22, 23], although many of those patients were likely

mismatched since low resolution typing methods were in use then. In the absence of active GVHD, persistently low CD4 counts and persistently low immunoglobulin levels have been associated with the risk for late infectious morbidity [2, 24].

Thus, the risk of late infection for patients with ongoing GVHD and prolonged immunosuppressive therapy remains substantial. In contrast, in most patients without GVHD the incidence of life-threatening infection is much lower and continues to decline with passing time after transplant.

Two large retrospective CIBMTR studies have investigated late deaths (defined as beyond 2 years) of allogeneic HCT survivors. The first one, with more than 6,000 two-year survivors and a median follow-up of 6.6 years, estimated a risk of death from infection in the absence of GVHD of approximately 6% [25]. Half of the infections were bacterial. A similar study ten years later of more than 10,000 two-year survivors with a median follow-up of 9 years estimated that 10–20% of all deaths were caused by infection in the absence of active GVHD [26]. Proportions of deaths due to infection were similar in all major categories of diseases for which the transplant was performed. Generally, the risk of infectious death decreased over time after transplant, less after ten years compared to 2–4 years. Unfortunately, this kind of large retrospective registry study lacks the capability to capture and analyze fine details regarding specific infections and risk factors.

In some small retrospective studies, pneumonia appeared to be the predominant type of late serious infection [21, 22, 27]. For example, in a small single-center study, two-thirds of infectious deaths were due to pneumonia, and a pathogen was detectable in 57% of pneumonias with Aspergillus and CMV predominating [21]. Concomitant GVHD was present in many of the patients with infection in such reports, limiting our ability to determine rates of infections in the absence of GVHD. Other risk factors were CMV infection, mismatched or unrelated donor grafts, and use of TBI [21]. Older reports noted the importance of late varicella-zoster virus infection [22], but today with routine prolonged acyclovir prophylaxis this is much less common except in patients with persistent GVHD [28]. Limitations of these older studies include small numbers, unique center-specific transplant practices, varying follow-up practices, and different case mix that might affect both types and frequency of infection as well as risk factors. In a preliminary (unpublished) analysis of CIBMTR survivors who died from late infection, antecedent GVHD had occurred in most, suggesting persistent immune deficits after recovery from GVHD. This study is ongoing.

Persistent viral infections often lead to additional clinically important complications late after HCT. Persistent immune deficits after CMV infection can confer susceptibility to other infectious pathogens. Of note, non-relapse mortality in patients with early CMV infection continued to increase beyond one year in a large CIBMTR analysis, with infection being a major cause of death, suggesting that there may be long-lasting immune deficits after CMV infection that predispose patients to later infection [12, 13]. Other viral infections also may lead to complications late after transplant. Viral hepatitis either before or early after transplant may be associated with late complications. Flares of hepatocellular injury can occur at the time of tapering of immunosuppressive therapy due to deleterious immune responses to viral replication. Chronic infection can also result in complications such as chronic active

hepatitis, cirrhosis, or hepatocellular carcinoma more than 10 years after transplant [29]. Improved screening of blood and transplant donors, use of the hepatitis B vaccine, and the use of hepatitis B antivirals and the recent introduction of potent hepatitis C antivirals have resulted in a lessening of the risk for late hepatitis complications. Recent recognition of HPV-associated gynecologic and head and neck carcinomas has led to calls for consideration of the HPV vaccine for prevention [30–32]. It is possible that other late viral associated complications will be identified with the increasing number of recipients surviving beyond 10 years and the identification of new viral pathogens and their associations with transplant complications.

The variability in the reporting of infectious disease data in the HCT population has several causes. First, the definition of infectious syndromes is complex, and changes as new diagnostic assays are developed. Important distinctions may be missed by transplant clinicians and data managers who are not familiar with the most current definitions. Second, there is no standardization between centers in the application of infectious disease diagnostic algorithms and variability of anti-infective practices, with some centers relying heavily on prophylaxis or empiric anti-infective therapies, while other centers pursue infectious disease diagnoses aggressively. Such variability may lead to confounding due to ascertainment bias. Third, the variability late after HCT is even greater. Clinical care of the HCT survivor after one year is not typically performed by many transplant centers, particularly in the U.S. Community practices, to which these patients have returned, may not find it important to capture detailed infection data in clinic encounters. In many cases aggressive diagnostic testing is not used or even possible and empirical therapy for suspected or presumptive therapies predominates. This is confounded moreover by inconsistent availability of knowledgeable personnel to collect follow-up data. The variability in the quality of such data is substantial and leads to even greater ascertainment bias. The net effect of these limitations is that audits of infection data reports frequently find errors in under-reporting of infectious events and in some cases over-reporting due to lack of use of standardized definitions. [8, 33]

Key research priorities and recommendations

1. A long-term, multicenter prospective study of late infectious events after HCT is highly desirable. One-year HCT survivors should be enrolled and followed up to 5 years to determine the incidence of serious infection, types of pathogens, the risk factors, and the immunologic correlates. The sample size should be large enough to capture important differences between key variables that influence infection risk. To provide valid, actionable information we recommend the following:
    - **a.** only centers with enough commitment and resourced to provide high quality infection data should participate
    - **b.** standardized definitions of infection events should be applied
    - **c.** standardization of the anti-infective practices and diagnostic approaches should be implemented
    - **d.** standardized follow-up protocols should be used

e. audits of data should be performed.

f. Samples should be collected for immunologic correlate testing to allow analysis of both clinical and immunological risk factors.

2. There is a growing recognition of the important role of the gut microbiome on the host immunity. Studies have identified associations between changes in the microbiota early after HCT on early infectious complications, GVHD, transplant-related mortality, and relapse [34–36]. However, there are no studies on how long-lasting such early patterns of microbiota are on both late microbiota and late infection risk. Thus, a second research priority would be a prospective study to examine the association of early and late microbiota changes after HCT and the association of such changes with late infections and immunity. Such a study could be incorporated into the prospective study of late infections described above.

3. Knowledge about the occurrence of certain specific late infections after HCT is lacking. For example, the effectiveness of consensus infection control guidelines on infection is of great interest. Are centers adhering to the vaccine guidelines; are they effective in reducing infection; what are the barriers that impede effectiveness? A third research priority is to create a registry of vaccine-preventable and other rare infectious diseases (e.g., late aspergillosis or *Pneumocystis* pneumonia). Case identification should be annotated with key information about risk factors, immunologic parameters and information about vaccination.

Section 2. Immune Reconstitution in the Laboratory

Functional Immune recovery after HCT depends on persistence of adoptively transferred mature donor immune cells present in the graft, and neogenesis of cells derived from donor hematopoietic progenitor cells (HPC). [37, 38] Early immune recovery following HCT has been studied by quantifying white cell subsets. Early immune recovery proceeds in the following order: NK cells, B cells, CD8 T cells first, followed later by CD4 T cells, plasma cells and dendritic cells. Detailed analyses of lymphocyte subset recovery and thymic function early after transplant have been published but beyond the first post-transplant year the data are limited. Despite normal white blood cell numbers, some HCT patients do not possess normal functional immunity. Methods to determine presence of absence of functional immunity have not been validated, even if CD4 lymphocyte numbers or CD4/CD8 ratios are sometimes considered appropriate surrogate markers [39]. Validated measures of immune function after HCT are urgently needed. Such methods could eventually guide infection prevention strategies after HCT.

Multiple factors have an impact on the immune parameters that can be measured in the laboratory. Table 2 highlights some of the relevant findings and others will be discussed in the subsections dedicated to T and B cell function. The key point is the dearth of data about immune function late after HSCT.

T cell immune reconstitution

Pathobiology of late immune dysregulation—Impaired thymopoiesis, lymphopenia and antigen exposure all contribute to TCR repertoire dysregulation [47]. Memory skewing of the T cell response and associated impairment of T cell repertoire diversity has been associated with poor control of chronic viral infection [48] and impaired anticancer immunity [49]. Late memory CD8+ T cells are less able to produce IL-2 in association with other cytokines. [50]

Measures of T cell immune reconstitution—The types of assays currently available to assess T cell immune reconstitution include enumeration of $CD4^+$ and $CD8^+$ T cells. T cell subset analyses by flow cytometry (naïve, memory, and effector) are performed primarily in the research setting. Furthermore, assessment of thymopoiesis and recent thymic emigrants (by TRECs and phenotyping), TCR repertoire analysis or sequencing, and antigen-specific functional assays including response to vaccines are also not routinely used in clinical settings.

Naive, central and effector memory and stem cell memory T cells may be enumerated by their expression of CD45 isoforms (e.g., CD45RA) in combination with maturation and homing markers (CCR7, CD31, CD103, CD27, CD62L, CD28, CD95 and CD57). Other critical T cell subsets include CD8+ memory stem cells ($CD8+CD161^{hi}$) [51], regulatory T cells ($CD4^+CD25^{hi}CD127^{low}FOXP3^+$) [5253], and T helper 17 cells [54].

