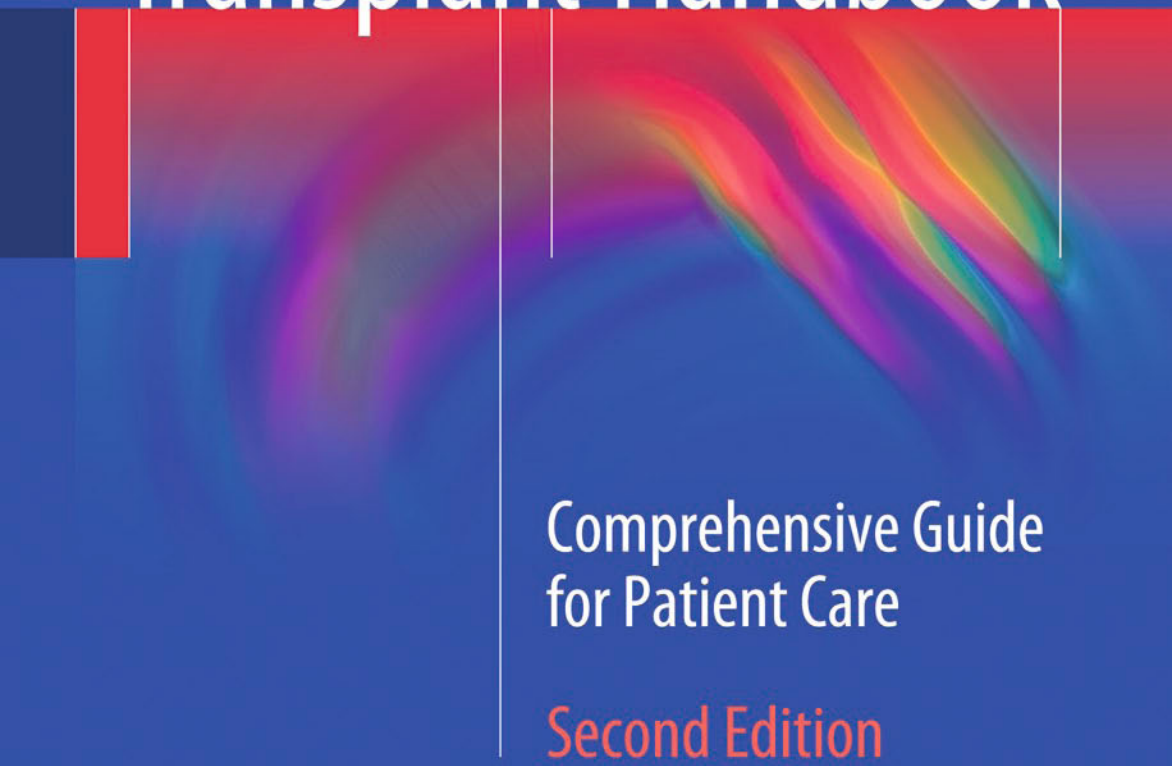
Richard T. Maziarz
Susan Slater *Editors*

Blood and Marrow Transplant Handbook



Comprehensive Guide for Patient Care

Second Edition

Springer

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Richard T. Maziarz • Susan Schubach Slater
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Introduction and Acknowledgments

Hematopoietic stem cell transplantation has experienced a dramatic increase of activity over the past decade with a continued marked escalation of procedures projected over the next 10–15 years. This expansion is not only a reflection of an ever-changing field with increasing demand but also the pursuit of innovation that contributes to continued improved outcomes with less risk of adverse events or deleterious long-term consequences for the transplant patient population. Cellular therapy is a dynamic field. It requires multispecialty input for the management of these complex patients. In the past, transplantation was the sole responsibility of a few academic centers and information resided within the hands of a few individuals. However, with the dissemination of technology and the ongoing proliferation of these procedures, there has been an obligatory need for the development of tools to provide standard guidelines and algorithms for the management of patients.

Most institutions have established their own set of guidelines and recommendations designed for consensus management as patients are in constant need of shared care. As new workforce demands have emerged, there have been changes in the workplace with ongoing predictions of a marked shortage of transplant-trained physicians, advanced practice providers, nurses, and pharmacists. Efforts to recruit health care providers to this field are paramount to continue to provide day-to-day care of the transplant patient. In light of these changes, it becomes imperative to provide detailed and shared consensus guidelines to achieve the best outcomes for our patients.

This guide to patient management is the product of 20 years of evolution of patient care at our institution. Wherever possible, the information herein has been altered to reflect the multiple options that exist for treatment of various conditions. However, *it is not meant to define the exact care pathway for all patients*. Rather, we have provided a practical set of guidelines that can be shared across institutions. This effort is our contribution to the workforce shortage for transplant providers. By providing an easy-to-use manual that covers the basics of care of the stem cell transplant patient which can be utilized to educate junior faculty, physician assistants, nurse practitioners, residents, fellows, and other providers that may be recruited to the day-to-day care of the patient, we have achieved our goal. As this second edition demonstrates, this pocket guide remains a work in progress, and we anticipate that

as time passes, even potentially quite quickly, a new set of guidelines will need to be generated.

We recognize that this manual is incomplete. We do not discuss graft engineering or stem cell expansion approaches to any great degree. We are not addressing the nuances of haploidentical transplantation or other therapies that remain in clinical trial development and are only now emerging into the clinical arena. Nor are we talking about regeneration medicine, its futures, and its overlap with hematopoietic stem cell transplantation. Rather, we provide information about standards of care and assimilate knowledge gained from others.

The work presented within this volume represents not the work of a few but the work of many. A number of our authors were members of the team that helped to create our institution-specific consensus guidelines. We have also recruited new members to assist in generating these ever changing set of standards. We wish to thank the many contributors, as well as our mentors and colleagues who have inspired us to pursue this field and who have provided us with the energy to make this contribution. Their contributions to our program cannot be underestimated. In addition, we thank our team of dedicated nurses, social workers, CMAs, CNAs, physical therapists, nutrition specialists and all providers that are present at the patients' bedside. We also thank our collaborating community partners: referring physicians, advanced practice providers and nurse coordinators. Finally, we acknowledge the national and international efforts focused on improving patient outcomes through organizations such as ASBMT, EBMT, NMDP, BMT CTN, FACT, JACIE, ISCT, AABB, CBMTG, APBMT, WBMT, SBTMO, and others. Through collaboration and shared information, we hope to assure the best outcome of our patients as they return to their communities across the country.

Richard T. Maziarz
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Part I
The Nuts and Bolts of Stem Cell Transplantation

Chapter 1
Overview of Hematopoietic Stem Cell Transplantation

Richard T. Maziarz

Hematopoietic stem cell transplantation (HSCT) is currently a standard-of-care procedure for many disorders. Frequently, HSCT procedures are curative in situations where no other curative treatment options exist. Specifically, the key element in HSCT as a therapy is the replacement of the host (recipient) marrow function by another source of hematopoietic stem cells (HSC). These sources could include HSC collected from the patient (autologous) or from another individual (allogeneic). Allogeneic sources include family-related or unrelated products, collected either directly from healthy donors or cryopreserved stem cell products, including umbilical cord blood. A few rare patients have a syngeneic (identical twin) donor. In the setting of allogeneic HSCT, products are preferentially matched at major histocompatibility complex (MHC) human leukocyte antigen (HLA) class I and II molecules located on chromosome 6, which guide immunologic recognition as self or nonself. Advances in immunogenetics and immunobiology, conditioning regimens, disease characterization and risk stratification, immune suppression, antimicrobials, and other types of supportive care have all contributed to improvements in disease control and overall survival. These outcomes have resulted in a marked increase in the number of procedures performed annually worldwide. However, it is critical to always recognize that HSCT requires substantial resources. Thus delivering this therapy requires large multidisciplinary teams of nursing, pharmacists, physicians, social workers, nurse practitioners, physician assistants, nutrition experts, and occupational and physical therapists, in addition to specialized facility and technical resources.

HSCT has been developed over the past 50–60 years since the first human clinical experimental transplants were performed in the 1950s. One of the earliest curative allogeneic bone marrow HSCT procedures transplant was performed in a young child with immune deficiency syndrome in 1968. By the early 1980s,

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bone marrow transplantation was no longer considered experimental but as the standard of care for a variety of disorders including acute and chronic leukemia, aplastic anemia, lymphoma, multiple myeloma, and a number of inherited disorders including severe combined immune deficiency, thalassemia, and other inborn errors of metabolism. With this recognition, the utilization of this procedure rapidly increased to the current state where over 50,000 procedures are performed worldwide each year as estimated by the Center for International Blood and Marrow Transplant Research (CIBMTR).

1.1 Key Principles

1. Bone marrow stem cells are capable of repopulating all hematopoietic and lymphocytic populations while maintaining capacity for self-regeneration, assuring long-term immunologic and hematopoietic viability.
2. Allogeneic HSCT achieves two goals: replacement of host HSC pools after conditioning and establishment of the donor immune system, either by expansion of naïve immune progenitors or by adoptive transfer of mature donor immune cells.
3. Treatment of nonmalignant disorders is directed at stem cell or immune system replacement while the treatment of malignant disorders requires both replacement of an underlying stem cell or immune system and eradication of malignancy.
4. The decision to use high-dose myeloablative chemoradiotherapy is based upon the identification of malignancies that (a) have a therapy sensitivity threshold that can be overcome and/or (b) have a short enough doubling time to allow the greatest number of malignant cells to be impacted by the conditioning regimen.
5. Conditioning agents whose dose-limiting toxicity is hematologic in nature are primarily selected for myeloablative chemotherapy.
6. Organ-specific toxicities can be experienced and represent “collateral damage” of myeloablative chemoradiotherapy, thus necessitating the need for evaluation of organ function reserve prior to HSCT.
7. The benefits of autologous HSCT are dependent upon dose escalation of conditioning regimens.
8. Graft-versus-host disease (GVHD) after allogeneic HSCT may be a consequence of the transfer of a competent donor immune system that recognizes host target antigens.
9. Prophylaxis for GVHD with immune suppressive medications is warranted in nearly all standard allogeneic HSCT settings.
10. GVHD can be eliminated by depletion of mature T cells from the donor allograft.
11. Depletion of mature T cells from an allograft is associated with an increased risk of relapse of the underlying malignancy.

12. In T cell replete allografts, the occurrence of GVHD has been associated with immunologic-based graft versus leukemia (GVL) therapeutic benefit and can be directly linked to improved survival. As populations of T cells are selectively separated, the relationship may become less linked.
13. The emergence of reduced intensity and nonmyeloablative allogeneic HSCT is the direct result of an effort to maximize the immunologic GVL effect while minimizing risk of regimen-related morbidity and mortality.
14. Patient selection influences outcomes; patients with better overall functional performance status, limited comorbidities and underlying organ damage, and stronger support systems have superior outcomes.

The material included within the following chapters of this patient management handbook provides details that substantiate these principles.

1.2 Research Efforts in HSCT

The success of HSCT has its origins in the research laboratories and clinical research units of many worldwide institutions. The HSCT community has also had the foresight to track outcomes of recipients in center-specific databases and in registry databases, which have been instrumental in providing opportunities for ongoing research. However, it is also recognized that HSCT patients still face significant morbidity and mortality substantiating the continued need for ongoing research. There have been measurable improvements in survival despite the growing number procedures performed in older patients and patients with preexisting comorbidities. However, there remains room for improvement.

Much of the material within this handbook reflects established standards of care of management in the HSCT patient. However, the field demands more. There are many areas of active research including new conditioning regimens, new immune suppressive approaches, vaccines (both prior to and after HSCT) focused at infectious pathogens as well as the primary malignancy, T regulatory cells, new indications for HSCT such as autoimmune disease or sickle cell disease, applications of natural killer cells, novel stem cell mobilization agents, and continued improvement in supportive care. Recently, the American Society for Blood and Marrow Transplant (ASBMT) published a set of research priorities to assist in the focus of attention to those fields that are most likely to lead to continued development of hematopoietic cellular therapy.

These include:

1. Stem cell biology
    a. Cell manipulation
    b. Stem cell sources
    c. Inducible pluripotent stem cells
    d. Cancer stem cells

2. Tumor relapse
    a. Prevention of and therapy for post-HSCT relapse
    b. Immunotherapy with T cells and dendritic cells
3. GVHD
    a. Separation of GVHD and graft-versus-tumor effects
    b. Immune reconstitution and GVHD
    c. Biomarkers predicting GVHD
    d. Role of regulatory T cells
4. Applying new technology to HSCT
    a. Genomics
    b. Proteomics
    c. Imaging
    d. Markers of immunologic recovery
    e. Phamacogenomics
5. Expanded indications for HSCT
    a. Solid tumors
    b. Regenerative medicine
    c. Autoimmune disease
    d. Response to bioterrorism in radiation accidents
6. Survivorship
    a. Long-term complications
    b. Longevity
    c. Quality of life
7. Transplants in older patients
    a. Biology of aging
    b. Indications for transplant
    c. Outcomes and quality of life
8. Improving current use of HSCT
    a. Graft sources
    b. Conditioning intensity
    c. Cost effectiveness

1.3 Horizons/Challenges

HSCT remains an ever-changing field. As described briefly above, these technologies have been applied to thousands of people within dozens of countries. The success of the varied research initiatives will extend these applications to a greater

degree. Currently, the National Marrow Donor Program (NMDP) projects the number of unrelated HSCT procedures to double over the next five years, from current levels of nearly 6000 annually to over 10,000 by 2020. This growth has been multifactorial and is impacted by broader indications, improved supportive care, changing age demographics with increased incidence of cancers reported, and improved survivorship of patients with cardiovascular disease.

With these predictions, one must also be aware that the development of molecular therapeutics may lead to an alternate future. Much of cancer therapy research today is focused on the "personalized" medicine approach in which small molecules that target the multiple signaling pathways might convert life-threatening malignancies to truly chronic diseases. The impact of imatinib mesylate (Gleevec®) on HSCT for chronic myeloid leukemia (CML) is a prime example. Recognizing that the vast majority of patients with CML do not proceed to early HSCT and the prevalence of CML in the general population has increased, patients who now undergo HSCT are those with advanced or resistant disease. Despite this observation, HSCT outcomes for patients with CML remain excellent. Additionally, data are emerging that aggressive pretreatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) with tyrosine kinase inhibitors (TKI) has actually led to improved outcomes after allogeneic HSCT. Similar observations with autologous HSCT for multiple myeloma have been made. The use of imides and proteasome inhibitors pre-HSCT and as maintenance therapy post-HSCT has led to marked improvements in progression-free survival and, in some studies, observations of improved overall survival. Active studies addressing the role of TKI oral therapy as adjuncts to HSCT for treatment of FLT3-ITD+ acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) are planned and/or underway. As a result, comparative effectiveness and outcomes research will remain essential as we compare HSCT therapies to these new options. The availability of registry databases has been vital for these analyses and will remain critical for the future.

It is not just small molecule therapy that has driven the personalized medicine efforts. One cannot underestimate the potential impact that will emerge from graft engineering efforts in immune mediated therapies. Both humoral and cellular immune systems are being exploited. Bi-specific antibodies and genetically modified T cells are actively being studied, either as a bridge to HSCT or for relapse after HSCT. The resounding success of small institutional investigator-initiated studies of chimeric antigen receptor-modified T cells (CAR-T) used for relapsed/refractory ALL and CLL have launched large multicenter, industry sponsored, as well as National Institutes of Health (NIH)-sponsored clinical trials to further explore these treatments in hematologic malignancies and multiple other disease settings.

However, we must be aware that the increased numbers of patients undergoing HSCT, as well as the observed improvement in survival, will lead to a greater demand for specialists in the field of HSCT. Not only are the patients who undergo HSCT in need of specialized providers, the rapidly expanding population of survivors, particularly those with chronic GVHD, have difficulty finding a medical home with their primary care providers or referring medical oncologists. One potential future is that the comprehensive care delivery systems developed for HSCT patients that resemble a medical home may become a model for other specialties. These

care delivery systems have evolved from capitated-risk contracts for HSCT patients and reflect the need for the mixed team of providers including HSCT physicians, advanced practice providers, nurses, social workers, and cell-processing laboratory technologists along with medical specialty assistance from infectious diseases, critical care, gastroenterology, etc. This evolution of care may become the model for survivor management.

A recent analysis suggested that within the very near future, that there will be a significant shortfall in physicians trained and focused on the care of HSCT patients. Thus, new paradigms must be developed for the delivery of care to the HSCT survivor, including expansion of the advanced practice provider workforce of physician assistants and nurse practitioners, as well as active recruitment of new trainees in the field of hematology and medical oncology. Most importantly, training programs and generation of training tools must be established for a new specialty of primary care providers focused on delivery of chronic care to the cancer survivor. Such a training curriculum for HSCT providers has been developed by the American Society of Blood and Marrow Transplantation (ASBMT) and is available through the ASBMT website (ASBMT.org).

This handbook of blood and marrow HSCT provides the background for medical providers to manage the HSCT recipient. Guidelines are provided for evaluating and selecting the appropriate transplant candidate, recognizing that medical but also socioeconomic factors influence outcomes. Detailed descriptions of appropriate pre-HSCT conditioning as well as identification of key prophylaxis strategies to avoid complications are provided. Supportive care efforts are critical, including appropriate selection of blood products, maintaining nutritional and functional abilities, as well as identifying the appropriate follow-up care for the recipient to minimize complications. However, consequences of the immunologic and chemoradiotherapeutic interventions are expected, and we have provided immediate hands-on, what to do, treatment recommendations for the provider. Finally, information on management of the long-term survivor as well as those that experienced post-HSCT relapse is included.

Management of the HSCT patient has never been accomplished as the effort of a sole individual. There is a saying that “It takes a village to raise a child,” allegedly attributed to an old African proverb. Similarly, a very large and extensive professional community has developed to care for the individual patients. The ASBMT and the European Group for Blood and Marrow Transplantation (EBMT) are two large societies focused at providing the research and educational forums to further the field and have sponsored the two principal professional journals of our field, *Biology of Blood and Marrow Transplantation* and *Bone Marrow Transplantation,* respectively. However, they are not alone. The American Society of Hematology, the NMDP (“Be the Match”), and the Foundation for Accreditation of Cell Therapy (FACT) all have instructional websites and literature that support the efforts. The National Heart, Lung and Blood Institute (NHLBI) and National Cancer Institute-funded Blood and Marrow Transplant Clinical Trial Network (BMT CTN) was created to facilitate the generation of multicenter, transplant-focused trials for the advancement of the field. These professional societies and groups represent our village.

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Chapter 2
The Business of Cellular Therapy and Hematopoietic Stem Cell Transplantation

Peggy Appel and Richard T. Maziarz

Hematopoietic stem cell transplantation (HSCT) is extremely complex and expensive, requiring significant personnel, pharmaceutical, supportive, and patient/family resources. Classically, after achieving primary disease control, the first step in HSCT involves high doses of chemotherapy and/or radiation in an attempt to eradicate residual disease. The subsequent infusion of the stem cell product leads to hematopoietic and immunologic recovery, of which the latter may often require months to years to achieve.

The first transplant procedures were successfully performed more than 40 years ago. As indications multiplied and transplant-related mortality declined, HSCT utilization expanded with a dramatic increase in the number of both autologous and allogeneic procedures performed over the past decade (see Fig. 2.1).

HSCT has demonstrated efficacy for the treatment of selected malignancies (e.g., multiple myeloma, acute and chronic leukemia, lymphoma), as well as for immunodeficiency, bone marrow failure, and infiltrative disorders such as amyloidosis. The development of reduced intensity-conditioning regimens has allowed successful treatment of older patients and those with comorbidities that would deem them ineligible for myeloablative therapy (see Fig. 2.2).

Finally, the expansion beyond human leukocyte antigen (HLA)-identical sibling allogeneic HSCT to unrelated donor transplants as well as alternative donors, including unrelated cord blood transplants and related haploidentical donors, has resulted in donor availability for nearly all patients in need.

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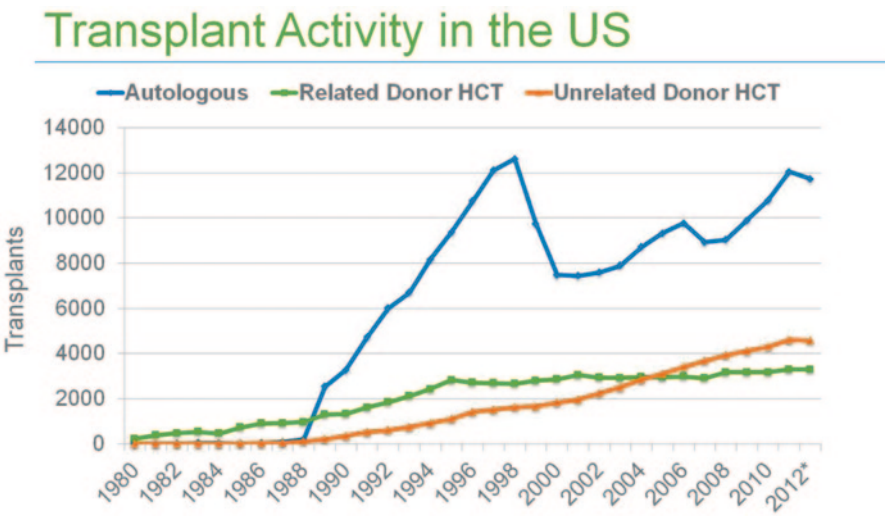

Fig. 2.1 Estimated annual numbers of transplants in the USA were compiled according to the number registered with CIBMTR. Estimates of how closely the numbers reported are representative of actual transplant activity vary according to the type of transplant and number of centers reporting data per year. Prior to 2007, all except unrelated donor allogeneic transplant facilitated by the NMDP were reported voluntarily. It was estimated that the CIBMTR captured 90 % of all unrelated donor transplants performed in the USA, 60–90 % of related donor allogeneic transplants and 65–75 % of autologous transplants. These estimates were extrapolated from other databases that capture transplant center activity, accreditation, or hospital discharges. After 2007, the Stem Cell Transplant Outcomes Database (SCTOD) was initiated which changed reporting requirements and data capture to an electronic format. The SCTOD requires that all allogeneic transplants performed in the USA be registered with CIBMTR. Data reporting of autologous transplants remains voluntary and the numbers in the CIBMTR database are estimated to be 80 %. US numbers of allogeneic transplants in the CIBMTR are representative of the actual transplant activity. The number of autologous transplants in the USA has steadily increased since 2000, mainly for treatment of plasma cell and lymphoproliferative disorders. The ongoing increase of autologous transplants is likely related to a higher number of patients older than 60 years being performed nationwide. Allogeneic transplants from unrelated donors surpassed the number of allogeneic transplants from related donors after 2006 and the gap between these two types of approaches continues to widen annually. The major contributing factors to this trend are the growth of unrelated donor databases, improvements in unrelated donor transplant, and increase in numbers of allogeneic transplants for patient older than 60 years with reduced intensity conditioning. (Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2013. Available at: http://www.cibmtr.org)

2.1 Increase in Utilization and Impact of HSCT on National Health-Care Costs

The amplification in numbers of HSCT procedures has been associated with a dramatic increase in overall costs. Utilization of unrelated cord blood products has further impacted expenditure, as those patients generally experience slower hematopoietic and immunologic recovery, requiring increased resource utilization.

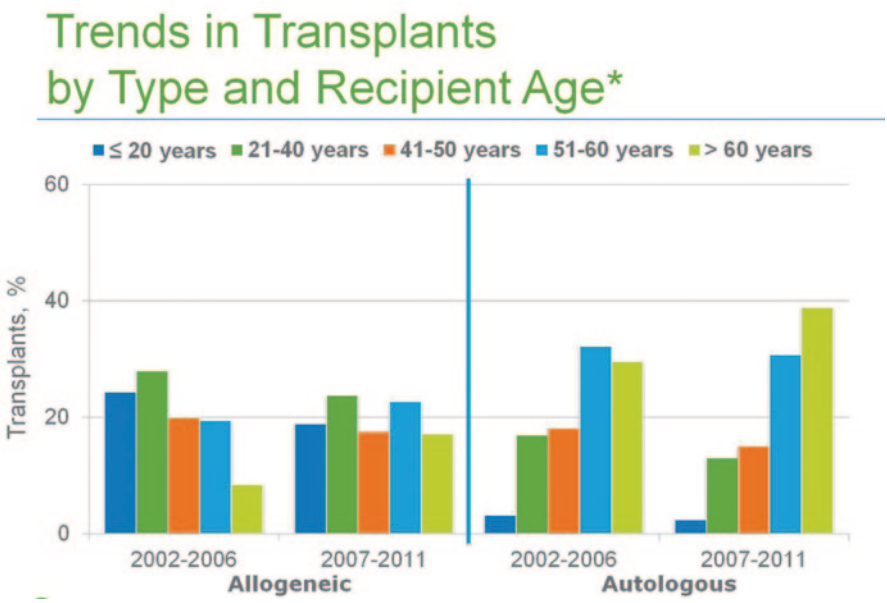

Fig. 2.2 The number of autologous and allogeneic transplants for treatment of malignant diseases in older patients continue to increase. Thirty-nine percent of autologous transplant recipients and 17% of allogeneic transplant recipients in 2007–2011 were older than 60. The majority of autologous transplant recipients (70%) and 40% of allogeneic transplant recipient were older than 50 in this later period. Among allogeneic transplant recipients, the proportion of patients older than 60 years doubled from 8% to 17% during the decade analyzed. (Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2013. Available at: http://www.cibmtr.org)

The improved survivorship of cancer patients has been confirmed as recently reported by the National Cancer Institute (NCI). Annual expenditures on cancer have also increased in the USA with cancer-care costs estimated at US $ 124.6 billion in 2010, of which, the transplantable malignancy of lymphoma was #3 and leukemia was #6 in expenditure by disease sites. Costs are estimated to exceed US $ 160 billion by 2020. The increase in HSCT utilization was substantiated in a recent report from the Agency for Healthcare Research and Quality (AHRQ) of an analysis performed by the Healthcare Cost and Utilization Project (HCUP) of the Nationwide Inpatient Sample, a database of hospitalization and inpatient stays, representative of all short-term, nonfederal hospitals. For activity between January 2004 and December 2007, it was shown that the HSCT procedure was ranked highest in percentage increase for commonly performed inpatient procedures for hospital costs (84.9%) and for total hospital stays (51.3%) with approximate costs of US $ 1.28 billion in 2007 (Table 2.1). Recognizing that the HSCT procedure represented approximately 1% of total hospital stays, 4.4% of the total costs were encumbered for HSCT.

This rapid increase in HSCT procedures took place in a 48-month interval within the past decade. However, these numbers are a small fraction of what is currently projected for the near future. Based on population demographics and surveillance,

Table 2.1 AHRQ analysis of medical and surgical procedures with increased utilization in the USA. Commonly performed procedures with the most rapidly increasing hospital inpatient costs, 2004–2007. (AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 2004 and 2007)

Principal procedure category	Total costs (2007) (US $)	Total hospital stays (2007)	Percentage change	
			Total costs (2004–2007) (%)	Total hospital stays (2004–2007) (%)
Bone marrow transplant	1,282,645,000	15,100	84.9	51.3
Open prostatectomy	1,032,016,000	88,500	68.6	40.8
Aortic resection; replacement or anastomosis	1,872,908,000	61,600	38.5	31.9
Cancer chemotherapy	2,616,504,000	187,400	33.2	14.2
Spinal fusion	8,863,922,000	350,700	29.5	15.6
Lobectomy or pneumonectomy	1,757,748,000	81,400	29.2	24.9
Incision and drainage, skin and subcutaneous tissue	1,108,187,000	158,600	28.6	31.5
Arthroplasty knee	9,217,740,000	605,200	27.5	25.7
Nephrotomy and nephrostomy	682,609,000	38,600	25.3	11.7
Mastectomy	660,173,000	70,100	23.8	3.6
Total for top 10 procedures[a]	*29,094,452,000*	*1,657,100*	*32.3*	*22.2*

[a] 2004 costs were adjusted to 2007 dollars using the overall consumer price index

epidemiology, and end results (SEER) data for the incidence and prevalence of malignancies, the National Marrow Donor Program (NMDP) anticipates a doubling of the current number of unrelated transplants performed (~5500 in 2011) as early as 2015 (estimated as high as 12,500 procedures). They also predict a concomitant 30% increase in autologous HSCT.

These reports from the HCUP and the NMDP are supported by the Milliman 2011 US Organ and Tissue Transplant Cost Estimates and Discussion report. The analysis suggests that there was a 110% increase in billed charges for allogeneic HSCT between 2003 and 2008. The estimates were based on billed charges (recognizing that charges do not equate to cost of procedures nor do charges indicate what percent of charges are paid by the governmental or private payer). Autologous transplant charges increased from approximately US $ 205,000 to US $ 370,000, and allogeneic transplant charges increased from approximately US $ 380,000 to US $ 805,000 in this short period of time. Also, recognizing that approximately 20,000 procedures were performed, these individual numbers suggest that transplantation may become a US $ 10 billion industry.

2.2 Complexity of Care Increases Costs

In the setting of increasing demand for HSCT and increasing cost of health care and novel technologies, it remains critical for providers and health systems to assure that adequate reimbursement is obtained to cover the costs of the individual procedures, costs associated with the defined incident of care, and the potential associated with medical complications and sequelae.

Reimbursement based on a fee-for-service indemnity approach no longer exists for the vast majority of patients. Insurance carriers have developed case rate contacts for HSCT with negotiated payments for pretransplant evaluation, HLA typing, transplant product acquisition, and patient care. In contrast, government payers (Medicaid and Medicare) have set reimbursement schedules:

1. Medicare coverage provides funding for a period of time surrounding the actual transplant procedure, typically in a diagnosis-related group (DRG)-based reimbursement structure.
2. It is important to recognize that DRG payments are provided with the presumption of a predictable resource consumption encountered by the recipient.
3. In some instances, the payer does not differentiate between autologous, allogeneic-related, and allogeneic-unrelated transplant in their rate-setting process:
    a. This approach ignores the greater complexity of workup, cell source selection, and post-treatment risk of complications for the allogeneic recipient.
4. Preexisting comorbidities as well as the disease state and donor type drive resource consumption. These variables, seen across the spectrum of patients for whom transplant services are provided, are not accounted for by the limited DRG codes.

Contractual arrangements with private/commercial payers will often carve out HSCT services from general medical services contracts:

1. Services related to HSCT will often have a bundled payment for all services performed within a boundary of time around the transplant, usually covering the first 30 days for an autologous and 100 days for an allogeneic HCST procedure.
2. These contracts should be designed to cover:
    a. Recipient evaluation and assessment of transplant eligibility
    b. Donor search benefits
    c. Harvest and acquisition of stem cell product
    d. The immediate peri-transplant period and the post-transplant phase
    e. Special circumstances (preplanned second transplant procedure, donor leukocyte infusion, retransplants, high-cost pharmaceuticals (e.g., plerixafor)

2.3 Contracts and Reimbursement Strategies

If structured appropriately, contracts should reflect mutual exposure to financial risk. Reimbursement methodologies vary in the degree to which financial risk is shared.

One of the confounding issues that those involved in the care of the transplant patient face is that the actual transplant procedure is generally an infusion that occurs at a precise moment in the midst of a complicated medical treatment course. The infusion defines the actual transplant. However, reimbursement usually is focused on providing coverage for that event and for a series of surrounding days, which defines an episode of care. Various reimbursement methodologies have been undertaken, including reimbursement of:

1. All charges generated by providers and health systems in care of an HSCT patient
2. A discount of charges which actually represents a fixed rate percent, discounting total billed charges
3. A case rate, which incorporates a fixed fee that covers all transplant-related hospital or clinic services for a specified period of time, predating and following the actual infusion event
4. A global case rate which represents a fixed fee that covers all hospital and physician charges for a specified period of time, typically involving post-transplant care

Recognizing the unique needs of individual patients, many of the case rate and global case rate methodologies will include provisions that protect the transplant center as well as the payer from financial risk. These provisions vary in the degree of financial protection they provide. Examples include:

1. *Outlier days*, which provide a per diem reimbursement for each inpatient day beyond a well-defined post-infusion time period
2. An *outlier threshold* which reimburses the provider and institutions a defined percentage of billed charges after a specified threshold beyond the case rate has been reached
3. A *floor provision* which assures that at no time will a hospital be reimbursed less than a specific percent of billed charges

The setting in which the HSCT procedure is performed, i.e., inpatient or outpatient, may influence reimbursement. Pharmaceuticals may be reimbursed at a higher level per dollar of charge in the outpatient setting. The differences in reimbursement based on setting can have a significant impact on the financial performance of the HSCT program.

2.4 Integrated Structure for Contract Management

The complexity of contracting for HSCT services is reinforced by the implementation of separate transplant specialty contracting personnel by hospitals and payers. Development of rate structures that support the center's strategic initiatives, monitoring of the center's performance on each contract, and providing assistance to patients in understanding their benefits as they relate to the contract require an integrated team approach:

1. A typical team for contract management would include:
    a. Managed care contracting
    b. HCST program medical director
    c. HSCT program administrator
    d. Patient billing services
    e. Financial counseling personnel
    f. Program's managed care clinical liaison/coordinator:
        i. Review of patient referral insurance information
        ii. Review of patients' benefits:
            - Lifetime maximum
            - Transplant maximum
            - Prescription coverage
        iii. Communication with patient regarding benefits
        iv. Liaison with insurance company in communication of patients' status in the process
    g. Medical social worker

2.5 Payer Types

Understanding reimbursement variability between governmental and private payers is a necessity. Traditionally, since HSCT was performed in younger patients, private payers dominated the health coverage. However, over the last half decade, there has been a significant change in the payer mix with an increase in patients with governmental insurance support (Medicare or Medicaid).

According to transplant center estimates, as many as 25–30 % of their patients were supported by governmental payers in 2012, an increase from previous estimates of approximately 15 % in 2007. This shift in payer mix can have a dramatic impact on transplant program financial viability, given the low average rates of reimbursement by Medicare and state Medicaid programs.

1. Affordable Care Act:
    a. The Patient Protection and Affordable Care Act (ACA) was signed into law on March 23, 2010 and could add more than 30 million Americans to the insured ranks by 2019.
    b. The intent of the law is to increase access while reducing the overall cost of health care.
    c. Patients who have had or who will need an HSCT should benefit from expanded access to affordable insurance options and the removal of long-standing benefit and coverage restrictions as provided under the ACA.
    d. Prior to the enactment and implementation of the ACA, HSCT patients seeking new insurance coverage faced the potential of a lack of insurers willing to insure them, limited benefit insurance plans with high premiums, and/or preexisting condition exclusions of HSCT-related costs.
    e. The ACA assures access to health insurance for HSCT patients in the following ways:
        i. A requirement that anyone eligible for insurance cannot be denied coverage.
        ii. Prevents insurers from rescinding coverage when diagnosed with an illness or condition.
        iii. Elimination of lifetime dollar limits on total paid benefits.
        iv. Annual dollar limits are allowed only in a more restricted manner, specifically for services not covered by the definition of the essential health benefits (EHB). While there is not a specific mention of HSCT as an EHB at the federal level, the components of the HSCT process all fall into covered categories.
        v. Removal of preexisting condition exclusions.
    f. In addition to access, the other significant principle of the ACA is an overall reduction in health-care spending, particularly in the Medicare program:
        i. The expected impact on transplant centers is uncertain but will likely be significant, given that Medicare eligible patients are the fastest growing segment of allogeneic HSCTs.
        ii. The elimination of lifetime, annual, and procedural financial caps and removal of preexisting condition exclusions could influence third-party reimbursement strategies.
    g. In conjunction with the ACA, the delivery of patient care by coordinated care organizations (CCOs) and accountable care organizations (ACOs) is focused on managing populations and efficient delivery of primary care. Hematology and oncology patients could be viewed differently by hospital systems as the resource consumption by these patients would be significant, based on current pricing of many cancer therapeutics and procedures.

h. Transplant centers should consider how to prepare for new models of payment bundling, pay-for-quality programs, and an increased focus on cost-effectiveness and value from all payer types.

    i. Transplant centers will be under pressure to document quality of care to avoid penalties and/or earn incentives.

2. Medicare services

a. Federal governmental payers are predominantly guided by Medicare coverage decisions.
b. Medicare coverage will be limited to items and services that are determined to be covered and within the scope of a Medicare benefit category.
c. HSCT is a procedure for which Medicare has developed a national coverage determination, and the coverage information is available to all online within the Medicare coverage database.
d. Medicare's two-midnight rule for inpatient admissions:

    i. As of October 1, 2013, Centers for Medicare & Medicaid Services (CMS) finalized a new way to identify/determine appropriate inpatient admissions: A patient admission is presumed to be an appropriate inpatient admission for purposes of a Medicare severity-diagnosis-related group (MS-DRG) payment when there is the expectation that the patient will require a stay for more than two midnights.
    ii. If the stay is expected to last fewer than two midnights, it generally would not be appropriate for an inpatient hospital admission.
    iii. An inpatient admission may be justified based on patient's medical history, comorbidities, severity of signs and symptoms, current medical needs, and the risk/probability of an adverse event occurring during the hospitalization period.
    iv. With reduced intensity regimens, transplant programs are able to treat certain Medicare patients mostly in the outpatient setting and admit them only for the cell infusion.
    v. Since patients can react differently, some may stay more than two midnights, while others may not, and it is often not known at the time of admission what the patients' clinical course will be. *Should a program change how care is provided*?
    vi. Page 50,945 of the final rule states: "…when it is difficult to make a reasonable prediction, the physician should not admit the beneficiary but should place the beneficiary in observation as an outpatient. As new information becomes available, the physician must then reassess the beneficiary to determine if discharge is possible or if it is evident that an inpatient stay is required."
    vii. This ruling has implications for reimbursement of donor search and product acquisition charges:

- Donor search and product acquisition fees are tied to the inpatient DRG payment for the transplant procedure and are not included in the daily incident of care ambulatory payment classification (APC) reimbursement used for outpatient services.

viii. In addition, reimbursement for Medicare day patients is considerably less than the average inpatient DRG rate for this procedure.
ix. Patient out-of-pocket expenses are also affected by a day-patient stay.