Estimation of TCR repertoire diversity historically used indirect methods like TCR Vβ repertoire analysis by microfluorimetry [55] or assessment of skewing within individual Vβ regions by TCRβ "Spectratyping." [56, 57] However, rapid evolution of the efficiency and cost of next generation sequencing technologies now allows direct assessment of repertoire diversity within surface marker-sorted T cell subsets or HLA-peptide multimer-sorted subsets of antigen-specific CD8+ T cells.[58–60]

Several antigen-specific T cell functional assays are available for evaluating virus-specific responses, for example, to CMV [61–63], EBV [64], aspergillus [65], as well as to tumor antigens like Wilms' tumor 1 (WT1) and proteinase-3 [66]). The relevant assays include cytokine flow cytometry [61], ELISPOT [67], and HLA-peptide tetramer staining [63, 68]. Cytokine secretion, measured by flow or ELISPOT, elicited CD4+ and CD8+ T cell responses to peptide antigens [69], proteins [61], or cells [70] can be detected [71].

Clinical correlates of measured T cell reconstitution—Some studies have found an association between early immune reconstitution and clinically relevant endpoints. Survival was better in children whose CD3+CD8+ counts rose to >5th percentile of age-matched normal levels during the first year compared to children who never attained these levels [44]. Similarly in adults, early reconstitution of CD3+ and $CD8^+$ T cells correlated with improved progression-free survival (PFS) [45]. Not surprisingly, impaired vaccine responses were associated with delayed T immune recovery [72]. In this study, of mostly young adults, vaccine responses to PnCRM7 and HIB tested at a median of 13 months post-HCT were better among those who had achieved CD4+ T cells >200/μL and IgG levels >500 mg/dL [72].

Overall, higher levels of circulating CD4+CD45RA cells correlated with improved PNCRM7 response [72].

Studies of functional assessments of CMV-specific T cells have primarily been performed in the early post-HCT interval, leading to incomplete understanding of why persistent deficits in CMV-specific immunity lead to viral reactivation in nearly a third of HCT recipients. In a large (n=269) single institution study examining the incidence of late CMV reactivation following allogeneic HCT, the incidence of late reactivation was 31% and was more likely to occur in patients with prior or ongoing GVHD, in recipients of mismatched or unrelated donors, and in individuals transplanted for a lymphoid diagnosis [73]. In contrast to studies of CMV- and EBV-specific T cell immunity, little is known about functional immunity to other herpesviruses important in HCT recipients, including HSV, VZV and HHV-6, some of which contribute to late morbidity and mortality in a subset of HCT recipients.

At 2 years post-HCT a CD4+ and CD8+ T cell defect was observed involving naive, terminally differentiated, memory and competent cells [74]. At 5 years post-HCT, another study showed that low numbers of CD4+ and CD4+CD45RA+ T cells and reversed CD4/CD8 ratios persisted; CD4+CD45RA+ T cell numbers were low despite the absence of cGVHD at 2 years [41].

In a study of patients who were beyond 10 years post-HCT and no longer taking immunosuppressive medication (with one exception), $CD4^+$ and $CD8^+$ T cell blood counts were not significantly different from those enumerated using donor samples that were cryopreserved at transplant. However, compared with donors, recipients had significantly fewer naive T cells, fewer $CD4^+$ central memory cells, more effector $CD8^+$ cells, and more regulatory T cells [16]. No clinical correlates were reported.

T cell reconstitution has been shown to be affected by the combined effects of GVHD prophylaxis and treatment, and acute and cGVHD itself [75, 76]. $CD4^+$ T cell reconstitution is impacted by the use of T-cell depletion and GVHD [72]. At 2 years post-HCT, the number of $CD4^+$ $CD29^+$ T cells was higher in recipients with extensive cGVHD suggesting that cGVHD affected T cell immune reconstitution [41]. In another study chronic GVHD did not influence $CD8^+$ T cell recovery, while naive $CD4^+$ subsets were strongly affected [74].

T cell immune reconstitution following autologous HCT—The timing of T cell reconstitution differs between autologous and allogeneic HCT, with some studies showing more prolonged CD4 lymphopenia after autologous HCT.[75] Renewed thymopoiesis is possible in adults >30 years old, but decreases with increasing age. [77] In a study of autologous HCT for breast cancer, TREC numbers correlated positively with naïve T cell recovery and TCR repertoire diversification. Naïve T cells were evident by 100 days after autologous HCT for myeloma; thymic function fully recovered by 2 years, was age dependent and positively correlated with naive T-cell recovery and TCR repertoire diversity [43]. In another study, prolonged total and naïve CD4+ T cell lymphopenia persisted until 2 years after autologous HCT [75]. After autologous HCT, T cell recovery predicted OS and PFS in patients with hematologic malignancies and breast cancer [78].

In contrast to the allogeneic HCT setting, fewer detailed studies of functional immune reconstitution have been performed in autologous HCT recipients, likely due to the lower incidence of infections associated with deficits in cell mediated immunity (e.g., CMV). However, even for infections occurring relatively frequently in autologous HCT recipients (e.g., reactivations of HSV, VZV), little is known about the pace or quality of functional T cell recovery.

Regulatory T cell immune reconstitution—The development and maintenance of immune tolerance after HCT requires the balanced reconstitution of "conventional" effector CD4+ (Tcons), tolerizing CD4+ regulatory T cells (Tregs) and CD8+ T cells, which may also be important in the pathogenesis of cGVHD [79]. Very limited data exist about Treg recovery beyond one year after HCT. As noted in one study, at 10 years after HCT recipients had significantly more Tregs compared to donors [16]. One study with 2 years of follow-up showed that Tregs and Tcons recover at similar pace and slower than CD8 T cells, and were predominantly of central and effector memory phenotype [80]. Thymic Treg production was very limited within the first two years in contrast to the production of naïve Tcons and CD8 T cells. Early recovery of naïve Tregs and Tcons correlated with the development of chronic GVHD particularly if there was an imbalance of Tcons over Tregs [80]. Low telomerase activity in Tregs has been associated with severe chronic GVHD after allo-HCT [81]. Lastly, the use of autologous HCT to treat autoimmune diseases via tolerance induction is thought to depend on increased Treg TCR diversification [82]. Another T cell population whose role is less understood in HCT, are the IL-10 producing TR1 cells [83] Moreover, other potentially important regulatory populations include regulatory B cells, NK cells, and macrophages [83, 84858687]. Their role in immune reconstitution and responses to exogenous stimuli late after HCT is poorly understood.

B cell immune reconstitution

Translational studies have led to a greater appreciation of post-HCT B-cell deficiencies and clinical determinants of B-cell recovery kinetics, including alloreactivity. Recovery of functional immune cells after autologous HCT has been likened to fetal ontogeny, requiring re-encounter of the new donor immune system to microbes over many years. Most patients after autologous HCT eventually regain functional immunity. By contrast, functional immune recovery in the presence of alloantigen is a lifelong process, especially when immune tolerance is not achieved (i.e., in cGVHD).

The paucity of IgD-negative post-GC cells and CD27+ B cells and a 'fetal-like' B cell compartment may persist for years. B cell dysregulation results in auto- and allo-antibody production, which is more profound in cGVHD patients.[88–90] Despite the clinical importance of these phenomena, the recovery of late B-cell function remains underexplored.

Hypogamaglobulinemia after HCT is associated with dramatically increased infection risk, including encapsulated organisms and viruses. [87, 91] Collectively, published data support the notion that patients with and without cGVHD achieve varying states of B-cell immune function and are variably immune tolerant, analogous to genetic immunodeficiency

patients.[92, 93] However, what molecular mechanisms account for persistent B cell dysfunction late after HCT remain largely unexplored.

The inability to mount a proper B-cell response to microbial insult after HCT has been associated with a paucity of memory B cell responses in the first 2 years after HCT [94, 95]. Flow cytometric analyses of blood in patients after allogeneic HCT and autologous HCT have afforded detailed enumeration of B-cell subsets with functional correlates in the healthy setting that can be defined by cell surface marker criteria in both autologous and allogeneic HCT patients [96]. Persistently low numbers of CD27+ memory B cells [97, 98], IgDLo, post-germinal center (GC) B cells [99] and immaturity of the B Cell Receptor (BCR) repertoire [100] suggest a failure of B cells to undergo key maturation steps including somatic hypermutation. In murine GVHD splenic atrophy and destruction of secondary lymphoid organs is evident and likely immune-mediated although limitatioins of tissue access make this difficult to study directly in humans [101–104]. Abnormal *ex vivo* B cell responses have been attributed to steroid therapy [105], mitogen defects [106, 107], T-dependent IgG defects [108], B-cell activation signaling [109] and Ig-switching defects [110]. Rare antigen-experienced B cell subsets are capable of constitutive IgG secretion but HCT patients are known to have poor recall responses to vaccination.[97, 111] HCT patients, especially those with cGVHD are unable to produce functional high affinity antibodies.

Factors contributing to long-term B cell functional aberrations after HCT remain largely unknown because, with few exceptions, most studies examine antibody and B cell responses within the first 2 years after HCT. One early study showed that patients (followed for nearly 5 years after HCT) who had been in vivo challenged with phage and pneumococcal antigen recovered normal primary and secondary antibody responses recovered if they did not have cGVHD.[112] Another study of patients followed for a median of 6.5 years after allogeneic HCT showed progressive loss of antibodies to measles, mumps and rubella over time, with most previously vaccinated patients becoming seronegative by 5 years.[113] A European study of patients receiving the pneumococcal vaccine after HCT revealed that even in the absence of GVHD, IgG responses several years after primary vaccination were not durable.[114] Ongoing susceptibility of patients, especially those with cGVHD to encapsulated organisms suggests that splenic B cell dysfunction may persist for years. Long-term reconstitution deficits and plasma Ig levels were determined in a study in which HCT patients with and without cGVHD were examined together. Low B cell numbers and low functional response to tetanus toxin were associated with increased infections at 6 years post HCT.[15]

While *ex vivo* assays have shown that B cells are constitutively activated in cGVHD,[115, 116] B lymphopenia and humoral immune deficiency are distinctive characteristics of cGVHD.[117–120]. Studies have characterized the composition of the peripheral blood B cell compartment and have begun to characterize factors leading to altered B cell homeostasis after HCT.[104, 121] While functional anti-microbial antibodies are often persistently absent and HCT patients are hypogammaglobulinemic, cGVHD, is paradoxically associated with high titers of allo- and autoantibody.[88, 89] In this regard, cGVHD patients appear to be similar to patients with common variable immune deficiency (CVID) given their common propensity toward B cell autoreactivity in the face of profound humoral immune deficiency.[89, 122] A preponderance of CD21LoCD27-B cells has been found to be associated

with infectious complications [97] suggesting that typical antimicrobial GC reactions do not occur. Muted B cell responses to microbial pattern recognition receptors like lipopolysaccharide (LPS) potentially contribute to this GVHD-associated immune deficiency.[123] Evidence suggests that similar immunodeficiency states are associated with variable levels of immune tolerance and autoimmunity.[124–126]

Reconstitution of innate immunity

Almost all studies evaluating innate immune populations (natural killer (NK) cells, invariant NKT cells, dendritic cells, macrophages, neutrophils, eosinophils, platelets, and monocytes.) have focused on immune constitution under one year after transplantation with the assumption that these populations normalize not only in numbers but function as well. Only a single study has shown that low early counts (up to day 180) of innate populations such as basophils, eosinophils, macrophages, and monocytes, may be associated with post-HCT infection risk after 1 year but the study is limited by very small numbers.[87] The few remaining studies have focused only on NK cells and shown that factors such as ATG, alemtuzumab [127, 128] can delay their immune reconstitution but the impact after 1 year, if any, is unknown. Interestingly, late EBV infection may impact innate immunity inducing hemophagocytic lymphohistiocytosis.[129] Studies of the late recovery of innate immune responses and their interaction with T and B cell populations are warranted.

Key research priorities and recommendations

The difficulties of conducting detailed immunologic studies late after HCT were already mentioned. Additionally, the quality of registry data, while typically reliable for survival and relapse, is less robust related to reporting of infectious events in the late post-transplant interval.

Immune cell intrinsic and extrinsic pathways responsible for prolonged immune deficiency after HCT remain unknown. Immune function assays that determine infection risk have not been validated. The ability to understand immune dysregulation that persists into the late post-HCT interval will depend on prospective correlative sample collection that continues beyond one year, and the correlation of phenotypic and functional data with clinical data regarding late infection events, the presence of ongoing GVHD and the incidence and competing risks of mortality. The development of patient immunologic profiles with calendar and event driven collection of samples, including serum and PBMC, and clinical data should be encouraged to facilitate a better understanding of the determinants of late immune recovery. We recommend the following research priorities:

1. Studies that identify late dysfunctional adaptive immunity and probe the molecular mechanisms underlying it in the presence and absence of cGVHD.
2. Studies that address adaptive immune system neogenesis, maturation and exhaustion. In particular, it is important for us to understand how these processes are influenced by persistent alloreactivity, inflammation and viral infection.
3. Studies to assess late functional pathogen-specific T and B cell responses (to bacterial vaccines as well as viral antigens) as well as to pathogens not historically assessed in published studies (e.g., VZV, HSV, HHV-6). These

studies should aim to identify what factors that are associated with poor responses.

The detailed prospective study suggested in section 1 should include assessments at 1, 2 and 5 years post-HCT that addresses adaptive immune system cell neogenesis, maturation and exhaustion in the context of alloantigen activation and viral infection. Consideration should be given to event-driven storage of samples for future analysis.

Section 3. Interventions to improve immune function

This section will focus on the active generation of immune responses by vaccination and the passive transference of immunity with immunoglobulin (IVIG). Adoptive cellular immunotherapy will be addressed only briefly. We discuss what is known and areas that need study. The potential for intervention on the microbiome and its effects on late immunity, an area of the utmost interest, as mentioned earlier, is not yet known and will not be discussed [137].

Vaccination post HCT is accepted as a basic principle of improving the immune response. [112] While international guidelines recommend the administration of killed organism vaccines as early as 3–6 months post-transplant, [3, 138] implementation of vaccination schedules remains variable.[139]

Passive transfer of immunity with IVIG provides short-term protection against infection. IVIG may be given to treat active infections or to prevent infection [140–142143–145146]. In addition, there are times when IVIG products are used as adjunctive therapy for infections that are out of control [140, 147, 148]. Hypogammaglobulinemia on its own is a potential indication for IVIG replacement, although the threshold for repletion differs from center to center, perhaps most commonly < 400 mg/dL [149]. The published evidence on the benefits of IVIG is non-conclusive. The lower rates of relevant CMV related endpoints identified by early controlled single center studies and supported by meta-analyses did not translate onto improved overall survival, maybe in part due to increase in sinusoidal obstruction syndrome (SOS) [150, 151152153, 154155]. Use of IVIG products is not without its problems, and overuse may impair long-term humoral recovery after BMT [156]. Moreover, studies of its use late after HCT have not been conducted.

Current knowledge gaps

Vaccinations—There are many gaps in our understanding of the development of post-HCT active immunity through vaccination due to a lack of standardization and/or adequate studies (see Table 4). The former originates from the fact that vaccination protocols vary among centers as well as from country to country. The latter has occurred because systematic vaccination studies in large enough cohorts that address different stem cell sources, variations in HLA-match, conditioning regimens and GVHD activity, have not been a recent area of funded research except for a few vaccines under development in which the sponsor desired to have data that included HCT recipients.

Passive Immunity with Immunoglobulin—There are several knowledge gaps in the use of immunoglobulin after HCT. In particular, the relevance of older randomized studies and meta-analyses data regarding the risks of SOS and benefits of IVIG therapy is an open question given the current practices of more universal liver prophylaxis with ursodeoxycholic acid and busulfan therapeutic dose monitoring. The most recent meta-analyses still focus on myeloablative conditioning and matched sibling HCT without any focus on unrelated or haploidentical donors, cord or peripheral blood graft sources, or reduced intensity conditioning [155, 157].

There is no strong evidence regarding the IgG level at which replacement IVIG should be administered,[3] and practices vary. The experience from the patients who underwent allogeneic HCT for primary immunodeficiency disease (PID) may provide some guidance.[158] Serum trough IgG levels are higher among PID patients when higher IVIG replacement doses are given, and the risk for pneumonia is lower.[159] IVIG replacement may be stopped once GVHD has resolved, immunosuppressive therapy has been discontinued, trough IgG levels are >600 mg/dL, and there is evidence of Ig-class switched B cells. However, specific antibody responses are followed. Correlative studies have not been performed for adults. Whether or not such observations are applicable for patients transplanted for other diseases has not been studied.

IVIG half-life varies widely from 1 to 10 days among HCT recipients, versus 18 to 23 days among healthy controls.[160–162] Active infections can accelerate immunoglobulin catabolism which necessitates dose adjustments to maintain target IgG levels [162]. So, knowledge gaps include defining the optimal frequency for measuring IgG levels after HCT, as well as the specific indications for its administration (severe hypogammaglobulinemia *versus* specific infections). In addition, if immunoglobulin products are used, which are the safest products and what is the most cost-effective way of administering them?

Adoptive cellular immunotherapy—Adoptive cellular immunotherapy has emerged as a promising strategy for the control of otherwise untreatable viral infections. Proof-of-concept trials show that this approach is safe and well tolerated [163]. Remaining issues include determining the best source of obtaining virus-specific cells (donor related or third-party [164]). This technique has the potential to revolutionize the management of refractory viral infections after HCT. Only a few transplant centers have the capability to prepare the cell products, a gap that is well-recognized, and these have rarely been studied in the late period post-HCT.