3. Medicaid services:

a. At the state level, there is wide variation in Medicaid reimbursement and coverage for HSCT:

i. There may be limitations based on indications for HSCT, maximal allowable inpatient stays, and medication support, as well as variation in inpatient or outpatient service provision.
ii. Clinical trial coverage variability also can be dramatically different:

- HSCT is not a mandatory covered benefit for adults, and all states have the discretion to choose whether to provide coverage or to determine the extent of coverage.
- In austere times, states may identify control of Medicaid costs as a means to reduce their deficits and balance their budgets.
- Recent data released by HCUP demonstrated that Medicaid coverage was provided to 3064 HSCT hospitalizations or 16 % of all discharges for HSCT in the USA in 2010.
  A recent analysis of the Medicaid programs in 47 states by the NMDP, assessing the degree of recommended benefit support which included transplant procedure and disease indications, donor search, medications, clinical trial support, and transportation and lodging, was unable to identify any state that provided minimal coverage benefits in all five categories and identified only three states that met minimum supports level in four of the five categories. Eight states had perceived adequate Medicaid support coverage in only one of the five categories.

b. The ACA mandated that all states must expand coverage under Medicaid to individuals up to 133 % of the federal poverty level (FPL) and provided federal funding to cover the cost of increased coverage:

i. The US Supreme Court declared that this requirement was unconstitutional and that each state had the right to decide whether or not to implement this provision. As a result, the extent of Medicaid coverage is to be determined on a state-by-state basis.

c. Expanded Medicaid will have both positive and negative repercussions for patients and HSCT programs:

   i. Increased access to coverage will mean more patients have HSCT as a treatment option, but this expansion does not improve the quality of benefits or the reimbursement rates associated with state Medicaid plans.
   ii. An increase in Medicaid patients with these less-than-ideal coverage provisions would predict an increased burden on already-limited transplant center resources.

4. Private payers:

   a. Private payers also have significant variability in aspects of HSCT coverage.
   b. Private payers often follow Medicare guidelines for coverage determinations for HSCT indications. However, significant variability within contractual agreements for reimbursement structures, donor search and acquisition, benefit packages, clinical trial coverage, and financial procedural or lifetime benefits are found.
   c. Coverage for the HSCT patient is generally not an issue of medical necessity, but a detailed contractual agreement between the insurance beneficiary, the payer, and the site of employment from which the group insurance has been elected:

      i. It is recognized that currently, for many payers, the majority of their members are in plans that are self-funded employer plans, for which benefits are individually selected by the employing company.
      ii. As a means to control costs, one could envision that selection of high cost benefits for what would be perceived as orphan diseases might fail to be elected.
      iii. Additionally, many small payer companies will have reinsurers who have their own set of contracted language, defining benefits for these high cost procedures (https://payor.bethematchclinical.org/WorkArea/DownloadAsset.aspx?id=7501).

   d. Detailed and specialized review of the recipient's insurance contract is necessary for comprehension of the benefit package.

5. Centers of excellence:

   a. Many of the larger private insurance and reinsurance companies have established center of excellence criteria and established national transplant networks.
   b. These programs may vary in size depending on the number of lives insured, the geographic regions covered by those insured, and the type of HSCT procedure offered.
   c. For the transplant center, participation in these "Center of Excellence" programs and national transplant networks may allow access to greater numbers of patients:

      i. Participation is often based on meeting selection criteria which is typically generated by a center's volume and outcome data.

ii. Selection of a network requires submission of detailed program information, disease-specific outcomes often with on-site inspection of facilities and review of program standards, as well as renewable review of outcome data over time.
iii. This payer requirement can be a challenge for individual patients if the Center of Excellence is not geographically close, as they will need to relocate themselves and at least have a caregiver family member's house near the transplant center for an extended period of time. This additional financial burden may or may not be reimbursed by the insurance company.

2.6 Quality

High-quality outcomes for HSCT patients have always been a goal of transplant providers and their teams. Determination of quality was often performed internally to evaluate systems and elements that could influence the HSCT product line and service delivery. Increasingly, there has been national attention on outcomes necessary to maintain eligibility within third-party payers' network facilities and, more recently, for governmental payer reimbursement. For instance, CMS has implemented a reimbursement program based on "value-based purchasing" in which a percentage of hospital reimbursement for CMS patients is held at risk while determining whether or not the hospital has met target goals for optimal patient experience and whether clinical measures are achieved. For HSCT programs, the incidence of catheter-associated bloodstream infections, readmissions, or falls with harm can negatively influence the reimbursement of services.

The establishment of a public, national Stem Cell Therapeutic Outcomes Database (SCTOD) for patients undergoing allogeneic blood, cord, and marrow transplant procedures was a component of the C.W. Bill Young Cell Transplantation Act. This allowed for assessment and comparison of inter-institutional overall mortality outcomes and procedural risk. Consistent with Center for International Blood and Marrow Transplant Research's (CIBMTR) goal to increase transparency of the Center Outcomes Report and at the urging of the Health Resources and Services Administration (HSRA), CIBMTR has made available unblinded center-specific outcomes reports (www.bethematch.org/access).

Comparative risk assessment based on patient pretransplant comorbidities and standardized determinations of severity of illness for the transplant stay, generated by evaluating the discharge diagnostic codes, are being utilized by groups such as the University Health Care Consortium (UHC). Available data are used to compare length of stay, percent of intensive care unit transfers, and observed-to-expected in-hospital mortality between member organizations. It is anticipated that quality initiatives will be increasingly scrutinized with a major focus on survival, quality of life, and presence or absence of clinical comorbidities. Efficient healthcare delivery via care pathways will also be examined, and their utilization will increasingly influence reimbursement, as well as maintaining Center of Excellence designation:

1. Foundation for the Accreditation of Cellular Therapies (FACT):
    a. FACT accreditation, which addresses clinical care, donor management, cell collection, cell processing, and cell administration, is voluntary. However, it has become an almost necessary qualification for a program to be acknowledged and remains competitive.
    b. Many insurers, Centers of Excellence programs, and national transplant networks include FACT accreditation as a requirement for selection/inclusion.
    c. Accreditation is awarded after successful documentation of compliance with FACT standards. Compliance is judged by evaluation of written documentation and through on-site inspections.
2. Data management:
    a. A transplant program's data management enterprise supports compliance with regulatory standards, internal assessment of quality and quality improvement initiatives, and research development.
    b. HSCT programs are expected to contribute data regarding transplant procedures to the NMDP, CIBMTR, SCTOD, or similar data repositories. These data are then available for research purposes on outcomes.
3. The Food and Drug Administration (FDA):
    a. The FDA's mission is to protect the public health.
    b. In May of 2005, the FDA created a registration system for establishments that collect, manipulate, and manufacture cellular therapy products:
        i. The registration system was created to establish procedures to prevent the introduction, transmission, and spread of communicable disease by cellular therapy products.
        ii. HSCT programs are required to register and submit a list of all types of cellular therapy products collected or infused in their institution. The registration must be updated annually.
    c. The FDA requires documentation of complaints involving the distribution of cellular therapy products that allege transmission of a communicable disease to the recipient of the product.
    d. Enforcement of the registration and reporting requirements is accomplished by FDA inspections.

2.7 Clinical Trials

The evolution of the HSCT field over the last 30 years has been marked by advances in basic, translational, and clinical science. Clinical trials have been instrumental in determining the efficacy of HSCT. Catalyzing the science of transplantation in the USA was the collaboration between the National Heart, Lung, and Blood Institute and the National Cancer Institute that led to the foundation of the Blood and Marrow Transplant Clinical Trials Network (BMTCTN). More than 5000 patients

have now been enrolled in BMTCTN trials including many who have participated in advanced phase III trials, defining new standards of care in the field. Additionally, most transplant centers contribute HSCT patient outcome data to the CIBMTR which has served as a central resource for retrospective analyses, answering questions that otherwise would not be answered in single-center prospective trials.

It is essential for a transplant program to verify that coverage is available for clinical trial participation. Wide variation exists with regard to coverage of clinical trial participation between governmental and nongovernmental payers:

1. CMS has a list of determined and nondetermined diagnoses for coverage. There are no preauthorization pathways. If one chooses to offer a transplant procedure for a disorder in which there are no determinations, reimbursement after the fact will be at the discretion of the local Medicare intermediary.
2. Additionally, Medicare does not provide support for participation in phase I toxicity trials unless there are clear secondary efficacy endpoints.
3. In contrast, Medicaid programs will determine at a state level whether clinical trials are supported and to what extent.
4. With private payers, coverage of clinical trials has become even more complex:
    a. Many of the national payers have provisions that if clinical trials are supported by the NIH, coverage is provided. Thus, funding would be provided if the recipient receives care at an NCI-designated cancer center or participates in a cancer intergroup or in a BMTCTN clinical trial.
    b. Participating in industry-sponsored clinical research trials or investigator-initiated research often requires strict scrutiny to verify that study-specific costs are not passed on to the payer, and that only designated standard of care coverage is the responsibility of the payer.
    c. The clinical trials' landscape becomes even more complex as many of the group health plans are self-funded, business-selected plans:
        i. Even when HSCT is considered standard care, if a portion of the care (e.g., choice of a prophylactic antifungal agent) is considered research, the entire transplant episode may be denied.
        ii. Often clinical trials are omitted from the selection of benefits of coverage for employees.
        iii. Recently, the National Business Group on Health (NBGH), in collaboration with the National Comprehensive Cancer Network, has published documents for review and implementation by employers outlining recommended benefits packages for cancer prevention and treatment among their employees.
5. Under the ACA, coverage for routine costs associated with an approved clinical trial will be required beginning in January 2014:
    a. Routine costs are defined as all aspects of care outside of the investigational drug, item, or procedure itself.
    b. Clinical trials must be approved or sponsored by the NIH, the Center for Disease Control and Prevention (CDC), AHRQ, and CMS.

   c. Trials may be any phase (I–IV) and must be conducted in relation to the prevention, detection, or treatment of cancer or other life-threatening disease or condition.

6. Transplant centers will need to provide clear communication to payers regarding the justification for the trial, the eligibility of the patient, and the portions of the treatment plan that are routine or investigational.

2.8 Future Considerations

HSCT procedures will continue to grow in demand as outcomes improve, novel therapeutic indications are identified, and the US population ages. New technologic advances in cellular therapy will continue to emerge. It is likely that some of the investigational cellular products, including dendritic cells, regulatory T cells, natural killer cells, mesenchymal stromal cells, chimeric antigen receptor-modified T cells (CAR-T), and viral-specific cloned T cells, will prove to be beneficial in the clinical course of the transplant patient. Similarly, the advances in small molecules and targeted therapies could diminish the demand for HSCT or, alternatively, could enhance the likelihood of improved outcomes, thus furthering the demand for procedures. Re-examination of reimbursement strategies, particularly regarding the contractual arrangements around an "incident of care," will be necessary to assure that the cost of goods and manufacturing of these novel therapies are included within the transplant patient benefit package.

Similarly, the demand for HSCT procedures may further expand if new indications emerge, such as autoimmune disorders or cotransplantation with solid organs.

On recognizing these potential advancements, it is also important to maintain awareness that, currently, demand within the USA for HSCT is not being met. The NMDP has recently performed a study of geographic market saturation within the USA, assessing actual allogeneic HSCT procedures versus the calculated demand (with recognition that there were limitations in the model). Their analysis suggested there may remain a significant number of patients for whom procedures could be performed and who are not yet in a position to access these services.

2.9 Summary

1. Well-designed prospective clinical trials and retrospective data analyses have provided the critical data that led to the designation of HSCT as standard of care for a variety of malignant and nonmalignant disorders.
2. The demand for evidence-based medicine will continue as will the demand for quality outcomes with efficiency in delivery. Coverage decisions will depend on whether evidence exists to justify the support. Ongoing attention to detail for

services rendered is necessary to identify whether or not payment is adequate and justified.
3. Multi-institutional comparison of outcomes will continue and will be expanded to determine if the services supported by private or governmental payers were delivered with high quality.
4. Additionally, one can anticipate that assuring that both patients and providers have all the information needed to make accurate decisions will be demanded as transparency has become central.
5. The need for more flexible models of reimbursement is required, as the current approach where contractual rules supersede medical necessity generally does not keep up with the technologic advances driving the field.
6. Recognition of these issues and the critical need for collaborative interactions between providers and health-care systems will be needed to continue to manage the HSCT patient population, going forward.

The ability to maintain and expand an HSCT program requires the efforts of a specialized business team to develop, implement, and manage contracts; personnel knowledgeable of the most current regulatory standards and data reporting requirements; and a clinical team dedicated to the critical ongoing communication with the referring physician. This partnership is critical to the promotion of long-term survivorship for the HSCT patient.

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Chapter 3
Hematopoietic Stem Cell Sources and Donor Selection

Jose F. Leis

3.1 Introduction

1. Human hematopoietic stem cells (HSC) express CD34 and Thy-1 (lo) on their surface and are capable of multi-lineage growth and supporting long-term hematopoiesis.
2. HSC can be isolated from bone marrow (BM), peripheral blood after mobilization (PBSC), and umbilical cord blood (UCB).
3. HSC may be obtained from autologous (BM or PBSC) or allogeneic (HLA-matched related (MRD), HLA-matched unrelated (MUD), or mismatched related or unrelated donors, and UCB) sources.
4. Bone Marrow Donors Worldwide (www.bmdw.org) maintains an international inventory of the majority of available adult unrelated donors and cord blood units. Seventy-one stem cell donor registries from 51 countries and 48 cord blood banks from 32 countries participate. As of late 2013, an estimated 22 million adult donors and 600,000 cord units are available.

3.2 Stem Cell Sources

1. Bone marrow:
   a. Gold standard for more than three decades
   b. Aspirated from posterior iliac crest under general or regional anesthesia
   c. Generally requires 10–20 ml/kg of marrow for adult recipients
   d. Donors can be primed with filgrastim prior to harvest which may improve HSC recovery in heavily pretreated patients

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e. Advantages:
   i. Fewer T cells in graft compared with PB source
      - Decreased risk of chronic graft-versus-host disease (GVHD)
   ii. Decreased mortality in children and adolescents
f. Disadvantages:
   i. Requires operating room and spinal or general anesthesia
   ii. Increased morbidity to donors:
      - Potential risks include pain, infection, blood loss, nerve damage.
      - May require blood transfusions for young pediatric donors.
   iii. Slower neutrophil and platelet engraftment
   iv. Increased risk of relapse in some studies
g. Target cell dose:
   i. Target cell dose 2×10^8 total mononuclear cells (TMNC)/kg recipient body weight
   ii. Minimum 1×10^8 TMNC/kg recipient body weight
   iii. Retrospective studies show better hematopoietic recovery, decreased treatment-related mortality (TRM), and improved overall survival (OS) when CD34 cell dose $> 3 \times 10^6$/kg

3.3 Peripheral Blood

1. Under normal circumstances, HSC are found in very low levels in PB:
   a. Thousandfold or more increase in circulating HSC seen after filgrastim stimulation or recovery from cytotoxic chemotherapy
   b. Has largely replaced BM as primary source of HSC
2. Advantages:
   a. Rapid recovery of hematopoiesis compared to BM
   b. Decreased morbidity to donors
   c. Increased disease-free survival (DFS) and OS in high-risk hematologic malignancies
3. Disadvantages:
   a. Must mobilize stem cells into circulation:
      i. Use of chemotherapy in autologous setting
      ii. High-dose filgrastim, sargramostim, +/− plerixafor (currently autologous setting only)

b. More T cells in circulation compared with BM:

i. Increased risk of chronic GVHD in the allogeneic setting

4. Target cell dose:

a. Minimum 2×10^6 CD34+ stem cells/kg recipient body weight
b. Target $3–5 \times 10^6$ CD34+ stem cells/kg recipient body weight, although this varies by institution
c. Doses $> 8 \times 10^6$ CD34+ stem cells/kg associated with increased risk of GVHD and decreased OS in some allogeneic transplant studies

5. Mobilization:

a. Autologous transplant:

i. Disease-specific chemotherapy followed by filgrastim at 10 μg/kg/day SC until PB CD34 count increases above institutional target levels, e.g., > 10 cells/μl before the onset of leukapheresis
ii. Filgrastim at 10 μg/kg/day SC for 4 days followed by leukapheresis on day 5
iii. Filgrastim at 10 μg/kg/day SC for 4 days in the morning + plerixafor 0.24 mg/kg SC (maximum dose 40 mg) in the evening on day 4
iv. Plerixafor (Mozobil®):

- Reversibly inhibits binding of SDF-1α, expressed on BM stromal cells, to the CXC chemokine receptor 4 (CXCR4), resulting in mobilization of HSC and progenitor cells from BM to the PB.
- Reduce dose to 0.16 mg/kg (max 27 mg) if estimated glomerular filtration rate (GFR) < 50 ml/min using the Cockroft–Gault equation.
- FDA approval in the autologous setting for patients with multiple myeloma and non-Hodgkin lymphoma. Currently not approved for allogeneic donors.

b. Factors associated with poor mobilization:

i. Prior chemotherapy: increased cycles and duration of treatment
ii. Prior radiation to BM
iii. Low pre-mobilization platelet count
iv. Female gender
v. Exposure to purine analogues, e.g., fludarabine
vi. Exposure to alkylating agents, e.g., prior melphalan in myeloma
vii. Exposure to lenalidomide
viii. BM involvement by lymphoma
ix. Low PB CD34 count during mobilization
x. PB CD34 count is proportional to CD34 apheresis yield
xi. PB CD34 < 10 cells/μl associated with mobilization failure

c. Strategies for the hard-to-mobilize patient:

i. BID dosing of filgrastim at 5–10 μg/kg/day SC for 4 days, then leukapheresis

ii. Double growth factor: BID dosing of filgrastim at 5–10 μg/kg SC plus sargramostim at 250 mg/m^2 once daily for 4 days, then leukapheresis
iii. High-dose filgrastim + plerixafor
iv. BM harvest

d. Risk-adapted approach by Mayo Clinic:

i. Start filgrastim alone at 10 μg/kg/day
ii. If day 4 or 5 PB CD34 < 10/μl, initiate leukapheresis the following day
iii. If day 5 PB CD34 < 10/μl, add plerixafor 0.24 mg/kg evening dose (dose adjusted for renal function), initiate leukapheresis the following morning
iv. If daily leukapheresis yield < 0.5×10^6 CD34/kg, repeat plerixafor and continue leukapheresis the following day
v. Continue daily filgrastim and plerixafor until goal is reached or STOP if < 0.5×10^6 CD34/kg collected despite use of plerixafor

3.4 Umbilical Cord Blood

1. High number of fetal HSC are present in UCB collected after delivery.
2. Each year, no suitable related or unrelated donor (URD) can be identified for 6–10,000 patients who could potentially benefit from an HSC transplant. This deficiency is particularly true for minority patients.
3. Typically, cord blood units are typed at intermediate resolution for HLA-A and HLA-B, and at high-resolution for HLA-DR.
4. Advantages:

a. Criteria for a "match"-less stringent:

i. 4/6 match acceptable
ii. Increases chance of finding a suitable donor

b. UCB lymphocytes are less alloreactive
c. Allows for greater HLA-disparity, can engraft with 4/6 match
d. Less GVHD for degree of mismatch
e. Rapid access: suitable cord unit can be identified in a few days and shipped overnight

6. Disadvantages:

a. Cell dose:

i. Need minimum of 3–4 × 10^7 total nucleated cells (TNC)/kg to ensure durable engraftment
ii. Only 10 % of UCB units have sufficient stem cells to transplant a patient > 50 kg in weight
iii. Increased nonrelapse mortality to 70 % in < 1.7×10^7 TNC/kg

b. Slow engraftment relative to related or URD BM or PBSC transplants.
c. Increased infectious complications from slow neutrophil engraftment.
d. No donor leukocyte infusion (DLI) available for the treatment of relapse or graft failure.
e. Currently, limited inventory is available.

7. Impact of cell dose:

a. Slow rate of hematopoietic recovery
b. High risk of graft rejection
c. High TRM
d. Poor OS if low dose
e. Magnified effect of HLA mismatch

8. Choosing the best cord unit (EuroCord recommendations):

a. 6/6 match $> 3 \times 10^7$ TNC/kg.
b. 5/6 match $> 4 \times 10^7$ TNC/kg.
c. 4/6 match $> 5 \times 10^7$ TNC/kg.
d. Do not perform single-unit UCB transplant with $< 4/6$ match or $< 3 \times 10^7$ TNC/kg.

9. Strategies to improve UCB transplant in adults:

a. Double UCB unit grafts to augment cell dose.
b. Most patients have more than one 4–6/6 HLA-matched UCB unit available.
c. Adult studies suggest improved engraftment and reduced TRM compared with single unit transplants.
d. Sustained engraftment seen from only one of the two units, not both.
e. Experimental approaches for *ex vivo* expansion are currently under investigation.

3.5 Donor Selection

1. HLA typing (see Fig. 3.1):

a. HLA is the name of the set of genes on chromosome 6 that encode the major histocompatibility complex (MHC) in humans.
b. HLA genes are highly polymorphic.
c. Each HLA allele is designated by the name of the gene/locus followed by an asterisk and a four- to eight-digit number indicating the allele. The first two numbers are based on the serologic type of the resultant protein "antigen" and the next two numbers on the specific allele designation based on the order in which the gene was discovered, e.g., A*0201 is an allele of the HLA-A2 gene.
d. HLA antigens are key components of immune function and are involved in recognizing self versus nonself, in organ or graft rejection, GVHD, infection control, autoimmunity, etc.

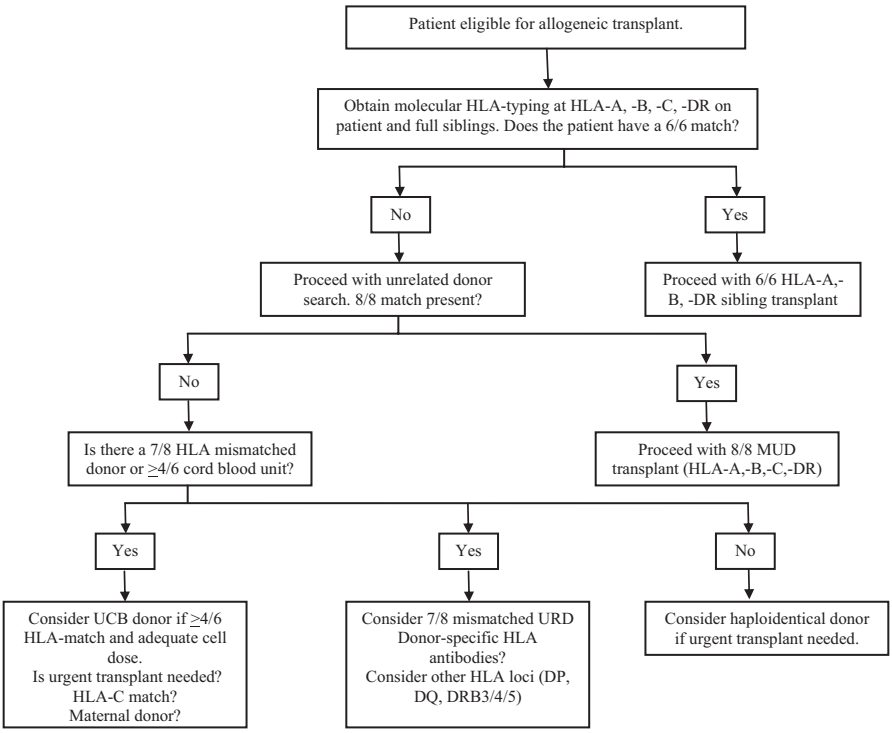

Fig. 3.1 Suggested algorithm for hematopoietic stem cell donor selection. *MUD* matched unrelated donor, *UCB* umbilical cord blood, *URD* unrelated donor

e. HLA class I molecules (HLA-A, HLA-B, HLA-C) are found on the surface of all nucleated cells.
f. HLA class II molecules (HLA-DR, HLA-DQ, HLA-DP) are found on the surface of immune system cells, i.e., B lymphocytes, dendritic/antigen presenting cells, and are inducible in most tissues.
g. Matching donor and recipient for HLA haplotypes is the most important factor of a successful allogeneic hematopoietic cell transplant.

2. Matched related donors

a. Twenty-five percent chance a given sibling will be HLA-matched at A, B, and DR loci
b. Preferred stem cell source over other donor sources
c. Associated with lower rates of acute and chronic GVHD
d. More rapid and less expensive donor workup and stem cell procurement
e. Improved clinical outcomes
f. Despite improvements in outcomes (TRM, relapse-free, and OS) of URD transplants, MRD are still favored in patients > 50 years of age:

1. Risks of acute GVHD grade 2–4 (hazard ratio (HR), 1.63; $P < 0.001$), acute GVHD grade 3–4 (HR 1.85; $P < 0.001$), and chronic GVHD (HR 1.48;

$P < 0.0001$) were all higher after MUD compared with MRD transplants in these older patients.

g. Higher risk of relapse of malignancy (AML, CML > ALL) if donor is an identical twin (syngeneic).

3. Matched unrelated donors

a. Only 30% of patients who require an allogeneic HSCT will have an HLA-MRD.
b. Large number of donors are needed in registries due to the large diversity in the HLA system (> 5500 class I alleles and > 1600 class II alleles resulting in millions of HLA combinations).
c. Certain racial and ethnic groups (e.g., African Americans are more polymorphic than Caucasians at HLA loci) have a large number of specific haplotypes and have more difficulty in finding suitable donors.
d. Identification of a suitable MUD can take 2–6 months.
e. The longer search times make MUD HSCT less feasible for high-risk leukemias. Donor searches should be started early in the treatment course of these diseases.
f. Each HLA antigen or allele mismatch is associated with approximately a 10% decrease in 5-year post-transplant survival. In a large retrospective study of 3857 myeloablative BM transplants done between 1988 and 2003 in the USA, a single mismatch detected by low- or high-resolution DNA testing at HLA-A, -B, -C, or DRB1 (7/8 match) was associated with higher mortality, lower 1-year OS 43 versus 52%, lower DFS, increased TRM, and acute GVHD. Single mismatches at HLA-B and -C were better tolerated than mismatches at HLA-A or DRB1. Mismatching at two or more loci increased the risks while mismatches at HLA-DP or DQ and other donor characteristics did not affect survival.
g. Retrospective analysis of 1933 unrelated donor–recipient pairs that received PBSC HSCT between 1999 and 2006 showed that an 8/8 match was associated with better 1-year survival than a 7/8 match (56% vs. 47%). Mismatch at HLA-C antigen correlated with decreased leukemia-free survival (LFS) and increased risk of mortality, TRM, and grade 3-4 acute GVHD.
h. Other donor factors such as age, sex, parity, cytomegalovirus (CMV) status, ABO matching may have weak effects on outcome.

4. Alternative donors:
Alternative donor sources (UCB or haploidentical donors) allow for shorter time to transplant but are associated with increased risk of transplant-related complications:

a. Haploidentical donors
b. Related haploidentical donors are matched at three of six loci (HLA-A, -B, -DR) sharing one chromosome 6 with the recipient.
c. Multiple individuals in a family including parents, siblings, and even children can potentially serve as the donor.

d. Increased donor availability in racial and ethnic groups.
e. Intensive GVHD prophylaxis is necessary. In one international study, ATG, cyclosporin, methotrexate, mycophenolate, and anti-CD25 antibody were utilized. Cumulative incidence of grade 2-4 acute GVHD was 24% (5% grade 3-4) and extensive chronic GVHD was 6% at 2 years. OS was estimated at 45% at 3 years.
f. Immunosuppression with post-transplant cyclophosphamide is emerging as a standard haploidentical GVHD prophylactic strategy with acceptable outcomes.
g. The BMT-CTN conducted two parallel phase II trials for patients without HLA-matched donors. Reduced intensity conditioning (RIC) with post-transplant cyclophosphamide was used, followed by either double UCB (BMT-CTN 0602; see Sect. 4.b.11) or haploidentical BM (BMT-CTN 0603). The 1-year OS and progression-free survival (PFS) were 62 and 48%, respectively, 100-day incidence of acute grade 2-4 GVHD 32%, 1-year incidence of NRM 7% and relapse 45% after haploidentical transplant. A prospective phase III trial comparing double UCB and haploidentical transplantation is underway (BMT-CTN 1101).
h. Mismatch of maternal antigens is better tolerated than mismatch of paternal antigens. Leukemia patients, who received myeloablative conditioning followed by T-cell depleted haploidentical maternal grafts, had superior 5-year event-free survival (EFS) than those who received paternal grafts (50.6 vs. 11.1%; $P<0.001$). Improved survival was the result of lower relapse rates and TRM. The protective effect was seen in both female and male recipients.

5. Umbilical Cord Blood:

a. Demand for UCB HSCT has increased rapidly due to lack of suitable HLA-matched donors, particularly in ethnic groups, time limitations due to aggressive disease, and the potential lower incidence of GVHD.
b. Advantages include expanded donor pool, ease of product procurement, lack of donor attrition, donor safety, and decreased incidence of GVHD.
c. Major disadvantages include delayed engraftment, prolonged defects in immune reconstitution, increased risk of graft failure, no opportunity for additional donations, and increased risk of infection.
d. In children with malignancy, HSCT with UCB units matched for 4/6, 5/6, or 6/6 HLA haplotypes produces results that are equal to an 8/8 HLA-matched BM HSCT.
e. Potential UCB units should be selected on the basis of greatest HLA-match that contains an adequate TNC count. Acceptable UCB units should contain $\geq 3\times10^7$ nucleated cells/kg and also, preferentially $\geq 2\times10^5$ CD34+cells/kg. In patients transplanted for nonmalignant disease, the risk of rejection is higher and a cutoff of $\geq 3.5\times10^7$ TNC/kg is recommended.
f. In a large retrospective study of adults transplanted for acute leukemia, LFS after UCB HSCT was comparable to 8/8 and 7/8 allele-matched URD PBSC or BM HSCT:

i. TRM was higher after UCB HSCT than after 8/8 allele-matched PBSC (HR 1.62, $P=0.003$) or BM HSCT (HR 1.69, $P=0.003$).
ii. Grades 2-4 acute and chronic GVHD were lower in UCB recipients compared with allele-matched PBSC (HR 0.57, $P=0.002$ and HR 0.38, $P=0.003$, respectively).
iii. The incidence of chronic GVHD was lower after UCB HSCT compared to 8/8 allele-matched BM HSCT (HR 0.63, $P=0.01$).

g. HLA-C matching appears to improve outcomes. In a retrospective analysis of 803 patients with leukemia or myelodysplastic syndrome (MDS), who underwent an unrelated UCB HSCT, patients matched for HLA-A, -B, and -DRB1, but mismatched for HLA-C and had higher TRM than those matched for HLA-C (HR 3.97).
h. Priority should be given to unidirectional mismatches in the GVHD direction; avoid mismatches in the host-versus-graft direction:

i. Unidirectional mismatches in the GVHD direction are associated with significantly earlier time to engraftment.
ii. Unidirectional mismatches in the host-versus-graft direction have delayed time to engraftment, higher rates of graft failure, and higher relapse rates.

i. Increased incidence of infection may account for up to half of the TRM associated with UCB HSCT.
j. A high incidence of infection after neutrophil recovery suggests intrinsic defects in immune reconstitution after UCB HSCT.
k. UCB HSCT after non-myeloablative conditioning is associated with more rapid neutrophil recovery and immune reconstitution.
l. Use of two UCB units (double UCB HSCT (dUCB)) is acceptable for patients who do not have a single unit with adequate cell count:

i. After myeloablative conditioning, transient mixed chimerism may be identified early but is followed by sustained engraftment of only one unit by day 100.
ii. Most studies suggest improved disease control with decreased relapse rate after dUCB HSCT compared to a single unit UCB HSCT:

- Some studies suggest that UCB units should be at least 3/6 HLA-matched to each other in the setting of dUCB HSCT.
- BMT-CTN 0604 (Evaluating the Safety and Effectiveness of an Umbilical Cord Blood Stem Cell Transplant that uses Low Dose Chemotherapy in People with Leukemia or Lymphoma).

  - Demonstrated 1-year probability of OS of 54% and PFS of 46% after a cyclophosphamide/fludarabine/TBI-conditioned dUCB HSCT with a day +100 cumulative incidence of grade 2-4 acute GVHD of 40%.
  - This study has laid the groundwork for CTN 1101 (A Multicenter, Phase III, Randomized Trial of Reduced-Intensity Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood vs. HLA Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies).

6. Single-antigen MRD
    a. Early studies suggest that single HLA-antigen MRD HSCT may lead to increased rates of GVHD, if the mismatch is in the GVHD vector, or increased incidence of graft failure, if the mismatch is in the host-versus-graft vector. There was no significant impact on OS.
    b. A retrospective registry study from Japan compared outcomes in 779 patients with acute leukemia, CML, or MDS who received a 1-antigen MRD versus 8/8 allele URD HSCT:
        i. Higher overall mortality rate was observed in patients who received the MRD graft, particularly in those patients with standard risk disease.
        ii. HLA-B antigen mismatch was associated with lower OS due to increased TRM.

3.6 Other Considerations

1. Donor-specific HLA antibodies:
    a. HLA mismatch should mandate screening for donor-specific HLA antibodies.
    b. Recipient anti-HLA antibodies directed at donor HLA antigens are associated with high graft rejection rates.
    c. Other donors should be pursued in this setting.
2. Donor age:
    a. Initial studies in HSCT performed in the 1990s suggested that younger donors (age < 30 years) were associated with improved DFS and OS and decreased acute and chronic GVHD.
    b. Older matched sibling donors (> age 50) are preferred over 8/8 HLA-matched younger URDs for leukemia/lymphoma patients who are more than the age of 50 years. Risks of acute GVHD grade 2-4 (HR, 1.63; $P < 0.001$), 3-4 (HR, 1.85; $P < 0.001$), and chronic GVHD (HR, 1.48; $P < 0.0001$) were higher after HSCT performed with younger URDs compared with older MSD HSCT.
3. Donor parity:
    a. In a 2001 NMDP study, nulliparous female donors were associated with lower risks for chronic GVHD.
    b. Male donor < nulliparous female donor < female donor with one prior pregnancy < female donor with two + prior pregnancies.
    c. No effect of parity was seen in acute GVHD.
    d. Parity has not been an independent risk factor for OS and DFS in recent studies.
4. CMV status:
    a. CMV seropositive recipients have a lower OS than seronegative recipients.

b. Donor CMV status does not impact survival of either CMV positive or negative recipients.
c. A European group for Blood and Marrow Transplantation (EBMT) study suggested that CMV seropositive recipients should receive cells from CMV seropositive donors, as the adoptive transfer of mature lymphoid cell populations was associated with more rapid development of recipient CMV immunity.

5. ABO status:

a. ABO compatibility between donor and recipient is not necessary for HSCT.
b. A recent meta-analysis demonstrated no adverse association between ABO mismatching and graft failure, GVHD, or survival.

6. Donor screening (see Chap. 4 for additional details):

a. Must be completed to ensure safety of the donor and that the HSC product is safe for the recipient.
b. Medical history questionnaire targets risk factors for transmission of genetic or infectious diseases.
c. Physical exam.
d. Baseline laboratory testing, electrocardiogram (ECG), chest X-ray.
e. Infectious disease testing.

3.7 Donor Complications

1. BM acquisition (harvest):

a. NMDP tracks complications of its donors.
b. Of the first 9245 harvests, 125 donors (1.34 %) experienced a serious medical complication including mechanical injury to tissue, bone, or nerve (55 %), anesthetic complications (36 %), and infection (< 1 %).
c. Pain was the most common symptom with 82 % reporting back or hip pain at the collection site with 33 % reporting anesthesia-related throat pain. Fatigue was reported in 59 %. Site reaction, insomnia, nausea, dizziness, and anorexia were far less common (< 15 %).
d. Transient changes in white blood cells (WBC), platelets, and hemoglobin were observed with most counts returning to baseline by 1 month post harvest. Anemia with a 3-g/dl decrease in hemoglobin was observed in both male and female donors with a mild decrease persisting at 1 month.
e. Marrow harvest appears safe in children with the EBMT, reporting no serious complications in 313 pediatric donors.

2. PBSC donors

a. Serious adverse events were uncommon (0.6 %).
b. In a prospective trial from the NMDP, 6768 PBSC donors who underwent collection between 2004 and 2009 were evaluated:

i. Central venous access was required in 5% of male donors and 21% of female donors.
ii. Leukocytosis with a mean WBC of 40,000/μl and 20% exceeding 50,000/μl was reported.
iii. Thrombocytopenia with platelets < 100,000/μl was seen in 26% of donors after one collection and 50% of donors after two collections.
iv. Musculoskeletal pain which peaked at day 5 of granulocyte colony-stimulating factor (G-CSF) administration was reported in nearly 90% with the majority grade I/II.
v. Other less common symptoms included fatigue (49–50%) and insomnia (30%).
vi. Female donors were more likely to require hospitalization (3 vs. 1%).