Key research priorities and recommendations

There are a number of recommendations that can be made with respect to these three categories of interventions and which could become more favorable with future contextual studies, cost-effective utilization and ease of implementation in the future:

1. A retrospective study from a small number of centers of basic numeric immune reconstitution markers correlated with vaccine responses might shed some light on standardizing thresholds for initiating vaccination for the current portfolio of transplant types.

2. Prospective multicenter clinical trials are needed to both define and address the knowledge gaps in achieving active immunity after vaccination in the aforementioned comprehensive range of posttransplant scenarios (Table 4). Key study variables will include: harmonized vaccine schedules (including start times), clinical variables, and harmonization of calendar driven vaccine specific titers. These data will provide the evidence to support development of a schedule of required and optional vaccines with guidelines for administration of and monitoring of success (and failure) in the prevention of infection.

3. Regarding passive transfer of immunity we would like to gain knowledge regarding the current practice of IVIG therapy, perhaps through the use of online surveys. The surveys could start with a relatively small number of centers, with all types of transplants, to determine the range of practice and rates of infections and use the data to guide development of a study to determine what dose schedules provide protection from infection.

BIBLIOGRAPHY

1. Pasquini, MC., Zhu, X. Current uses and outcomes of hematopoietic stem cell transplantation: CIBMTR Summary Slides. 2015. Available at:http://www.cibmtr.org/
2. Leather HL, Wingard JR. Infections following hematopoietic stem cell transplantation. Infect Dis Clin North Am. 2001; 15:483–520. [PubMed: 11447707]
3. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2009; 15:1143–1238.
4. Alsharif M, Cameron SE, Young JA, et al. Time trends in fungal infections as a cause of death in hematopoietic stem cell transplant recipients: an autopsy study. Am J Clin Pathol. 2009; 132:746–755. [PubMed: 19846817]
5. Bachanova V, Brunstein CG, Burns LJ, et al. Fewer infections and lower infection-related mortality following non-myeloablative versus myeloablative conditioning for allotransplantation of patients with lymphoma. Bone Marrow Transplant. 2009; 43:237–244. [PubMed: 18806838]
6. Tomblyn M, Young JA, Haagenson MD, et al. Decreased infections in recipients of unrelated donor hematopoietic cell transplantation from donors with an activating KIR genotype. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2010; 16:1155–1161.
7. van Burik JA, Carter SL, Freifeld AG, et al. Higher risk of cytomegalovirus and aspergillus infections in recipients of T cell-depleted unrelated bone marrow: analysis of infectious complications in patients treated with T cell depletion versus immunosuppressive therapy to prevent graft-versus-host disease. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2007; 13:1487–1498.
8. Young JA, Logan BR, Wu J, et al. Infections after Transplantation of Bone Marrow or Peripheral Blood Stem Cells from Unrelated Donors. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2016; 22:359–370.
9. Srinivasan A, Wang C, Srivastava DK, et al. Timeline, epidemiology, and risk factors for bacterial, fungal, and viral infections in children and adolescents after allogeneic hematopoietic stem cell transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2013; 19:94–101.
10. Robin M, Porcher R, De Castro Araujo R, et al. Risk factors for late infections after allogeneic hematopoietic stem cell transplantation from a matched related donor. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2007; 13:1304–1312.

11. Servais S, Lengline E, Porcher R, et al. Long-term immune reconstitution and infection burden after mismatched hematopoietic stem cell transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2014; 20:507–517.
12. Itzykson R, Robin M, Moins-Teisserenc H, et al. Cytomegalovirus shapes long-term immune reconstitution after allogeneic stem cell transplantation. Haematologica. 2015; 100:114–123. [PubMed: 25261095]
13. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. Blood. 2016; 127:2427–2438. [PubMed: 26884374]
14. Petropoulou AD, Porcher R, Peffault de Latour R, et al. Increased infection rate after preemptive rituximab treatment for Epstein-Barr virus reactivation after allogeneic hematopoietic stem-cell transplantation. Transplantation. 2012; 94:879–883. [PubMed: 23001354]
15. Maury S, Mary JY, Rabian C, et al. Prolonged immune deficiency following allogeneic stem cell transplantation: risk factors and complications in adult patients. Br J Haematol. 2001; 115:630–641. [PubMed: 11736948]
16. Le RQ, Melenhorst JJ, Battiwalla M, et al. Evolution of the donor T-cell repertoire in recipients in the second decade after allogeneic stem cell transplantation. Blood. 2011; 117:5250–5256. [PubMed: 21421838]
17. Storek J, Joseph A, Espino G, et al. Immunity of patients surviving 20 to 30 years after allogeneic or syngeneic bone marrow transplantation. Blood. 2001; 98:3505–3512. [PubMed: 11739150]
18. Abrahamsen IW, Somme S, Heldal D, Egeland T, Kvale D, Tjonnfjord GE. Immune reconstitution after allogeneic stem cell transplantation: the impact of stem cell source and graft-versus-host disease. Haematologica. 2005; 90:86–93. [PubMed: 15642674]
19. Antin JH. Immune reconstitution: the major barrier to successful stem cell transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2005; 11:43–45.
20. Kalhs P, Panzer S, Kletter K, et al. Functional asplenia after bone marrow transplantation. A late complication related to extensive chronic graft-versus-host disease. Ann Intern Med. 1988; 109:461–464. [PubMed: 3046449]
21. Bjorklund A, Aschan J, Labopin M, et al. Risk factors for fatal infectious complications developing late after allogeneic stem cell transplantation. Bone Marrow Transplant. 2007; 40:1055–1062. [PubMed: 17891187]
22. Atkinson K, Farewell V, Storb R, et al. Analysis of late infections after human bone marrow transplantation: role of genotypic nonidentity between marrow donor and recipient and of nonspecific suppressor cells in patients with chronic graft-versus-host disease. Blood. 1982; 60:714–720. [PubMed: 6213276]
23. Ochs L, Shu XO, Miller J, et al. Late infections after allogeneic bone marrow transplantations: comparison of incidence in related and unrelated donor transplant recipients. Blood. 1995; 86:3979–3986. [PubMed: 7579369]
24. Storek J, Gooley T, Witherspoon RP, Sullivan KM, Storb R. Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts. Am J Hematol. 1997; 54:131–138. [PubMed: 9034287]
25. Socie G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med. 1999; 341:14–21. [PubMed: 10387937]
26. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2011; 29:2230–2239. [PubMed: 21464398]
27. Sullivan KM. Longterm followup and quality of life after hematopoietic stem cell transplantation. J Rheumatol Suppl. 1997; 48:46–52. [PubMed: 9150118]
28. Boeckh M, Kim HW, Flowers ME, Meyers JD, Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation--a randomized double-blind placebo-controlled study. Blood. 2006; 107:1800–1805. [PubMed: 16282339]

29. McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology. 2010; 51:1450–1460. [PubMed: 20373370]
30. Katz J, Islam MN, Bhattacharyya I, Sandow P, Moreb JS. Oral squamous cell carcinoma positive for p16/human papilloma virus in post allogeneic stem cell transplantation: 2 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014; 118:e74–78. [PubMed: 25151594]
31. Tedeschi SK, Savani BN, Jagasia M, et al. Time to consider HPV vaccination after allogeneic stem cell transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2010; 16:1033–1036.
32. Zhang L, Epstein JB, Poh CF, et al. Comparison of HPV infection, p53 mutation and allelic losses in post-transplant and non-posttransplant oral squamous cell carcinomas. J Oral Pathol Med. 2002; 31:134–141. [PubMed: 11903818]
33. Copelan E, Casper JT, Carter SL, et al. A scheme for defining cause of death and its application in the T cell depletion trial. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2007; 13:1469–1476.
34. Holler E, Butzhammer P, Schmid K, et al. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2014; 20:640–645.
35. Jenq RR, Ubeda C, Taur Y, et al. Regulation of intestinal inflammation by microbiota following allogeneic bone marrow transplantation. The Journal of experimental medicine. 2012; 209:903–911. [PubMed: 22547653]
36. Taur Y, Jenq RR, Perales MA, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood. 2014; 124:1174–1182. [PubMed: 24939656]
37. Hakim FT, Gress RE. Reconstitution of the lymphocyte compartment after lymphocyte depletion: a key issue in clinical immunology. European journal of immunology. 2005; 35:3099–3102. [PubMed: 16231288]
38. van den Brink, MR., Velardi, E., Perales, MA. Hematology/the Education Program of the American Society of Hematology. Vol. 2015. American Society of Hematology Education Program; 2015. Immune reconstitution following stem cell transplantation; p. 215-219.
39. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2012; 18:348–371.
40. Small TN, Papadopoulos EB, Boulad F, et al. Comparison of immune reconstitution after unrelated and related T-cell-depleted bone marrow transplantation: effect of patient age and donor leukocyte infusions. Blood. 1999; 93:467–480. [PubMed: 9885208]
41. Fujimaki K, Maruta A, Yoshida M, et al. Immune reconstitution assessed during five years after allogeneic bone marrow transplantation. Bone Marrow Transplant. 2001; 27:1275–1281. [PubMed: 11548845]
42. Lewin SR, Heller G, Zhang L, et al. Direct evidence for new T-cell generation by patients after either T-cell-depleted or unmodified allogeneic hematopoietic stem cell transplantations. Blood. 2002; 100:2235–2242. [PubMed: 12200390]
43. Douek DC, Vescio RA, Betts MR, et al. Assessment of thymic output in adults after haematopoietic stem-cell transplantation and prediction of T-cell reconstitution. Lancet. 2000; 355:1875–1881. [PubMed: 10866444]
44. Koehl U, Bochennek K, Zimmermann SY, et al. Immune recovery in children undergoing allogeneic stem cell transplantation: absolute CD8+ CD3+ count reconstitution is associated with survival. Bone Marrow Transplant. 2007; 39:269–278. [PubMed: 17311085]
45. Kanda J, Chiou LW, Szabolcs P, et al. Immune recovery in adult patients after myeloablative dual umbilical cord blood, matched sibling, and matched unrelated donor hematopoietic cell

transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2012; 18:1664–1676. e1661.