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Chapter 4
Pre-transplant Medical Evaluation

Andy Chen

Conventional autologous and allogeneic hematopoietic stem cell transplant (HSCT) can be a life-saving or life-extending procedure but is associated with significant risk for noninfectious and infectious complications. Reduced intensity allogeneic HSCT is often offered to recipients with advanced age and/or significant comorbid clinical conditions. Appropriate identification of recipients likely to benefit from these rigorous procedures is essential. Screening of donors is necessary to identify all potential risk of harm to the donor and to identify potential transmissible illnesses to the recipient.

Referral to a transplant center does not mandate a patient to undergo a transplant procedure. It is the role of the HSCT specialist to determine if transplant should be considered as an option for disease consolidation with final decision to be made in conjunction with the patient and the referral provider team.

4.1 Considerations and/or Indications for Transplant

1. Adult acute myelogenous leukemia (AML; see Tables 4.1 and 4.2):
    a. Complete remission 1 (CR1)—all AML except for good risk
    b. Antecedent hematologic disease
    c. Therapy-related AML
    d. Primary induction failure or relapse
    e. Presence of minimal residual disease after therapy

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Table 4.1 Transplant types by disease

Disease	Autologous	Allogeneic
AML	X	X
ALL	–	X
MDS	–	X
CML	–	X
Lymphoma	X	X
Myeloma	X	X
Germ cell	X	–
Bone marrow failure	–	X
Congenital disorders	–	X

AML acute myeloid leukemia, *ALL* acute lymphoid leukemia, *MDS* myelodysplastic syndrome, *CML* chronic myeloid leukemia

2. Pediatric AML:
    a. CR1—all except good risk
    b. Induction failure or relapse
    c. Monosomy 5 or 7
    d. Age <2 years at diagnosis
    e. Treatment-related AML
    f. Presence of minimal residual disease after therapy
3. Adult acute lymphoblastic leukemia (ALL):
    a. CR1—all except for young adults treated on pediatric protocols (recent data suggest that adults have improved outcomes when treated on highly aggressive pediatric regimens as compared to standard adult treatment regimens)

Table 4.2 Risk stratification for AML

Risk group	Cytogenetics	Molecular markers
Favorable	Inv(16) or t(16;16) t(8;21) t(15;17)	Isolated NPM1 mutation (normal karyotype) Isolated CEBPA mutation (normal karyotype)
Intermediate	Normal +8 only t(9;11) Other abnormalities not defined	c-KIT mutation with core binding factor leukemia
Poor	Complex (≥3 abnormalities) −5, del 5q −7, del 7q 3q21q26 t(6;9) t(9;22) 11q23 abnormalities except t(9;11) 17p abnormalities	FLT3 ITD (normal karyotype)

AML acute myeloid leukemia

b. High risk

i. Ph+t(9;22)
ii. MLL (11q23) rearrangements
iii. High white blood cell (WBC) at diagnosis (>30 K for B cell, >100 K for T cell)

c. Induction failure or relapse
d. Presence of minimal residual disease after therapy

4. Pediatric ALL:

a. High-risk CR1:

i. Ph+t(9;22)
ii. MLL (11q23) rearrangement
iii. Infant
iv. WBC at diagnosis >100 K

b. Induction failure or relapse
c. Presence of minimal residual disease after therapy

5. Myelodysplastic syndrome (MDS):

a. Intermediate or high-risk revised international prognostic staging score (IPSS-R)—see Table 4.3:

Table 4.3 International prognostic staging system for myelodysplasia

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	–	Good	–	Interme-diate	Poor	Very poor
Marrow blast %	≤2%	>2–<5%	–	–	5–10%	>10%	–
Hemoglobin	≥10	–	8–<10	<8	–	–	–
Platelets	≥100	50–<100	<50	–	–	–	–
ANC	≥0.8	<0.8	–	–	–	–	–

ANC absolute neutrophil count

IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤1.5
Low	>1.5–3
Intermediate	>3–4.5
High	>4.5–6
Very high	>6

IPSS-R revised international prognostic scoring system

1. Cytogenetics:
   - Very good: del(11q), -Y
   - Good: normal, del(20q), del(5q) alone and double
   - Intermediate: +8, 7q-, i(17q), +19, +21, any other single or double, independent clones
   - Poor: der(3)q21/q26, -7, double including 7q-, complex (three abnormalities)
   - Very poor: complex (>3 abnormalities)

b. Treatment-related MDS
c. Transfusion dependence or refractory cytopenias

6. Chronic myelogenous leukemia (CML):

a. Chronic phase:

1. Failure to achieve a hematologic or cytogenetic response to either nilotinib (Tasigna®) or dasatinib (Sprycel®)
2. Intolerance to/failure of two tyrosine kinase inhibitors (TKIs)
3. Any T3151 mutation

b. Accelerated phase:

1. Newly diagnosed patients who do not achieve an optimal response to TKIs
2. TKI-treated patients who progress from chronic phase

c. Blast crisis (myeloid or lymphoid)

7. Myeloproliferative disorders (BCR-ABL negative):

a. High-risk cytogenetics
b. Poor initial response or at progression

8. Follicular and low-grade non-Hodgkin's lymphoma (NHL):

a. Less than partial response to initial treatment
b. Initial remission duration < 12 months
c. Second or subsequent relapse
d. Transformation to diffuse large B cell lymphoma (DLBCL)

9. DLBCL and aggressive NHL:

a. First or subsequent relapse
b. No CR with initial treatment
c. CR1 with high-intermediate or high-risk international prognostic index (IPI; see Table 4.4)
d. Double- or triple-hit lymphoma
e. Peripheral T cell lymphoma

10. Mantle cell NHL:

a. Following initial therapy

11. Hodgkin lymphoma:

a. Primary induction failure
b. First or subsequent relapse

Table 4.4 International prognostic index (IPI) for large-cell lymphoma

Risk factors
Age > 60
Performance status > 1
Elevated LDH
Extranodal sites > 1
Stage III–IV

Risk group	Number factors
Low	0–1
Low intermediate	2
High intermediate	3
High	4–5

12. Multiple myeloma:
    a. After initiation of therapy
    b. At first progression
    c. Second transplant for relapsed disease
13. Germ cell cancer:
    a. Refractory to induction
    b. Second or subsequent relapse
14. Neuroblastoma:
    a. Short initial remission
    b. Poor initial response or at progression
15. Bone marrow failure syndromes:
    a. At diagnosis of marrow failure:
        1. Severe aplastic anemia
        2. Fanconi anemia
        3. Pure red cell aplasia
        4. Amegakaryotosis
        5. Paroxysmal nocturnal hemoglobinuria
        6. Other
16. Congenital/inherited immune deficiencies:
    a. At diagnosis:
        1. Severe combined immunodeficiency (SCIDs)
        2. Wiskott–Aldrich syndrome
        3. Familial hemophagocytic lymphohistiocytosis (HLH)
        4. Other

17. Hemoglobinopathies:
    a. Transfusion-dependent thalassemia at diagnosis
    b. Sickle cell disease with aggressive course
18. Inherited metabolic disorders:
    a. At diagnosis:
        1. Hurler's syndrome
        2. Adrenoleukodystrophy
        3. Metachromatic leukodystrophy
        4. Other

4.2 Sources of Hematopoietic Stem Cells

1. Autologous (see Chap. 3):
    a. Peripheral blood
    b. Bone marrow
2. Allogeneic:
    a. Related, unrelated
        1. Well matched (either no identified human leukocyte antigen (HLA) mismatch and informative data at four loci or allele matching at HLA-A, -B, -C and –DRB1)
        2. Partial match (defined, single-locus mismatch determined by high-resolution DNA typing)
        3. Mismatched ($\geq$2 allele or antigen mismatches)
        4. Haploidentical
    b. Peripheral blood, bone marrow, single cord, double cord

4.3 Patient Evaluation

1. History:
    a. Signs/symptoms, pathology, staging, risk stratification, relapses
    b. Treatment history with responses and dates
    c. Complications, both therapy and disease related
    d. Infectious disease history
2. Current disease status (depending on disease type):
    a. PET/CT (positron emission tomography/computed tomography)

   b. Bone marrow biopsy
   c. Tumor markers

3. Allergies and medications (including supplements)
4. Past medical history:

   a. Chronic or serious illnesses and surgeries
   b. Transfusion history
   c. Vaccinations
   d. Menstrual status & pregnancies (if applicable)

5. Family history:

   a. Health status and malignancy history
   b. Potential donors

6. Psychosocial evaluation (see Chap. 5 for additional details):

   a. Caregiver availability
   b. Psychiatric history
   c. Substance abuse
   d. Work and living situation
   e. Travel history
   f. Financial screening and evaluation

7. Systems evaluation:

   a. Dentition
   b. Respiratory, including pulmonary function, tests with diffusion capacity of carbon monoxide (DLCO)
   c. Cardiac including electrocardiogram (EKG) and ejection fraction (see Chap. 23 for additional details)
   d. Hepatic—liver function tests (LFTs)
   e. Renal—electrolytes, blood urea nitrogen (BUN), creatinine
   f. Neurologic—assess for central nervous system involvement if indicated
   g. Hematologic—complete blood count (CBC), blood type (ABO/Rh)

8. Other laboratories/testing:

   a. Pathology review
   b. Pregnancy test (if applicable)
   c. Infectious disease testing:

      1. Required by Foundation for the Accreditation of Cellular Therapy (FACT):

         − HIV-1 and 2, hepatitis B, hepatitis C, syphilis

      2. Recommended (required by some authorities):

         − Cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), human T-lymphotropic virus (HTLV) 1 and 2, West Nile virus, Chagas disease, Toxoplasmosis

Table 4.5 ECOG/WHO performance scale

Score	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care and confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG Eastern Cooperative Oncology Group, *WHO* World Health Organization

3. Selected cases:
   - Tuberculosis—exposure risk
   - Fungus—past history, allogeneic transplant
   - Parasites—exposure risk, travel history

d. HLA typing (for allo candidates):

4. HLA-A, -B, -DRB1 (also -C if unrelated)

9. Performance status (see Tables 4.5 and 4.6)

Table 4.6 Karnofsky performance scale

Score	
100%	Normal, no symptoms or signs of active disease
90%	Able to carry on normal activity, minor signs or symptoms of active disease
80%	Normal activity with effort
70%	Unable to do active work, cares for self
60%	Requires occasional assistance
50%	Requires considerable assistance and frequent medical care
40%	Disabled, needs special care
30%	Hospitalized, death not imminent
20%	Hospitalized, critical condition
10%	Moribund
0	Dead

4.4 General Guidelines for Patient Eligibility

1. Disease meets indication for transplant
2. Chemosensitive disease:
   a. Minimal marrow involvement for autologous transplant
3. Adequate performance status (see above):
   a. Eastern Cooperative Oncology Group (ECOG) ≤2 or Karnofsky ≥70% for conventional ablative regimen
   b. ECOG ≤3 or Karnofsky ≥50% for reduced intensity transplant
4. Adequate non-hematopoietic organ function
   a. Creatinine ≤2× upper limit of normal (ULN) or CrCl ≥50 (except amyloid/myeloma)
   b. Cardiac ejection fraction (EF) ≥40%, no clinically significant indications of heart failure, no uncontrolled arrhythmia
   c. Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and DLCO Adjusted ≥45% predicted
   d. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤3× ULN; total bilirubin ≤2× ULN, unless Gilbert's syndrome
5. Psychosocial:
   a. Ability to provide informed consent
   b. Willing and able to comply with therapy
   c. Available caregiver
   d. Insurance coverage
6. Adequately matched available donor or adequate collection of autologous stem cells (see Chap. 3 for additional details):
   a. Auto collection: minimum $\geq 2 \times 10^6$ CD34+cells/kg (target $\geq 5 \times 10^6$)
   b. Allogeneic matching:
      1. Related: 5–6 of 6 (HLA-A, B, DRB1)
      2. Unrelated: 7–8 of 8 (HLA-A, B, C, DRB1)
      3. Cord: 4–6 of 6 (HLA-A, B, DRB1)
      4. HLA-A mismatching is highest risk
      5. Antigen mismatch is higher risk than allele mismatch
      6. National Marrow Donor Program (NMDP) does not currently recommend the need for matching at HLA-DRB3, 4, 5 or HLA-DQ
7. No active infections require ongoing therapy, except:
   a. Adequately treated fungal infection on chronic suppressive therapy
   b. Prophylactic therapy
   c. HIV positive patients on highly active anti-retroviral therapy (HAART)

8. Exclusion criteria:
    a. Chemorefractory
    b. Life expectancy severely limited by other illness
    c. Inability to tolerate preparative regimen
    d. Pregnancy
9. Relative contraindications:
    a. Major medical comorbidities
    b. Major psychiatric illness
    c. Substance abuse
    d. Lack of insurance/financial resources
    e. Lack of caregiver
10. Hematopoietic cell transplant comorbidity index (see Table 4.7):
    a. Predictor of nonrelapse mortality
    b. Consider reduced intensity regimen if comorbidity index ≥4

Table 4.7 Comorbidity index

Comorbidity	Definition	Points
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmia	1
Cardiac	Coronary artery disease[a], congestive heart failure, myocardial infarction, or EF ≤50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic agents, but not diet alone	1
Cerebrovascular accident	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic—mild	Chronic hepatitis, bilirubin >ULN -1.5×ULN, or AST/ALT >ULN -2.5×ULN	1
Obesity	Body mass index >35 kg/m²	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV1 66–80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in patient's past history, excluding non-melanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3

Table 4.7 (continued)

Comorbidity	Definition	Points
Severe pulmonary	DLCO and/or FEV1 ≤65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 × ULN or AST/ALT > 2.5 × ULN	3

[a] One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft
EF ejection fraction, *ULN* upper limit of normal, *SLE* systemic lupus erythematosis, *RA* rheumatoid arthritis, *CTD* connective tissue disease, *DLCO* diffusion capacity of carbon monoxide, *FEV1* forced expiratory volume in 1 s, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

4.5 Allogeneic Donor Evaluation

1. HLA typing for HLA-A, -B, -DRB1 (also -C if unrelated)
2. History and physical
3. Transmissible disease screen:
    a. Recent vaccinations
    b. Travel outside of the USA
    c. Transfusion history
    d. High-risk history or behaviors
    e. Inherited, hematologic, autoimmune, or malignant conditions
4. Pregnancy history
5. Laboratories
    a. CBC, chemistries, LFTs, coagulation
    b. Blood type and compatibility
    c. Serum pregnancy test (if applicable)
6. Infectious disease:
    a. Required by FACT:
        i. HIV-1/2, HBV, HCV, syphilis
    b. Recommended (required by some authorities):
        ii. CMV, EBV, HSV-1/2, HTLV-1, HTLV-2, VZV, West Nile, Chagas Toxo
7. Consents and notifications
    a. Donor consent for mobilization therapy and possible central venous catheter placement.
    b. Notify prospective donor of abnormal findings.
    c. Document rationale and consent for use of ineligible donor.
    d. Notify apheresis unit of health issues which could affect safety of collection.
    e. To avoid a conflict of interest, the physician consenting the donor should not be the physician of the recipient.

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Chapter 5
Social Work: Evaluation and Support

Nancy Boyle and Keren McCord

Hematopoietic stem cell transplant (HSCT) is a complex treatment that often results in high levels of psychological distress and social/financial strain for patients and their families. The procedure and the ensuing recovery can test even the most adaptive functional patient and support system. Indeed, it is the psychosocial issue that can be the most vexing for transplant teams.

HSCT patients and their support teams require information as well as physical and emotional resources in order to maximize the benefit of the procedure. Each patient brings their past medical, emotional, financial, and personal experiences which impact their ability to tolerate the ardors of transplant.

Five phases of the HSCT process have been described:

1. The decision to undergo HSCT
2. Pre-HSCT preparation
3. HSCT hospitalization
4. Hospital discharge and early recovery
5. Long-term recovery

This chapter focuses on the psychosocial issues along this continuum.

Each patient has a unique diagnosis, staging, and comorbidities that affect his/her journey through transplant. Psychologically, an individual adjusts to each transition utilizing their adaptive to maladaptive coping mechanisms. An early study on "returning to normal" revealed that patients least likely to report return to normalcy were those with unrealistic expectations. While there will be patients who will remain unrealistic, a majority can be assisted by providing realistic information and support.

A patient-centered approach is at the forefront of new accreditation standards for hospital cancer programs released by the Commission on Cancer (CoC) of the

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American College of Surgeons (ACS). Four national cancer patient support/advocacy organizations worked closely with the CoC to develop patient-centered standards to better enable cancer patients to work with their interdisciplinary cancer treatment team: American Cancer Society, Cancer Support Community, National Coalition for Cancer Survivorship, and LIVE**STRONG™**. The CoC includes *Distress Treatment Guidelines for Patients* as a standard to be established for accreditation (http://www.facs.org/cancer/coc/whatis.html).

Distress in pre-HSCT patients was first described in 1995 as demonstrated by scores on the Profile of Mood States Scale. Study results showed that a decreased sense of control (intrapersonal mastery) and decreased sense of optimism were related to a higher level of distress. In a 2005 study, it was identified that pre-transplant distress is highly predictive of post-transplant distress, and there was a statistically significant association between self-reported distress and medication noncompliance. The distress thermometer (DT) with HSCT patients, when studied for validation in comparison to the Center for Epidemiological Studies-Depression Scale (CES-D) and the State–Trait Anxiety Inventory-State Version (STAI-S), showed that the single-item DT compares well with the longer measures to assess psychological distress. The DT cutoff score of four supports significant distress to warrant further assessment, and while the DT is being promoted as a screening tool by the National Comprehensive Cancer Network (NCCN), they suggest a cutoff of five or above for further assessment. Additional study is indicated in the HCST population.

Seven causes of distress in patients who undergo HCST have been identified:

1. Uncertainty regarding treatment outcome, recurrence, and mortality
2. Impact of the treatment on their family
3. Changes in appearance and impact on sexuality
4. Long-term burden of treatment such as reduced functional status
5. Interaction with the medical system
6. Communication with medical personnel and obtaining information
7. Financial considerations, such as insurance coverage, the cost of treatment, and supporting self/family

Although no consensus guidelines regarding psychosocial eligibility for HSCT have been developed, there are data-identifying psychosocial factors associated with pre-HSCT vulnerability that influence outcomes. In a study of HSCT clinicians deciding whether to proceed with transplant given specific psychosocial risk factors, 75 % of responding physicians recommended not to proceed in cases of suicidal ideation, use of illicit drugs, and history of noncompliance. Additionally, 69 % recommended not to proceed in cases where no caregiver support was identified.

Psychosocial issues have been studied in the solid organ transplant population, as these patients require psychosocial evaluation prior to being added to the waiting list. In HSCT, autologous or allogeneic donors are used which also require appropriate psychosocial evaluation. Pretransplant screening for HSCT has borrowed from solid organ transplant in the format of the Psychosocial Assessment of Candidates for Transplant (*PACT*) and Transplant Evaluation Rating Scale (*TERS*).

While transplant programs vary in size and funding, there is value in having a mental health professional assess a patient's ability to withstand the psychological stresses of HSCT, including assessment of preexisting psychiatric morbidities. Individuals with anxiety and depression are at risk for poor health outcomes. Patients who experience overall mood, anxiety, or adjustment disorder have 8% longer lengths of stay.

5.1 Psychosocial Evaluation and Assessment

The key aspects for assessment are the characteristics and needs of the patient, family, and caregiver(s), including financial status, employment/disability, insurance, past/current mental health, and/or substance abuse history, and details about their care plan: who, what, and where.

1. Demographics:
    a. Marital status
    b. Family composition
    c. Current living situation
    d. Developmental stage
    e. Formal education
    f. Legal issues
    g. Children's issues/preparation
2. Employment and financial information:
    a. Employment and/or disability status
    b. Source of income
    c. Primary wage earner
    d. Insurance status
    e. Out-of-pocket obligation
    f. Prescription coverage
    g. Ability to maintain insurance and income
    h. Other (alimony, outstanding debts, financial planning, power of attorney, etc.)
3. Cognitive/mental health/substance abuse:
    a. Cognitive deficits
    b. Literacy
    c. Learning ability
    d. Mental health history
    e. Psychiatric medications
    f. Counseling or hospitalization history
    g. Significant recent stressors (marriage, divorce, death, job loss, moves, etc.)
    h. Substance-abuse history

4. Coping skills:
    a. Strengths/weaknesses
    b. Coping approach
    c. Avoidance mechanism
    d. History of significant losses
    e. Use of alternative/complementary treatments
    f. Adaptation to illness
5. Relationships/support systems:
    a. Partner relationship (cohesion)
    b. Extended family support/availability
    c. Identification of caregivers
    d. Familial coping patterns
    e. Adaptation
    f. Spiritual/faith-based support
    g. Cultural traditions, informal, and community support
6. Medical concerns:
    a. Level of understanding of the HSCT process
    b. Decision-making issues (and agreement of support persons)
    c. Pain issues
    d. Expectations
    e. Optimism
    f. Ability to make post-HCST plans
    g. Advance care planning/directives

5.2 Preparation and Planning

1. Issues:
    a. Comprehension of the medical circumstance (e.g., remission vs. recurrence, intensity of therapy, prognosis)
    b. Mode of learning of the patient and caregiver (i.e., written or verbal? Are they literate? Is English their primary language?)
    c. Informed consent and decision making
    d. Anxiety/fear
    e. Practical arrangements (e.g., distance from transplant center, housing arrangements, caregiver support)
2. Interventions:
    a. Education about medical status and proposed treatment, as well as duties and duration of commitment of a caregiver
    b. Maximizing information delivery (e.g., repetition, multiple formats including written information, audiovisual aids, support groups, internet sites)

c. Institution-specific expectations and requirements
d. Preparative counseling

3. Referrals:

a. Educational classes are a way to reinforce prior teaching and discussions with HSCT staff; orient the patient to the hospital campus, the inpatient unit, and outpatient clinic; begin discharge planning; review advance directives and patient/caregiver agreement forms; and provide a forum to share anxiety and distress.
b. Connect with community resources, i.e., Leukemia & Lymphoma Society, Medicaid, counseling services, etc.
c. HSCT assistance resources available on the internet (see Table 5.1).

Table 5.1 HSCT internet resources. (Also see Chap. 9 for AYA-specific resources)

Organization	URL
Transplant resources	
Be the match	www.marrow.org
Blood and marrow transplant information network (BMT Infonet)	www.bmtinfonet.org
BMT support online	www.bmtsupport.org
Explore BMT	www.explorebmt.org
National bone marrow transplant link	www.nbmtlink.org
General resources	
American cancer society	www.cancer.org
Cancer.net	www.cancer.net
Cancers and careers	www.cancerandcareers.org
Cancer legal resource center	www.disabilityrightslegalcenter.org
Kids konnected	www.kidskonnected.org
Lotsa helping hands	www.lotsahelpinghands.com
LIVE**STRONG**	www.livestrong.org
Leukemia and lymphoma society	www.lls.org
Lymphoma research foundation	www.lymphoma.org
Multiple myeloma research foundation	www.multiplemyeloma.org
Financial resources	
Be the match	http://bethematch.org/For-Patients-and-Families/Getting-a-transplant/Planning-for-transplant-costs/Financial-Assistance-for-Transplant-Patients
Bone marrow foundation	www.bonemarrow.org
CancerCare, Inc.	www.cancercare.org
Patient advocate foundation	www.patientadvocate.org
RX assist	www.rxassist.org

BMT blood and marrow transplant, *RX* prescription, *AYA* adolescent and young adult

5.3 Active Treatment: Inpatient and Outpatient

1. Issues:
    a. Patient/caregiver anxiety and uncertainty about the HSCT process and outcome
    b. Disruption of patient/family roles
    c. Fears of recurrence, infection, death
    d. Interpersonal stressors (e.g., poor coping strategies, mental health issues, etc.)
    e. Uncertainty about discharge plans
2. Interventions:
    a. Negotiate personal control
    b. Build on previous experiences/successes
    c. Ongoing self-assessment and training
    d. Educate about outpatient process (e.g., medications, expected appointments, availability of 24-h medical advice/support)

5.4 Immediate Short Term

1. Issues:
    a. Transition to outpatient setting post HSCT
    b. Increased stress on relationship between patient and caregiver
    c. Caregiver burden and feelings of incompetence
    d. Patient's dependency and loss of control
    e. Graft-versus-host disease (GVHD) risk in allogeneic recipients
2. Interventions:
    a. Assess the meaning of uncertainty and stressors
    b. Evaluate burdensome tasks
    c. Assist patient/family to identify and mobilize available resources
    d. Assist in evaluating relationship enhancements
    e. Assure continuation of medical support/management in transitions to outpatient setting

5.5 Long Term/Survivorship

1. Issues:
    a. Transition back to home, work, and/or previous family roles
    b. Changes in patient's emotional and physical functions due to complications and long-term effects of HSCT

c. Fear of recurrence
d. Feelings of "being different"

2. Interventions:

a. Assess transitional needs and provide referrals to the Department of Vocational Rehabilitation, Social Security Disability, etc.
b. Evaluate the effect of complications/late effects on relationships
c. Problem-solve positive steps to build on strengths
d. Assess and support survival techniques
e. Provide support groups and reunions for survivors (NBMTlink webinars, Peer to Peer, BMTinfonet, etc.)

5.6 End-of-Life Care

1. Issues:

a. Emotions including fear, sadness, failure
b. Effects on the family, especially young children
c. Physical changes, pain, comfort
d. Spiritual needs
e. Home versus hospital versus skilled facility

2. Intervention:

a. Assess the source of expressed emotions
b. Assess the impact on the family and assist with children, involve child life services when appropriate
c. Foster hope
d. Consider home hospice as an option for patient and family
e. Advocate with provider team and family to meet patient's wishes as possible

3. Special considerations:

a. Patient questioning if they should have had the transplant? Did it matter?
b. Related donor's grief and feelings about transplant outcome. Are they responsible for the outcome?

5.7 Palliative Care and Hematologic Malignancy

A U.S. retrospective study showed patients with a hematologic malignancy accessed palliative care less frequently than those with solid tumors (11% vs. 89% respectively; see Chap. 33). Research suggests that while hematology staff are aware of the needs for palliative care, the lack of access and integration to care has an adverse effect on families and caregivers. Qualitative analysis suggests family

members were aware of patient dying, but were reluctant to speak to staff about it and felt inadequately assisted in preparing for the dying experience.

Barriers to integration of palliative care in the setting of hematologic malignancies include:

1. The course of the illness
2. Availability of community resources including hospice support with no reimbursement for palliative care or ongoing transfusion support
3. Unpredictability of the illness
4. Unclear goals of care
5. Availability of early-phase clinical trials and the patient's comprehension of the study objective
6. Availability of ongoing supportive therapies
7. Psychological dependency and the ongoing relationship between patient/family and providers

Provider skills needed for provision of palliative care:

1. Assessment
2. Information sharing
3. Decision-making capacity
4. Ability to determine patient's capacity for decision making
5. Ability to clearly define goals of care
6. Capacity for objective discussion of withdrawal of therapy
7. Openness to discussion of *Death with Dignity* where allowed
8. Advance care planning and delivery
9. Surrogate decision making
10. Conflict resolution
11. Affirmation of patient/family understanding, satisfaction, concerns

5.8 Caregiving Needs and Requirements

Individuals who undergo HSCT require caregiver support until otherwise told by their transplant provider team. Autologous HSCT recipients typically require a 24-hour caregiver for approximately 2–3 weeks after discharge from the hospital, while allogeneic HSCT recipients may require a caregiver anywhere from 2–6 months depending on complications that may arise.

Changes in health-care delivery systems and policy highlighting reduction of costs have moved much of the HSCT process from the inpatient to the outpatient setting, which may extend the caregiver's commitment by weeks to months. These changes also add an additional layer of responsibility to the caregiver, as greater involvement during the earlier phases of HSCT is required. Payer contracts may not reimburse for post-HSCT caregiver support. Therefore, the responsibility lies with the patient's natural supports, i.e., family members or friends. This incredible commitment requires even further time away from work and other personal responsibilities.

5.9 Psychosocial Impact of Caregiving and Protective Factors

While there has been a breadth of research that explores the psychosocial implications for the HSCT recipient, less is known about the experience of the caregiver. Research has shown that the psychosocial health of the caregiver has a direct impact on the health and well-being of the patient. Caregivers suffer from anxiety and depression, sleep deprivation and fatigue, sexual dysfunction, and greater vulnerability to illness, and may experience fear, frustration, and isolation. Adaptation of the caregiver is important not only for his/her own wellbeing but also in achieving optimal patient outcomes.

Studies have shown female caregivers tend to report higher levels of distress than male caregivers, because they are more likely to assume the role of primary caregiver while maintaining responsibility for the care of the rest of the family. Additionally, small studies suggest females to be more empathetic.

Control refers to the caregiver's ability to maintain a sense of predictability and manageability within their life and the lives of their loved ones. Adaptation to the caregiving role, as indicated by lower levels of distress, was noted in caregivers who reported a higher sense of personal control and spiritual well-being. Providing caregivers with detailed information about a patient's treatment course may offer more predictability. Caregivers who identified with a form of spiritual practice also showed increased adaptation to distress. Their faith allowed them to navigate the burdens of caregiving by applying meaning to their role and the role of illness in the life of their loved one.

Developing strategies and interventions to support caregivers can prove to be an important part of a patient's care. Support groups, online resources, and web-based tools to assist caregivers in managing their role are emerging. These resources are likely to be more beneficial when provided early in the planning process, as coping patterns established early can prove to be an essential part of the overall effectiveness of stress management.

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Chapter 6
Conditioning Regimens

Joseph S. Bubalo

The preferred conditioning regimen for hematopoietic stem cell transplantation (HSCT) should be capable of reducing the tumor load in the setting of a malignant disorder, provide adequate immunosuppression to prevent graft rejection, and have manageable side effects or regimen-related toxicities. Traditionally, allogeneic conditioning regimens were ablative (Table 6.1), meaning that stem cell support was required in order to attain hematopoietic recovery of the bone marrow. Beginning in the early twenty-first century, there has been a trend in multiple patient populations to move towards reduced-intensity conditioning regimens (RICs; Table 6.2) which are defined as any regimen which does not require stem cell support for hematopoietic recovery, yet results in low hematologic toxicity and mixed donor–recipient chimerism in a substantial proportion of patients in the early post-transplantation period. Most transplantation experts agree that any regimen which includes (i) total body irradiation (TBI) of < 500 cGy as a single fraction or < 800 cGy if fractionated, (ii) < 9 mg/kg of oral busulfan, (iii) < 140 mg/m^2 of melphalan, or (iv) < 10 mg/kg of thiotepa is an RIC regimen.

Increasingly, in both adult and children who do not have a related stem cell donor, cord blood progenitor cells are being used as a stem cell source for their allogeneic HSCT. These require different conditioning regimens (Table 6.3) as well as changes in associated supportive care and immune suppression.

In the autologous setting, high-dose therapy with stem cell support is frequently used to salvage relapsed or persistent disease, as well as to consolidate or prolong cancer remission. Sequential or tandem stem cell transplants are used in some disease states to further deepen a remission, increase the chance for cure, or facilitate delivery of a high dose regimen (Table 6.4).

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Table 6.1 Common ablative conditioning regimens. (see Sect. 6.E for dosing recommendations)

Regimen	Disease states treated	Comments
Cy+ATG +/-TBI	Aplastic anemia	TBI added for unrelated donors (URD)
tBu–Cy	AML, ALL, CLL, CML, NHL, MM, MDS	The busulfan exposure target varies by disease which is attained by pharmacokinetic monitoring
Cy–TBI	AML, ALL, CLL, NHL, MDS	–
BEAM	NHL, HD, MM	–

Cy cyclophosphamide, *ATG* antithymocyte globulin (equine), *tBu* targeted busulfan, *AML* acute myelogenous leukemia, *ALL* acute lymphocytic leukemia, *CML* chronic myelogenous leukemia, *CLL* chronic lymphocytic leukemia, *NHL* non-Hodgkin's lymphoma, *HD* Hodgkin's disease, *MM* multiple myeloma, *MDS* myelodysplasia, *BEAM* carmustine, etoposide, cytarabine, melphalan

Table 6.2 Common RIC regimens

Regimen	Disease states treated	Comments
Bu–Flu	AML, ALL, CLL	–
Bu–Flu–TBI	AML, ALL, CLL	–
Flu–Mel	NHL, MM	–
Flu–TBI	AML, ALL, CLL	–
TBI–200 cGY	AML, ALL, CLL	More rapidly paced disease may require more aggressive therapy. This is considered a nonmyeloablative regimen which is the least intense of the RIC regimens
Flu–Cy–R	NHL, CLL	–

AML acute myelogenous leukemia, *ALL* acute lymphocytic leukemia, *Bu* busulfan, *CLL* chronic lymphocytic leukemia, *Flu* fludarabine, *Mel* melphalan, *NHL* non-Hodgkin's lymphoma, *R* Rituximab, *RIC* reduced-intensity conditioning regimens

Table 6.3 Common conditioning regimens for cord blood transplants

Regimens	Disease states treated	Comments
Flu–TBI (ablative)	AML, ALL, CML, MDS, NHL	Engraftment occurs approximately 2–3 weeks later than with other stem cell sources. Dual cord blood units often used for adults
Cy–Flu–TT–TBI	AML, ALL MDS	Dual cord blood units often used for adults
Cy–Flu–TBI	AML	–
TT–Bu–Flu–rATG	AML, ALL, NHL, CML, MDS	Single cord blood unit used for adults and children

AML acute myelogenous leukemia, *ALL* acute lymphocytic leukemia, *Bu* busulfan, *CML* chronic myelogenous leukemia, *Flu* fludarabine, *MDS* myelodysplasia, *NHL* non-Hodgkin's lymphoma, *TT* thiotepa, *rATG* Thymoglobulin® (rabbit)

Table 6.4 Common autologous conditioning regimens

Regimen	Disease states treated	Comments
Bu16–Etoposide	AML	Note: despite ablative dose of Bu this is used in the autologous setting
BEAM	NHL, HD	–
BuMelTT	NHL, HD	–
Carbo–Etoposide	Germ cell	May be done in tandem
Carbo–Etoposide–Cy	Germ cell	May be done in tandem
Cy–Etoposide–TBI	NHL, HD	–
CBV	NHL, HD	–
Melphalan	MM, Amyloid	May be done in tandem

AML acute myelogenous leukemia, *Bu* busulfan, *CML* chronic myelogenous leukemia, *Carbo* carboplatin, *CBV* cyclophosphamide, carmustine, etoposide, *HD* Hodgkin's disease *NHL* non-Hodgkin's lymphoma

6.1 Conditioning Agents

Most conditioning agents are associated with pancytopenia, sterility, and alopecia in the doses used in myeloablative regimens. Mucositis may encompass the entire gastrointestinal (GI) tract and result in stomatitis, esophagitis, nausea, vomiting (see Table 6.5 for prophylaxis), and diarrhea (see Chap. 21). Selected toxicities and important aspects of care are presented, as these are unique or more prevalent in the high-dose therapy setting. On a day-to-day basis, these effects may require additional therapy or attention to specific patient-care techniques to manage the patient and minimize morbidity (see Table 6.6 for dosing guidance to individualize dose for specific patients attributes):

1. Anti-thymocytic immune globulin equine (ATG or ATGAM®):
    a. Type: immune modulator, polyclonal antibody mixture
    b. Dose: 30 mg/kg IV daily for 3 days
    c. Toxicities:
        i. Fatal allergic reactions. Requires test dose prior to initiation of treatment.
        ii. Serum sickness (or maturation syndrome) symptoms including fever, chills, hypotension, rash, arthralgias, joint pain and renal insufficiency.
    d. Patient care points:
        i. Intradermal test dose prior to first dose with contralateral saline dose
        ii. Premedicate with diphenhydramine, acetaminophen, and corticosteroids
        iii. Run slowly to begin then may accelerate rate as tolerated
        iv. Have emergency medications at bedside (epinephrine, hydrocortisone, diphenhydramine)
    e. Rabbit ATG (Thymoglobulin®) can be substituted in some circumstances, often based on institutional guidelines Dose is different than the equine ATG, see specific protocol for dosing.