46. Schulenburg A, Fischer M, Kalhs P, et al. Immune recovery after conventional and non-myeloablative allogeneic stem cell transplantation. Leukemia & lymphoma. 2005; 46:1755–1760. [PubMed: 16263578]
47. Mackall CL, Bare CV, Granger LA, Sharrow SO, Titus JA, Gress RE. Thymic-independent T cell regeneration occurs via antigen-driven expansion of peripheral T cells resulting in a repertoire that is limited in diversity and prone to skewing. J Immunol. 1996; 156:4609–4616. [PubMed: 8648103]
48. Betts MR, Nason MC, West SM, et al. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. Blood. 2006; 107:4781–4789. [PubMed: 16467198]
49. Gattinoni L, Klebanoff CA, Palmer DC, et al. Acquisition of full effector function in vitro paradoxically impairs the in vivo antitumor efficacy of adoptively transferred CD8+ T cells. The Journal of clinical investigation. 2005; 115:1616–1626. [PubMed: 15931392]
50. Kim TK, St John LS, Wieder ED, Khalili J, Ma Q, Komanduri KV. Human late memory CD8+ T cells have a distinct cytokine signature characterized by CC chemokine production without IL-2 production. J Immunol. 2009; 183:6167–6174. [PubMed: 19841187]
51. Turtle CJ, Swanson HM, Fujii N, Estey EH, Riddell SR. A distinct subset of self-renewing human memory CD8+ T cells survives cytotoxic chemotherapy. Immunity. 2009; 31:834–844. [PubMed: 19879163]
52. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003; 299:1057–1061. [PubMed: 12522256]
53. Cozzo C, Larkin J 3rd, Caton AJ. Cutting edge: self-peptides drive the peripheral expansion of CD4+CD25+ regulatory T cells. J Immunol. 2003; 171:5678–5682. [PubMed: 14634074]
54. Duggleby RC, Madrigal JA. Methods of detection of immune reconstitution and T regulatory cells by flow cytometry. Methods in molecular biology. 2014; 1109:159–186. [PubMed: 24473784]
55. Komanduri KV, Salha MD, Sekaly RP, McCune JM. Superantigen-mediated deletion of specific T cell receptor V beta subsets in the SCID-hu Thy/Liv mouse is induced by staphylococcal enterotoxin B, but not HIV-1. J Immunol. 1997; 158:544–549. [PubMed: 8992966]
56. Arstila TP, Casrouge A, Baron V, Even J, Kanellopoulos J, Kourilsky P. A direct estimate of the human alphabeta T cell receptor diversity. Science. 1999; 286:958–961. [PubMed: 10542151]
57. Arstila TP, Casrouge A, Baron V, Even J, Kanellopoulos J, Kourilsky P. Diversity of human alpha beta T cell receptors. Science. 2000; 288:1135. [PubMed: 10841721]
58. Krell PF, Reuther S, Fischer U, et al. Next-generation-sequencing-spectratyping reveals public T-cell receptor repertoires in pediatric very severe aplastic anemia and identifies a beta chain CDR3 sequence associated with hepatitis-induced pathogenesis. Haematologica. 2013; 98:1388–1396. [PubMed: 23716544]
59. van Heijst JW, Ceberio I, Lipuma LB, et al. Quantitative assessment of T cell repertoire recovery after hematopoietic stem cell transplantation. Nature medicine. 2013; 19:372–377.
60. Meyer EH, Hsu AR, Liliental J, et al. A distinct evolution of the T-cell repertoire categorizes treatment refractory gastrointestinal acute graft-versus-host disease. Blood. 2013; 121:4955–4962. [PubMed: 23652802]
61. Komanduri KV, Viswanathan MN, Wieder ED, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. Nature medicine. 1998; 4:953–956.
62. Ozdemir E, St John LS, Gillespie G, et al. Cytomegalovirus reactivation following allogeneic stem cell transplantation is associated with the presence of dysfunctional antigen-specific CD8+ T cells. Blood. 2002; 100:3690–3697. [PubMed: 12393402]
63. Komanduri KV, Donahoe SM, Moretto WJ, et al. Direct measurement of CD4+ and CD8+ T-cell responses to CMV in HIV-1-infected subjects. Virology. 2001; 279:459–470. [PubMed: 11162802]
64. Callan MF, Tan L, Annels N, et al. Direct visualization of antigen-specific CD8+ T cells during the primary immune response to Epstein-Barr virus In vivo. The Journal of experimental medicine. 1998; 187:1395–1402. [PubMed: 9565632]

65. Stanzani M, Orciuolo E, Lewis R, et al. Aspergillus fumigatus suppresses the human cellular immune response via gliotoxin-mediated apoptosis of monocytes. Blood. 2005; 105:2258–2265. [PubMed: 15546954]
66. Molldrem JJ, Lee PP, Wang C, et al. Evidence that specific T lymphocytes may participate in the elimination of chronic myelogenous leukemia. Nature medicine. 2000; 6:1018–1023.
67. Kostense S, Otto SA, Knol GJ, et al. Functional restoration of human immunodeficiency virus and Epstein-Barr virus-specific CD8(+) T cells during highly active antiretroviral therapy is associated with an increase in CD4(+) T cells. European journal of immunology. 2002; 32:1080–1089. [PubMed: 11920575]
68. Altman JD, Moss PA, Goulder PJ, et al. Phenotypic analysis of antigen-specific T lymphocytes. Science. 1996; 274:94–96. [PubMed: 8810254]
69. Kern F, Surel IP, Brock C, et al. T-cell epitope mapping by flow cytometry. Nature medicine. 1998; 4:975–978.
70. Martins SL, St John LS, Champlin RE, et al. Functional assessment and specific depletion of alloreactive human T cells using flow cytometry. Blood. 2004; 104:3429–3436. [PubMed: 15284108]
71. Trivedi D, Williams RY, O'Reilly RJ, Koehne G. Generation of CMV-specific T lymphocytes using protein-spanning pools of pp65-derived overlapping pentadecapeptides for adoptive immunotherapy. Blood. 2005; 105:2793–2801. [PubMed: 15514011]
72. Pao M, Papadopoulos EB, Chou J, et al. Response to pneumococcal (PNCRM7) and haemophilus influenzae conjugate vaccines (HIB) in pediatric and adult recipients of an allogeneic hematopoietic cell transplantation (alloHCT). Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2008; 14:1022–1030.
73. Ozdemir E, Saliba RM, Champlin RE, et al. Risk factors associated with late cytomegalovirus reactivation after allogeneic stem cell transplantation for hematological malignancies. Bone Marrow Transplant. 2007; 40:125–136. [PubMed: 17530009]
74. Corre E, Carmagnat M, Busson M, et al. Long-term immune deficiency after allogeneic stem cell transplantation: B-cell deficiency is associated with late infections. Haematologica. 2010; 95:1025–1029. [PubMed: 20133894]
75. Kalwak K, Gorczynska E, Toporski J, et al. Immune reconstitution after haematopoietic cell transplantation in children: immunophenotype analysis with regard to factors affecting the speed of recovery. Br J Haematol. 2002; 118:74–89. [PubMed: 12100130]
76. Perlingeiro Beltrame M, Malvezzi M, Bonfim C, Covas DT, Orfao A, Pasquini R. Immune reconstitution in patients with Fanconi anemia after allogeneic bone marrow transplantation. Cytotherapy. 2014; 16:976–989. [PubMed: 24831839]
77. Hakim FT, Memon SA, Cepeda R, et al. Age-dependent incidence, time course, and consequences of thymic renewal in adults. The Journal of clinical investigation. 2005; 115:930–939. [PubMed: 15776111]
78. Porrata LF, Markovic SN. Timely reconstitution of immune competence affects clinical outcome following autologous stem cell transplantation. Clinical and experimental medicine. 2004; 4:78–85. [PubMed: 15672944]
79. Socie G, Ritz J. Current issues in chronic graft-versus-host disease. Blood. 2014; 124:374–384. [PubMed: 24914139]
80. Alho AC, Kim HT, Chammas MJ, et al. Unbalanced recovery of regulatory and effector T cells after allogeneic stem cell transplantation contributes to chronic GVHD. Blood. 2016; 127:646–657. [PubMed: 26670634]
81. Kawano Y, Kim HT, Matsuoka K, et al. Low telomerase activity in CD4+ regulatory T cells in patients with severe chronic GVHD after hematopoietic stem cell transplantation. Blood. 2011; 118:5021–5030. [PubMed: 21900196]
82. Delemarre EM, van den Broek T, Mijnheer G, et al. Autologous stem cell transplantation aids autoimmune patients by functional renewal and TCR diversification of regulatory T cells. Blood. 2016; 127:91–101. [PubMed: 26480932]