Table 6.5 Antiemetic dosing

Agent	Risk	Antiemetic regimen	Comments
Antithymocyte globulin	Low	None needed	Other premedications required
Busulfan	Moderate to high	Ondansetron 8 mg PO Q 6 h or 24 mg PO daily	Dexamethasone 20 mg daily with once daily ondansetron no dexamethasone required for every 6 hour busulfan dosing
Carboplatin	High	Ondansetron 24 mg PO or 8 mg IV prior to first daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron
Carmustine	High	Ondansetron 24 mg PO or 8 mg IV prior to first daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron
Clofarabine	Low	Ondansetron 8 mg PO daily. 16 mg (8 mg IV) if other chemotherapy agents given	Dexamethasone 8–12 mg daily with each daily ondansetron
Cyclophosphamide	High	Ondansetron 24 mg PO or 8 mg IV prior to first daily chemotherapy dose. Consider adding aprepitant each day cyclophosphamide is given plus 1 additional day or fosaprepitant once on first day of cyclophosphamide	Dexamethasone 20 mg daily with each daily ondansetron. Dose adjust dexamethasone if aprepitant used
Cytarabine	Low (< 1000 mg/m^2/day)	Ondansetron 8 mg PO daily. 16 mg PO (8 mg IV) if other chemotherapy agents given	Dexamethasone 8 mg daily with each daily ondansetron
Etoposide	Moderate to high	Ondansetron 24 mg PO or 8 mg IV prior to first daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron
Fludarabine	Low	Ondansetron 8 mg PO daily.16 mg PO (8 mg IV) if other chemotherapy agents given. If only agent used that day may substitute 10 mg prochlorperazine for the ondansetron	Dexamethasone 8 mg daily with each daily ondansetron
Melphalan	High	Ondansetron 24 mg PO or 8 mg IV prior to first daily chemotherapy dose. Consider adding aprepitant each day melphalan is given and for one additional day or fosaprepitant once on first day of cyclophosphamide	Dexamethasone 20 mg daily with each daily ondansetron. Dose adjust dexamethasone if aprepitant used

Table 6.5 (continued)

Agent	Risk	Antiemetic regimen	Comments
Total body irradiation	High	Ondansetron 8 mg PO prior to each radiation fraction	Dexamethasone 20 mg daily with the first daily ondansetron
Thiotepa	High	Ondansetron 24 mg PO or 8 mg IV prior to first daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron

Ondansetron is interchangeable with granisetron at equivalent doses.Palonosetron and dolasetron dosing for optimal effect is unclear
Lorazepam 0.5 mg PO/IV should be offered if needed prior to each day's first chemotherapy dose

Table 6.6 Chemotherapy dosing in conditioning regimens

Agent	Dosing	Dose adjustment for renal insufficiency	Additional information
Alemtuzumab	Flat dosing in adults based upon regimen selected	No dose adjustment required for renal dysfunction	No dose adjustments for small or obese individuals
Busulfan	Dose on ABW25 in adults (obese and nonobese) receiving per kilogram dosing or BSA based on TBW for square meter dosing. All regimens > 12 mg/kg PO equivalent are recommended to have PK targeting as appropriate for the disease state. Regimens using doses ≤ 12 mg/kg PO equivalent do not have sufficient information to recommend routine PK monitoring at this time Pediatrics should be dosed upon TBW with similar monitoring guidelines	No dose adjustment required for renal dysfunction	-PK monitoring has reduced rate of SOS from ~ 20% to < 5% -AUC/Css targeting varies by regimen -For BuCy regimens, the MTD is 16 mg/kg PO equivalent over 4 days for adults
Carboplatin	Dose adults on BSA based on TBW	If CrCl < 50, dose based on an AUC of seven per day using 24-h urine collection to estimate GFR or calculated CrCl	No dose adjustment required for BSA-dosed obese individuals. If using Calvert formula, dose based on 24-h urine collection derived from CrCl
Carmustine	Dose adults on BSA based on TBW unless > 120% IBW, then dose on BSA based on ABW25	No dose adjustment required for renal dysfunction	Pulmonary toxicity > 50% at 600 mg/m^2 with multiple agent regimens. MTD of 1200 mg/m^2 as single agent with 9.5% pulmonary toxicity
Clofarabine	Dose on BSA based on TBW	reduce 50% for CrCl 30–60 mL/min. Do not use for < 30 mL/min	No dose adjustments for obese individuals

Table 6.6 (continued)

Agent	Dosing	Dose adjustment for renal insufficiency	Additional information
Cyclophosphamide	Dose on IBW for Cy 120 or 200 *Exception*: aplastic anemia for Cy 120 dose on TBW unless > 120% IBW then ABW25	For CrCl < 30, dose at 75% of protocol dose	For obese patients, see dosing column
Cytarabine	Dose on BSA based on TBW	No dose adjustment required if < 500 mg/m^2	No dose adjustment for obese patients
Etoposide	Dose on ABW25 for milligrams per kilogram dosing and BSA based on TBW for BSA based dosing	Dose at 50% for CrCl < 30; do not exceed 30 mg/kg	DLT of mucositis
Fludarabine	Dose on BSA based on TBW	CrCl 17–40 ml/min dose at 80% CrCl < 17 ml/min dose at 60%	Post-treatment leukoencephalopathy still being studied for conditioning regimen doses more than 125 mg/m^2 No dose adjustment for obesity
Melphalan	Dose on BSA based on TBW	For CrCl < 40, dose at 70 mg/m^2/day × 2 or 140 mg/m^2 on 1 day for goal dose 200 mg/m^2	DLT of mucositis No dose adjustment for obesity as long as dose is < 3.6 mg/kg of ABW
Pentostatin	Dose on BSA based on TBW	CrCl < 60, 75% dose CrCl < 30, 40% dose	No dose adjustment for obesity
Thiotepa	Dose adults on BSA based on TBW unless > 120% IBW then dose on BSA based on ABW40	No dose adjustment required for renal dysfunction	Multiagent MTD is 500–750 mg/m^2, single agent MTD is 900 mg/m^2
Antithymocyte globulin—Equine	Dose on milligrams per kilogram based on TBW	No dose adjustments for renal dysfunction	No dose adjustments for obese individuals
Antithymocyte globulin—Rabbit	Dose on milligrams per kilogram based on TBW	No dose adjustments for renal dysfunction	No dose adjustments for obese individuals

Patients with a CrCl < 10 ml/min or requiring dialysis at the time of transplant should have their doses reviewed by a pharmacist trained in the care of HCT patients

ABW25 adjusted body weight (IBW + 0.25 (TBW–IBW)), *ABW40* adjusted body weight (IBW + 0.4 (TBW—IBW)), *AUC* area under curve, *BSA* body surface area, *CrCl* creatinine clearance, *DLT* dose-limiting toxicity, *HCT* hematopoietic cell transplantation, *IBW* ideal body weight, *MTD* maximally tolerated dose, *PK* pharmacokinetics, *TBW* total or actual body weight

Obesity defined as BMI >30 if not otherwise defined in agent dosing column

2. Carmustine (BiCNU®, BCNU®):
   a. Type: nitrosourea alkylating agent
   b. Dose: 300 mg/m^2 IV for 1 day or 150 mg/m^2 daily for 3 days are common dose schedules
   c. Toxicities:
      i. Infusional hypotension related to rate of administration. See maximum infusion rate.
      ii. Nausea and vomiting (N/V).
      iii. Progressive pulmonary fibrosis; acute onset usually responds to steroids but, if unresponsive, may be fatal. Symptoms include cough, dyspnea, or restrictive pattern on pulmonary function tests (PFTs).
      iv. Mucositis.
   d. Patient care points:
      i. Preadministration baseline PFTs with diffusion capacity of carbon monoxide (DLCO)
      ii. Administer at a maximum rate of 3 mg/m² per minute
      iii. Requires prehydration and posthydration
3. Busulfan (Myleran®, Busulfex®):
   a. Type: alkylating agent
   b. Dose (adjusted body weight = IBW + 0.25 (Actual—ideal body weight)):
      i. Myeloablative = 1 mg/kg/dose oral (PO) for total of 12–16 mg/kg or 0.8 mg/kg/dose IV every 6 h or 3.2 mg/kg/day × 3–4 days for a total of 9.6–12.8 mg/kg
      ii. Reduced intensity = 3.2 mg/kg IV once
      iii. 0.8 mg IV is equivalent to 1 mg PO
   c. Toxicities:
      i. Lowers seizure threshold
      ii. nausea/vomiting
      iii. Pulmonary fibrosis (busulfan lung): symptoms of cough, dyspnea, low grade fever
      iv. Hepatitis/sinusoidal obstructive syndrome (SOS; may have late onset)
      v. Mucositis
      vi. Hyperpigmentation/skin blistering
   d. Patient care points:
      i. Anticonvulsants required to prevent seizures. Loading dose of phenytoin, levetiracetam +/- clonazepam, lorazepam, etc. given the evening prior to first dose of busulfan with maintenance dosing daily, continuing through the morning after the administration of the last dose.

ii. Pharmacokinetic targeting is ideal for oral delivery and can optimize IV administration. Target levels of busulfan with cyclophosphamide only, not BuMelTt or other busulfan conditioning schedules: < 16 mg/kg PO equivalent

- AUC 950–1350 micromole minutes for leukemias other than myeloid leukemia (ML) or myelodysplastic syndrome (MDS)
- AUC 1315–1500 micromole minutes for chronic myelogenous leukemia (CML)
- AUC 1000–1350 micromole minutes for non-Hodgkin lymphoma (NHL)
- AUC 1169–1315 micromole minutes for MDS

iii. Give oral drug on an empty stomach.
iv. If patient vomits within 30 min or less of drug administration and tablets are visible, count tablets and repeat that number of pills. If unsure, repeat entire dose.
v. If patient vomits within 30–60 min of drug administration and tablets are visible, count tablets and repeat that number of pills. If unsure, repeat one-half the dose.
vi. Tablets should be placed in gelatin capsules for ease of consumption.
vii. If there is more than one episode of emesis requiring redosing, consider changing to IV busulfan.

4. Carboplatin (Paraplatin®):

a. Type: alkylating agent
b. Dose: 600–700 mg/m2/day IV for 3 days
c. Toxicities:

i. Irreversible ototoxicity
ii. Delayed Nausea/Vomiting
iii. Renal insufficiency
iv. Electrolyte disturbances—acidosis, hyponatremia
v. Neurotoxicity

d. Patient care points:

i. Maintain adequate hydration

5. Cyclophosphamide (Cytoxan®)

a. Type: alkylating agent
b. Dose: 60 mg/kg/day IV daily for 2 days (based on IBW) incorporated into conventional hematologic malignancy conditioning regimens:

i. Aplastic anemia: 50 mg/kg IV daily for 4 days (based on IBW) is commonly used

c. Toxicities:

i. Hemorrhagic cystitis
ii. Cardiomyopathy
iii. Nausea/Vomiting
iv. Mucositis
v. Syndrome of inappropriate antidiuretic hormone (SIADH)
vi. Histamine-type reaction characterized by sinus burning, cough, itchy/watery eyes, chest discomfort/tightness
vii. Gonadal failure

d. Patient care points:

i. Multigated radionuclide angiography (MUGA) or transthoracic echocardiogram (TTE) pretreatment with baseline left ventricular ejection fraction (LVEF) > 45 %.
ii. Adequately hydrate patient for 12 h prior to cyclophosphamide dose with normal saline (NS). The cyclophosphamide should run concurrently with 2-mercaptoethane sulfonate (MESNA) to protect bladder. The patient is asked to void every 1–2 h during cyclophosphamide administration. Check for hematuria with each void. If the patient should develop hemorrhagic cystitis, continuous bladder irrigation is indicated.
iii. Diurese to maintain euvolemia.
iv. Monitor daily intake/output and weights.
v. Daily chemistries (Na, K^+) during infusion days
vi. Infuse slowly if histamine reaction occurs and consider pseudoephedrine 60 mg PO every 4 hours × 2 for subsequent doses.

6. Cytosine arabinoside (ARA-C, Cytosar-U®):

a. Type: antimetabolite
b. Dose: 400 mg/m^2 IV daily for 4 days as part of the (carmustine, etoposide, cytarabine, melphalan) BEAM regimen
c. Toxicities:

i. Mucositis
ii. Cerebellar dysfunction: ataxia, nystagmus, slurred speech
iii. Chemical conjunctivitis prophylactic eye drops not required at this dose
iv. Acral erythema
v. Biliary stasis and elevated liver function tests (LFTs)
vi. Fevers, myalgia, bone pain, chest pain
vii. Capillary leak syndrome

7. Etoposide (VP-16, Vepesid®):

a. Type: plant alkaloid, inhibits topoisomerase II
b. Dose:

i. With carboplatin: 750 mg/m^2 IV daily for 3 days
ii. With TBI or busulfan: 30–60 mg/kg IV for 1 day
iii. With BEAM 2–400 mg/m^2/day IV for 4 days

c. Selected toxicities:

i. Hypersensitivity, anaphylactic-type reaction
ii. Hypotension, usually an infusional reaction Infuse over a minimum of 1 hour
iii. Mucositis
iv. Large-volume diarrhea
v. Elevated LFTs. Evaluate dose for bilirubin > 5 mg/dL
vi. Erythema multiforme, plantar palmer erythemia
vii. Fever
viii. Peripheral neuropathy
ix. Cystitis

d. Patient care points:

i. Premedicate for infusion with steroids and diphenhydramine and repeat for 2 h into the infusion if using undiluted etoposide hydrochloride
ii. Fluid bolus with 500–1000 mL NS for hypotension (systolic blood pressure (SBP) < 85 mmHg or blood pressure decrease > 20 mmHg from baseline) during infusion
iii. If unresponsive to fluid bolus, stop infusion. May consider restarting at a lower dose after blood pressure stabilizes with additional corticosteroids, antihistamines, and blood pressure support, including dopamine 2–5 mcg/kg/min.
iv. Maintain adequate hydration before and after infusion.
v. Do not give diuretics or antihypertensive medications on days of etoposide administration.
vi. Skin rash may require topical steroid treatment.

8. Fludarabine (Fludara®):

a. Type: antimetabolite, purine analogue
b. Dose: 30–40 mg/m^2/day for 3–5 days
c. Selected toxicities:

i. Rare, severe neurologic toxicity (cortical blindness, coma, death), risk increases above doses of 140 mg/m^2/regimen.
ii. Rare hemolytic anemia.
iii. Combination use with pentostatin has resulted in severe pulmonary toxicity.

d. Patient care points:

i. Causes profound lymphopenia; therefore, prophylaxis and surveillance for opportunistic infections are important.

9. Melphalan (Alkeran®):

a. Type: alkylating agent
b. Dose:

i. Single agent: 100 mg/m2 IV daily for 2 days (standard) or 200 mg/m2 × 1 day; can be used at a total dose of 100 mg/m2 or 140 mg/m2 in some settings in patients with amyloid light-chain (AL) amyloidosis or multiple myeloma
ii. BEAM: 140 mg/m^2 IV for 1 day
iii. BuMelTt: 50 mg/m^2 IV daily for 2 days
iv. Creatinine clearance < 10 or dialysis: 70 mg/m² IV daily for 2 days (multiple myeloma (MM) or Amyloid)
v. Age > 75: 70 mg/m² IV daily for 2 days (MM or Amyloid)

c. Selected toxicities:

i. Mucositis
ii. Hyperpigmentation
iii. Nausea/Vomiting
iv. Arrythmias

d. Patient care points:

i. Give immediately after mixing as stability in solution is limited.
ii. Ask patient to suck on ice chips before, during, and after infusion (at least 30 min) to decrease blood flow to oral mucosa to help prevent mucositis. Cryotherapy has been shown to decrease stomatitis.

10. Thiotepa (Thioplex®):

a. Type: alkylating agent
b. Dose: 250 mg/m2 IV daily for 2 days with BuMelTt
c. Selected toxicities:

i. Nausea/Vomiting
ii. Central nervous system (CNS) changes including decline in mental status
iii. Hepatic changes including late sinusoidal obstruction syndrome (SOS) and elevated LFTs
iv. Pulmonary toxicity
v. Headache
vi. Skin desquamation, especially in intertriginous areas, as thiotepa is excreted in sweat
vii. Mucositis

d. Patient care points:

i. Consider having patient shower two to three times daily during and for 24 h post high-dose thiotepa administration. Use hydrocortisone cream 1% underarms, in groin area or face or triamicinolone cream 0.1% for all other areas of desquamation.
ii. Round dose to nearest 15 mg due to vial size.

11. TBI:
    a. Dose:
        i. Nonablative transplants: 200–500 cGy in a single dose
        ii. Conventional transplantation: 1200–1400 cGy given in divided fractions; dose, number, and delivery per institutional guidelines
        iii. Examples of conventional TBI:
            - Low-risk disease: 1200 cGy divided into eight doses delivered twice daily (BID) over 4 days
            - High-risk disease: 1400 cGy divided into eight doses delivered BID over 4 days
    b. Selected toxicities:
        i. Sunburn-like rash, diffuse erythema
        ii. Parotiditis
        iii. Cataracts
        iv. Thyroid dysfunction, usually seen late
        v. Nausea/Vomiting
        vi. CNS toxicity, leukoencephalopathy
        vii. Acute pneumonitis/alveolar hemorrhage
        viii. Fatigue
        ix. Growth failure
        x. Gonadal failure
        xi. Diarrhea
    c. Patient care points:
        i. Premed before each treatment
        ii. Shield lungs as per protocol
        iii. Pretreatment thyroid stimulating hormone (TSH)

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Chapter 7
Nutrition

Stacey Evert

Hematopoietic stem cell transplant (HSCT) patients have huge metabolic demands related to wound healing after conditioning regimens and infectious events with associated febrile states, and in allogeneic HSCT recipients, the systemic inflammatory state and local tissue damage imposed by acute graft-versus-host disease (GVHD). In the long term, ongoing inflammatory conditions and maldigestion/malabsorption can contribute to a chronic wasting syndrome. The central and critical importance of maintaining adequate nutritional balance throughout the transplant process cannot be understated. Understanding the anabolic and catabolic states seen in the HSCT population as well as issues related to the restriction of diet for these patients is essential.

While we seek to optimize the nutritional state of the patient, it is also important to recognize that the gastrointestinal (GI) tract can be a portal of infection. As such, the identification of an appropriate diet that limits further infectious risk in this immune compromised patient population is essential.

Within this section, the rationale for a controlled low-bacteria diet, GVHD dietary restrictions, and general diet guidelines are provided. Additionally, details regarding the goals for nutrition during HSCT and guidelines for initiation of total parenteral nutrition (TPN) and enteral nutrition (EN) are given, with additional recommendations including a discussion of the ongoing debate regarding L-glutamine.

7.1 Low-Bacteria Diet

Patients undergoing intensive conditioning regimens for HSCT who develop a period of cytopenia have an increased risk for developing a food-related infection from bacteria, yeasts, molds, viruses, and parasites. To help prevent food-related

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infections, many institutions have implemented some form of low-bacteria or low-microbial diet. Variations include sterile diet, well-cooked foods only, or a modified house diet which omits fresh fruits and vegetables from an otherwise regular diet. While the effect of a low-bacteria diet on preventing infection is unknown, HSCT patients who are neutropenic should avoid foods associated with increased infection risk. More studies are needed to determine the safety, efficacy, and necessity of a low-bacteria diet in this setting.

The Center for Disease Control (CDC) has developed a list of foods that an HSCT patient should avoid as well as food safety guidelines. These guidelines should be the building blocks that individual institutions can utilize to develop their own version of a low-bacteria diet. These guidelines include the use of separate cutting boards for raw meats and vegetables, meticulous hand hygiene after handling of raw meats, and cooking meats to the appropriate internal temperature for that product.

Foods patients should avoid include:

1. Foods containing raw and undercooked eggs
2. Unpasteurized dairy products
3. Unpasteurized fruit and vegetable juices
4. Unpasteurized cheeses or cheeses containing molds
5. Undercooked or raw poultry, meats, fish, and seafood
6. Vegetable sprouts (e.g., alfalfa, bean, and other seed sprouts)
7. Raw fruits with a rough texture (e.g., raspberries)
8. Smooth raw fruits (unless washed under running water, peeled, or cooked)
9. Unwashed raw vegetables (unless washed under running water, peeled or cooked)
10. Undercooked or raw tofu
11. Raw or unpasteurized honey
12. Deli meats, hot dogs, and processed meats
13. Raw, uncooked grain products
14. Mate tea
15. All moldy and outdated food products
16. Unpasteurized beer
17. Raw, uncooked brewer's yeast
18. Unroasted raw nuts
19. Roasted nuts in the shell

In general, some version of a low-bacteria diet should be followed for 2–3 months post-autologous HSCT; allogeneic patients should continue until at least day + 100. In the end, it is up to the patient's provider to determine when the dietary restrictions can be discontinued.

Probiotics are under study for the management of a variety of medical conditions. Their use is gaining popularity by both the medical community and general population. Probiotics can be found in over-the-counter capsules or in foods such as yogurt, kefir, and fortified milk. Strong evidence has been found for probiotic use for the treatment of infectious diarrhea and prevention/treatment of antibiotic-

induced diarrhea. Theoretically, probiotic use in the HSCT population could be viewed as a way to treat antibiotic-induced or radiation-induced diarrhea; however, this could promote infectious complications in this immunocompromised population. While probiotics are being utilized to treat medical conditions in the immune competent population, there have been no studies done to evaluate their efficacy in patients undergoing HSCT. Without those data, the safety of probiotics in HSCT recipients is unknown and use should be avoided, recognizing the risk of bacterial translocation though the GI tract wall potentially resulting in systemic infection.

Water safety is also a concern for these patients. HSCT recipients should avoid using well water as water testing is performed too infrequently. If patients choose to use tap water, they should heed public health advisories on water safety. Use of a water filtering system or home distiller may reduce the risk for waterborne pathogens found in tap water. The filter "should be capable of removing particles ≥ 1 μm in diameter or filter by reverse osmosis." Bottled water should be used with caution and checked to be sure that reverse osmosis, distillation, or 1-μm particulate absolute filtration is used to remove *Cryptosporidium* (patients may need to check with the bottler to see whether this has been done). Also, patients should be aware that the water used to make ice, tea, coffee, etc. must be free of *Cryptosporidium* (especially important if patients are not residing in their own homes).

7.2 GVHD Diet

GVHD is a T-cell-mediated immunologic reaction of engrafted lymphoid cells against the host tissue that may involve major organs, most commonly the skin, GI tract, and liver typically occurring within the first 100 days (acute GVHD). Clinical symptoms seen in patients with acute GVHD of GI tract may include abdominal pain/cramping, diarrhea, dysphagia, nausea, and vomiting. Chronic GVHD (commonly identified after the first 100 days) may be seen in some patients with symptoms of weight fluctuation, xerostomia, stomatitis, anorexia, reflux symptom, and diarrhea. All of these clinical findings can lead to malabsorption, bacterial translocation across the GI mucosa, dehydration, and weight loss in a patient population already at risk for these complications.

GVHD of the GI tract is especially challenging. Nutritional assessment and support of patients with GVHD of GI tract may be difficult due to inaccurate output measurement (large volume diarrhea, incontinence, or mix of stool/urine) as well as fluid retention which could mask weight loss.

Nutrition therapy can range from bowel rest and TPN to a diet that is low in GI stimulants/irritants (i.e., caffeine, lactose, acid, fat, and fiber) based on the severity of their symptoms. For patients with acute GVHD who present with large volume watery diarrhea and GI cramping, bowel rest and TPN are the initial steps of nutrition therapy. Once signs and symptoms have begun to improve (decreased abdominal cramping and decreased stool output, typically < 500 ml per day), patients may start a limited isotonic clear liquid diet. Once stools start to become formed, and the

patient reports minimal cramping, one could start a diet that is low fat (20–40 gm/day), low fiber, and lactose restricted, with a gradual advancement to regular diet as tolerated. Regular monitoring for tolerance to advancement of diet is important. Increased diarrhea, emesis, or abdominal cramping should warrant a return to the previous dietary restrictions. Patients should remain on TPN until tolerating adequate calories and protein. EN in the form of tube feedings can be entertained at this time. The addition of new foods and diet advancement will vary by patient based on symptoms and tolerance. In patients with long-term chronic GVHD of GI tract, low-fat diet education and pancreatic enzymes may be beneficial.

7.3 Goals of Nutrition During HSCT

Because HSCT patients are predisposed to malnutrition related to the disease process and conditioning regimen toxicities, they should receive ongoing nutrition assessment throughout the HSCT process, including nutritional and medical histories, anthropometry, chemistry review, and assessment of additional factors that may interfere with the patient taking adequate nutrition (pain control, activity level, etc.). This information will assist in determining the nutrient requirement for individual patients.

In general, patients who are in the immediate post-HSCT phase have the following energy and protein requirements:

1. Energy needs (BEE = basal energy expenditure)
    a. Calculated by Harris Benedict equations:
        i. For men, the BEE = 66.5 + (13.75 x kg) + (5.0 x cm) − (6.78 x age)
        ii. For women, the BEE = 655.1 × (9.56 × kg) + (1.85 × cm) − (4.68 x age)
    b. Baseline needs: BEE × 1.3–1.5 (30–35 kcal/kg, ASPEN Core Curriculum)
        i. Typically used with patients with evidence of engraftment and no metabolic stressors
    c. Stressed needs: BEE × 1.5−1.6
        i. Typically used in the immediate post-HSCT period.
2. Protein needs
    a. Estimated as approximately 2 × the recommended dietary allowance
    b. 1.5 gm/kg − use adjusted weight for obesity: (ideal weight + 0.025(actual weight − ideal weight)). Increased in the immediate post HSCT period or with corticosteroid treatment
    c. Protein requirements may need to be adjusted due to other medical conditions:
        i. Increase requirements due to muscle wasting, steroid myopathy, GHVD, etc.

   ii. Decrease requirements in the setting of renal insufficiency, hepatic encephalopathy, etc.
3. Fluid requirements
   a. Individualized based on the patients clinical status (i.e., increased in the setting of excessive GI loss, nephrotoxic medications, etc., and decreased in the setting of compromised organ function and iatrogenic fluid overload)
   b. Maintenance fluid needs for adults is 1500 mL/m^2 body surface area

Oral nutrition should be encouraged as much as possible throughout the transplant process. Autologous and some allogeneic HSCT recipients may be able to maintain adequate oral intake and avoid TPN during the transplant period with attention to symptom management. Symptom control via medication or adjustments to diet may help the patient avoid TPN and maintain adequate oral intake. However, the majority of allogeneic HSCT recipients, and all patients with severe mucositis, will likely require TPN to maintain positive nitrogen balance and prevent significant weight loss.

7.4 Use of TPN

Patients who are undergoing myeloablative HSCT have a higher incidence of various oral and GI complications. Examples of these complications can include but are not limited to oral/esophageal mucositis, anorexia, and nausea/vomiting/diarrhea (see Chap. 21). These complications can impair nutritional status by limiting oral intake in the immediate post-HSCT period. It is common practice to utilize TPN during this period for those patients unable to tolerate oral intake:

1. TPN initiation guidelines
   a. TPN should be considered if the following conditions exist:
      i. Weight loss of > = 5 % of usual body weight
      ii. Patient unable to consume at least 50 % of BEE for > = 3 days (see Sect. B.1)
      iii. Negligible oral intake (or < 50 % of BEE) is anticipated for at least seven consecutive days
      iv. Severe GI toxicity lasting > 5 days expected with the conditioning regimen (e.g., busulfan, etoposide, melphalan, and/or total body irradiation combinations)
   b. Recommend a baseline of 25–30 kcal/kg/day, 1.5 gm protein/kg/day and 20–30 % of kcal from lipids:
      i. Adjusted body weight should be used for patients > = 125 % ideal weight or BMI > = 30
      ii. Calories and protein provided should be adjusted based on patient's medical condition (i.e., acute kidney injury, fluid status, etc.)

iii. Lipids are not contraindicated in HSCT patients unless the patient has excessive hypertriglyceridemia. Recommendations in the setting of hypertriglyceridemia:
   - For fasting triglycerides > 500, consider holding lipids until triglycerides decrease but for no longer than 2 weeks. Then reintroduce at 4–8 % and monitor triglycerides. As triglyceride levels stabilize, increase back to 20–30 %
   - Consider other causes of hypertriglyceridemia if this remains an ongoing issue
   - Minimum amount of lipid necessary to prevent essential fatty acid deficiency is 4–8 % of total energy intake
   - Evidence of essential fatty acid deficiency will appear in 1–2 weeks in HSCT patients not receiving lipids

c. Vitamin C at a dose of 500 mg/day should be provided to promote tissue recovery via collagen biosynthesis
d. Additional zinc should be added to TPN for patients with diarrhea at a dose of 1 mg/100 mL
e. For patients with persistent hyperbilirubinemia (serum bilirubin > 10 mg/dL), the trace elements of copper and manganese should be removed from TPN

2. TPN administration recommendations:

a. When oral caloric intake is > 50 % of caloric needs × 2 consecutive days, discontinue TPN
b. Taper TPN to 50 % of caloric needs as soon as possible when oral intake resumes to stimulate appetite (minimum Kcal in TPN will be 1000/day)
c. Discontinue TPN at least 1 day prior to anticipated discharge to ensure adequate oral intake
d. If prolonged nutritional support is anticipated, EN should be considered in patients who have resolution of severe mucositis, esophagitis, and/or diarrhea

7.5 Use of EN

EN is the preferred method of feeding patients to maintain the integrity of the GI tract and prevent bacterial translocation through the GI mucosa. However, TPN has long been the commonly utilized method of nutritional support due to the availability of central access and consistent delivery of calories and protein. Initiating and maintaining EN in patients after an HSCT can be difficult due to the risk of bleeding during tube placement and dislodgement of tube or aspiration during vomiting related to treatment toxicity.

Placing the feeding tube after completion of the conditioning regimen but prior to the onset of mucositis, using a nasogastric tube instead of nasojejunal tube due to the ease of placement, and/or gradual increase in volume to overcome the gastroparesis effect may help patients tolerate enteral feedings.

The benefits of EN over TPN include reduction of risk of venous access device infection, venous thrombosis, and metabolic disturbances, as well as decreased risk of bacterial translocation across the GI tract. Some studies have shown that patients who received EN when unable to consume oral intake were less likely to develop acute GVHD of GI tract. EN after HSCT may provide a direct trophic effect on the GI mucosa, thus maintaining the integrity of the GI wall and limiting excess cytokine production, and therefore may ultimately influence the development of acute gut GVHD.

7.6 Catabolic/Anabolic States

An anabolic state is part of the metabolic process where an individual builds muscle mass and loses fat mass, achieved through adequate nutrition and exercise. Multiple factors may prevent achieving anabolic status by cancer patients including a general systemic effect, a local effect (depending on tumor location), and the type of therapy used to treat the cancer. Despite a patient consuming what appears to be an adequate amount of nutrients, they still may not be able to maintain a state of anabolism due to alterations in host metabolism, inefficiency of nutrient use, or competition for nutrients between the malignancy and normal host elements.

The catabolic process occurs when the body needs to break down its own tissue for energy use because there is not enough energy available in the form of food. During times of illness and stress, as in the settings of active disease processes such as cancer, the body's response is both hypermetabolic and hypercatabolic. The tissue catabolism that happens during this time is mediated through cytokine and counterregulatory hormone release. If left uncorrected, the process of catabolism can lead to loss of lean body mass and total protein body deficiency, impairing the ability to recover from illness.

Tissue catabolism in cancer patients is likely a factor of inadequate energy intake, hypermetabolism, or both. While hypermetabolism is not present in all patients with cancer, a significant correlation between the disease duration and hypermetabolism has been shown. Recently data suggested that hypermetabolism in cancer patients can be related to tumor-induced changes in host hormones, neuropeptides, cytokines, and neurotransmitters which can have negative effects on appetite and increase protein breakdown.

7.7 Discussion of Glutamine Controversy

Glutamine, normally a nonessential amino acid, is important in many metabolic processes including proliferation of lymphocytes, macrophages, and fuel for enterocytes, as well as preserving the integrity of the GI mucosa and function of the intestines. The body may not be able to synthesize adequate amounts of glutamine

in times of severe physiological stress causing a deficiency and thus may require either oral or IV glutamine supplementation.

In regard to IV glutamine, the American Society for Parenteral and Enteral Nutrition Clinical Guidelines concluded, "pharmacologic doses of parenteral glutamine may benefit patients undergoing hematopoietic cell transplantation." It should be noted that parenteral glutamine is not made readily available by US Food and Drug Administration (FDA)-approved manufacturers but instead as a prescription prepared by a compounding pharmacy. In three separate meta-analyses of using IV glutamine, the conclusion was the same; IV glutamine could possibly decrease the number of blood stream infections. There was no benefit with regard to length of stay, duration of TPN use, or improvement in morbidity/mortality. Oral glutamine has been shown to decrease the incidence or severity of mucositis developed by patients undergoing HSCT. Despite these positive reports, these particular studies were small, and drug dosing and administration schedules were inconsistent. More studies of glutamine supplementation, either IV or oral, are needed to determine the benefit in the HSCT population.

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Chapter 8
Physical and Occupational Therapy

Jennifer Pidkowicz

An important component of care in the spectrum of treatment of patients with cancer is assuring ongoing physical activity. Patients undergoing hematopoietic stem cell transplant (HSCT) face a multitude of side effects often resulting in diminished physical functioning and lack of engagement in physical activity of any type. An array of studies have been performed utilizing aerobic exercise with or without a strengthening component to evaluate the effect of exercise on physical functioning, cancer-related fatigue, quality of life, and cognitive functioning. Results suggest that the implementation of physical exercise is beneficial over the continuum of treatment and is a promising adjuvant intervention. This chapter summarizes the current literature and introduces the role of rehabilitation services as a part of the treatment team and recovery process.

8.1 Benefits of Physical Exercise

Prior to HSCT, many patients are at or near their "normal" level of functioning; however, others may be poorly conditioned. The side effects of the HSCT process may result in a significant loss of their baseline function. Nausea, mucositis, diarrhea, fatigue, cytopenias, graft-versus-host disease (GVHD), and compromised nutritional intake may result in prolonged bed rest and inactivity which decrease the patient's ability to engage in physical activity. It has been well studied that inactivity can have detrimental outcomes including diminished cardiovascular function, significant loss of muscle mass, pneumonia, orthostatic hypotension, and venous thrombosis with the greatest loss of physical function occurring within the first 10 days of inactivity. It has also been shown that the use of long-term corticosteroids, such as those used to treat GVHD, cause muscle fiber atrophy which contributes to clinically significant steroid myopathy.

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Multiple studies have demonstrated that engagement in a physical exercise routine can improve physical capacity. Increased walking speed and strength have been correlated with physical exercise participation, as well as the decreased potential loss of endurance. Additional studies have demonstrated that skeletal muscle mass was preserved and muscle strength was improved in cancer patients who participated in a supervised aerobic and resistive exercise routine. Improved physical capacity can minimize functional loss and restore or maintain independence in activities of daily living (ADLs).

The use of physical exercise has been shown to be effective as an adjuvant therapy for cancer-related fatigue. The National Comprehensive Cancer Network (NCCN) describes cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." HSCT may result in incapacitating fatigue, more common in allogeneic than autologous recipients. Additionally, mean fatigue scores decreased after completion of a physical exercise program. The use of exercise has been proposed to be effective in management of both acute and chronic fatigue.

Positive changes in physical functioning have been found to correlate with improvement in quality of life. Positive changes in physical, emotional, and social well-being were associated with improved muscle strength and improved aerobic capacity which correlated with decreased depression.

In summary, physical exercise may help prevent and remediate the loss of physical functioning, decrease in fatigue, and improved quality of life that is associated with HSCT.

8.2 Areas of Consideration

1. General observations from relevant research studies:
    a. All studies included some form of aerobic activity +/− strengthening exercises.
    b. Many of the studies were retrospective.
    c. Similar observations were found between studies of inpatient and outpatient recipients.
    d. There is no specified program that has been validated as the optimal combination of intensity, frequency, and duration.
2. Thrombocytopenia and anemia may often limit participation in a structured physical exercise program.
3. Programs can be graded based upon the patient's medical condition.
4. Aerobic and strengthening programs:
    a. Aerobic exercise consisted of ergometry via a stationary bicycle or bed ergometer and/or walking either around the hospital ward or on a treadmill.
    b. The average time spent on aerobic activity was between 15 and 30 min, either consecutively or in intervals.

c. The frequency over the period of 1 week varied between daily, three times/week, and five times/week.
d. The definition of moderate intensity varied greatly, ranging from 40 to 80% of the maximum heart rate or the use of the Borg Rate of Perceived Exertion Scale (see Table 8.1).
e. Studies also suggested the inclusion of strength training, using exercise bands, and/or body weight for resistance.
f. The American College of Sports Medicine (ACSM) concluded that aerobic activity should follow the Physical Activity Guidelines for Americans, which "suggests at least 150 min/week of moderate-intensity activity or 75 min/week of vigorous-intensity activity (or an equivalent combination)" with a lighter intensity and slower progression for those who have undergone HSCT.
g. As for strength training, the ACSM recommends "muscle-strengthening activities of at least moderate intensity at least 2 days/week for each major muscle group":
    i. It is important to note that these guidelines are for "survivors" or those who have completed treatment.
    ii. It has been shown that flexibility in the regimen may empower patients to continue to participate in a program by allowing them to regulate their own behavior.
    iii. This approach may also increase the patient's self-reliance and result in behavior change, especially for those who were sedentary prior to HSCT.
h. A proposed physical exercise program is outlined in Table 8.2.

Table 8.1 Borg rating of perceived exertion scale

6		How you feel when lying in bed or sitting in a chair, relaxed. Little or no effort
7	Very, very light	
8		
9	Very light	
10		
11	Fairly light	
12		Target range: how you should feel with exercise or activity
13	Somewhat hard	
14		
15	Hard	
16		
17	Very hard	How you felt with the hardest work you have ever done
18		
19	Very, very hard	
20	Maximum exertion	

Table 8.2 Recommendations for physical exercise. (Reprinted by permission from Macmillan Publishers Ltd: [BONE MARROW TRANSPLANTATION] Wiskemann and Huber (2008))

Phase of therapy	Type of exercise
Before HSCT	Mixed exercise (3–5×/week)
	Duration (session): up to 30 min
	Intensity: moderate (12–14 Borg scale, 70–80 % maximum HR)
During HSCT	Starting with endurance training (5×/week up to daily), adding resistance training with increasing platelet counts in the last third of hospitalization (2–3×/week)
	Duration (session): 10–15 min at the beginning (if helpful use the interval method), up to 30 min in the end
	Intensity: moderate (12–14 Borg scale, 70–80 % maximum HR)
After HSCT	Mixed exercise (3–5×/week)
	Duration (session): up to 30 min and more
	Intensity: moderate (12–14 Borg scale, 70–80 % maximum HR)

HR heart rate, *HSCT* hematopoietic stem cell transplant

5. Cytopenias:
   a. Historical perspectives:
      i. A study completed in 1986 suggested that physical exercise should be discontinued when a patient experienced severe thrombocytopenia (platelets < 50,000/mL) and anemia (hemoglobin < 8 g/dL).
      ii. In 1989, another study recommended that those with acute leukemia receiving chemotherapy should not complete any form of physical activity until complete remission was obtained.
   b. It has since been shown, however, that it is possible for physical exercise to be safely performed in the setting of severe cytopenias:
      i. Elter et al. demonstrated that no patients suffered bleeding complications with a platelet count < 10,000 mL or critical tachycardias with hemoglobin < 8 g/dl.
      ii. Rather than blood counts, the criteria used for terminating physical exercise were based on either bleeding or cardiac complications.
      iii. Physical exercise was also recommended to be limited in the setting of active infections and/or fever.

8.3 The Role of Rehabilitation Services

Rehabilitation services consist of occupational therapy (OT), physical therapy (PT), and speech therapy services. This section focuses on the role of OT and PT in assisting in prevention, remediation, and compensation. These two specialties comple-

ment each other; both services are beneficial and are invaluable members of the treatment team:

1. Occupational therapy:
    a. Defined by the American Occupational Therapy Association as the "therapeutic use of occupations, including everyday life activities."
    b. OT services are provided for "habilitation, rehabilitation, and the promotion of health and wellness to those who have or are at risk for developing an illness, injury, disease, disorder, condition, impairment, disability, activity limitation, or participation restriction."
    c. Addresses the "physical, cognitive, psychosocial, sensory-perceptual, and other aspects of performance to support engagement in occupations that affect physical and mental health, well-being, and quality of life."
    d. The occupational therapist strives to assist those with cancer to live within the limitations of the diagnosis itself as well as the side effects of the treatment.
    e. The individual undergoing treatment for his/her disease faces many burdens including fatigue, loss of strength, loss of independence, cognitive deficits, and anxiety. These areas may be addressed by utilization of the following methods:
        i. Adaptation and management of ADLs including but not limited to the use of adaptive techniques to both task and environment, adaptive equipment, and caregiver training to promote independence.
        ii. Utilization of energy conservation techniques via a variety of techniques including pacing, planning, delegation, and priority setting.
        iii. Addressing psychosocial concerns by engaging in lifestyle changes, relaxation techniques, coping strategies, and exploration of new valuable occupations.
        iv. Implementation of cognitive strategies to address "chemo brain" via compensatory techniques and the use of a variety of aids and adaptations.
        v. Use of physical activity including exercise, range of motion, stretching, and strengthening.
    f. Utilizes a collaborative and client-centered approach to address the side effects of cancer. The holistic nature of OT brings a broad view of the individual's needs beyond the cancer treatment. This allows the individual to be able to successfully participate in many areas of life.
2. Physical therapy:
    a. PT is defined by the World Confederation for Physical Therapy as "services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan. This includes providing services in circumstances where movement and function are threatened by aging, injury, pain, diseases, disorders, conditions or environmental factors."

b. The general goals of PT include the prevention and reduction of weakness, avoidance of loss of pulmonary function, maintenance of range of motion and joint integrity, and preservation of balance, coordination, and endurance.
c. The physical therapist may address these aims in the following ways:
    i. Functional rehabilitation and exercise including, but not limited to, aerobic activity and strengthening while monitoring the medical effects of the physical activity including cardiac and pulmonary function.
    ii. Assessment and treatment of mobility deficits.
    iii. Fall prevention strategies including the use of balance and gait training and incorporation of assistive devices (walkers, canes, etc.) as necessary.
    iv. Management of edema.
    v. Pulmonary and cardiovascular strengthening.
d. PT may provide the greatest benefit if initiated in the pre-HSCT time frame to assist with prevention rather than remediation.
e. If PT begins during the hospitalization, it is best to begin immediately after hospital admission and before the onset of treatment side effects.

Conclusion

The side effects associated with high-dose chemotherapy and HSCT may result in physical debilitation. The incorporation of physical activity has been shown to minimize the loss of strength, independence, energy, and quality of life. Although the majority of research has been performed on limited sample sizes, it can be inferred by the multitude of studies across the spectrum of cancer diagnoses that physical activity is likely to be beneficial for the HSCT population.

An optimal exercise program has not been defined; however, it has been shown that moderate aerobic activity along with a strengthening routine may help prevent steroid myopathy and improve cancer-related fatigue quality of life.

Occupational and physical therapists are essential members of the HSCT treatment team who provide recommendations on the implementation of physical activity, as well as assist with prevention, remediation, and compensation of the complications associated with treatment.

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Chapter 9
Adolescent and Young Adult Concerns

Brandon Hayes-Lattin

Since the publication of the National Cancer Institute Progress Review Group report, Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer, there has been an increasing effort to address the unique needs of patients between the ages of 15 and 39 diagnosed with cancer who often feel isolated between the worlds of pediatric and adult oncology. This group of individuals is now identified in clinical trials and in clinical care as the adolescent and young adult (AYA) population.

Historically, hematopoietic stem cell transplant (HSCT) has been applied selectively to younger, healthier patients, and hematologic malignancies are among the most common cancers of the AYA population. Therefore, attention to their age-specific needs constitutes quality care. Each domain of AYA cancer care (Table 9.1) should be approached with the patient's age and developmental status in mind. An ideal AYA team consists of medical providers, nurse specialists, social workers, vocational counselors, fertility experts, geneticists, physical and occupational therapists, and community-based services with peer support.

Priority concerns for these domains are listed below:

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Table 9.1 Domains of AYA cancer care

Domain	Examples
Medical	Oncology, palliation, nutrition, endocrinology, etc.
Emotional	Psychology, coping, distress
Physical	Exercise, activities of daily living, myopathy
Neurocognitive	Education, vocation
Social	Relationships with peers and providers
Reproductive	Fertility preservation, parenting options
Financial	Disability, insurance
Lifestyle issues	Environment, risky behaviors, balance with treatment
Late effects	Prevention, monitoring
Care community	Caregivers, family, friends

AYA adolescent and young adult

9.1 Medical

1. Leukemias, lymphomas, and germ cell tumors are common cancers among AYA-aged patients; HSCT may play an important role in the therapy of these malignancies:
   a. Compared to children, the treatment-related morbidity and mortality may be increased for AYAs, but less so than for older adults.
   b. Changes in initial treatment (such as pediatric-inspired therapies for acute lymphoblastic leukemia) have led to a reconsideration of the role of HSCT in first remission in some circumstances.
   c. An increased understanding of unique biologic features in cancers among AYAs compared to children or older adults may alter prognostic tools and the recommended role and timing of HSCT for the AYA patient.
2. Attention to age-specific details related to growth and development may influence medical needs and care, including issues in endocrinology (see also Chap. 26) and nutrition:
   a. Growth hormone
   b. Thyroid
   c. Gonadotropins
   d. Adrenal
3. A variety of genetic syndromes may present with cancer in the AYA age range including Fanconi anemia, Li–Fraumeni syndrome, dyskeratosis congenita, and others.

9.2 Emotional

1. Distress, depression, anxiety
2. Issues of existentialism
3. Sexuality
4. Development of coping mechanisms

9.3 Physical

1. Changes in appearance
2. Sexual development and function
3. Activity limitations

9.4 Neurocognitive

1. Neuropsychological assessments
    a. Consider formal assessment at baseline with follow-up assessments as indicated
2. Vocational training

9.5 Social

1. Changes in peer relationships
2. Family relationships (spouse, children, parents):
    a. Loss of autonomy
    b. Changes in roles and responsibilities
3. Coworkers and employer
4. Health-care providers, many of whom may also be young adults

9.6 Reproductive

1. Guidelines from the American Society of Clinical Oncology recommend that a discussion of the possibility of infertility be part of education and informed consent for all patients of reproductive age:

a. Discussion should include risks, fertility preservation options, and appropriate referrals to reproductive specialists:

   i. Every effort should be made to discuss fertility as early as possible after a cancer diagnosis
   ii. Published guidelines also state that fertility preservation should be readdressed prior to HSCT.
   iii. In addition to fertility preservation options, alternative parenting methods including adoption or surrogacy should also be discussed.

2. Males:

   a. Risk: Rates of azoospermia after high-dose conditioning regimens are as high as 90 %, although rates for those treated with busulfan and cyclophosphamide are 50 %, and with cyclophosphamide alone 10 %
   b. Assessment: Semen analysis for quantitative analysis and motility
   c. Fertility preservation options:

      i. Sperm banking:

         - Pros:

            o Inexpensive
            o Noninvasive

         - Cons:

            o Hampered by findings of decreased sperm motility, azoospermia
            o Psychological/emotional stress leading to inability to ejaculate

   d. Gonadal tissue cryopreservation:

      i. This is the only method available for preserving fertility in prepubertal males and remains investigational.
      ii. Theoretical risk of reseeding tumor cells after reimplantation of tissue

3. Females:

   a. Risk: Rates of ovarian failure after high-dose conditioning regimens are as high as 65–85 %. However, this statistic may not be accurate as studies do not account for whether patients are trying to conceive. Younger age at HSCT may be associated with lower risks of infertility.
   b. Assessment: Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), estradiol level, ovarian follicle assessment by ultrasound
   c. Fertility preservation options:

      i. *In vitro* fertilization and embryo cryopreservation:

         - Pros:

            o Well-established therapy
            o Success rate of 26–36 %

- Cons:
  - Requires 2–3 weeks from initiation of therapy to oocyte retrieval
  - Requires a partner for sperm donation or willingness to accept banked sperm
  - High cost

ii. Oocyte cryopreservation:

- Pros:
  - No fertilization required prior to cryopreservation
- Cons:
  - Oocytes more susceptible than embryos to damage during freezing/thawing
  - Requires 2–3 weeks from initiation of therapy to oocyte retrieval
  - High cost

iii. Hormonal suppression with gonadotropin-releasing hormone (GnRH) analogue:

- Pros:
  - Easy to administer with no delay in therapy
- Cons:
  - Efficacy is not well established
  - Not sufficient alone to preserve fertility in HSCT recipients
  - Associated with bone loss which may cause other long-term complications

iv. Ovarian tissue banking:

- Pros:
  - No hormonal stimulation required, therefore minimal risk of delay in therapy
- Cons
  - Theoretical risk for reseeding tumor cells after reimplantation of tissue

v. Gonadal tissue banking:

- This is the only method available for preserving fertility in prepubertal girls and remains investigational.

9.7 Financial

1. Insurance (medical, life, disability)
2. Employment
3. Housing and transportation
4. Financial loss or bankruptcy

9.8 Lifestyle Issues

1. Substance use (alcohol, tobacco, recreational drugs)
2. Sleep patterns
3. Attention to flexibility in scheduling
4. Modifications to increase adherence

9.9 Late Effects

9.10 Care Community

1. Family (parents, spouse, siblings; see Chap. 34)
2. Partner
3. Peers (friends, AYA organizations)
4. Community (religious organizations, clubs, networks)

9.11 AYA-Specific Resources

1. National Cancer Institute (http://www.cancer.gov/cancertopics/aya)
2. NCCN guidelines (http://www.nccn.org/professionals/physician_gls/pdf/aya.pdf)
3. American Society of Clinic Oncology (http://university.asco.org/focus-under-forty)
4. Critical Mass: The Young Adult Cancer Alliance (http://criticalmass.org)

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Chapter 10
Infection Prophylaxis

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Abstract Infection remains an important cause of non-relapse morbidity in hematopoietic stem cell transplant (HSCT). Recipients, specific risk for infection is related to prior exposure history (e.g. replace of latent infection) intensity of the conditioning regimen, immunosuppressive agents utilized, and new exposure in the setting of altered host immune response. Prevention of infection by way of prophylactic and preemptive strategies has been associated with improvement in transplant outcomes over the past few decades.

10.1 Herpes Simplex Virus/Varicella Zoster Virus Prophylaxis

1. If nausea or mucositis precludes oral intake, change to intravenous (IV) acyclovir until patient is able to tolerate oral intake (Table 10.1). Valacyclovir is an acceptable alternative for prophylaxis. For dosing recommendations, see Tables 10.1 and 10.2.
2. If patient develops overt signs of oral or genital mucocutaneous herpes simplex virus (HSV) infection while on prophylactic dosing, increase to treatment doses of oral acyclovir (400 mg po 5×/day) or valacyclovir (500–1000 mg po twise daily (BID)) or change to acyclovir 5 mg/kg IV q8hr (adjusted for renal function).
3. If symptoms persist despite therapeutic doses of acyclovir, consider the possibility of acyclovir-resistant HSV which may entail treatment with foscarnet or other approaches. In this instance, obtaining viral culture (for growth of an isolate) and resistance testing should be considered, along with consultation to the infectious diseases service.
4. Varicella zoster virus (VZV)-seronegative allogeneic recipients who are <24 months post-transplant, >24 months post-transplant and on immunosuppressive therapy or who have active chronic graft-versus-host disease (GVHD)*,

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Table 10.1 Post–transplant acyclovir prophylaxis

	VZV−/HSV−	VZV−/HSV+	VZV+/HSV−/+
Autologous	No prophylaxis required	Acyclovir 800 mg po daily through day +365	Acyclovir 800 mg po daily through day +365
Allogeneic	No prophylaxis required[a]	Acyclovir 800 mg po BID through day +365 or off all immune suppression	Acyclovir 800 mg po BID through day +365 or until off all immune suppression, whichever comes later

[a] Prophylaxis should be considered on a case-by-case basis, acknowledging serology may not be informative following use of agents such as rituximab and alemtuzumab
VZV Varicella zoster virus, *HSV* Herpes simplex virus, *BID* twice daily

Table 10.2 Dosing recommendations for acyclovir and valacyclovir

			Renal impairment	
		CrCl ≥ 50 mL/min	CrCl 30–49 mL/min	CrCl < 30 mL/min
Acyclovir PO	Autologous Allogeneic	800 mg po daily 800 mg po BID	800 mg po daily 800 mg po daily	400 mg po daily 400 mg po daily
Valacyclovir PO	Autologous Allogeneic	500 mg po daily 500 mg po BID	500 mg po daily 500 mg po daily	500 mg po daily 500 mg po daily
Acyclovir IV	Autologous or allogeneic	250 mg/m^2 IV Q12H	250 mg/m^2 IV Q24H	250 mg IV Q24H

PO per osal, *IV* intravenous, *BID* twice daily

who have had close contact with a person with either primary VZV infection (chickenpox) or herpes zoster (shingles) should receive VZV-specific immunoglobulin as soon as possible for up to 10 days following the exposure. VariZIG® (Cangene Corporation, Winnipeg, Canada) is a purified human varicella zoster immune globulin preparation. If VariZIG® cannot be obtained, consider IV immunoglobulin 400 mg/kg × 1 dose, although the data to support efficacy are limited.

*Note: These patients are *not* candidates for postexposure varicella immunization as it is a live attenuated virus vaccine.

5. Family members and close contacts who receive the Varivax® or Zostavax® vaccine and develop a rash within 3–6 weeks after vaccination should avoid contact with the hematopoietic stem cell transplantation (HSCT) recipient to decrease risk for transmission of vaccine-strain virus.
6. If a transplant recipient is hospitalized with or develops VZV infection during hospitalization (either primary infection or reactivation infection with or without dissemination), isolation should consist of contact and airborne precautions in a negative airflow room to limit the risk for transmission on the transplant unit. Placement off the transplant ward should be considered.

10.2 Cytomegalovirus Disease Prevention

1. HSCT candidates who are cytomegalovirus (CMV)-seronegative should receive either CMV serongative or leukocyte-reduced blood products to decrease the risk of primary CMV infection. In this setting, a CMV-seronegative donor is preferred if other factors (e.g., human leukocyte antigen (HLA) match, etc.) are equal.
2. *Autologous recipients*: No CMV surveillance is required for unselected autologous recipients, unless clinically indicated (e.g., patients with protracted fevers, gastrointestinal (GI) symptoms). If patient has documented CMV disease within 1 year prior to transplant, CMV polymerase chain reactions (PCRs) should be followed weekly through day +100.
    a. CMV-seropositive autologous recipients who have received major T cell suppression prior to HSCT (e.g., alemtuzumab), total body irradiation as part of the conditioning regimen, high-dose corticosteroids for another indication, and/or T cell depleted (CD34 + selected) grafts are at risk for symptomatic CMV infection or disease and should have preemptive monitoring post–transplant.
3. *Allogeneic recipients*: Both prophylactic and preemptive strategies can be used to prevent CMV disease in allogeneic recipients. A preemptive approach is used most commonly, but prophylaxis is undertaken by some centers and in certain circumstances, particularly for high-risk patients such as recipients of cord blood or haploidentical products.
    a. Given the poor outcomes associated with CMV disease prior to allogeneic transplantation, patients with documented pre-transplant CMV infections warrant special consideration with regard to preemptive monitoring strategies, and even consideration for prophylaxis in some settings.
4. For *preemptive monitoring,* CMV DNA viral load is the standard test, supplanting CMV pp65 antigenemia which has its limitations in the setting of leukopenia. Ideally, measurement of CMV DNA should be with the international reference standard to decrease inter-laboratory variability.
5. Preemptive monitoring should occur with sufficient regularity so as to allow time for intervention prior to the onset of CMV end-organ disease.
6. *At our center,* we use the following protocol for preemptive monitoring:
    a. Patients who are CMV-seronegative with a CMV-seronegative donor should have monthly CMV PCRs through day +100, and when clinically indicated (e.g., if protracted fevers, GI symptoms, unexpected cytopenias, etc.).
    b. Patients who are CMV-seropositive or who have a CMV-seropositive donor should have weekly CMV PCRs through day +100.
    c. *Any patient with CMV infection prior to or after day +100* should have prolonged surveillance.

i. If no GVHD is present, continue surveillance weekly for 3 months following infection, then every other week for 3 months.
ii. If GVHD is present, continue surveillance weekly for 1 year following CMV infection.

7. *Preemptive therapy* is typically initiated after the detection of CMV DNA (or antigenemia); it should be recognized, however, that there are no standardized or validated thresholds. Prophylactic acyclovir should be discontinued if preemptive therapy for CMV infection is initiated.
8. While there is a growing literature to support the safety and efficacy of oral valganciclovir as an approach to preemptive therapy in HSCT recipients, IV ganciclovir or foscarnet remain the guideline recommendation at this writing.
9. Chest X-ray should be performed at the time of documentation of CMV reactivation, with finer imaging reserved for symptomatic presentation.
10. *At our center***,** we incorporate oral valganciclovir as preemptive therapy for any patient without signs/symptoms suggestive of CMV end-organ disease and meeting all of the following criteria:

a. No signs/symptoms or suspicion of CMV end-organ disease
b. Normal chest X-ray
c. Absence of GI complaints (nausea, vomiting, diarrhea)
d. Afebrile
e. CMV viral load < 5000 copies/mL
f. No history of medication noncompliance
g. Able to tolerate adequate oral intake/medications
h. No evidence of active gut GVHD

i. Preemptive valganciclovir consists of induction dosing until quantitative PCR assays are negative for two consecutive weeks, then maintenance dosing for 2 weeks (renal dose adjustment as indicated, outlined in Table 10.3).

Table 10.3 Dosing recommendations for valganciclovir in renal impairment

	Normal renal function	Renal impairment[a]			
CrCl	≥60 mL/min	40–59 mL/min	25–39 mL/min	10–24 mL/min	<10 mL/min (hemodialysis)
Induction	900 mg po BID	450 mg po BID	450 mg po daily	450 mg po QOD	*Do not* use–no dosing guidlines available
Maintenance	900 mg po daily	450 mg po daily	450 mg po QOD	450 mg po twice weekly	*Do not* use–no dosing guidlines available

[a] Patients with renal insufficiency should receive valganciclovir 900mg po BID x 2 doses; the dose should then be adjusted for their renal function as outlined in Table 10.4
BID twice daily. QOD every other day.

Table 10.4 Dosing recommendations for ganciclovir in renal impairment

	Normal renal function	Renal impairment[a]			
CrCl	≥70 mL/min	50–69 mL/min	25–49 mL/min	10–24 mL/min	<10 mL/min (hemodialysis)
Induction	5 mg/kg IV q12hr	2.5–5 mg/kg IV q12hr	2.5 mg/kg IV q24hr	1.25 mg/kg IV q24hr	1.25–2.5 mg/kg IV 3×/week (dose following dialysis)
Maintenance	5 mg/kg IV q24hr	2.5 mg/kg IVq24hr	1.25 mg/kg IV q24hr	0.625 mg/kg IV q24hr	0.625 mg/kg IV 3×/week (dose following dialysis)

[a] Patients with renal insufficiency should receive ganciclovir 5 mg/kg IV q12hr × two doses. The dose should then be adjusted for renal function as outlined above
IV Intravenous

ii. If viral load continues to rise after 14 days of valganciclovir therapy, change to induction dose IV ganciclovir (renal dose adjustment as indicated, outlined in Table 10.4) and consider the possibility of ganciclovir-resistant CMV. In this setting, consultation with the infectious diseases service is advised. If concern for ganciclovir resistance is sufficiently high, resistance testing (typically by genotypic analysis) should be obtained, with consideration for an empiric switch to foscarnet in patients who develop life- or sight-threatening disease (see Chap. 17).

iii. If the patient does not meet criteria for preemptive valganciclovir as outlined above, preemptive therapy should consist of ganciclovir 5 mg/kg IV BID* until quantitative PCR assays are negative for two consecutive weeks, then 5 mg/kg IV daily* for 2 weeks. Then, if PCR assays remain negative, discontinue ganciclovir and restart prophylactic acyclovir. *All doses should be adjusted based on renal function, as indicated in Table 10.4.

11. If CMV reactivation occurs after day +100, the decision to treat preemptively will depend on the height of the circulating viral load as well as host immune status. Preemptive treatment should be with either oral valganciclovir or IV ganciclovir, as outlined above.

10.3 Antibacterial Prophylaxis

1. Fluoroquinolone prophylaxis should be considered for patients with expected duration of profound neutropenia (absolute neutrophil count (ANC) ≤100 cells/mm^3) >7 days. Both levofloxacin and ciprofloxacin are reasonable options

for this indication, though levofloxacin offers an advantage in situations with increased risk for mucositis-related viridans group streptococcal infection. If fluoroquinolone prophylaxis is undertaken by a center, systematic monitoring for the emergence of fluoroquinolone-resistant Gram-negative bacilli is important.
2. *At our center,* autologous and allogeneic recipients receive levofloxacin 500 mg po daily from day 1 until ANC > 500/mm^3 on 2 consecutive days or until first neutropenic fever (temperature ≥ 38.0 ℃) occurs, at which time, empiric broad-spectrum parenteral antibiotic therapy is begun (see Chap. 17) after appropriate cultures are obtained.
3. If patient is unable to tolerate oral medications, use IV formulation of quinolone (e.g., levofloxacin 500 mg IV daily).
4. In the case of a documented quinolone allergy or intolerance, IV cefepime could be considered as a substitute after consideration of risks/benefits.

10.4 Encapsulated Organism Prophylaxis for Patients with Chronic GVHD

1. All patients with chronic GVHD and all asplenic patients should receive prophylaxis for encapsulated organisms with oral penicillin (250–500 mg po twice daily or 500–1000 mg po once daily).
2. Alternatives for patients who are penicillin-allergic include azithromycin 250 mg po daily (in particular in patients with chronic bronchiolitis obliterans syndrome) or trimethoprim/sulfamethoxazole single strength 1 tablet po daily.

10.5 Antifungal Prophylaxis

1. Autologous and allogeneic recipients should receive antifungal prophylaxis post–transplant, acknowledging the survival benefit associated with the use of fluconazole for this indication.
2. *At our* center:
   a. Autologous recipients receive fluconazole 400 mg po/IV daily beginning day 0 and continuing through day + 30, with consideration for continuation until day + 75.
   b. Allogeneic recipients receive fluconazole 400 mg po/IV daily beginning day 0 and continuing until day + 75 for nonmyeloablative transplants or day + 100 for myeloablative transplants, longer for those patients with prolonged neutropenia or steroid dosing > 20 mg per day of prednisone equivalent.
3. In patients at risk for invasive aspergillosis (large, allogeneic recipients) who are receiving fluconazole prophylaxis, weekly serum galactomannan monitoring

Table 10.5 Dosing recommendations for azole antifungals

Drug	Adult dose (Prophylaxis)	Comments
Fluconazole	400 mg po/IV daily[a]	
Posaconazole[b]	300 mg po BID for one day, then 300 mg po QD (tablet)[c] 200 mg po TID (suspension)	To maximize absorption, dose with meals and ensure no proton-pump inhibitor/ H2-blocker therapy
Voriconazole[b]	6 mg/kg IV q12 × 2 doses (loading dose), then maintenance weight-based dosing: <40 kg: 100 mg BID 41–50 kg: 200 mg BID 51–60 kg: 250 mg BID >60 kg: 300 mg BID *(round to nearest 50 mg for oral, with maximum dose 300 mg BID)*	Oral dosing on an empty stomach to maximize absorption

[a] Renal dose adjustment required, dose at 200 mg daily for CrCl < 50 mL/min.
[b] Newer azoles are metabolized primarily by cytochrome P450 enzymes, and as such there are numerous critical drug–drug interactions to be mindful of, including by not limited to the calcineurin inhibitors and sirolimus as well as multiple chemotherapeutic agents. Consult package insert, Bruggemann et al. (2009), transplant pharmacist, and/or infectious diseases consultation service before prescribing these medications.
[c]Tablet from prefered, given superior absorption
TID the times daily, *BID* twice dalily, *IV* Intravenous

should be considered through day +100 and longer for those patients with prolonged neutropenia or steroid dosing >20 mg per day of prednisone equivalent.

4. Alternatives to fluconazole prophylaxis (if dose-limiting liver function test abnormalities, documented allergy, or significant drug–drug interactions) include an echinocandin (e.g., micafungin 100 mg IV daily) or low-dose liposomal amphotericin B products (eg., 3 mg/kg three times weekly).
5. Patients who receive high-dose steroids after transplant (≥0.4 mg/kg/day of methylprednisolone equivalent) for treatment of GVHD or for any other indications (e.g., idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, etc.) should receive extended-spectrum azole prophylaxis, ideally with posaconazole. See Table 10.5 for azole antifungal dosing recommendations.
6. Patients with pre–transplant history of invasive aspegillosis should receive secondary prophylaxis with a mold–active agent (e.g. voriconazole or posaconazole).
7. If enteral aborption is problematic or if oral intake is insufficient, change posaconazole prophylaxis to voriconazole. See Table 10.5 for azole antifungal dosing recommendations.
8. Alternatives to extended-spectrum azole prophylaxis (if dose-limiting liver function test abnormalities, documented allergy, QT_c prolongation, or significant drug–drug interactions) include liposomal amphotericin products (eg., 3 mg/kg three times weekly, with close monitoring of renal function) or an echinocandin product (e.g., micafungin 100 mg IV daily), though noting echinocandins are less optimal given the risk for breakthrough mold infection.

10.6 Azole Antifungal Monitoring Guidelines

At our center, we monitor voriconazole/posaconazole drug levels for all patients on these agents, given the variability in achievable serum concentration and the suggestion that therapeutic outcomes, as well as toxicity in the case of voriconazole, are dependent on drug level.

1. Voriconazole level should be checked within 1 h prior to dose on/about day 5–7 after drug initiation. Target level for voriconazole prophylaxis is: 1–5 mcg/mL.
    a. If subtherapeutic voriconazole levels are found, dose adjustment by 50 or 100 mg/dose may be made, with repeat level checked 5–7 days after dose adjustment.
2. A posaconazole level should be checked within 1 hour prior to dose on/about day 10 (days 7–10) after drug initiation. Target level for posaconazole prophylaxis is: 0.5–1.5 mcg/mL.
    a. If subtherapeutic levels of posaconazole are found, posaconazole absorption can be increased by increasing the dose up to 200 mg po Q10, administering with food (high-fat meals) or nutritional supplement, and avoiding acid suppressants (proton pump inhibitors and H2 antagonists). Due to saturable absorption, the posaconazole dose should not be increased beyond 800 mg/day (suspension); for the tablet formulation, doses exceeding 300 mg/day have not been studied.
3. If drug level does not fall within suggested target range despite dose adjustment, consult with transplant pharmacist, and/or infectious diseases service for advice on dose adjustment or other maneuvers to optimize dosing.

10.7 *Pneumocystis Jirovechii* Prophylaxis

1. All HSCT recipients should receive *Pneumocystis* prophylaxis.
2. *At our center,* patients receive trimethoprim/sulfamethoxazole DS 1 tablet po BID beginning on the first day of their conditioning regimen, continuing through day + 2.
3. Both autologous and allogeneic patients should resume *Pneumocystis* prophylaxis following engraftment, typically between day + 30 and + 40.
4. Standard prophylaxis is trimethoprim/sulfamethoxazole DS 1 tablet po BID twice weekly.
5. Alternatives in sulfa-allergic patients or patients with limited marrow reserve post-HSCT include*:
    a. Dapsone 100 mg po daily (consider checking G-6PD level prior to initiation and monitor for methemoglobinemia if the long-term use is required)

b. Pentamidine 4 mg/kg IV or 300 mg aerosolized q4 weeks
c. Atovaquone 750 mg BID or 1500 mg po daily

*Barring clear contraindications to trimethoprim/sulfamethoxazole, this is the agent of choice for *Pneumocystis* prophylaxis given its superior efficacy for this indication, as well as some degree of protection against atypical bacteria such as *Listeria* and *Nocardia* which the alternatives lack.

6. *Pneumocystis pneumonia* (PCP) prophylaxis should continue for a total of 6 months for autologous recipients and until discontinuation of all immunosuppressive therapy in allogeneic recipients.

10.8 Viral Hepatitis

1. Patients who are hepatitis B virus (HBV) infected (HBV surface antigen and/or HBV DNA positive) should be evaluated by hepatology and/or the infectious diseases services prior to transplant, with consideration for HBV-active antiviral therapy (e.g., lamivudine or entecavir) prior to proceeding with the transplant conditioning regimen.
   a. During the course of antiviral therapy, HBV DNA should be monitored to ensure suppression, in particular in the setting of abnormal liver function tests.
   b. HBV-active antiviral therapy should be continued for at least 6 months post-transplant in autologous recipients and at least 6 months following discontinuation of immunosuppressive therapy in allogeneic recipients.
2. Patients who are hepatitis C virus (HCV) infected (HCV RNA positive) prior to transplant should be evaluated by hepatology for evidence of underlying cirrhosis, with consideration for liver biopsy when indicated.
   a. Those patients with documented cirrhosis or hepatic fibrosis should receive a conditioning regimen that does not contain either cyclophosphamide or total body irradiation, as those regimens pose an increased risk of hepatic sinusoidal obstruction syndrome.
   b. Treatment for chronic HCV should be considered in HSCT recipients who are in remission from their underlying disease, ≥ 2 years post–transplant without active GVHD, and off immune suppression for at least 6 months
   c. With the introduction of direct-acting antiviral agents, associated with greatly improved cure rates and less regimen-related toxicity, it is anticipated that recommendations regarding management of HCV infection in transplant candidates/recipients will evolve in the near future.

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Chapter 11
Graft-Versus-Host Disease Prophylaxis

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Acute graft-versus-host disease (aGVHD) is the leading cause of nonrelapse mortality in allogeneic transplant patients. Efforts have been made to identify patient, donor, graft, and genetic risk factors for the development of aGVHD. Common risk factors include increased age of recipient, gender disparity, indication for transplant, use of unrelated donor, human leukocyte antigen (HLA) mismatch, ABO antigen disparity, graft stem cell source and dose, and low quantity of regulatory T cells (Tregs). In addition, conditioning regimens and posttransplant medication management can have a significant impact on rates of both aGVHD and chronic GVHD (cGVHD). Current conditioning regimens are considered myeloablative, low intensity, or nonmyeloablative in nature. The combination of medications and doses used in conditioning regimens is associated with varying degrees of recipient toxicity and creates complex host/graft environments.

It has been proposed that there is a sequence of events leading to the development of aGVHD. First, the host environment is damaged by the transplant-conditioning regimen. As a result, pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interferon (IFN) are released and host antigen-presenting cells (APCs) are activated. Second, donor T cells activate when they bind to host APCs. Organ damage, most commonly skin, gut, and liver, may result as a consequence of donor T cell proliferation and differentiation. The aim of recent efforts has been to decrease host damage, reduce host inflammation, and regulate donor T cell quantity and type.

This chapter focuses on standard management, new approaches, and future directions of GVHD prophylaxis as they relate to conditioning regimens, donor T cell manipulation, and posttransplant medication management.

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11.1 Standard Prophylaxis

Despite the type of conditioning regimen used, standard aGVHD prophylaxis to date has focused on the use of double or triple drug combinations which include calcineurin inhibitors (CNIs; such as cyclosporine and tacrolimus), methotrexate, prednisone, mycophenolate mofetil (MMF), and sirolimus:

1. The backbone of the prophylactic regimen has utilized CNIs.
2. Long-course methotrexate (four doses, days +1, 3, 6, and 11) is often added as a second agent.
3. Phase III data has demonstrated the use of sirolimus as an acceptable alternative to methotrexate as a second agent. Blood and Marrow Transplant-Clinical Trials Network (BMT-CTN) 0402 trial demonstrated no difference in the rate of aGVHD-free survival between the two arms for patients undergoing myeloablative hematopoietic stem cell transplantation (HSCT) with cyclophosphamide/total body irradiation conditioning. Nephrotoxicity was encountered when utilized with busulfan/cyclophosphamide.
4. The addition of prednisone as a third agent can be employed when short-course methotrexate (days +1, 3, and 6) is used.
5. As an alternative approach, MMF may be added to CNI.

11.2 New Approaches

Only 30% of patients who require an allogeneic transplant have an HLA-matched sibling donor. An alternate donor source must be identified. These options include an unrelated donor, a suitable cord blood unit(s), or a haploidentical family member. The development of novel strategies for preventing GVHD such as antibody-mediated in vivo T cell depletion and in vitro T cell depletion of donor grafts has contributed to the increased use of single and double cord blood and haploidentical donor transplants:

1. Antithymocyte globulin (ATG) and alemtuzumab (Campath®) have been studied as mechanisms for preventing GVHD by creating antibody-mediated in vivo T cell depletion:
    a. ATG is primarily used as part of the conditioning regimen in unrelated donor and unmanipulated haploidentical transplants with a goal of obtaining GVHD rates similar to those of HLA-matched sibling donor transplants.
    b. Alemtuzumab can also be used as part of the conditioning regimen for unrelated donor transplants and has been shown to be an acceptable alternative to ATG in decreasing rates of aGVHD.
    c. Post-transplant high-dose cyclophosphamide has been used with the goal of lysing activated, replicating, alloreactive donor T cells. Piloted at Johns Hopkins Medical Center, this approach for haploidentical transplantation was validated in a multicenter trial, BMT-CTN 0603, and is being considered in more standard transplant settings.

2. Although ATG, alemtuzumab, and cyclophosphamide may provide the ability to infuse T-cell-replete grafts in mismatched transplants with low rates of GVHD, the use of T cell depletion techniques is reemerging as a viable option:
   a. Single agent or no pharmacologic GVHD prophylaxis may be possible in patients receiving T-cell-depleted grafts (BMT-CTN 0303):
      i. Modified and unmodified T cell add back is currently being studied in a variety of clinical trials.
      ii. The roles of alloreactive natural killer (NK) cells and Tregs in standard and haploidentical transplants are being defined.
      iii. Add back of genetically modified T cell populations designed to allow for a "suicide gene" may have benefits in limiting the development of life-threatening GVHD.

11.3 Future Directions

1. Both bortezomib (Velcade®) and maraviroc (Selzentry®) are currently under study as GVHD prophylactic agents:
   a. Bortezomib:
      i. Immunomodulatory properties allow for in vivo depletion of alloreactive T cells and are hypothesized to spare Tregs.
      ii. Phase I/II trials have examined the effects of post-transplant bortezomib on the rates of aGVHD in HLA-mismatched patients and have shown both acute and chronic rates similar to those in HLA-matched transplant patients.
   b. Maraviroc:
      i. This drug's chemokine receptor 5 (CCR5) antagonist effects are hypothesized to result in a reduction of lymphocyte recruitment to tissues involved in GVHD.
      ii. A combined phase I/II study of maraviroc with standard GVHD prophylaxis in reduced-intensity allogeneic transplants has demonstrated a low incidence of GVHD, warranting further investigation.