83. Roncarolo MG, Gregori S, Bacchetta R, Battaglia M. Tr1 cells and the counter-regulation of immunity: natural mechanisms and therapeutic applications. Curr Top Microbiol Immunol. 2014; 380:39–68. [PubMed: 25004813]
84. de Masson A, Bouaziz JD, Le Buanec H, et al. CD24(hi)CD27(+) and plasmablast-like regulatory B cells in human chronic graft-versus-host disease. Blood. 2015; 125:1830–1839. [PubMed: 25605369]
85. Kariminia A, Holtan SG, Ivison S, et al. Heterogeneity of chronic graft-versus-host disease biomarkers: the only consistent association is with CXCL10 and CXCR3+ NK cells. Blood. 2016
86. Koreth J, Matsuoka K, Kim HT, et al. Interleukin-2 and regulatory T cells in graft-versus-host disease. N Engl J Med. 2011; 365:2055–2066. [PubMed: 22129252]
87. Podgorny PJ, Pratt LM, Liu Y, et al. Low Counts of B Cells, Natural Killer Cells, Monocytes, Dendritic Cells, Basophils, and Eosinophils are Associated with Postengraftment Infections after Allogeneic Hematopoietic Cell Transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2016; 22:37–46.
88. Miklos DB, Kim HT, Miller KH, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood. 2005; 105:2973–2978. [PubMed: 15613541]
89. Patriarca F, Skert C, Sperotto A, et al. The development of autoantibodies after allogeneic stem cell transplantation is related with chronic graft-vs-host disease and immune recovery. Experimental hematology. 2006; 34:389–396. [PubMed: 16543073]
90. Storek J, Ferrara S, Ku N, Giorgi JV, Champlin RE, Saxon A. B cell reconstitution after human bone marrow transplantation: recapitulation of ontogeny? Bone Marrow Transplant. 1993; 12:387–398. [PubMed: 8275039]
91. Storek J, Espino G, Dawson MA, Storer B, Flowers ME, Maloney DG. Low B-cell and monocyte counts on day 80 are associated with high infection rates between days 100 and 365 after allogeneic marrow transplantation. Blood. 2000; 96:3290–3293. [PubMed: 11050018]
92. Stewart DM, McAvoy MJ, Hilbert DM, Nelson DL. B lymphocytes from individuals with common variable immunodeficiency respond to B lymphocyte stimulator (BLyS protein) in vitro. Clinical immunology. 2003; 109:137–143. [PubMed: 14597212]
93. Warnatz K, Wehr C, Drager R, et al. Expansion of CD19(hi)CD21(lo/neg) B cells in common variable immunodeficiency (CVID) patients with autoimmune cytopenia. Immunobiology. 2002; 206:502–513. [PubMed: 12607725]
94. Storek J. B-cell immunity after allogeneic hematopoietic cell transplantation. Cytotherapy. 2002; 4:423–424. [PubMed: 12473209]
95. Storek J, Viganego F, Dawson MA, et al. Factors affecting antibody levels after allogeneic hematopoietic cell transplantation. Blood. 2003; 101:3319–3324. [PubMed: 12506030]
96. Ault KA, Antin JH, Ginsburg D, et al. Phenotype of recovering lymphoid cell populations after marrow transplantation. The Journal of experimental medicine. 1985; 161:1483–1502. [PubMed: 3159819]
97. Greinix HT, Pohlreich D, Kouba M, et al. Elevated numbers of immature/transitional CD21- B lymphocytes and deficiency of memory CD27+ B cells identify patients with active chronic graft-versus-host disease. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2008; 14:208–219.
98. Avanzini MA, Locatelli F, Dos Santos C, et al. B lymphocyte reconstitution after hematopoietic stem cell transplantation: functional immaturity and slow recovery of memory CD27+ B cells. Experimental hematology. 2005; 33:480–486. [PubMed: 15781339]
99. Storek J, Zhao Z, Lin E, et al. Recovery from and consequences of severe iatrogenic lymphopenia (induced to treat autoimmune diseases). Clinical immunology. 2004; 113:285–298. [PubMed: 15507394]
100. Omazic B, Lundkvist I, Mattsson J, Permert J, Nasman-Bjork I. Memory B lymphocytes determine repertoire oligoclonality early after haematopoietic stem cell transplantation. Clin Exp Immunol. 2003; 134:159–166. [PubMed: 12974769]
101. Sale GE, Alavaikko M, Schaefers KM, Mahan CT. Abnormal CD4:CD8 ratios and delayed germinal center reconstitution in lymph nodes of human graft recipients with graft-versus-host

disease (GVHD): an immunohistological study. Experimental hematology. 1992; 20:1017–1021. [PubMed: 1505636]

102. Al-Eid MA, Tutschka PJ, Wagner HN Jr, Santos GW, Tsan MF. Functional asplenia in patients with chronic graft-versus-host disease: concise communication. Journal of nuclear medicine: official publication, Society of Nuclear Medicine. 1983; 24:1123–1126.
103. Jin H, Ni X, Deng R, et al. Antibodies from donor B cells perpetuate cutaneous chronic graft-versus-host disease in mice. Blood. 2016; 127:2249–2260. [PubMed: 26884373]
104. Sarantopoulos S. Antibodies are back for thymic attack in cGVHD. Blood. 2016; 127:2170–2171. [PubMed: 27151737]
105. D'Costa S, Slobod KS, Benaim E, et al. Effect of extended immunosuppressive drug treatment on B cell vs T cell reconstitution in pediatric bone marrow transplant recipients. Bone Marrow Transplant. 2001; 28:573–580. [PubMed: 11607770]
106. Keever CA, Small TN, Flomenberg N, et al. Immune reconstitution following bone marrow transplantation: comparison of recipients of T-cell depleted marrow with recipients of conventional marrow grafts. Blood. 1989; 73:1340–1350. [PubMed: 2649174]
107. Small TN, Keever CA, Weiner-Fedus S, Heller G, O'Reilly RJ, Flomenberg N. B-cell differentiation following autologous, conventional, or T-cell depleted bone marrow transplantation: a recapitulation of normal B-cell ontogeny. Blood. 1990; 76:1647–1656. [PubMed: 1698484]
108. Lum LG, Seigneuret MC, Storb RF, Witherspoon RP, Thomas ED. In vitro regulation of immunoglobulin synthesis after marrow transplantation. I. T-cell and B-cell deficiencies in patients with and without chronic graft-versus-host disease. Blood. 1981; 58:431–439. [PubMed: 6455127]
109. Allen JL, Tata PV, Fore MS, et al. Increased BCR responsiveness in B cells from patients with chronic GVHD. Blood. 2014; 123:2108–2115. [PubMed: 24532806]
110. Storek J, Saxon A. Reconstitution of B cell immunity following bone marrow transplantation. Bone Marrow Transplant. 1992; 9:395–408. [PubMed: 1628122]
111. Sarantopoulos S, Stevenson KE, Kim HT, et al. Altered B-cell homeostasis and excess BAFF in human chronic graft-versus-host disease. Blood. 2009; 113:3865–3874. [PubMed: 19168788]
112. Witherspoon RP, Storb R, Ochs HD, et al. Recovery of antibody production in human allogeneic marrow graft recipients: influence of time posttransplantation, the presence or absence of chronic graft-versus-host disease, and antithymocyte globulin treatment. Blood. 1981; 58:360–368. [PubMed: 6454452]
113. Ljungman P, Lewensohn-Fuchs I, Hammarstrom V, et al. Long-term immunity to measles, mumps, and rubella after allogeneic bone marrow transplantation. Blood. 1994; 84:657–663. [PubMed: 8025290]
114. Cordonnier C, Labopin M, Robin C, et al. Long-term persistence of the immune response to antipneumococcal vaccines after Allo-SCT: 10-year follow-up of the EBMT-IDWP01 trial. Bone Marrow Transplant. 2015; 50:978–983. [PubMed: 25867652]
115. Perrett KP, Jin C, Clutterbuck E, et al. B cell memory to a serogroup C meningococcal conjugate vaccine in childhood and response to booster: little association with serum IgG antibody. J Immunol. 2012; 189:2673–2681. [PubMed: 22855707]
116. Giesecke C, Frolich D, Reiter K, et al. Tissue distribution and dependence of responsiveness of human antigen-specific memory B cells. J Immunol. 2014; 192:3091–3100. [PubMed: 24567530]
117. Pullerits R, Brisslert M, Jonsson IM, Tarkowski A. Soluble receptor for advanced glycation end products triggers a proinflammatory cytokine cascade via beta2 integrin Mac-1. Arthritis and rheumatism. 2006; 54:3898–3907. [PubMed: 17133598]
118. Flynn RAJ, Luznik L, MacDonald KP, Paz K, Alexander KA, Vulic A, Du J, Panoskaltsis-Mortari A, Taylor PA, Poe JC, Serody JS, Murphy WJ, Hill GR, Maillard I, Koreth J, Cutler CS, Soiffer RJ, Antin JH, Ritz J, Chao NJ, Clynes RA, Sarantopoulos S, Blazar BR. Targeting Syk activated B cells in murine and human chronic graft-versus host disease. Blood. 2015 [Accepted March 16, 2015]