11.4 Agents used for GVHD Prophylaxis

1. Cyclosporine and tacrolimus:
   a. Mechanism of action/place in therapy:
      i. Inhibit calcineurin resulting in a decreased production of interleukin 2 (IL-2). IL-2 is one of the major cytokines responsible for activation and proliferation of T cells

ii. Used in conjunction with methotrexate for the prevention of GVHD in myeloablative transplants and in conjunction with mycophenolate for prevention of GVHD in nonmyeloablative transplants

b. Dose and administration:

i. Cyclosporine in myeloablative transplants:

- Continuous infusion:
  - 3 mg/kg/day IV beginning day −1
  - May begin with 5 mg/kg/day IV from day −1 to day +3 before converting to 3 mg/kg/day
- Bolus dosing:
  - IV: 1.5–2 mg/kg/dose IV every 12 hours beginning day −2. Infuse over 2–4 hours.

ii. Cyclosporine in nonmyeloablative transplants:

- Continuous infusion:
  - 3 mg/kg/day IV beginning anywhere from day −3 to day −1
  - May begin with 1 mg/kg/day IV from day −7 to day −2 before converting to 3 mg/kg/day on day −1
- Bolus dosing:
  - PO: 4 mg/kg/dose PO every 12 hours beginning day −3

iii. Tacrolimus in myeloablative transplants:

- Continuous infusion:
  - 0.02–0.03 mg/kg/day IV beginning anywhere from day −3 to day −1
- Bolus dosing:
  - IV: 0.015 mg/kg/dose IV every 12 hours beginning day −1. Infuse over 2–4 hours.
  - PO: 0.05–0.075 mg/kg/dose PO every 12 hours beginning day −1

iv. Tacrolimus in nonmyeloablative transplants:

- Bolus dosing:
  - PO: 0.025–0.03 mg/kg/dose PO every 12 hours beginning day −3

v. Conversion from IV to PO

- Cyclosporine: convert to PO Gengraf or equivalent using an IV:PO conversion factor of 1:1.8 or 1:2. Gengraf or equivalent must be used; *do not* use Sandimmune®.
- Tacrolimus: convert to PO as soon as possible using an IV:PO conversion factor of 1:3 or 1:4

vi. Conversion from cyclosporine to tacrolimus:

- Monitor daily cyclosporine levels and begin tacrolimus when cyclosporine level is < 100–125 ng/mL.

- Begin tacrolimus at 1/3 the normal starting dose and titrate up slowly if using in conjunction with an azole antifungal.

vii. Tapering doses:

- Tapering schedule varies based on protocol and institutional standards. Day of taper initiation and duration of therapy vary from center to center.
- General rules:
  - Taper dose approximately 10 % each week if no GVHD
  - Begin taper at approximately day +100 and discontinue by day +365 (earlier for nonmyeloablative transplants)

viii. Other information:

- Hold cyclosporine or tacrolimus dose on day 0 if scheduled within 4 hours of stem cell infusion.
- Cyclosporine IV is usually given as bolus doses. Patients may experience an increased rate of aGVHD grade II–IV when cyclosporine is given as a continuous IV infusion. However, continuous infusion may confer better disease-free survival in high-risk patients.
- There is no statistically significant benefit to administering cyclosporine for 24 months versus 6 months with regard to the development of cGVHD.
- Tacrolimus IV is usually given as a continuous infusion rather than bolus doses due to increased renal and neurologic toxicity seen with bolus doses.

c. Monitoring:

i. Trough concentrations vary based on protocol and institutional standards.
ii. Trough concentrations:

- Cyclosporine in myeloablative transplants: 150–450 ng/mL.Usual range is 200–300 ng/mL.
- Cyclosporine in nonmyeloablative transplants: 100–300 ng/mL.In higher concentrations, early posttransplant may be warranted:
  - Day +3 through day +28: 300–400 ng/mL
  - Day +29 through day +56: 250–350 ng/mL
- Tacrolimus in myeloablative transplants: 5–20 ng/mL. Usual range is 5–10 ng/mL.
- Tacrolimus in nonmyeloablative transplants: 5–20 ng/mL.

iii. Checking levels:

- Levels are to be checked no sooner than 36 hours following a change in dose or schedule (at least 6 doses if given every 12 hours).
- Routine monitoring of levels should occur twice a week.

- If giving drug by continuous infusion, hold infusion for a minimum of 15 minutes prior to collecting level.

iv. Other information:

- IV infusions should always occur through the same IV line. An alternate site should be used for collecting trough levels.
- Patient will have a spuriously high level if sample is drawn from the line used for infusion. Draw an additional level from a peripheral stick to confirm the accuracy of an abnormally high level.
- Achieving target cyclosporine concentrations in the second week of transplant and the week prior to engraftment will significantly reduce the chance of developing aGVHD.

d. Dose adjustments:

i. Adjust doses by 10–15% each time serum levels are outside of goal range.
ii. Adjust doses by up to 30% each time depending on severity of hepatic insufficiency.
iii. Adjust doses for renal insufficiency caused by cyclosporine or tacrolimus (see Table 11.1):

- The risk of creatinine >2× baseline increases by 94% when the mean concentration of cyclosporine is >300 for 7–14 days.
- The risk of creatinine >2× baseline increases by 41% when the mean concentration of tacrolimus is >20 for 7–14 days.

iv. Dose adjust for drug interactions with CYP 3A4 inhibitors such as amiodarone, azole antifungals, calcium channel blockers, nicardipine, macrolide antibiotics, protease inhibitors, and some tyrosine kinase inhibitors:

- Depending on the strength of azole antifungal as an inhibitor, cyclosporine doses may need to be reduced as much as 60% when given concomitantly with the azole.
- Adjust doses by up to 20% each time.

Table 11.1. Dose adjustment for renal insufficiency

Creatinine (mg/dL)	Cyclosporine/tacrolimus dose
1.5–1.75 (or 1–1.5× baseline)	50–75% of current dose
1.76–2 (or 1.6–1.9× baseline)	25–50% of current dose
>2 (or >1.9× baseline)	Hold until creatinine <2 then resume at 50–75% of prior dose

v. Dose adjust for drug interactions with CYP 3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin.

e. Adverse effects (*Note:* There is no strict correlation between toxicity and level):

i. Adverse effects common to cyclosporine and tacrolimus:

- Hypertension:
  - Treat with a calcium blocker, such as nifedepine ER or amlodipine.
  - Avoid angiotensin converting enzyme (ACE) inhibitors and diuretics with cyclosporine. They can exacerbate the already reduced renal blood flow caused by cyclosporine due to afferent arteriole vasoconstriction.
  - It is critically important to maintain DBP < 90.
- Renal impairment:
  - Decrease dose to avoid continued damage to kidneys. See dose adjustments listed above.
- Electrolyte abnormalities: hypomagnesemia, hyperkalemia
- Neurotoxicity: tremors, ataxia, headache, seizures
  - Obtain MRI. If posterior leukoencephalopathy is evidenced by MRI, hold doses. The condition is reversible.
  - Treat seizures with antiepileptic agents such as phenytoin or levetiracetam.
  - Reduce tremors with propranolol 10 mg PO every 6 hours.
- Hepatic impairment: hyperbilirubinemia:
  - Cyclosporine and tacrolimus are excreted through the bile in feces.
  - Monitor levels closely and decrease dose.
- Hemolytic uremic syndrome/microangiopathic hemolytic anemia (MAHA)/transplant-associated thrombotic microangiopathy (TATMA)
- Diabetes

ii. Adverse effects specific to cyclosporine:

- Infusion reaction: burning hands and feet, whole body flushing, and/or muscle cramping:
  - May be reaction to the cremaphor diluent.
  - Slow the every 12 hours infusion or give the daily dose as a continuous infusion.
  - Premedication or oral administration of cyclosporine may be required.
- Hypertrichosis/hirsutism
- Gingival hyperplasia
- Arthralgias and myalgias:
  - Can be seen with first dose. Treat with narcotic analgesics.

iii. Adverse effects specific to tacrolimus:

- Neurotoxicity: hallucinations, nightmares
- Infusion reaction:
  - May be reaction to the castor oil and dehydrated alcohol in the formulation.
  - Use premedication and give tacrolimus orally if possible.

2. Methotrexate

a. Mechanism of action/place in therapy:

i. Inhibits dihydrofolate reductase, resulting in a lack of reduced folates available for thymidylate and purine synthesis. As a result, lymphocytes are unable to proliferate.
ii. Used in conjunction with cyclosporine, tacrolimus, or sirolimus for prevention of GVHD in myeloablative transplants.

b. Dose and administration:

i. Standard regimen:

- 15 mg/m^2 IV push on day +1. Administer at least 24 hours after infusion of stem cells.
- 10 mg/m^2 IV push on day +3, +6 (+/– day +11)
- Patients receiving peripheral blood stem cells (PBSCs) have an increased disease-free and overall survival when given day +11 methotrexate versus those receiving BM and day +11 methotrexate.

ii. Mini dose:

- 5 mg/m^2 IV push on day +1, +3, +6, +11

iii. Assess patient prior to each dose and consider holding the dose for third spacing (pleural or pericardial effusions, ascites), liver insufficiency, or renal failure.

c. Monitoring:

i. High serum methotrexate levels can be toxic to an early graft
ii. Check serum methotrexate level 24 hours after the dose is given if suspect toxicity.
iii. May use folinic acid rescue if serum levels are >0.05 μmol/L.

d. Dose adjustments (see Table 11.2):

i. Dose adjust for liver insufficiency
ii. Check with provider if patient has renal failure/compromise

Table 11.2. Methotrexate dosing in liver insufficiency

Bilirubin (mg/dL)	Methotrexate dose
<3.0	100%
3.1–6.0	50%
>6.0	Hold

e. Adverse effects:

i. Minimal toxicity at low doses
ii. Mucositis:

- May hold the dose or decrease to 5 mg/m^2 if grade IV mucositis is present.
- May use folinic acid rescue 10 mg IV every 6 hours × 6–8 doses to prevent exacerbation of existing mucositis. Begin 24 hours after administration of methotrexate dose.
- Use of folinic acid does not affect aGVHD outcomes.

iii. Hyperbilirubinemia
iv. Delayed neutrophil and platelet recovery

3. Corticosteroids:

a. Mechanism of action/place in therapy:

i. Suppresses immune response to stimuli
ii. Used in conjunction with cyclosporine or tacrolimus and methotrexate for prevention of GVHD in myeloablative transplants

b. Dose and administration:

i. Methylprednisolone (Solumedrol®, Medrol®):

- 0.25 mg/kg/dose IV every 12 hours beginning day +7 or day +12
- May increase dose to 0.5 mg/kg/dose IV every 12 hours during weeks 2 and 3 after initiation

ii. Conversion from IV to PO:

- Convert to PO prednisone using an IV:PO conversion factor of 1:1.
- Standard conversion factor is 4:5; however, no loss of efficacy has been observed in practice using 1:1.

iii. Tapering doses:

- Tapering schedule varies based on protocol and institutional standards. Day of taper initiation and duration of therapy vary from center to center.

- General rules:
  - Taper dose approximately 5 % each week if no GVHD
  - Begin taper at approximately day +30 with the goal of reaching 10 mg PO daily by day +84
  - Hold prednisone dose at 10 mg PO daily when beginning to taper calcineurin inhibitor at approximately day +100.

c. Monitoring/adverse effects:

i. Diabetes:

- Monitor blood glucose levels on a regular basis and supplement patient with insulin and short-acting insulin on an as-needed basis and intermediate-acting insulin on a scheduled basis

ii. Infection:

- Patients should receive antifungal prophylaxis when taking >30 mg/day of prednisone

d. Additional information:

i. The addition of corticosteroids to a prophylaxis regimen will significantly reduce the patient's risk for grade I–IV aGVHD but does not decrease the incidence of grade III–IV aGVHD or cGVHD.

4. Mycophenolate mofetil (Cellcept®):

a. Mechanism of action/place in therapy:

i. Inhibits both T and B lymphocyte proliferation via inhibition of inosine monophosphate dehydrogenase (IMPDH).
ii. Used in conjunction with cyclosporine and tacrolimus for prevention of GVHD in nonmyeloablative transplants. Replaces methotrexate in two- to three-drug combinations.

b. Dose and administration:

i. Myeloablative transplants:

- 500–1500 mg PO/IV two to three times daily or 15 mg/kg/dose PO/IV two to three times daily beginning day 0 or +1
- Administration of 15 mg/kg/dose three times daily will provide serum concentrations of mycophenolate similar to those seen in the solid organ transplant setting

ii. Nonmyeloablative transplants:

- 1000 mg PO/IV two to three times daily or 15 mg/kg/dose PO/IV two to three times daily
- First dose should be at least 4–6 hours after the infusion of stem cells

- Related donor transplant recipients can receive twice daily dosing, while unrelated donor transplants recipients should receive three times daily dosing

iii. Conversion from IV to PO:

- Do not crush/open capsules and administer on an empty stomach if possible.
- Dose can be given as an IV infusion over 2 hours if necessary. The IV:PO conversion is 1:1.

iv. Tapering doses:

- Tapering schedule varies based on protocol and institutional standards. Day of taper initiation and duration of therapy varies from center to center.
- General rules:
  - Related donor transplants: stop mycophenolate at day +28
  - Unrelated donor transplants: begin taper at approximately day +29 with the goal of discontinuing therapy by day +56.

c. Monitoring/adverse effects:

i. Cardiovascular:

- Hypertension
- Edema

ii. Gastrointestinal:

- Diarrhea
- Nausea/vomiting

iii. Infection:

- Mycophenolate has been shown to be an independent risk factor for the development of cytomegalovirus (CMV) infections.
- Preemptive treatment of positive CMV antigenemia is required to prevent active CMV infection.

5. Sirolimus:

a. Mechanism of action/place in therapy:

i. Inhibits both T and B lymphocyte proliferation by binding to FK binding protein 12, resulting in a complex that directly affects the function of mammalian target of rapamycin (mTOR), an enzyme responsible for growth of cells in the G phase

ii. Thought to have synergy with calcineurin inhibitors, sirolimus is used in conjunction with tacrolimus +/– methotrexate for myeloablative and non-myeloablative transplants

b. Dose and administration:

i. Myeloablative and nonmyeloablative transplants:

- Load with 12 mg PO × 1 beginning day − 3 followed by 4 mg PO daily
- If body surface area (BSA) is < 1.5 m^2, load with 6 mg/ m^2 PO × 1 followed by 2 mg/m^2 PO daily

ii. Other information:

- There is no IV formulation.
- Consistently taking medication with or without meals will help with monitoring of levels and dose adjustments.
- Repeat dose if patient vomits within 15 min of administration. However, t-1/2 life is very long (60 hours) so missing a dose is not likely to affect serum levels.

c. Monitoring:

i. Goal trough concentration is 3–12 ng/mL

ii. Checking levels:

- Levels are to be checked no sooner than 5 days following a change in dose or schedule.
- Routine monitoring of levels should occur once a week.

d. Dose adjustments:

i. Dose adjust for drug interactions with CYP 3A4 inhibitors such as amiodarone, azole antifungals, calcium channel blockers, nicardipine, macrolide antibiotics, protease inhibitors, and some tyrosine kinase inhibitors:

- Depending on the strength of azole antifungal as an inhibitor, sirolimus doses may need to be reduced as much as 60% when given concomitantly with the azole.
- Concomitant administration with voriconazole may require sirolimus to be taken every other day. Inhibition of 3A4 in the gut wall by voriconazole can result in a 100-fold increase in sirolimus concentration.

ii. Dose adjust for drug interactions with CYP 3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin

e. Common toxicities:

i. Cardiovascular:

- Hypertension
- Edema

ii. Pulmonary:

- Epistaxis

- Interstitial pneumonitis

iii. Headache
iv. Hypercholesterolemia/hypertriglyceridemia
v. Mild, reversible, leucopenia/anemia/thrombocytopenia with chronic use
vi. Sirolimus may potentate TATMA when given in conjunction with calcineurin inhibitors
vii. Arthralgia
viii. Hypokalemia

6. ATG:

a. Mechanism of action/place in therapy

i. Polyclonal immune globulin preparations created by immunizing either rabbits or horses with human thymocytes or rabbits with the T lymphoblastic cell line Jurkat (ATG-Fresenius)
ii. Used for prevention of GVHD in myeloablative and nonmyeloablative transplants as part of conditioning regimen

b. Dose and administration:

i. Rabbit ATG: 3–4.5 mg/kg/dose given for 2–5 days pretransplant for a total of 7.5–15 mg/kg/regimen
ii. Rabbit ATG-Fresenius: 20–30 mg/kg/dose given for 3 days pretransplant (days −4, −3, −2) for a total of 60–90 mg/kg/regimen
iii. Premedicate with acetaminophen 650 mg PO, diphenhydramine 50 mg PO/IV, and dexamethasone 20 mg IV 1 hour prior to each dose
iv. Infuse through central line over a minimum of 6 hours on first infusion and 4 hours on consecutive infusions
v. Requires test dose of 0.1 mL of 1:1000 dilution intradermally with control of normal saline (NS) 0.1 mL intradermally to the contralateral forearm:

- Observation required every 15 minutes.
- A positive skin test is a wheal $\geq$10 mm in diameter.
- Provider should be notified for positive skin test, itching, or marked local swelling.
- If reaction occurs, consider increasing steroid premedications. And if reaction is severe, hold administration of medication.

c. Monitoring/adverse effects:

i. Anaphylaxis:

- Have emergency medications at bedside including: epinephrine 1:1000 SQ (usual dose 0.3 mg), diphenhydramine 50 mg IV, hydrocortisone 100 mg IV

ii. Fevers/chills
iii. Rash
iv. Joint pain/weakness (serum sickness)
v. Renal impairment

vi. Leukopenia/thrombocytopenia

7. Alemtuzumab (Campath®):
   a. Mechanism of action/place in therapy:
      i. Humanized monoclonal antibody directed against CD52, which induces complement mediated lysis
      ii. Reduces T and B lymphocytes as well as NK cells
      iii. Used as part of the transplant induction regimen
   b. Dose and administration:
      i. Standard dose schedules include:
         - 0.16–0.2 mg/kg/day IV for 6 days pretransplant or 0.5 mg/kg/day IV for 3 days pretransplant
      ii. Current management approaches include:
         - 3 mg on the first day of conditioning and titrate up to target dose
      iii. Low-dose regimens: 10 or 20 mg daily
      iv. Maximum dose 30 mg daily
      v. Premedicate with acetaminophen 650 mg PO, diphenhydramine 50 mg PO/IV
      vi. Administer as IV infusion over 2 hours
   c. Monitoring/adverse effects:
      i. Anaphylaxis:
         - Have emergency medications at bedside including: epinephrine 1:1000 SQ (usual dose 0.3 mg), diphenhydramine 50 mg IV, hydrocortisone 100 mg IV
      ii. Hypotension
      iii. Fevers/chills
      iv. Urticaria/rash
      v. Pancytopenia
      vi. Infection

8. Cyclophosphamide (Cytoxan®):
   a. Mechanism of action/place in therapy:
      i. Inhibits DNA replication, causing selective destruction of alloreactive T cell clones. This leads to induction of immunological tolerance post HSCT.
      ii. Used post HSCT for donor T cell depletion, typically with single-agent CNI prophylaxis

b. Dose and administration:

i. 50 mg/kg/day IV on days +3 and +4
ii. Doses should be given with 2-mercaptoethane sulfonate (MESNA) and hydration
iii. Infuse per institutional protocol
iv. Requires antiemetic prophylaxis

c. Monitoring/adverse effects:

i. Hemorrhagic cystitis
ii. Arrhythmias/cardiac tamponade/heart failure/myocarditis
iii. Pneumonitis and ARDS

9. Bortezomib (Velcade®)

a. Mechanism of action/place in therapy

i. Proteasome inhibitor which selectively depletes proliferating alloreactive T lymphocytes, reduces T-helper type 1 cytokines, and blocks activation of antigen presenting cells.
ii. Used peri-transplant for donor T cell depletion
iii. Remains under investigation at this time

b. Dose and administration

i. 1.3 mg/m^2 IV on days + 1, +4, and +7
ii. Administer via rapid IV push

c. Monitoring/adverse effects

i. Pneumonitis, lung infiltrates and acute respiratory distress syndrome (ARDS)
ii. Edema/hypotension
iii. Weakness
iv. Peripheral neuropathy
v. Gastrointestinal disturbances

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Chapter 12
Transfusion Medicine

Susan Schubach Slater and James Gajewski

The unique transfusion needs of the hematopoietic stem cell transplant (HSCT) recipient require collaboration between the clinical transplant and transfusion medicine services. Successful interaction is essential to the optimal management of HSCT recipients with the goals of reducing the risk of alloimmunization and infection transmission and avoiding potential medical errors.

12.1 General Transfusion Considerations

1. All HSCT candidates should receive leukocyte-reduced red blood cell (RBC) and platelet products:
   a. Decreases the incidence of alloimmunization to human leukocyte antigens (HLA):
      i. Positive lymphocytotoxic and flow cytometric crossmatch studies are associated with increased risk of primary graft failure and graft rejection
   b. Reduces the risk of transfusion-associated cytomegalovirus (CMV) transmission:
      i. All patients should have a pre-HSCT assessment of CMV exposure as determined by serum anti-CMV titers
      ii. Leukofiltration has been shown in randomized trials to be effective at decreasing donor-derived CMV transmission
      iii. Utilization of CMV negative blood products is the most effective intervention to prevent CMV transmission in a CMV negative recipient receiving

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a stem cell product from a CMV negative hematopoietic stem cell (HSC) donor

2. All blood products should also be irradiated to a dose of 1500–2500 cGy:
    a. Reduces the incidence of transfusion-associated graft-versus-host disease (TA-GVHD) secondary to exposure to donor lymphocytes:
        i. Clinical symptoms of TA-GVHD occur between 4 and 30 days post HSCT and may include:
            - Fever
            - Macular papular rash
            - Nausea, vomiting, diarrhea
            - Liver function abnormalities
        ii. Occurs rarely but is associated with a mortality rate of ~88%
        iii. Corticosteroids, cyclosporine and antithymocyte globulin have shown little efficacy in treatment of TA-GVHD
    b. There are no data available to verify lifetime need for irradiated blood products; however, most centers recommend this safety maneuver as standard practice:
        i. There are no reliable tests to measure complete immunologic reconstitution and therefore not reliable measure of decreased risk for TA-GVHD
    c. HSC donors should also receive irradiated blood products if required during stem cell collection to reduce the theoretical transmission risk of TA-GVHD associated with transfusions of nonirradiated blood products.
    d. Exact transfusion thresholds have not been defined; however, these are typically influenced by comorbid conditions and transplant complications:
        i. Conventional threshold for platelet transfusions is a platelet count of $\leq 10{,}000/mm^3$.
        ii. Patients who are febrile or who are actively bleeding may require a higher platelet transfusion threshold and more frequent transfusions.
        iii. For patients who do not demonstrate an incremental increase to transfused platelet products as assessed by a 15–30 min post-platelet count, a platelet-refractory workup should be initiated to determine extent of alloimmunization.
            - The expected corrected count increment (CCI) after a platelet transfusion is approximately $15{,}000\ \mu L \times 10^{11}/m^2$ of body surface area.
            - CCI of < 5000–7500 is indicative of platelet refractoriness:
            - Ensure patients are receiving platelet products that are no more than 48 h old
            - Ensure platelet products are ABO identical

- If these measures do not result in appropriate CCI, consider the use of crossmatched or HLA-matched platelet products

e. Conventional threshold for packed red blood cells (PRBC) transfusions is Hgb ≤ 8 g/dL:

i. There are little data that show blood transfusions significantly improve oxygen delivery or clinical outcomes in any setting.
ii. Observational studies demonstrated Hgb of 5–6 g/dL are generally well tolerated in the setting of critical illness and acute bleeds without evidence of cardiac ischemia.
iii. Recent meta-analysis of randomized studies restricting transfusions to Hgb < 7 g/dL showed a significant reduction in pulmonary edema, acute coronary syndrome, rebleeding, bacterial infections, and overall mortality:

- These studies included both children and adults, not limited to the transplant nor oncology settings.

iv. There is no evidence that demonstrates a therapeutic benefit to maintaining a Hgb > 10 g/dL.

3. Special concerns for patient with aplastic anemia:

a. Increased number of transfusions is associated with increased rates of graft rejection resulting in decreased overall survival
b. Transfusions should be minimized whenever possible
c. Platelet products should be single-donor products to reduce the number of donor exposures
d. Use of blood components from family members who are potential donors should be discouraged to avoid immunologically sensitizing the recipient to the potential donor's minor histocompatibility antigens and HLA

4. Transfusion-related acute lung injury (TRALI):

a. US National Heart, Lung, and Blood Institute consensus definition for symptoms of suspected, possible, and delayed TRALI (see Table 12.1)
b. Occurs in 1 in 5000 PRBC transfusions and 1 in 2000 units of plasma-containing products:

i. The exact mechanism of injury is unknown. However, it is proposed that due to underlying host factors, neutrophils adhere to the pulmonary epithelium. The neutrophils and endothelial cells are then activated by mediators in the blood product which results in capillary leak and pulmonary edema.
ii. Due to nonspecific symptoms and absence of specific disease markers and diagnostic tests, the incidence is likely to be higher.
iii. Incidence is higher in ICU patients than in the general hospital population.

Table 12.1 Definition of transfusion-related acute lung injury (TRALI). (Reprinted with permission from Vlaar and Juffermans (2013) with permission from Elsevier)

Suspected TRALI
Acute onset within 6 h of blood transfusion
$PaO_2/F_iO_2 < 300$ mmHg, or worsening of P to F ratio
Bilateral infiltrative changes on chest radiograph
No sign of hydrostatic pulmonary edema (pulmonary arterial occlusion pressure ≤ 18 mmHg or central venous pressure ≤ 15 mmHg
No other risk factor for acute lung injury
Possible TRALI
Same as for suspected TRALI but another risk factor present for acute lung injury
Delayed TRALI
Same as for (possible) TRALI and onset within 6–72 h of blood transfusion

c. Clinical presentation:
    i. Dyspnea, tachypnea, and hypoxia
    ii. Possibly fevers +/− rigors
    iii. Tachycardia
    iv. Hypotension
d. Overall mortality of 5–10 % making it the leading cause of transfusion-associated deaths in the United States
e. Proposed risk factors:
    i. Presence of mechanical ventilation
    ii. Emergency cardiac surgery
    iii. Hematologic malignancy
    iv. Positive fluid balance
    v. Sepsis/shock
f. Differential diagnoses:
    i. Transfusion-associated circulatory overload
    ii. Anaphylaxis
    iii. Sepsis
    iv. Acute hemolytic transfusion reaction
g. Treatment:
    i. Supportive measures:
        - Supplemental O_2
        - Mechanical ventilation with low tidal volumes
        - Maintain euvolemic status
        - No evidence for use of corticosteroids
    ii. If reaction occurs during product infusion, the product should be returned to the blood bank for culture and rechecking of ABO compatibility
    iii. Symptoms typically resolve within 96 h of onset

12.2 Peri-HSCT Considerations

1. Major ABO incompatibility:
   a. This circumstance exists when the recipient's plasma has anti-donor RBC antibodies (i.e., recipient is blood group O (absence of A, B substances), donor is blood group A or B or AB)
   b. Complications of major ABO incompatible HSCT
      i. Acute hemolytic reaction during infusion of the HSCT product
      ii. Delayed RBC engraftment
      iii. Pure red cell aplasia
   c. Recommend HSC product hematocrit be kept to <2% to minimize exposure to incompatible RBC volume; however, there are no regulations regarding the volume of RBCs allowed in an HSC product
   d. To reduce the complications associated with infusion of ABO-incompatible HSC marrow products:
      i. Red cell depletion by:
         - Hetastarch separation
         - Mononuclear cell separation by machine centrifugation
         - Chemical separation via density gradient separation
      ii. Reduce the titer of incompatible recipient isohemagglutinin:
         - Plasma exchange
         - Immunoadsorption columns
         - In vivo reduction by infusion of pre-HSCT donor-type secretor plasma
         - Slow infusion of donor-type RBCs
         - Despite aggressive hydration and premedication with antihistamines, serious transfusion reaction may occur resulting in fever/rigors, hematuria, and/or hemolysis
   e. Manipulation of the marrow HSC product may result in decreased overall CD34+cell count of the product
2. Minor ABO incompatibility:
   a. This circumstance exists when the donor's plasma is incompatible with the recipient's RBCs
      i. Group AB recipient/ group non-AB donor
      ii. Group A recipient/ group B or O donor
      iii. Group B recipient/ group A or O donor
   b. Marrow HSC products may require plasma reduction if donor anti-recipient titer is high:
      i To decrease risk, many centers will plasma-deplete all minor ABO-incompatible products

Table 12.2 Guidelines for selecting ABO group for erythrocyte and platelet-containing components for patients undergoing HSCT.

Recipient ABO group	Donor ABO group	Transfuse RBCs	Transfuse platelets/ plasma products[a]
A	B	O	AB
A	O	O	A
A	AB	O	AB
B	A	O	AB
B	O	O	B
B	AB	O	AB
O	A	O	A
O	B	O	B
O	AB	O	AB
AB	A	O	AB
AB	B	O	AB
AB	O	O	AB

[a] First choice for platelet transfusions. If first choice is unavailable, use any ABO group for platelet support

ii. Peripheral blood HSC products are already plasma- and RBC-reduced but are easily further plasma-depleted.
iii. There is always concern for minor RBC antibodies not detectable by crossmatch:

- In the case of a reaction, the HSC infusion should be stopped immediately and donor/recipient identity, crossmatch, and antibody screens reviewed.
- If no error is identified, an immediate density gradient, mononuclear cell separation is required.

3. Major–minor ABO incompatibility:

   a. Mononuclear cell concentration or density gradient mononuclear separation is required
   b. Consider pre-HSCT infusion of donor-type plasma

4. Due to major and minor ABO incompatibility between donors and recipients, guidelines for transfusion of blood products have been established to decrease the risk of complications (see Table 12.2).

12.3 Day 0 Transplant Infusion Considerations

1. Product identification:
   a. Physician must confirm and document the HSC product is appropriate for infusion:
      i. Review source documents to confirm the product is from the correct donor
      ii. Verify correct cell dose for the intended transplant indication
      iii. Verify patient identity
   b. Additional requirements for meeting Current Procedural Terminology (CPT) code standards:
      i. Physician must be in attendance at the start of the infusion to monitor for acute toxicity
      ii. Remain immediately available to manage and report infusion toxicities
      iii. Document all above data in the medical record
   c. CPT codes:
      i. 38240: Hematopoietic progenitor cell; allogeneic transplantation
      ii. 38241: Hematopoietic progenitor cell; autologous transplantation
      iii. 38242: Donor leukocyte infusion (DLI) to treat relapse after allogeneic transplant
      iv. 38243: Hematopoietic progenitor cell boost
2. It is standard practice to premedicate all patients with acetaminophen 650 mg po, diphenhydramine 25–50 mg IV/po and IV steroids (hydrocortisone 100 mg IV or equivalent) prior to infusion of both autologous and allogeneic HSC products.
   a. These standards are institution specific and may be mandated by clinical trial protocol.
   b. Donor–recipient HLA disparity and graft manipulation (i.e., ex vivo or in vivo T cell depletion) are additional determinants of premedication needs.
   c. Emergency medications should be at the bedside during HSC infusion:
      i. Acetaminophen po
      ii. Diphenhydramine IV
      iii. Hydrocortisone IV (or equivalent)
      iv. Epinephrine (1:1000) SC
      v. Dopamine (or alternate vasopressor) IV
3. Marrow HSC product:
   a. Potential for volume overload with transfusion of 2–3 units of PRBC equivalent infusion; diuresis may be needed
   b. Fat emboli syndrome occurs rarely and is less common with the advent of in-line filters
   c. Potential for bone emboli with unfiltered product

d. Anaphylaxis:

   i. Typically seen due to incompatibility from major or minor RBC cell surface antigens
   ii. May also result from additives used in cell processing

4. Peripheral blood HSC product:

   a. Noncryopreserved (fresh) product:

      i. Anaphylaxis:

         • Typically seen due to incompatibility from major or minor RBC cell surface antigens
         • May also result from additives used in cell processing

      ii. Infusion-related toxicities:

         • Hypertension/hypotension
         • Fever
         • Cough
         • Nausea, vomiting
         • Flushing

   b. Cryopreserved product infusion:

      i. 10% dimethylsulfoxide (DMSO) is a very lipid soluble product; therefore, during the HSC infusion, as thawed cryopreserved product reaches the pulmonary vascular bed, transalveolar diffusion occurs

         • Patients may experience dysphoric sensations of taste, throat constriction, cough, and nausea/vomiting
         • Neurologic toxicity has also been reported
         • Toxicity (i.e., hypotension, systemic symptoms) is influenced by the rate of infusion
         • Number of granulocytes in the product influences risk of DMSO toxicity
         • DMSO removal has not adversely affected outcomes and allows for more rapid infusion of the HSC product

5. Transplant-associated hemolysis:

   a. There is always a risk of immediate hemolysis due to recipient anti-donor antibodies:

      i. This occasionally occurs in the autologous transplant setting and is typically an allergic reaction to DMSO used in the cryopreservation process:

         • With the cryopreservation process, red cells often fracture; interaction between these red cells and circulating red cells can mimic a transfusion reaction
         • Some centers routinely wash DMSO from cryopreserved products prior to infusion

ii. In the allogeneic setting, if all correct pathways for donor/recipient identification were followed, an immediate mononuclear separation should be performed.
iii. In the setting of mother/child transplant, there is an increased risk of reaction during infusion due to minor erythrocyte incompatibility not detected by crossmatch:

- If this occurs, consider mononuclear cell separation

b. Symptoms:

i. Fever
ii. Hypotension
iii. Anxiety
iv. Hematuria
v. May progress to disseminated intravascular coagulation (DIC)

12.4 Post-HSCT Considerations

1. Immune hemolysis:

a. Hemolysis immediately post-allogeneic HSCT results from recipient-derived anti-erythrocyte antibodies while delayed hemolysis is likely due to donor ABO antibodies
b. Passenger lymphocyte syndrome (PLS):

i. Results from production of incompatible blood group antibodies from transplanted donor-derived B lymphocytes
ii. Typically occurs 5–15 days post-HSCT; rarely occurs after 6–8 weeks post-HSCT
iii. Reported incidence varies between 6 and 30%
iv. Risk factors:

- Peripheral blood stem cell (PBSC) product > marrow
- Use of a calcineurin inhibitor without methotrexate for GVHD prophylaxis
- Reduced-intensity conditioning regimen
- Use of a non-HLA-matched sibling donor
- Group A or group AB recipient with group B donor
- Female donor

v. Diagnosis:

- Direct antiglobulin testing (Coombs)
- Lactate dehydrogenase (LDH), direct/indirect bilirubin
- Haptoglobin

vi. Prevention and management strategies:

- Rituxan for GVHD prophylaxis reportedly decreases the incidence of PLS
- Include an antiproliferative agent (i.e., methotrexate) for GVHD prophylaxis
- Pre-HSCT RBC exchange using donor-type RBCs
- Close monitoring for signs of acute hemolysis during the first 14 days post-HSCT
- Typically self-limited, therefore supportive care measures such as transfusion of compatible RBCs, maintenance of adequate renal perfusion, and in some cases empiric corticosteroids, is generally sufficient
- In cases of massive hemolysis, exchange transfusion should be considered

c. Pure red cell aplasia:

i. May result after major ABO mismatched HSCT:

- Persistence of recipient's lymphocytes and/or plasma cells after completion of the conditioning regimen which produce antibodies to donor-derived erythrocytes, resulting in destruction of erythroid precursors and anemia.

ii. Can occur either early or late (> 100 days) post transplant.
iii. Reported incidence varies from 0 to 29 %.
iv. Diagnosis requires the absence of marrow erythrocyte precursors in the setting of adequate myeloid, lymphoid, and megakaryocyte populations with absence of donor RBCs on forward typing of the recipients RBCs.
v. Risk factors are not clearly defined, differing from study to study:

- Fludarabine/busulfan conditioning regimen
- Blood group A/O donor/recipient pairs

vi. Differential diagnosis includes parvovirus B-19:

- Check parvovirus immunoglobulin M (IgM) or parvovirus DNA

vii. Treatment:

- Often self-limited, resolving within a few weeks to months; small studies have shown no beneficial effects of treatment
- Plasma exchange to remove hemagglutinins, although this has not been shown to be effective due to its short effect and rapid rebound
- Taper of immune suppression
- Small studies have demonstrated effectiveness of additional agents; however, risk/benefit ratio must be considered:
  - Rituximab
  - Erythropoietin
  - DLI

d. Autoimmune hemolytic anemia (AIHA):

   i. Occasionally occurs post-allogeneic HSCT with no specific time frame.
   ii. Diagnosis should be considered for a positive direct Coombs
   iii. Study results may show a warm-type (IgG) panagglutinin, cold-type (IgM) agglutinin or an antibody with relative serologic specificity for other blood group antigens.
   iv. Late AIHA is associated with poor survival.
   v. More common in T-cell-depleted grafts.
   vi. Usually associated with either T-cell dysregulation or viral infection but can often be an early sign of impending relapse.

2. Engraftment syndrome (see Chap. 14):

   a. Typically presents with fever and hypoxia which coincide with white blood cell (WBC) recovery
   b. May progress to diffuse alveolar hemorrhage (see Chap. 22)
   c. High-dose steroids are used for initial therapy; however, an increased platelet transfusion parameter may be required for patients who develop diffuse alveolar hemorrhage

      i. Consider recombinant factor VIIa (NovoSeven®) or aminocaproic acid (Amikar®) for persistent bleeding

12.5 Transfer Back to Community Setting

It is important to advise local medical providers of HSCT-specific transfusion practice including ABO-type changes that occur following allogeneic HSCT and the need for irradiated blood products in all transplant recipients. Transfer-of-care letters should consider including information on appropriate transfusion practice.

Patients should also be made aware of their unique transfusion needs. They should be advised to carry appropriate identification, e.g., medical alert bracelets, alerting care providers in case the patient is rendered unconscious or unable to provide medical history.

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Chapter 13
Antithrombotic Guidelines

Thomas DeLoughery

13.1 Patients on Antithrombotic Therapy

1. Antiplatelet therapy (see Table 13.1):
   a. Primary prevention:
      i. A significant portion of the population is on aspirin or other antiplatelet agents.
      ii. In recent years, the use of these drugs for primary prevention of first myocardial infarction (MI) or cerebrovascular accident (CVA) has been become controversial.
      iii. The absolute reduction in events is very small and almost balanced by the increase risk in bleeding. Therefore, for a hematopoietic stem cell transplantation (HSCT) recipient taking antiplatelet agents for primary prevention, the most reasonable strategy would be to stop the medication.
   b. Secondary prevention:
      i. The benefits of antiplatelet therapy in patients who have suffered a MI or CVA are more robust with patients seeing a 22% reduction in vascular events.
      ii. A reasonable strategy would be to stop the drug when conditioning starts and then resume when platelets have recovered to > 50,000/ul.
      iii. Patients with a history of MI, CVA, or vascular disease but not previously on therapy should be started on aspirin 81 mg po daily (or clopidogrel 75 mg po daily if aspirin intolerant) when platelets have recovered to > 50,000/ul.

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Table 13.1 Management guidelines

Aspirin	–
Primary prevention	Stop
Secondary prevention	Stop during conditioning, resume when platelets > 50,000
Coronary stent	–
Bare metal	Combined therapy (ASA = aspirin + P2Y12 Inhibitor) 4 weeks, then ASA thereafter. Continue ASA until platelet count < 20,000, then resume when > 20,000
Drug eluting	If possible, delay transplant until 1 year after stent placement. If unable, combined therapy throughout transplant. After 1 year, continue ASA until platelet count < 20,000 then resuming when > 20,000
Atrial fibrillation	–
$CHADS_2$ 0–2	Stop ASA during conditioning, resume when platelets > 50,000
$CHADS_2$ > 2	Therapeutic LMWH until platelets < 50,000, prophylactic dosing when platelets 20–50,000
Mechanical heart valve	Therapeutic LMWH until platelets < 50,000, prophylactic doses 20–50,000
Acute events	–
Catheter thrombosis	Remove catheter, consider anticoagulation if symptomatic and platelets > 50,000
Distal thrombosis	Follow-up scans in 3 days, then weekly
Proximal thrombosis and PE	Therapeutic LMWH if platelets > 50,000, prophylactic doses 20–50,000, IVC filter if platelets < 20,000
Acute coronary syndrome	ASA for all patients regardless of platelet count
–	Individual therapy for patient per cardiology recommendations

LMWH low molecular weight heparin, *IVC* inferior vena cava

c. Patients with coronary stents:

   i. Management of patients with coronary stents is difficult because stopping antiplatelet therapy is strongly associated with stent thrombosis. This can be fatal in up to 50% of patients.
   ii. The risk is most extreme for bare metal stents for 4 weeks after placement and with first generation drug-eluting stents (DES) up to 1 year after placement. During this period, even stopping just clopidogrel is associated with adverse outcomes.
   iii. For a patient with a DES who requires HSCT during the "at-risk" period, it may be prudent to continue dual antiplatelet therapy throughout the phase of thrombocytopenia unless bleeding develops.
   iv. If possible, consideration should be given to delaying transplant until 1 year after DES placement. Consultation with cardiology is mandatory to determine safe timing for HSCT.

v. For patients with stents outside the high-risk period, continuing aspirin until the platelet count is < 20,000/ul, then resuming when > 20,000/ul can be considered.

13.2 Antithrombotic Therapy

1. Choice of therapy during HSCT:
   a. Although warfarin (Coumadin®) is the antithrombotic agent of choice for most patients, many of its properties make it undesirable for the HSCT patient:
      i. Warfarin requires close monitoring, has many drug–drug and food interactions, and its half-life is 36 h making it impractical to quickly start and stop if necessitated by changes in clinical condition.
      ii. Measurements of anticoagulation are influenced by vitamin K intake.
   b. The most practical antithrombotic agents for use during HSCT are the low molecular weight heparins (LMWH). The lack of interactions and the relatively short half-life (~4 h) simplifies their use in this setting. All of these agents are renally cleared so close monitoring is required (Table 13.2).
   c. There are no clear guidelines for anticoagulation in the setting of thrombocytopenia; however, most experts would recommend no full-dose anticoagulation below a platelet count of 50,000/ul and no prophylactic anticoagulation below a platelet count of 20,000/ul.
   d. In theory, one can transfuse platelets to try to maintain the platelet count above these thresholds; however, in practice this is difficult and associated with excess bleeding.

2. Atrial fibrillation:
   a. The leading indication for warfarin in older patients is CVA prevention from atrial fibrillation.
      i. It is estimated that 15 % of all CVAs can be attributed to atrial fibrillation. Warfarin has reduced the CVA rate from 5 % per year to 1 %.
      ii. While warfarin benefits most patients, those who previously have had CVAs are at a higher risk of recurrent CVA and appear to benefit the most from anticoagulation.

Table 13.2 Low molecular weight heparins

Drug	Prophylactic dosing	Therapeutic dosing	Pediatric dosing[a]
Dalteparin	2500 units/day	100 units/kg q 12 h	–
Enoxaparin	40 mg/day	1 mg/kg q 12 h or 1.5 mg/kg/day in low risk patients	< 5 kg: 1.5 mg/kg q 12 h > 5 kg: 1 mg/kg q 12 h
Tinzaparin	3500 units/day	175 units/day	–

[a] Safety and efficacy of dalteparin and tinzaparin have not been established

Table 13.3 $CHADS_2$ scoring system

$CHADS_2$ score	Yearly risk of CVA	Therapy
0	1.9	Aspirin
1	2.8	Aspirin
2	4.0	Warfarin
3	5.9	Warfarin
4	8.5	Warfarin
5	12.5	Warfarin
6	18.2	Warfarin

One point each for recent heart failure, hypertension, age > 75, and diabetes. Two points assigned for history of CVA
CVA cerebrovascular accident

b. Data now exist to risk-stratify patients and help to choose between warfarin and aspirin therapy.

   i. Clinically, the most useful prediction rule appears to be the $CHADS_2$ rule with one point being assessing for presence of congestive heart failure, hypertension, age over 75, and/or diabetes and two points for prior history of CVA (Table 13.3).
   ii. For the average patient, a $CHADS_2$ score of 0–1 would suggest low risk of CVA and aspirin therapy while a higher score (≥ 2) supports the use of warfarin.
   iii. For individuals with a $CHADS_2$ score ≥ 2, lifelong anticoagulation is recommended unless a contraindication emerges.
   iv. For management of an HSCT patient with expected periods of thrombocytopenia, those patients with $CHADS_2$ scores of 0–1 should stop aspirin at a platelet count of 50,000/ul and resume when platelets recover to over that level.
   v. Patients with $CHADS_2$ score ≥ 2 should be anticoagulated with LMWH as outlined above in Sect. B.1.b.

3. Mechanical cardiac valves:

   a. Patients with mechanical heart valves have a high risk for embolization/valve thrombosis, and anticoagulation is strongly recommended:

      i. The estimated risk of thrombosis without anticoagulant ranges from 12 to 30% per year.
      ii. Data support the idea that the newer generation of mechanical valves is less thrombogenic than the older ball–cage valves.

iii. Even with anticoagulation, the yearly rate of thrombosis ranges from 2.5 % with ball–cage valves to 0.5 % with a bileaflet valve.
iv. For management of an HSCT patient with their expected periods of thrombocytopenia, no full-dose anticoagulation below a platelet count of 50,000/ul nor prophylactic anticoagulation below a platelet count of 20,000/ul is recommended.
v. The daily risk of CVA off anticoagulation is uncertain, but recent data suggest it may be as high a 0.5–1 %, and this risk needs to be factored into risk assessment for transplantation.
vi. For patients perceived to be at a very high thrombosis risk (i.e., mitral valve with atrial fibrillation and history of CVA), one may consider platelet threshold of 30,000 /ul for therapeutic LMWH however this is associated with increased risk of bleeding.
vii. Patients with mechanical aortic valves are at a lesser risk of thrombosis than those with mitral valves; however, the rates of embolism and valve thrombosis are still substantial with newer valves, and anticoagulation is still mandatory.

b. Although the risk is lower than with mechanical valves, bioprosthetic heart valves have a definite risk of associated embolization and aspirin therapy is recommended. For HSCT patients with bioprosthetic valves, aspirin should be stopped at a platelet count of 50,000 /ul and resumed when platelets recover to over that level:

i. Patients with bioprosthetic valves with other risk factors such as atrial fibrillation or history of thromboembolic CVA should be anticoagulated with LMWH as outlined in Sect. B.1.b.

4. Deep venous thrombosis (DVT):

a. The duration of therapy for a DVT is determined by both the circumstances of the thrombosis and its location:

i. Provoked DVT (due to surgery, estrogen, trauma, etc.) requires only 3 months of anticoagulation.
ii. Provoked DVTs below the popliteal vein require at the most 6 weeks of anticoagulation.
iii. Patients with idiopathic thrombosis, especially pulmonary embolism (PE), should be considered for lifelong anticoagulation.

b. The risk of recurrent thrombosis is thought to be highest 6–12 weeks after the event so for most patients, even those requiring long-term anticoagulation, LMWH may be the therapy of choice, as outlined in Sect. B.1.b.
c. Although rare, DVT can complicate HSCT:

i. Rates are reported to be higher as the patient recovers and are hospitalized later for complications.
ii. Thrombosis incidences are similar to any general medicine patient (~1 % symptomatic and 15 % on screening).
iii. Given the risk of bleeding, intermittent compression stockings should be used.
iv. For hospitalized patients who have recovered their platelet counts, LMWH or other pharmacological prophylaxis should be used, especially in the setting of severe infection or other major complications.

13.3 Patients Who Develop Thrombosis

1. Catheter thrombosis:

a. Central venous catheters are essential to many aspects of cancer therapy. The clinically apparent thrombosis incidence for catheters ranges from 5 to 30 % and can be as high as 40 % with peripherally inserted central catheters (PICCs).
b. Signs of catheter thrombosis are nonspecific resulting in underestimation of incidence; this can be as high as 50 % if screening is performed.
c. Unlike lower extremity thrombosis, the incidence of PE with upper thrombosis is much less—only 8 % versus 31 % in one study.
d. Prevention of catheter thrombosis is controversial and most likely futile:

i. Most studies have not shown a benefit to prophylaxis with LMWH or warfarin in preventing thrombosis, and prophylaxis is not warranted in the transplant setting.

e. Therapy starts with removing the catheter because this will remove the provoker of the thrombus. For PICCs, this intervention may be the only stem required for recanalization of the vein:

i. If the patient is not severely thrombocytopenic but symptomatic, consideration could be given to a 4–6-week course of anticoagulation. There are data that one can try to "salvage" the catheter by keeping it in and using anticoagulation, but this was associated with a 4 % incidence of serious bleeding in a pilot study.
ii. Given the low risk of long-term sequela, there is little indication for thrombolytic therapy unless there is massive thrombosis (i.e., superior vena cava syndrome).

f. Rarely catheter thrombosis can be a sign of heparin-induced thrombocytopenia since heparin is often used to ensure patency. This diagnosis should be considered if there is massive thrombosis or coincidental thrombosis in other vascular fields.

2. Deep venous thrombosis
    a. If diagnosed during the thrombocytopenic phase, distal (calf vein) thrombosis can just be observed with a Doppler scan 3 days after initial diagnosis and then weekly, or sooner if symptoms increase.
    b. For the thrombocytopenic patient with a proximal vein thrombosis or PE, an inferior vena cava filter should be placed until the patient can be anticoagulated:
        i. A platelet threshold of 50,000/ul should be used to start anticoagulation.
        ii. Patients should be anticoagulated for 3 months since these would be considered "provoked thrombosis."
        iii. Given the complex medical regimens of these patients, long-term LMWH should be used for therapy.
3. Acute coronary syndrome (ACS):
    a. Modern management of ACS involves intense anticoagulation therapy.
    b. The presence of severe thrombocytopenia precludes the use of combined therapy with aspirin, clopidogrel, heparin, and intravenous platelet inhibitors:
        i. However, the use of aspirin is crucial for any patient with ACS and should be given regardless of the platelet count.
    c. Further management of the transplant patient with ACS needs to be individualized depending on their stage of transplant and overall clinical condition. Care must be coordinated between cardiology and transplant providers.

13.4 Role of New Direct Oral Antithrombotic Agents

There have been significant advances in the past 5 years in the field of thrombosis. New highly efficacious agents with low-risk profiles have been emerged for clinical use:

1. Advantages of director oral agents:
    a. No monitoring
    b. Limited drug–drug interactions
    c. Less risk of intracranial hemorrhage
    d. Xa inhibitors have been proven to be safer than warfarin in treatment of venous thrombosis
2. Patients who should be considered for treatment with new agents:
    a. Erratic international normalized ratio (INR) control
    b. Need to start or stop anticoagulation rapidly

c. Treatment of acute venous thrombosis
d. CVA prevention in atrial fibrillation

3. Novel agents:

a. Oral direct thrombin inhibitor: Dabigatran (Pradaxa®)

i. Indication: CVA prevention in patients with atrial fibrillation and treatment of venous thrombosis
ii. Dosing: 150 mg po bid
iii. Half-life: 12–14 h
iv. Drug-drug interactions: P-gp inhibitors: Dronedarone, ketoconazole - dose reduced to 75mg bid or contraindicated if renal impairment. P-gp inducers: Rifampin, St John's wort - contraindicated.

- No monitoring required
- Use alternative agents if CrCl < 50 ml/min

b. Direct factor Xa inhibitors

i. Rivaroxaban (Xarelto®)

- Indication
- Prevention of venous thrombosis: 10 mg po daily
- Treatment of venous thrombosis: 15 mg po bid × 3 weeks then 20 mg po daily
- CVA prevention in patients with atrial fibrillation: 20 mg po daily, reduced to 15 mg if CrCl 15–49 ml/min
- Half-life: 5–9 h
- Drug–drug interactions: Azoles and anti-HIV agents

ii. Apixaban (Eliquis®)

- Indication
- Prevention of venous thrombosis: 2.5 mg po bid
- Treatment of venous thrombosis: 10 mg po bid × 1 week then 5 mg po bid
- CVA prevention in patients with atrial fibrillation: 5 mg po bid. Decrease to 2.5 mg po bid if patient has two of these three characteristics:
  - Age > 80
  - Weight < 60 kg
  - Creatinine > 1.5 mg/dl
- Half-life: 12 h
- Drug–drug interactions: Azoles and anti-HIV agents decrease dose to 2.5 mg po bid

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Chapter 14
Engraftment

Sara Murray

Engraftment after hematopoietic stem cell transplant (HSCT) appears to occur as "overlapping waves" of hematopoiesis. Initial increases in absolute neutrophil counts result from a transferred population of relatively mature committed progenitor cells that are capable of only transient engraftment. Immature multipotent stem cells generate the second phase of neutrophil engraftment. Finally, pluripotent stem cells from the transplanted graft sustain trilineage hematopoiesis. Generally, engraftment begins to be observed 10–21 days after the stem cell infusion. Engraftment kinetics can be influenced by a number of factors including the underlying disease, pre-HSCT therapy, conditioning regimen, use of cytokines post HSCT, graft quality, and post-HSCT complications/events (e.g., graft-versus-host disease (GVHD), medications, infections).

Engraftment is defined in a variety of ways by different institutions, but generally has minimum criteria of:

1. Absolute neutrophil count of $\geq 500/mm^3$ for three consecutive days
2. Platelet count of $\geq 20{,}000/m^3$ for three consecutive days (and without transfusions for 7 days)
3. Hematocrit $\geq 25\%$ for at least 20 days (without transfusions)

14.1 Autologous

1. Initial white blood cell recovery is typically seen 10–14 days after stem cell infusion with platelet and red cell independence occurring at more variable rates.
2. There are no routinely scheduled bone marrow biopsy/aspirate procedures post-autologous HSCT to assess engraftment.

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14.2 Allogeneic

1. Generally a rise in the peripheral blood granulocyte count is detected in the third week after the stem cell source is infused:
   a. Peripheral blood stem cells average 10–14 days until the first evidence of recovery.
   b. Bone marrow stem cells average 21 days post infusion.
   c. Umbilical cord blood engraftment may be even longer but can be facilitated by identifying compatible donor cord blood products with higher cell counts.
2. Recovery of platelet production is more delayed, but transfusion independence is usually achieved within 5–7 weeks post HSCT and may occur much earlier.
3. Hematocrit and hemoglobin levels are not good indicators of hematopoietic recovery:
   a. Patients receiving an ABO incompatible donor stem cell infusion may continue to produce isohemagglutinins (host specific) for months to years.
   b. This circumstance may result in diminished reticulocyte activity and delayed red cell transfusion independence.
4. Neutrophil engraftment time lines are influenced by GVHD prophylaxis:
   a. Cyclosporine/prednisone showing the shortest engraftment time (10–15 days)
   b. Long-course methotrexate/cyclosporine having the longest engraftment time (21–26 days).
   c. These observations apply to marrow allografts. Blood stem cell allografts typically recover 2–3 days sooner.
5. Engraftment following a myeloablative allogeneic HSCT is documented by a bone marrow biopsy often performed between days +60 to 80.
6. Chimerisms are evaluated by either variable nucleotide tandem repeats (VNTR; same sex donor) or fluorescent in situ hybridization (FISH for XY; different sex donor].
7. For nonmyeloablative allogeneic HSCT recipients, peripheral chimerisms of both CD3+ (T cell lymphocytes) and CD 33+ (myeloid lineage) populations are assessed in schedules determined by institutional guidelines.
   a. Example of a typical schedule includes assessments at days +28, +56, +84, 6 months, 12 months, 18 months, and 24 months, then annually until 5 years post HSCT.
   b. Marrow chimerisms are often checked at similar intervals as standard marrow assessments.

14.3 Engraftment Syndrome

1. Engraftment syndrome (ES) typically occurs within 96 h of neutrophil recovery and presents as a combination of signs and symptoms that may include fever, rash, fluid retention, weight gain, hypoxia, noncardiogenic pulmonary edema, pulmonary infiltrates, and/or diffuse alveolar hemorrhage.
2. The pathophysiology of ES is not well understood. However, it is thought to involve interactions of activated cellular elements (T cells, monocytes, complement and effector cells) with a systemic response to cytokine release.
3. While this syndrome is most commonly described after autologous HSCT, ES may also occur after allogeneic HSCT.
4. Signs and symptoms mimic those of what has been considered "hyperacute" GVHD, often making a definitive diagnosis difficult:

a. It has been considered that ES is an early manifestation of GVHD in some cases; it may be a manifestation of host-versus-graft alloresponse in others.

5. Lack of well-defined criteria for diagnosis has led to a wide variation in the reported incidence, risk factors, and mortality associated with ES. Spitzer (Spitzer 2001) has proposed criteria for a uniform diagnosis based on the most commonly reported clinical findings (see Table 14.1):

a. The diagnosis of ES is made when a patient develops all three major criteria or two major and at least one minor criterion within 96 h of engraftment.

6. This syndrome is often self-limited, resolving with discontinuation of growth factors:

   a. In more severe cases with symptomatic pulmonary involvement, corticosteroids (1 mg/kg/day) have been shown to decrease mortality.
   b. Additionally, C1 esterase inhibitor concentrates have been shown to improve outcome in small studies.

Table 14.1 Proposed uniform definition of ES

Major criteria	Minor criteria
$T \geq 38.3$ °C with no identifiable infectious etiology	Hepatic dysfunction with either total bilirubin ≥2 mg/dL or transaminase levels ≥2x ULN
Erythrodermatous rash involving >25% BSA and not attributable to a medication	Renal insufficiency (SCr≥2x baselines)
Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with the diagnosis of hypoxia	Weight gain ≥2.5% of baseline body weight
	Transient encephalopathy unexplained by other causes

BSA body surface area, *ULN* upper limit of normal, *SCr* serum creatinine

14.4 Foundation for the Accreditation of Cellular Therapy Standards for Review of Engraftment

The major objective of Foundation for the Accreditation of Cellular Therapy (FACT) is to promote quality medical and laboratory practice in HSCT and other therapies using cellular products. FACT Standards were formed from laboratory standards developed by the International Society for Cellular Therapy (ISCT) and from the clinical and training guidelines developed by the American Society of Blood and Marrow Transplantation (ASBMT). Consensus in medical literature and contributions of experts in the cellular therapy field also led to the development of the standards:

1. FACT standards define engraftment as "the reconstitution of recipient hematopoiesis with blood cells and platelets from a donor". The standards require:
    a. Policies and procedures to describe the review of time to engraftment by the collection facility, processing facility, and clinical transplant program following cellular therapy product administration.
    b. Evaluation of engraftment to ensure that the highest quality product has been manufactured and distributed.
    c. Any unexpected engraftment outcomes should be investigated and corrective aspects or process improvement implemented.
    d. Personnel of the clinical HSCT program should evaluate all aspects of the collection, processing, and/or administration procedure related to any unexpected engraftment outcome including delayed or failed engraftment. The evaluation should be documented, and both short- and/or long-term corrective action be initiated.
2. Timely engraftment of the hematopoietic progenitor cell (HPC) product in a recipient following a dose intensive regimen is directly related to the quality of the HPC product:
    a. The collection facility, processing facility and clinical transplant program must be aware of the time to neutrophil and platelet engraftment for all patients for whom they have supplied products.
    b. The engraftment information can be solicited directly by the collection facility, the processing facility, or by another section of the clinical transplant program and presented at a common quality management meeting where select members of the clinical transplant program are in attendance.
3. There must be evidence of ongoing analysis of engraftment data by the clinical transplant program (see Table 14.2):
    a. The analysis should include the average (or median) and observed ranges of engraftment for the various products and transplant procedures performed by the program.

Table 14.2 Patient/product characteristics considered in engraftment analysis

Collection facility	Processing facility	Clinical transplant program
Number of collections per patient	CD34+ dose at time of transplant	# of prior chemotherapy regimens
Cell yield per collection	WBC concentration pre-cryopreservation	Conditioning regimen
Duration of each collection	Age of cellular product	Presence or absence of GVHD
	Viability of cellular product	Disease status
		CMV status

   b. The clinical transplant program is the most qualified to determine what constitutes an acceptable time to engraftment and all sections of the program should have access to the engraftment data.

4. Cellular product characteristics, especially CD34 cell dose should be considered in such analysis:
   a. The collection facility may consider the number of collections per patient, cell yield per collection, or duration of each collection in its analysis.
   b. The processing facility may consider white blood cell concentration at the time of cryopreservation, age of the product upon receipt, or viability of the product at time of transplant.
   c. These data can be used to identify changes that might require further investigation.
5. Chimerism assays can be used as a tool for the assessment of the product quality of allogeneic HPC products infused after nonmyeloablative treatment.
6. Product efficacy may be more difficult to assess for other non-HPC products and that assessment will differ for each product type.

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Chapter 15
Follow-Up Care

Carol Jacoby

In caring for the hematopoietic stem cell transplant (HSCT) patient, each transplant center must determine their own programmatic guidelines to ensure the continuity of care of their patients in the immediate post-transplant period. These guidelines typically include anticipated frequency of clinician visits and laboratory assessments, parameters for drug adjustments, and protocols for infectious disease prophylaxis and treatment. *Suggestions for follow-up guidelines are highlighted in this chapter based on our own institutional practice*. While institutional standards vary, it is clear that communication with the patient's primary referring oncologist is critical for optimal patient outcomes.

15.1 Outpatient Follow-up

1. Autologous HSCT:
    a. Follow-up in clinic twice weekly after discharge until the patient is clinically stable, then weekly until day +25–30.
    b. Subsequent follow-up at 2-week intervals through day +90, monthly for 3 months, every 2 months until 1 year, every 3–6 months for 2–5 years, then annually.
    c. At the time of transfer of care to the patient's primary oncologist, recommendations for length of antimicrobial prophylaxis and follow-up should be communicated.
    d. Restaging studies may be completed between days +80 and +100 with future restaging based upon the patient's primary disease (see Table 15.1)

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Table 15.1 Disease-specific evaluations

–	Day 100 evaluation	Additional evaluation
Aplastic anemia	Bone marrow biopsy/aspirate for path, flow, and FISH for MDS panel	EBV titers monthly posttransplant × 12 months
–	Chimerisms[a]	–
–	CBC with diff/chemistry panel	–
–	Reticulocyte count (uncorrected)	–
Acute lymphocytic leukemia (ALL)	Bone marrow biopsy/aspirate path, flow, and cytogenetics with FISH probes for prior abnormalities	–
–	Chimerisms[a]	–
–	CBC with diff/chemistry panel	–
–	Molecular markers (BCR/abl, TEL) only if previously abnormal	–
–	LP if CNS disease	–
Acute myeloid leukemia (AML)	Bone marrow biopsy/aspirate path, flow and cytogenetics with FISH probes for prior abnormalities	–
–	Chimerisms[a]	–
–	CBC with diff/chemistry panel	–
–	Molecular markers (FLT3, NPM) if previously abnormal	–
–	LP if history of CNS disease	–
Amyloidosis	Bone marrow biopsy/aspirate path, flow, and cytogenetics, and FISH for myeloma panel	Quantitative immunoglobulins monthly
–	Quantitative serum immunoglobulins	Serum-free light chains monthly
–	SPEP	CBC
–	Serum free light chains	Chem panel
–	CBC with diff/Chemistry panel	TTE every month for 1 year
	Troponin, BNP, PT/PTT	–
	TTE	–
	PFTs if hx of pulmonary involvement	–
Chronic lymphocytic leukemia (CLL)	Bone marrow biopsy/aspirate path, flow, and cytogenetics with FISH for CLL probes only if previously abnormal	–
–	Chimerisms[a]	–
–	CT scan chest/abd/pelvis if previously abnormal	–
–	CBC with diff/chemistry panel with LDH	–
CML	Bone marrow biopsy/aspirate path, flow, and cytogenetics, with FISH for BCR/abl and any prior abnormalities	Peripheral blood for quant PCR for BCR/abl at 2, 4, 6, 9, and 12 months post transplant, then q3 months during year 2. If PCR negative × 3 measurements, continue annual evaluation

Table 15.1 (continued)

–	Day 100 evaluation	Additional evaluation
–	Chimerisms[a]	–
–	Peripheral blood for quant PCR for BCR/abl	–
–	CBC with diff/chemistry panel	–
–	LP if hx of CNS disease	–
Germ cell	CT abdomen/pelvis with contrast	MRI brain
–	CXR	CT abd/pelvis with contrast every 3 months for 1 year, then every 6 months for 1 year
–	MRI brain if positive pre-transplant	AFP, HCG monthly for 1 year, then every 3 months for 1 year
–	Tumor markers (HCG, AFP, LDH)	–
–	CBC with diff/chemistry panel	–
Hodgkin/ non-Hodgkin lymphoma	Bone marrow biopsy/aspirate path, and flow with cytogenetics and FISH if previously abnormal (all allogeneic recipients; autologous recipients only if positive pre-transplant)	Aggressive disease (DLBCL, mantle cell, Burkitt, Hodgkin): Repeat laboratory tests and imaging at 3, 6, 12,18, and 24 months post-HSCT
–	Chimerisms[a]	Indolent disease: Repeat laboratory tests and imaging every 6 months for 2 years
–	CT/PET	–
–	CBC with diff/chemistry panel with serum LDH	–
–	LP if hx of CNS disease	–
Myelodysplastic syndrome	Bone marrow biopsy/aspirate path, flow, and cytogenetics with FISH probes for prior abnormalities	–
–	Chimerisms[a]	–
–	CBC with diff/chemistry panel	–
Multiple myeloma	Bone marrow biopsy/aspirate path, flow, and cytogenetics with FISH for myeloma panel	CBC, chemistries monthly
–	Chimerisms[a]	SPEP monthly
–	Quantitative serum immunoglobulins	Quantitative immunoglobulins monthly
–	SPEP	–
–	Serum-free light chains	Serum-free light chains monthly
–	24-h urine for creatinine and protein	–
–	CBC with diff/chemistry panel	–
–	Bone survey	–

FISH fluorescent in situ hybridization, *MDS* myelodysplastic syndrome, *CBC* complete blood count, *EBV* Epstein–Barr virus, *LP* lumbar puncture, *CNS* central nervous system, *SPEP* serum protein electrophoresis, *BNP* B-type natriuretic peptide, *TTE* transthoracic echocardiogram, *PFTs* pulmonary function tests, *PCR* polymerase chain reaction, *DLBCL* diffuse large B cell lymphoma

[a] allogeneic recipients only

2. Allogeneic HSCT:
    a. Follow-up in clinic twice weekly after discharge through day +50–60, then weekly through day +100. Visits may occur more frequently for patients with complications.
    b. After day +100, patients may be seen at least every 1–2 weeks for 6 months, then monthly. Visits may occur more frequently for patients with chronic graft-versus-host disease (cGVHD) or other post-HSCT complications.
    c. All allogeneic HSCT recipients should be checked thoroughly for signs and symptoms of GVHD at every follow-up visit.
    d. Restaging studies may be completed between days +80 and +100 with future restaging based upon the patient's primary disease (see Table 15.1).
    e. Generally, around day +100, the patient returns to their primary oncologist:
        i. At the time of transfer of care, complete documentation should be shared to assure continuity of care.
        ii. Depending on the distance to the patient's home, visits are often shared with the local care provider. This approach is particularly helpful for patients with cGVHD.
        iii. If the patient is unable to travel to the transplant center, thorough communication with the local oncologist is essential.
3. Cord blood HSCT:
    a. Follow-up in clinic twice weekly through day +50–60, then weekly through day +100.
    b. Visits may occur more often for patients with post-HSCT complications.
    c. After day +100, patients may follow-up at least every 1–2 weeks for 6 months, then monthly.
    d. Visits should occur more frequently for patients with cGVHD or with other post-HSCT complications.
    e. All patients should be thoroughly assessed for signs and symptoms of GVHD at every follow-up visit.
    f. Restaging studies may be completed between days +80 and +100 with future restaging based upon the patient's primary disease (see Table 15.1).
    g. Generally, around day +100, the patient returns to their primary oncologist:
        i. At the time of transfer of care, complete documentation should be shared to assure continuity of care.
        ii. Depending on the distance to the patient's home, visits are often shared with the local care provider. This approach is particularly helpful for patients with cGVHD.
        iii. If the patient is unable to travel to the transplant center, thorough communication with the local oncologist is essential.

4. Laboratory and radiologic studies:
   a. Autologous HSCT:
      i. Complete blood count (CBC) with differential twice weekly until stable, then weekly through day +30, then at each follow-up visit.
      ii. Complete chemistry profile that includes magnesium, lactate dehydrogenase (LDH), and renal and liver function tests twice weekly until stable, then weekly through day +30; reassess at each follow-up visit.
      iii. Consider assessment of immunoglobulin G (IgG) levels in patients experiencing repeated infections.
      iv. Cytomegalovirus polymerase chain reaction (CMV PCR) in patients with CD34-selected HSCT procedures.
   b. Myeloablative allogeneic HSCT:
      i. CBC with differential twice weekly through day +56, then weekly if clinically appropriate through day +100. Frequency after day +100 is dictated by the patient's clinical status.
      ii. Complete chemistry profile that includes renal and liver function studies, LDH, electrolytes and magnesium twice weekly through day +56, then weekly if clinically appropriate through day +100. Frequency after day +100 is dictated by the patient's clinical status.
      iii. CMV by PCR weekly through day +100 in seropositive recipients or if the donor is seropositive; monthly in seronegative recipients with seronegative donors (see Chap. 10 for additional CMV monitoring recommendations).
      iv. Consider surveillance blood cultures weekly while the patient is receiving prednisone ≥10 mg/day and has an indwelling catheter. Positive surveillance cultures in asymptomatic patients should be repeated before initiation of antibiotic therapy (see Chap. 17 for additional therapy guidelines).
      v. Galactomannan assays weekly through day +100 for patients receiving fluconazole prophylaxis.
      vi. IgG levels every other week through day +100. Intravenous immunoglobulin (IVIG) should be administered per institutional replacement guidelines. If GVHD is present, consider continued monitoring with IVIG replacement per institutional replacement guidelines.
      vii. Calcineurin inhibitor (CNI) troughs twice weekly and prn through day +60. Levels may then be assessed weekly while targeting therapeutic trough levels. CNI levels may be discontinued on initiation of taper:
         - If the patient is enrolled on a clinical trial, trough goals may be determined by the protocol.
         - If the patient is not on clinical trial, trough goals are determined institutionally.
         - An example of a common trough goal is 200–250 ng/dL for cyclosporine and 5–10 ng/dL for tacrolimus. Of note, these blood levels are trough goals (blood drawn approximately 12 h after the last dose).

viii. Immune reconstitution panels for humoral and cellular immunity may be evaluated at days +28, +56, +100, and +180, then at 1 year, and annually through 5 years or until reconstitution complete.

c. Nonmyeloablative transplant (outpatient setting):

i. For patients enrolled on a clinical trial, laboratory studies should be drawn per study protocol. For patients not receiving care on a clinical trial, consider:

- CBC with differential daily until nadir is reached and ANC returns to >500/mm^3. If the patient's absolute neutrophil count (ANC) does not fall below 500/mm^3, daily CBCs continue until there is a clear increase of ANC × 2 consecutive days. After daily CBCs are no longer required, monitor CBCs three times weekly until day +28.
- Chemistry profile that includes renal and liver function studies, LDH, electrolytes, and magnesium three times weekly until day +28, then weekly through day +100.
- CMV by PCR weekly through day +100 in seropositive recipients or if the donor is seropositive; monthly in seronegative recipients with seronegative donors (see Chap. 10 for additional CMV monitoring recommendations).
- If the patient has GVHD and requires steroid therapy, surveillance blood cultures can be considered weekly as long as the patient is receiving prednisone ≥10 mg/day and has an indwelling catheter. Consider repeating cultures prior to initiation of antibiotic therapy in asymptomatic patients (see Chap. 17 for additional therapy guidelines).
- Galactomannan assays weekly through day +100 for patients receiving fluconazole prophylaxis.
- IgG levels every other week through day +100. IVIG should be administered per institutional replacement guidelines. If GVHD is present, consider continued monitoring with IVIG replacement per institutional replacement guidelines.
- CNI trough levels twice weekly until day +56, then discontinued if patient begins a drug taper. Therapeutic CNI trough levels are typically determined by protocol:
- A common standard cyclosporine trough goal is 300–400 ng/dL through day +28 and then 250–350 ng/dL from day +28–56.
- 5–10 ng/dL for tacrolimus.
- Of note, these blood levels are trough goals (blood drawn approx 12 h after the last dose).

ii. Peripheral chimerisms may be drawn on days +28, +56, +84, +180, at 12 months, 18 and 24 months, then annually for 5 years.

iii. Immune reconstitution panels for humoral and cellular immunity may be evaluated at days +28, +56, +100, and +180, then at 1 year, and annually through 5 years or until reconstitution complete.

iv. Bone marrow aspirate/biopsy can be done on varying schedules:

- One example includes procedures on days +56 and +84, then at 6 months, 12 months, 18 months, 2 years, and then annually through year 5.

5. Other follow-up studies are determined by disease state (see Table 15.1).

d. Cord blood transplants:

i. For patients enrolled on a clinical trial, laboratory studies should be drawn per study protocol. For patients not receiving care on a clinical trial, consider:

- CBC with differential daily until ANC returns to >500/mm^3. After daily CBCs are no longer required, check CBC twice weekly until day +28, then weekly through day +100
- Chemistry profile that includes renal and liver function studies, LDH, electrolytes, and magnesium three times weekly until day +28, then weekly through day +100.
- Viral testing should include CMV by PCR and Epstein–Barr virus (EBV) by PCR weekly and human herpes virus 6 (HHV6) every 2 weeks until day +100 (see Chap. 10 for additional viral monitoring recommendations).
- If the patient has GVHD and requires steroid therapy, surveillance blood cultures can be considered weekly as long as the patient is receiving prednisone ≥10 mg/day and has an indwelling catheter. Consider repeating cultures prior to initiation of antibiotic therapy on asymptomatic patients.
- Galactomannan assays weekly through day +100 for patients receiving fluconazole prophylaxis.
- IgG levels every other week through day +100. IVIG should be administered per institutional replacement guidelines. If GVHD is present, consider continued monitoring with IVIG replacement per institutional replacement guidelines.
- CNI trough levels twice weekly until day +56, then weekly until the patient begins a drug taper:
  Therapeutic CNI trough levels are typically determined by protocol:
  A common standard cyclosporine trough goal is 200–250.
  A common standard tacrolimus trough goal is 5–10 ng/dL.
  Of note, these blood levels are trough goals (blood drawn approx 12 h after the last dose).
- Chimerism studies:
  Peripheral blood for sorted cells for CD3+ and CD33+ chimerism are evaluated at days +28, 56, and 84.
  Some institutions may require more extensive chimerism studies, also including CD14+ and CD56+ cell sorting as frequently as day +7, +14, and day +21 and day +28 if the patient does not have >95% donor engraftment.