119. Allen JL, Fore MS, Wooten J, et al. B cells from patients with chronic GVHD are activated and primed for survival via BAFF-mediated pathways. Blood. 2012; 120:2529–2536. [PubMed: 22896003]
120. Zhang S, Readinger JA, DuBois W, et al. Constitutive reductions in mTOR alter cell size, immune cell development, and antibody production. Blood. 2011; 117:1228–1238. [PubMed: 21079150]
121. Kuzmina Z, Greinix HT, Weigl R, et al. Significant differences in B-cell subpopulations characterize patients with chronic graft-versus-host disease-associated dysgammaglobulinemia. Blood. 2011; 117:2265–2274. [PubMed: 21063025]
122. Isnardi I, Ng YS, Menard L, et al. Complement receptor 2/CD21- human naive B cells contain mostly autoreactive unresponsive clones. Blood. 2010; 115:5026–5036. [PubMed: 20231422]
123. Falzarano G, Krenger W, Snyder KM, Delmonte J Jr, Karandikar M, Ferrara JL. Suppression of B-cell proliferation to lipopolysaccharide is mediated through induction of the nitric oxide pathway by tumor necrosis factor-alpha in mice with acute graft-versus-host disease. Blood. 1996; 87:2853–2860. [PubMed: 8639904]
124. Lothe RA, Blomhoff HK. Tumor suppressors--genes and proteins. Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke. 1998; 118:1887–1892.
125. Agarwal S, Smereka P, Harpaz N, Cunningham-Rundles C, Mayer L. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. Inflammatory bowel diseases. 2011; 17:251–259. [PubMed: 20629103]
126. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Current allergy and asthma reports. 2009; 9:347–352. [PubMed: 19671377]
127. Penack O, Fischer L, Stroux A, et al. Serotherapy with thymoglobulin and alemtuzumab differentially influences frequency and function of natural killer cells after allogeneic stem cell transplantation. Bone Marrow Transplant. 2008; 41:377–383. [PubMed: 17982494]
128. Stauch D, Dernier A, Sarmiento Marchese E, et al. Targeting of natural killer cells by rabbit antithymocyte globulin and campath-1H: similar effects independent of specificity. PLoS One. 2009; 4:e4709. [PubMed: 19266059]
129. Kawabata Y, Hirokawa M, Saitoh Y, et al. Late-onset fatal Epstein-Barr virus-associated hemophagocytic syndrome following cord blood cell transplantation for adult acute lymphoblastic leukemia. Int J Hematol. 2006; 84:445–448. [PubMed: 17189228]
130. Kim HT, Armand P, Frederick D, et al. Absolute lymphocyte count recovery after allogeneic hematopoietic stem cell transplantation predicts clinical outcome. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2015; 21:873–880.
131. Kim DH, Sohn SK, Won DI, Lee NY, Suh JS, Lee KB. Rapid helper T-cell recovery above 200 × 10 6/l at 3 months correlates to successful transplant outcomes after allogeneic stem cell transplantation. Bone Marrow Transplant. 2006; 37:1119–1128. [PubMed: 16699530]
132. Cohen G, Carter SL, Weinberg KI, et al. Antigen-specific T-lymphocyte function after cord blood transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2006; 12:1335–1342.
133. Rozmus J, Mallhi K, Ke J, Schultz KR. Functional hyposplenism after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2015; 50:1343–1347. [PubMed: 26168071]
134. Kulkarni S, Powles R, Treleaven J, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplants. Blood. 2000; 95:3683–3686. [PubMed: 10845897]
135. Cuthbert RJ, Iqbal A, Gates A, Toghill PJ, Russell NH. Functional hyposplenism following allogeneic bone marrow transplantation. J Clin Pathol. 1995; 48:257–259. [PubMed: 7730489]
136. Brinkman DM, Jol-van der Zijde CM, ten Dam MM, et al. Resetting the adaptive immune system after autologous stem cell transplantation: lessons from responses to vaccines. J Clin Immunol. 2007; 27:647–658. [PubMed: 17690955]
137. Nellore A, Fishman JA. The Microbiome, Systemic Immune Function, and Allotransplantation. Clin Microbiol Rev. 2016; 29:191–199. [PubMed: 26656674]
138. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014; 58:309–318. [PubMed: 24421306]

139. Carpenter PA, Englund JA. How I vaccinate blood and marrow transplant recipients. Blood. 2016; 127:2824–2832. [PubMed: 27048212]
140. Ljungman P, Cordonnier C, Einsele H, et al. Use of intravenous immune globulin in addition to antiviral therapy in the treatment of CMV gastrointestinal disease in allogeneic bone marrow transplant patients: a report from the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 1998; 21:473–476. [PubMed: 9535039]
141. Meyers JD. Prevention and treatment of cytomegalovirus infections with interferons and immune globulins. Infection. 1984; 12:143–150. [PubMed: 6203842]
142. Boeckh M. Current antiviral strategies for controlling cytomegalovirus in hematopoietic stem cell transplant recipients: prevention and therapy. Transpl Infect Dis. 1999; 1:165–178. [PubMed: 11428987]
143. Cortez K, Murphy BR, Almeida KN, et al. Immune-globulin prophylaxis of respiratory syncytial virus infection in patients undergoing stem-cell transplantation. J Infect Dis. 2002; 186:834–838. [PubMed: 12198619]
144. Khushalani NI, Bakri FG, Wentling D, et al. Respiratory syncytial virus infection in the late bone marrow transplant period: report of three cases and review. Bone Marrow Transplant. 2001; 27:1071–1073. [PubMed: 11438823]
145. Whimbey E, Champlin RE, Englund JA, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. Bone Marrow Transplant. 1995; 16:393–399. [PubMed: 8535312]
146. Straus SE, Ostrove JM, Inchauspe G, et al. NIH conference. Varicella-zoster virus infections. Biology, natural history, treatment, and prevention. Ann Intern Med. 1988; 108:221–237. [PubMed: 2829675]
147. Reed EC, Bowden RA, Dandliker PS, Gleaves CA, Meyers JD. Efficacy of cytomegalovirus immunoglobulin in marrow transplant recipients with cytomegalovirus pneumonia. J Infect Dis. 1987; 156:641–645. [PubMed: 3040870]
148. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med. 1988; 109:783–788. [PubMed: 2847610]
149. Carpenter PA, Kitko CL, Elad S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2015; 21:1167–1187.
150. Winston DJ, Ho WG, Lin CH, et al. Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. Ann Intern Med. 1987; 106:12–18. [PubMed: 3024542]
151. Sullivan KM, Kopecky KJ, Jocom J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med. 1990; 323:705–712. [PubMed: 2167452]
152. Wolff SN, Fay JW, Herzig RH, et al. High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med. 1993; 118:937–942. [PubMed: 8489107]
153. Messori A, Rampazzo R, Scroccaro G, Martini N. Efficacy of hyperimmune anti-cytomegalovirus immunoglobulins for the prevention of cytomegalovirus infection in recipients of allogeneic bone marrow transplantation: a meta-analysis. Bone Marrow Transplant. 1994; 13:163–167. [PubMed: 8205085]
154. Bass EB, Powe NR, Goodman SN, et al. Efficacy of immune globulin in preventing complications of bone marrow transplantation: a meta-analysis. Bone Marrow Transplant. 1993; 12:273–282. [PubMed: 8241987]
155. Cordonnier C, Chevret S, Legrand M, et al. Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. Ann Intern Med. 2003; 139:8–18. [PubMed: 12834313]

156. Sullivan KM, Storek J, Kopecky KJ, et al. A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 1996; 2:44–53.

157. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009; 27:770–781. [PubMed: 19114702]

158. Griffith LM, Cowan MJ, Notarangelo LD, et al. Improving cellular therapy for primary immune deficiency diseases: recognition, diagnosis, and management. The Journal of allergy and clinical immunology. 2009; 124:1152–1160. e1112. [PubMed: 20004776]

159. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clinical immunology. 2010; 137:21–30. [PubMed: 20675197]

160. Bosi A, De Majo E, Guidi S, et al. Kinetics of anti-CMV antibodies after administration of intravenous immunoglobulins to bone marrow transplant recipients. Haematologica. 1990; 75:109–112. [PubMed: 2162799]

161. Rand KH, Houck H, Ganju A, Babington RG, Elfenbein GJ. Pharmacokinetics of cytomegalovirus specific IgG antibody following intravenous immunoglobulin in bone marrow transplant patients. Bone Marrow Transplant. 1989; 4:679–683. [PubMed: 2555005]

162. Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. N Engl J Med. 1991; 325:110–117. [PubMed: 2052044]

163. Leen AM, Bollard CM, Mendizabal AM, et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. Blood. 2013; 121:5113–5123. [PubMed: 23610374]

164. Feuchtinger T, Richard C, Joachim S, et al. Clinical grade generation of hexon-specific T cells for adoptive T-cell transfer as a treatment of adenovirus infection after allogeneic stem cell transplantation. J Immunother. 2008; 31:199–206. [PubMed: 18481389]

165. Karras NA, Weeres M, Sessions W, et al. A randomized trial of one versus two doses of influenza vaccine after allogeneic transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2013; 19:109–116.

Table 1

Selected Factors that influence late infections after HCT

Factor		References
Age	Higher incidence of late fungal infections in older patients	9
Preparative regimen	Fewer early infections with non-myeloablative (NMA) vs myeloablative conditioning (MAC) Higher infection rate with total body irradiation (TBI)	5, 10
T cell depletion	More CMV and Aspergillus seen with T cell depletion in MUD	7
Peripheral blood (PBSC) vs bone marrow (BM)	Higher incidence of infection over 2 years with BM	8
Alternative donors	High incidence of infection in recipients of mismatched unrelated donor (MMUD) and umbilical cord blood (UCB)	11
Chronic graft versus host disease (cGVHD)	In many studies cGVHD turns out to be the only independent risk factor for severe infection	107
CMV infection	CMV seropositivity and reactivation has been associated with delayed immune reconstitution and increased infectious mortality	10, 12, 13
Post-HCT rituximab	Patients treated with pre-emptive rituximab for EBV reactivation had increased late infections	14

Table 2

Determinants of late immune recovery after HCT:

Factor	Study Characteristics, time period, subject numbers	Findings in Children	Findings in Adults	Reference
Age	≥18 months, n=71, T-cell depletion, related or URD	Majority had normal numbers by 6–12 months	Majority had CD4 < 200/ul for 12–18 months.	40
	≥5 years Chronic GVHD and age affect immune reconstitution		Low CD4+ CD45RA+ T cells up to 5 years. The number of CD4+ CD45RA+ cells in 10–19- year old patients > 40– 49-year-old patients	41
	18–36 months Majority T-cell depleted	No data	TRECSs recovered during the second year in adults.	42
Source of graft and TCD				
CD34+ selected vs unmanipulated	≥ 2 years, n=40, Autologous, Multiple Myeloma, unmanipulated or CD34+ selected		At 2 years, No difference in CD4 and CD8 numbers; in the CD34-selected group, TRECs > than both baseline TRECs and unselected group-TRECs	43
T cell depletion	18–36 months Majority T-cell depleted (127/158)	TREC from T cell depleted catch up at 9 months (all ages) as high as healthy controls	TREC from T cell depleted catch up at 9 months (all ages) as high as healthy controls; no later observations	42
PBMC vs. CD34+ vs BM	13–18 months n=32 *Higher numbers of Long-term survivors (>12 Months-4y) among patients with CD8+ above 5th and the 50th percentile of age-matched normal levels.*	No difference in CD4+CD45RA+ and CD +CD45RA+ between the 3 groups after 13–18 months		44
Cord Blood	Dual UCB vs MSD vs MUD n=95		No difference in T cell numbers at 1 year	45
Preparative regimen RIC vs MA, NMA, RIC	NMA vs MA-ASCT n=66		No difference in T cell numbers at 1 year	46

Table 3

Measurement of Immune Function Late after HCT

Test	What is evaluated	What we have learned about Outcomes from use of the test	References
ALC	Early lymphoid recovery ALC > .2 × 10(9) cells/L	Higher OS and PFS	130, 37
Donor:recipient chimerism (whole blood)	Availability of donor cells		
T cell phenotyping for CD3/CD4/CD8	Anti-viral and fungal immunity	Early reconstitution of $CD4^+$ $CD8^+$ T cells correlated with overall survival (OS), non- relapse mortality. and improved progression- free survival (PFS).	131
B cell phenotyping for CD19+ B cells	Ability to respond to vaccines		
NK phenotyping for CD56+ and CD16+ NK cells	Early viral immunity		
Immunoglobulin IgG, IgA, IgM	General B cell functional reconstitution		
Specific antibody evaluations Tetanus Diphtheria Pertussis Measles, Mumps Rubella	Memory T and B cell function post HCT		132
RBC pit counts	Splenic function	Decreased immunity of encapsulated organisms can result in rapid overwhelming sepsis	133–135
Specific response to neoantigens • HPV - peptide • Pneumococcus–polysaccharide	Ability of Naïve T cells and B cell to respond to an antigen		132, 136
Dendritic cell phenotyping	Overall evaluation of immune function	Higher numbers of myeloid DC associated with improved PFS	45, 87
Donor:recipient chimerism (T cell, B cells, myeloid, and dendritic cell)	More complete evaluation of donor immunity	If incomplete myeloid chimerism, can affect T and B cell repertoire. Incomplete B cell chimerism can affect immune repsonses to viral antigens	
Tregs and TR1 cells, Bregs, NKregs	Evaluation of regulatory function	Associated with immune tolerance and suppression of GvHD	83, 848586
Memory/CM/EM T cells			
Allergy testing if donor has known allergies	Evaluation of transfer of allergies from the donor	Significant allergies can be transferred to recipients from donors resulting and severe reactions	87

Table 4

Vaccination Strategy

Goal	Current variables	Recommendation
Vaccination is universal:	What vaccines can be given when still receiving immunosuppression?	The effects of GVHD and use of corticosteroids and ATG remain unclear
	How do post-HCT therapies like anti-B cell monoclonal antibodies, CAR-T cells, tyrosine kinase inhibitors, proteasome inhibitors affect ability to respond to vaccines?	These variables need to be included in the clinically annotated data that will accompany proposed immune reconstitution studies.
	Do vaccine responses need to be measured routinely or can responses be assumed?	Future vaccine studies need to incorporate post-vaccination titers so that if responses are shown to be near universal then practice guidelines could assume protection without measuring responses or identify subgroups in which it is important.
	Can pediatric combination vaccines (e.g. Pediarix = DTaP/IPV/HepB) be used conveniently and cost-effectively in adults	Among centers with good research infrastructure that give Pediarix versus separate Tdap/Td/Td, IPV and Hep B, it could be beneficial to retrospectively compare the response rates.
	Functional (i.e chronic GVHD) and/or surgical asplenia	Try to move from a pragmatic schedule that starts with conjugate vaccines (Hib, PCV13, MCV4) by studying vaccine responses in this important high-risk subgroup.
Killed organism	How early post-HCT can a successful immune response be obtained from vaccination? Data supporting early vaccination is strongest for the conjugate vaccines in matched sibling BMT without significant hypogammaglobulinemia or severe chronic GVHD	Studies have not adequately addressed different stem cell sources, variations in HLA-match, conditioning regimens and GVHD activity, hypogammaglobulinemia and this needs to be studied prospectively.
	Should seasonal influenza vaccination differ from other vaccination policy; specifically how early after HCT can flu shots be given? One study found 2 doses of flu vaccine (vs. standard 1 dose) did not enhance response and, response rates were double among recipients > 1 y vs <1 y post-HCT [165].	Consensus guidelines advise giving the flu shot from 6 months post-HCT and to giving earlier during influenza outbreaks but evidence to support these recommendations is lacking. Additional studies are needed to confirm that post-HCT recipients do not benefit from 2 shots or higher dose influenza vaccine. Quadrivalent versus high-dose trivalent needs to be studied.
	Do CD4, CD19 cell counts, IgG, IgA and IgM levels or IViG therapy influence administration of vaccines? Receiving IVIG for hypogammaglobulinemia might be a surrogate for delayed immune reconstitution.	We need to study how levels of basic numeric immune reconstitution (CD4, CD19, IgG, IgA, IgM) influence when to vaccinate because existing guidelines don't adequately address this for the wide range of HCT scenarios.
Select live organism vaccines	When should MMR, or Varicella vaccine be given?	There is only scant evidence to support consensus guidelines that advise at least 2 years post-HCT and long enough off immunosuppressive therapy that resumption of immunosuppression is unlikely.