It is important to become familiar with study protocols and follow recommendations for chimerism monitoring.
Bone marrow aspirate/biopsy are typically performed on day +28, then repeated again between day 80 and 100. However, this may be dictated by specific study protocol guidelines.
Immune reconstitution panels for humoral and cellular immunity may be evaluated at days +28, +56, +100, and +180, then at 1 year, and annually through 5 years or until reconstitution complete.
Additional evaluations should be completed per institution standards or study protocol.

15.2 Immunosuppression

1. Myeloablative HSCT:
   a. CNIs and prednisone should be gradually tapered post-HSCT, accomplished by decreasing the drugs in a stepwise, linear fashion. As a general rule, multiple immunosuppressive drugs should not be tapered at the same time, but done sequentially.
   b. For patients receiving steroid prophylaxis, consider tapering 10% of the starting steroid dose weekly beginning around day +30–35, with the goal of tapering to 10 mg/daily by day +84.
   c. CNIs may be tapered by 10% every week beginning at day +84 in the absence of GVHD. This taper may be adjusted by the primary provider based upon the patient status, risk of relapse, and presence of GVHD.
2. Nonmyeloablative HSCT:
   a. Many trials recommend specific guidelines for tapering immunosuppressive agents in the absence of GVHD. An example of a study-driven protocol for immunosuppressive is as follows:
      i. Sibling-donor HSCT recipients
         - Mycophenolate mofetil (Cellcept®) 15 mg/kg po BID beginning day 0, continuing through day +28; no taper required.
         - Cyclosporine (Gengraf®, Neoral®) begins on day -3 at a dose of 4 mg/kg po BID and is adjusted to maintain a trough goal of 300–400 ng/dL through day +28. The trough goal then decreases to 250–350 ng/dl through day +56. In the absence of GVHD, patients may begin a 6% per week at day +56 with a goal of ending therapy by day +180.

      ii. Unrelated-donor HSCT recipients
         - Mycophenolate mofetil (Cellcept®) 15 mg/kg po TID beginning day 0 through day +28, then decreasing to BID dosing through day +56. Therapy is stopped at day +56, no taper required.

Table 15.2 CNI dose adjustment for renal insufficiency

Creatinine (mg/dL)	Cyclosporine/tacrolimus taper
1.5–1.75 (or 1–1.5x baseline)	50% of current dose
1.76–2 (or 1.6–1.9x baseline)	25% of current dose
> 2.0 (or > 1.9 × baseline)	Hold until creatinine <2.0, then resume at 75% of prior dose

- Cyclosporine (Gengraf®, Neoral®) begins on day −3 at a dose of 4 mg/kg po BID and is adjusted to maintain a trough goal of 300–400 ng/dL through day +28. The trough goal then decreases to 250–350 ng/dl through day +56. In the absence of GVHD, patients may begin a 6% per week at day +56 with a goal of ending therapy by day +180.

3. Renal insufficiency and CNI dosing (see Table 15.2):
   a. Renal function should be followed closely in patients receiving CNIs. These drugs are held for serum creatinine levels ≥2.0 mg/dL.
   b. IV hydration may be beneficial to correct an elevated creatinine. Creatinine levels can rise unexpectedly, even in patients who have been tolerating CNIs for weeks to months and have had stable renal function.
   c. CNIs are associated with electrolyte wasting, particularly magnesium. Repletion of magnesium can be accomplished by oral means (dosing may be limited by diarrhea) or by intravenous route.

15.3 Immunizations

Recommendations for post-HSCT immunization are frequently debated and updated:

1. Current opinion suggests treating both autologous and allogeneic recipients as though they have never been vaccinated, recommending revaccination for both subsets of patients.
2. Presently, no pre-vaccination testing is recommended; however, consideration should be given for monitoring immune reconstitution in allogeneic patients prior to vaccination:
   a. Reconstitution of the immune system may take months to years and is affected by infection, length of immunosuppressive therapy, and GVHD.
   b. The best predictive marker of cellular immune recovery is the peripheral blood CD4 + count; recovering IgG levels is a crude indicator of humoral (B cell) immune recovery.
   c. One could measure antigen-specific antibodies prior to and after administering a killed vaccine to document an appropriate rise in the antibody levels demonstrating any humoral response.

3. It is not recommended to begin post-HSCT immunizations in the presence of stage III of IV GVHD or active infection. Vaccination should start as soon as possible as soon as these conditions are resolved.
4. General recommendations:

   a. The safety of administering live vaccinations is still controversial. However, it is agreed that at a minimum, live vaccines (measles, mumps, and rubella (MMR), yellow fever, and FluMist®) should be avoided for at least 2 years following transplant and for as long as patient is on significant immunosuppressive therapy.
   b. Oral polio vaccine (OPV) is no longer available in the USA. Therefore, injectable polio vaccine (IPV) is utilized.
   c. Immunization of family members is often recommended and should be based upon each transplant center's protocol:

      i. For varicella zoster virus (VZV) seronegative caregivers or those with no history of VZV, it is recommended they receive the Varivax® vaccine. Isolation from the transplant patient is necessary if the recipient of the vaccine experiences a rash post vaccination; continue isolation until the rash resolves.
      ii. Family members and close contacts are recommended to receive the inactivated influenza vaccine annually.
      iii. HSCT patients should avoid diaper changing of infants and children who receive the rotavirus vaccine (RV). If this is not possible, practice good hand hygiene:

         - RV5 is dosed at 2, 4, and 6 months of age and is shed in the stool for up to 15 days after vaccination.
         - RV1 is dosed at 2 and 4 months of age and is shed in the stool for up to 30 days after vaccination.

      iv. Caregivers and family members over the age of 60 should receive the Zostavax® vaccine. Isolation from the transplant patient is necessary if the recipient of the vaccine experiences a rash post vaccination; continue isolation until the rash resolves.
      v. Family members may receive the MMR vaccine per recommended scheduling; they should avoid contact with the HSCT recipient if they develop a fever and/or rash post vaccination until symptoms are resolved.

   d. It is recommended that HSCT recipients receiving immunosuppressive therapy who are exposed to VZV receive VariZig; this is currently only available by an expanded access protocol or compassionate use by the Cangene Corporation in Canada:

      i. An alternative option is IVIG if VariZig is not available.

5. Immunization-specific recommendations (see Table 15.3):
   a. Pneumococcal vaccine:
      i. Timing of initiation of dosing remains controversial:
         - One study showed similar responses in patients vaccinated at 3 months versus 9 months post transplant.
         - Early vaccination may be preferred as it protects against both early and late pneumococcal infection but may result in a shorter lasting antibody response.
         - If vaccinations started early, it is crucial to evaluate antibody levels to determine if revaccination is necessary

      ii. Pneumococcal conjugate vaccine (PCV) 13 is the preferred vaccine for the first three doses. However, consider pneumococcal polysaccharide (PPSV23) for the fourth dose to provide broader immune response.
   b. Diphtheria-tetanus vaccine:
      i. DT is full-dose diphtheria toxoid while Td is reduced dose. The dose of tetanus toxoid is the same in both.
      ii. Full toxoid (T) vaccines should be used whenever possible.
      iii. DT vaccine is not currently approved for children >age 7 due to side effects. However, it is usually tolerated well in HSCT recipients as they are similar to vaccine-naïve patients.
      iv. Diphtheria antibody levels after vaccination may be warranted in areas of increased risk of diphtheria.
   c. Pertussis vaccine:
      i. HSCT patients are more susceptible to complications from pertussis due to underlying pulmonary damage secondary to the conditioning regimen and/or GVHD.
      ii. Patients should receive full-dose acellular pertussis toxoid (DTaP)>. However, in the USA, this vaccine is not approved for patients > 7 years old.
      iii. The tetanus, diphtheria, pertussis (Tdap) vaccine contains lower doses of diphtheria and pertussis proteins; preliminary data show poor response to Tdap in autologous and allogeneic HSCT patients, regardless of timing of the dose.
   d. Influenza:
      i. Lifelong seasonal vaccination is recommended.
      ii. If possible, the inactivated influenza vaccine should be given up to 2 weeks prior to admission to pre-transplant patients who have not yet been vaccinated if admission falls during flu season.
      iii. All transplant recipients should receive the inactivated influenza vaccine after day +120, then annually:

Table 15.3 Suggested recommendations for autologous and allogeneic HSCT recipients[a]

Time posttransplant	Vaccine	Comments
3 months	PCV13	–
6 months	PCV13	–
12 months	PCV13	–
–	HPV	Females and males age ≤26 years
–	Hep A[b]	–
–	IPV	–
–	HBV	–
–	Tdap	–
–	HiB	–
–	Meningococcal conjugate	–
14 months	IPV	–
–	HBV	–
–	Td	–
–	HiB	–
18 months	PPSV23	If cGvHD or ineligible by criteria[c], substitute PCV13
–	Hep A[b]	Omit this dose for patients who did not receive initial dose at 12 months
–	IPV	–
–	HBV	Check HBsAb 1–2 months after last HBV injection. If negative, repeat series with doses at 1, 2, and 6 months; consider double-dose formulation
–	Td	–
–	HiB	–
24 months	MMR	Patient must meet dosing criteria to receive this immunization[d]
Annually	Inactivated influenza vaccine	–
Vaccines to avoid	Zostavax®	Live vaccine with high viral load
–	Varivax®	Safety data not established

PCV13 pneumococcal conjugate vaccine, *HPV* human papilloma virus, *Hep A* hepatitis A, *IPV* inactivated polio, *HBV* hepatitis B, *Tdap* tetanus, reduced-dose diphtheria and reduced-dose pertussis, *HiB Haemophilus influenza, PPSV23* pneumococcal polysaccharide, *MMR* measles, mumps, rubella

[a] Vaccines should be given at indicated time points to all autologous and allogeneic transplant recipients except those with active stage III–IV GVHD; with active infections; those receiving chemotherapy for relapse or posttransplant rituxan maintenance, autoimmune hemolytic anemia, etc

[b] For recipients who are HepB or HepC positive or those with cGVHD of the liver, nonalcoholic steatohepatitis, hemochromatosis, or other chronic liver disease, assess hepatitis A antibody titers at 12 months post-HSCT. If negative, proceed with hepatitis A vaccine

[c] Patient must meet all dosing criteria to receive PPSV23: IgG > 500, CD4 > 200, *and* no to minimal immune activation as documented by immune reconstitution panel

[d] Patient may receive this vaccine if off all immune suppression for at least 1 year, > 5 months since last IVIG infusion, IgG > 500, CD4 > 200, *and* minimal to no immune activation as documented by immune reconstitution panel

- Mandatory consideration should be given for a second dose in allogeneic recipients 60 days after the initial injection if within flu season (as defined by Centers for Disease Control and Prevention (CDC) criteria).

iv. Use of the quadrivalent inactivated influenza vaccine is recommended, when available. The trivalent egg-free vaccine should be used, only for those patients with a documented egg allergy.
v. High-dose vaccine should be used for patients ≥65 years old.
vi. The live intranasal influenza vaccination (FluMist®) should never be administered in this patient population and their close contacts.
vii. It is recommended that all caretakers and family members receive the inactivated influenza vaccine annually.

e. Varicella vaccines

i. Varivax® (varicella zoster vaccine) and Zostavax® (herpes zoster vaccine) should be avoided as there are insufficient safety data at this time.

f. Hepatitis B vaccine:

i. All patients should receive hepatitis B vaccines post-HSCT:

- For hepatitis B surface antigen (HBsAg)- or HBcAg-positive patients, vaccination should be given to prevent the risk of reverse seroconversion.
- For HBsAG- or HBcAg-negative patients, vaccination should be given to prevent new acquisition of the virus.
- Assess the HBsAb 1–2 months after the last vaccination. If negative, repeat the series administering double dose vaccines, then repeat the HBsAb; if negative, no additional vaccination is recommended.

g. Meningococcal vaccine:

i. There is a reasonable assumption that conjugated meningococcal vaccines give more stable immune responses than polysaccharide-based vaccines, although no comparative studies have been performed.

h. MMR vaccine:

1. MMRs are typically given in a combination vaccine.
2. MMR is a live vaccine. Immunization should be considered in patients who are at least 2 years post-HSCT, off all immune suppressive therapy for >1 year, and who have not received an infusion of IVIG or plasma for at least 5 months. Additionally, minimal or no immune reactivation should be documented by an immune reconstitution panel.

i. Human papillomavirus:

i. Vaccination can be considered in patients who meet age criteria.

15.4 Central Venous Catheters

1. In general, autologous HSCT recipients may have their central catheter removed once their platelet count is consistently $>50{,}000/mm^3$ without transfusional support:
   a. Assessment of peripheral venous access should be undertaken prior to catheter removal. In patients with very limited peripheral access, the provider should consider retaining their catheters.
2. Allogeneic HSCT recipients may expect to have a central catheter for at least 3–6 months post-HSCT, longer if they develop GVHD:
   a. It is not uncommon for patients to become bacteremic (symptomatic or asymptomatic) while on immunosuppression therapy. Attempts can be made to sterilize the catheter with appropriate antibiotic therapy. However, in cases of sepsis, hemodynamic instability, endocarditis, or persistent bacteremia, the catheter must be removed (see Chap. 17 for additional guidelines).
3. Allogeneic HSCT recipients with severe cGVHD should maintain venous access.

15.5 Activities of Daily Living Guidelines

1. Continue conscientious hand washing.
2. Avoid exposure to contacts with upper respiratory illnesses. If friends/family members are ill, they should not visit. Avoid crowds, but when unavoidable, the HSCT recipient should wear a mask. Guidelines vary. However, these recommendations should continue for approximately 30 days post autologous HSCT. For the allogeneic HSCT recipient, a minimum of 60 days is recommended. However, this is also dependent on the patient's dose of immunosuppressive therapy.
3. Avoid all tobacco products and exposure to smoke.
4. Encourage exercise with slow acceleration, as tolerated.
5. No swimming in public or private pools until 2 weeks after central catheter removed and patient is not receiving immunosuppression therapy.
6. Contact with pets (but not feces) is safe with the exception of reptiles, amphibians, and birds. Patients should wash their hands after contact with pets.
7. Gardening (with gloves) is safe after 3 months for autologous patients and 6 months for allogeneic patients without active GVHD.
8. No contact with barnyard animals for at least 6 months after HSCT. This timeline should be extended for patients who remain on immunosuppressants. Contact with exotic or wild animals should be avoided for approximately 6 months after autologous HSCT and as long as the patient is on immunosuppressive therapy for the allogeneic SCT recipient.

9. Avoid use of pesticides, solvents, or fertilizers for 9–12 months after HSCT.
10. Return to work or school:
    a. Autologous HSCT recipients may consider returning to work as early as 3–6 months after HSCT. Part-time work is advised for 2–4 months after returning to the work place.
    b. Allogeneic HSCT recipients may consider returning to work 6–12 months after HSCT if stable. Part-time work is advised for the first 2–6 months after returning to the workplace.
11. Sexual activities:
    a. May be resumed after day +30 if the patient has a neutrophil count > 1000/mm^3 and a platelet count > 50,000/mm^3.
    b. Limiting the number of sexual partners is advised.
    c. Safe sex practices are advised particularly in circumstances of prolonged immune suppression, thrombocytopenia, or epithelial surface/barrier disruption.
    d. Condoms should be used for the first year post transplant.
    e. Vaginal moisturizers, lubricants, or vaginal dilators may be required to preserve vaginal functioning.
12. Skin care:
    a. Sunblock with > 30 sun protection factor (SPF) should be worn at all times of sun exposure. Excessive sun exposure can activate an inflammatory response resulting in a flare of cutaneous GVHD.

15.6 Osteoporosis

HSCT recipients are at high risk of developing osteoporosis due to multiple predisposing factors (see Chap. 28 for additional details):

1. Pre-HSCT factors:
    a. Age: Men > 50, postmenopausal women
    b. Chronic illnesses: anorexia, systemic lupus erythematosis, rheumatoid arthritis, emphysema, and end-stage renal disease
    c. Endocrine abnormalities: adrenal insufficiency, Cushing's syndrome, diabetes mellitus, hyperparathyroidism, and thyrotoxicosis
    d. Gastrointestinal (GI) disorders: celiac disease, GI surgery, inflammatory bowel disease, and malabsorption
    e. Hematologic disorders: hemophilia, multiple myeloma, systemic mastocytosis, leukemia, lymphoma, sickle cell disease, and thalassemia
    f. Lifestyle factors: smoking, alcohol use (> 3 drinks/day), high caffeine intake, inadequate physical activity, vitamin D deficiency, and immobility

g. Medications: anticoagulants, anticonvulsants, tacrolimus, cyclosporine, glucocorticoids > 5 mg/day or for > 3 months, and chemotherapy agents (including methotrexate, ifosfamide, cyclophosphamide, doxorubicin, interferon alpha)

2. Post-HSCT factors:

a. Immunosuppressive therapy (especially glucocorticoids)
b. Poor nutrition
c. Hypogonadism
d. Inactivity

3. Prevention for allogeneic recipients on steroid therapy:

a. At day +60, consider beginning calcium 1000 mg + vitamin D 1000 units po TID and bisphosphonate therapy. This therapy should be held if the patient develops GVHD of the GI tract:

i. Parenteral bisphosphonates:

- Pamidronate (Aredia®) 60–90 mg IV every 3 –6 months
- Zolendric acid (Reclast®) 5 mg IV yearly

ii. Oral bisphosphonates:

- Alendronate (Fosamax®) 70 mg po weekly
- Ibandronate (Boniva®) 7.5 mg daily or 150 mg monthly
- Risedronate (Actonel®) 5 mg daily, 35 mg weekly, 75 mg × 2 consecutive days every month, or 150 mg monthly

iii. Estrogen/hormone therapy (e.g., Estrace®, Estraderm®, Ortho-EST®, Premarin®, Prempo®). Only indicated for prevention and lowest dose for shortest period of time recommended. Please see prescribing information with specific medication
iv. Estrogen agonist/antagonist (Evista®) 60 mg po daily

b. Consider obtaining a dual energy x-ray absorptiometry (DEXA) scan at 1 year post-HSCT, then annually if patient remains on glucocorticoid therapy:

i. Discontinue bisphosphonate therapy if DEXA scan is normal and patient is off steroids.
ii. DEXA scan should be repeated at age 50 if therapy stopped.

c. If patient's DEXA scan is consistent with osteoporosis, calcium + vitamin D and bisphosphonates should continue with consideration for the addition of:

i. Parathyroid hormone (teriparatide (Forteo®)) 20 mcg SQ daily. *This medication *should not* be used in patients with a history of bone metastases, hypercalcemia, skeletal malignancy, or any history of prior radiation therapy to skeleton.
ii. Assess vitamin D 25-OH annually and prn with replacement therapy if a deficiency is identified

– Vitamin D 50,000 units po weekly × 8–12 weeks, then repeat vitamin D 25-OH

15.7 Diet and Food Preparation

1. HSCT recipients are discouraged from preparing food, particularly early in the post-HSCT course (see Chap. 7 for additional recommendations):
   a. If they choose to cook for themselves, they should be encouraged to follow all safety recommendations:
      i. This includes washing food thoroughly as well as cooking foods to appropriate temperatures.
      ii. Cooked foods should be refrigerated within 2 h of cooking and then reheated to proper temperatures before eating.
2. A low-bacteria diet is recommended in most HSCT programs to prevent food-borne infections, although there are little clear data to support its benefit:
   a. In general, a low-bacteria diet felt to be most important when patients are neutropenic or while receiving immunosuppressive therapy.
   b. The length of time a patient is requested to continue this diet varies but is generally through day +60 for autologous and day +100 allogeneic HSCT recipients, longer if the patient remains on immune suppressive therapy.

15.8 Travel Safety

1. Traveling may expose the autologous HSCT recipient to many infectious risks. Therefore, the patient must be educated to limit his/her exposure.
   a. In general it is safe to start traveling 3–6 months post-HSCT including travel to developing countries.
   b. Airline travel is considered safe, but does pose an increased risk of airborne illnesses:
      i. Prevention is limited to attempting social distancing from obviously ill passengers and frequent hand washing.
   c. Cruise ships are also considered safe. However, the patient must be cognizant of food preparation:
      i. It is safest to stay with hot foods, fruits peeled by the patient or family member, processed drinks, hot coffee, and/or tea.
      ii. The patient must be hypervigilant about hand washing throughout the cruise.

2. Traveling for the allogeneic HSCT recipient is more restricted if they require chronic immunosuppressive therapy:
   a. The same guidelines apply as for the autologous HSCT recipient. However, it is recommended patients avoid travel to developing countries for a minimum of 1 year post-HSCT and ideally, until all immunosuppressive therapy has been discontinued.
   b. Patients should be encouraged to discuss plans for extensive travel with their transplant provider.
3. For immunization recommendations for the immunocompromised traveler, visit wwwnc.cdc.gov/travel/yellowbook/2010/chapter-8/immunocompromised-traveler.aspx.

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Part II
Transplant Complications and Ongoing Care

Chapter 16
Radiology Pearls for the Transplant Provider

Lyudmila Morozova and Marc Gosselin

A wide variety of pulmonary and abdominal complications can occur in HSCT patients and are a major cause of morbidity and mortality. Imaging plays a critical role in detection of pulmonary and abdominal abnormalities.

16.1 Chest

A wide variety of pulmonary complications, infectious and noninfectious, can occur following hematopoietic stem cell transplantation (HSCT). Pulmonary complications occur in approximately 70% of HSCT patients and play an important role in transplant-related deaths (Bolanos-Meade et al 2005; Coy et al. 2005). The type of pulmonary complication depends on the type of HSCT (autologous vs. syngeneic vs. allogenic), type of conditioning regimen (myeloablative vs. nonmyeloablative), and time-elapsed post HSCT (Fig. 16.1).

1. First, important definitions:
    a. *Consolidation:* increased attenuation of lung parenchyma with complete obscuration of normal lung architecture/blood vessels.
    b. *Ground glass:* increased attenuation of lung parenchyma through which blood vessels/normal lung architecture appear indistinct but still visible.
    c. *Air bronchograms:* visualization of air-filled airways surrounded by consolidated lung parenchyma.
    d. *Halo sign:* a zone of ground-glass attenuation surrounding a pulmonary consolidation/nodule/mass.

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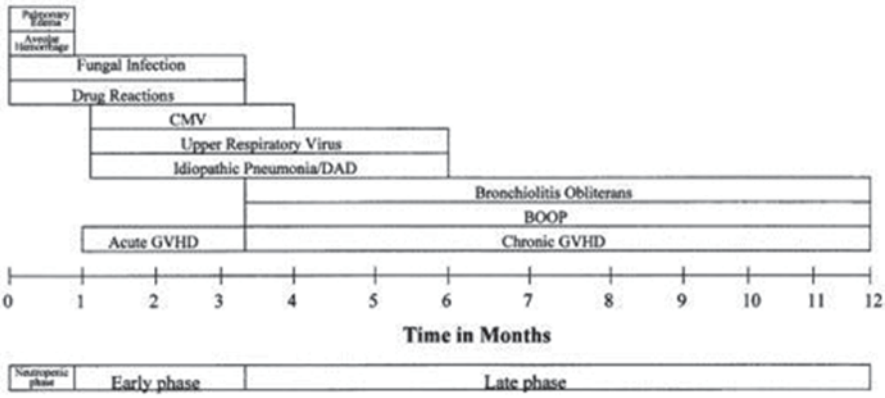

Fig. 16.1 Pulmonary complications after HSCT (borrowed from Gosselin and Adams 2002). *HSCT* hematopoietic stem cell transplantation

e. *Nodule:* increased attenuation on radiograph that is ≤3 cm in greatest dimension
f. *Mass:* increased attenuation on radiograph that is > 3 cm in greatest dimension.
g. *Reticulation:* fine curvilinear opacities.
h. *Infarct:* consolidation that does not enhance and does not have air bronchograms, most of the time in peripheral distribution.

2. Neutropenic phase (0–30 days)
   During this period, patients essentially have no effective immune system and therefore are susceptible to a wide range of infections. Supportive care and empiric antibiotic therapy are important in successful passage through the early post-transplant period. The most common noninfectious complications during the neutropenic phase are pulmonary edema, drug toxicity, and diffuse alveolar hemorrhage (DAH) (*Gosselin and Adams* 2002):

   a. Pulmonary edema

      Pulmonary edema, both cardiogenic and noncardiogenic, is very common in the immediate post-HSCT period. Patients receive large volumes of fluid in the form of medications, blood products, total parenteral nutrition, etc. This large-volume fluid infusion is further confounded by cardiac and renal impairment (consequences from chemotherapy administration) and concomitant hypoalbuminemia:

      i. Cardiogenic pulmonary edema:

         - Clinical symptoms
         - Dyspnea
         - Orthopnea
         - Lower extremity edema
         - Weight gain

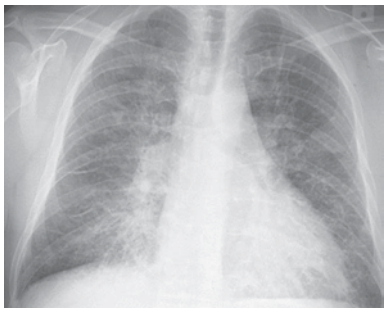

Fig. 16.2 Hydrostatic heart failure: The consolidation (water) is most severe in the lung bases symmetrically. Septal lines are seen throughout the lungs

ii. Radiographic findings (Fig. 16.2):

- Enlarged cardiac silhouette and pulmonary vessels.
- Pleural effusions.
- Septal and fissural thickening.
- Ground-glass and consolidative opacities.
- Of note, vascular indistinctness is best seen in the lung bases medially. The lungs are like two towels drying on a clothesline, the excess water collects mostly at the bases.

b. Noncardiogenic pulmonary edema:

i. Also called capillary leak/increased capillary permeability edema

ii. Factors other than elevated intravascular pressure result in fluid and protein accumulation in the lungs, commonly including:

- Total body irradiation
- Multiple transfusions
- Drug toxicity
- Sepsis

iii. May also be associated with engraftment syndrome (see Chap. 14) which manifests as:

- Fever
- Erythrodermatous skin rash
- Noncardiogenic pulmonary edema

iv. Radiographic findings (Fig. 16.3):

- Diffuse symmetric consolidative and ground-glass opacities.
- Typically, there is no clinical or radiographic evidence to suggest a cardiac etiology (cardiomegaly, septal lines).
- The diffuse distribution is a very important clue, reflecting the systemic causes that induce the vascular leak throughout the lungs, as opposed to that of hydrostatic edema (which affects lower lobes predominantly).
- The accumulation of fluid and protein in the lung tissue leads to decreased diffusing capacity, hypoxemia, and dyspnea and as a result, response to fluid restriction and diuresis is minimal.

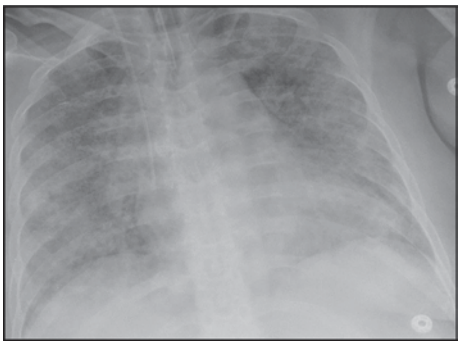

Fig. 16.3 Noncardiogenic edema: Diffuse ground glass reflecting the systemic cause of the vascular injury throughout the lungs, sepsis in this case

c. Drug toxicity:
   i. Drug toxicity can occur during both the neutropenic and early post-HSCT periods; see Sect. 16.3a for discussion.

d. DAH:

   i. In the early history of HSCT, DAH was identified in as many as 20% of patients. Currently, DAH is relatively uncommon and occurs most frequently in the 2–3 weeks post HSCT. It remains associated with very high mortality.

   ii. The exact pathophysiology of DAH is unclear but risk factors include:

      - Age >40
      - Severe mucositis
      - Solid malignancy
      - Rapid neutrophil recovery
      - Allogeneic HSCT
      - Grades III–IV acute graft-versus-host disease (GVHD)
      - Conventional myeloablative transplant

   iii. Typical presentation:

      - Acute onset of dyspnea
      - Cough
      - Hypoxemia
      - Occasional hemoptysis
      - Fever

   iv. Radiographic findings:

      - Rapidly progressive consolidative and ground-glass opacities.
      - Septal thickening.
      - Sparing of the most peripheral aspects of lung parenchyma.
      - Absence of pleural effusions.

   v. Definite diagnosis requires bronchoalveolar lavage that demonstrates increasingly bloody return without identification of any infectious organism. Hemosiderin-laden macrophages are seen in lavage fluid.

e. Bacterial/fungal infections:

i. Pulmonary manifestations of bacterial and fungal infections are not commonly seen during the neutropenia period despite high prevalence of bacteremia.
ii. The common empiric use of broad-spectrum antimicrobial agents may prevent development of infectious pneumonia.
iii. Incidental septic emboli, which on radiography manifest as peripheral poorly marginated nodules which rapidly cavitate, is an exception.
iv. Radiologic manifestation of other pulmonary bacterial and fungal infections will be discussed in Sects. 16.3.b and 13.3.c, as they are more common during the early/late post-transplant period.

f. Acute GVHD:

Historically, pulmonary complications were thought to be a common complication of acute GVHD. Typically, other organ systems (skin, liver, and gut) are involved prior to lung involvement. Currently, acute GVHD involving the lung is considered a very rare event.

3. Early phase (1–3 months) and late phase (3 months–1 year)
During the early period, 1–3 months after HSCT, the most common pulmonary complications are drug toxicity (allogeneic and autologous), and invasive aspergillosis and cytomegalovirus (CMV) pneumonia (allogeneic).
The late post-HSCT period extends from 3 months to 1 year. During this time, immune function continues to recover, and there is a reduction in pulmonary complications in autologous and syngeneic HSCT recipients. In contrast, allogeneic HSCT recipients often develop chronic GVHD which increases their risk of other infectious and noninfectious pulmonary complications:

a. Drug toxicity:

i. Occurs most often in the first 100 days post HSCT.
ii. Multiple cytotoxic mediations, such as carmustine, busulfan, and methotrexate, as well as radiation injury to the lung parenchyma are common offending agents.
iii. Clinically, patients present with dry cough, dyspnea, and low-grade fevers.
iv. Radiographic findings develop within days of the onset of symptoms.
v. The pattern of injury varies and may manifest as noncardiogenic edema, hypersensitivity reaction, diffuse alveolar damage (DAD), or nonspecific interstitial pulmonary pneumonitis:

- Hypersensitivity drug reaction pattern is the most common, presenting as bilateral patchy ill-defined areas of ground-glass and consolidative opacities; posterior segments of lower lobes are frequently involved.
- The findings may be very subtle on radiograph, and chest computed tomography (CT) is often required to evaluate parenchymal abnormality.

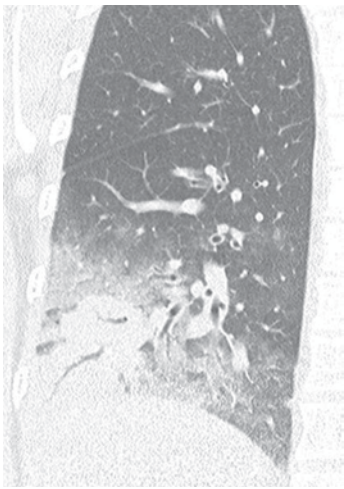

Fig. 16.4 Bacterial pneumonia: Peripheral consolidation with air bronchograms is the most common and characteristic imaging manifestation

- With continuous/repeated exposure to the offending agent, nonspecific interstitial pneumonitis, and pulmonary fibrosis ensue.

b. Bacterial infection:

i. There is high prevalence of bacteremia during early post-HSCT period; pulmonary bacterial infections are also commonly identified.
ii. Gram-negative bacteria, likely originating from oral mucosa or gastrointestinal (GI) tract, are most commonly identified.
iii. Gram-positive bacteremia is often identified in the setting of long-term central catheter utilization and upper GI tract mucositis.
iv. Presence of GVHD drastically increases the incidence of bacterial pneumonia.
v. Radiographic appearance (Fig. 16.4) of bacterial pneumonia is very similar to an immunocompetent host with focal pulmonary consolidation containing air bronchograms, often peripheral in distribution.

c. Opportunistic fungal/mold infections:

i. Account for approximately 0.9–13.2% of all pneumonias in allogeneic HSCT recipients, and is less common in autologous HSCT recipients.
ii. Aspergillus species are the most common pathogens. These can be angioinvasive or less frequently, airway invasive.
iii. Most frequently seen 1–4 months post HSCT. In patients with chronic GVHD, this period is extended even further.
iv. Primary prevention with the use of N-95 masks and high-efficiency particulate absorption (HEPA) filtration can be effective.
v. Clinically, patients often present with a cough and persistent fever. Hemoptysis is rarely seen.
vi. Radiographic findings (Fig. 16.5):

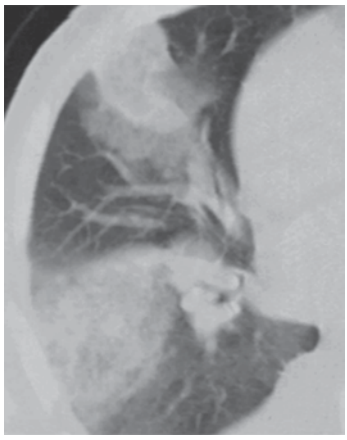

Fig. 16.5 Angioinvasive Aspergillus: Two focal consolidations with surrounding ground glass but without air bronchograms (infarct)

- Angioinvasive Aspergillus initially manifests as a single or multiple ill-defined infarcted nodules or masses.
- Focal or multifocal segmental or subsegmental nonenhancing consolidations, typically in a peripheral distribution, without air bronchograms are also commonly seen; all features of a pulmonary infarct.
- Later in the disease course, the nodules may cavitate and demonstrate an "air-crescent" sign on chest CT. This development signifies neutrophil recovery and better prognosis.
  - On CT, solitary or multiple nodules surrounded by a halo of faint ground glass may be seen ("halo sign"). This finding is highly suggestive of angioinvasive Aspergillus:
  - In a minority of cases, fungus invades the airways. On chest CT, *airway invasive* Aspergillus is identified by focal nodules or consolidation without air bronchograms.
  - Characteristic radiographic appearance in a neutropenic patient combined with isolation of Aspergillus from bronchoalveolar lavage is considered diagnostic of the infection.

d. CMV

i. CMV pneumonia most commonly occurs 6–12 weeks post HSCT.
ii. Patients with concurrent GVHD are at higher risk of CMV infection.
iii. Typically, there is reactivation of latent virus in seropositive patients. Seronegative recipients acquire infection from a CMV-positive donor or CMV-positive blood products. Aggressive clinical screening of CMV-positive recipients for CMV reactivation with initiation of preemptive therapy as early as possible, and the use of leukocyte-reduced blood products transfused to CMV-negative recipients have significantly decreased the development of clinical disease (see Chap. 10).

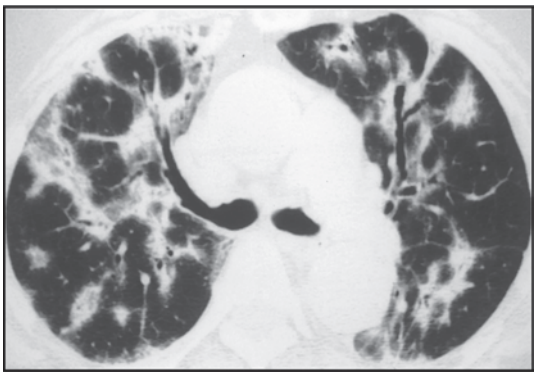

Fig. 16.6 Organizing pneumonia: Multifocal, somewhat peribronchial consolidations. This case was a "graft-versus-host" etiology

iv. Clinically, patients develop fever, dyspnea, nonproductive cough, and hypoxia.
v. Without treatment, respiratory failure rapidly develops and mortality rates are high.
vi. Chest radiographs demonstrate patchy ill-defined ground-glass opacities and scattered ill-defined sub-centimeter nodules. There is lower lobe predominance but pleural effusions are not commonly seen.

e. GVHD

During the late period, while autologous and syngeneic transplant recipients recover their immune function with reduction of pulmonary complications, allogeneic HSCT recipients face another challenge: GVHD:

i. Patients with GVHD are predisposed to bacterial, viral, and fungal pneumonias, either from primary immune dysfunction caused by GVHD itself, associated hypogammaglobulinemia, or from secondary immune dysfunction due to immune suppressive therapies.
ii. Noninfectious complications include bronchiolitis obliterans syndrome (BOS) and cryptogenic organizing pneumonia (COP; see Chap. 22).

f. BOS:

i. About 10% of allogeneic HSCT recipient with chronic GVHD develop BOS.
ii. Pulmonary viral infections also predispose HSCT recipients to BOS.
iii. Present with cough and dyspnea on exertion. Fever is uncommon.
iv. Initial chest radiograph may be normal or may show subtle pulmonary hyperinflation.
v. Chest CT is more telling and typically demonstrates mosaic attenuation and bronchial dilation. Expiratory views usually demonstrate air trapping.
vi. There is no effective treatment and mortality is high.

g. COP:

i. COP affects 1–2 % of allogeneic HSCT recipients. The etiology of COP is typically infection or drug toxicity.
ii. Patients present with dry cough, dyspnea, and low-grade fevers.
iii. On radiography and CT, multifocal consolidative opacities in a peribronchial and peripheral/subpleural distribution are observed (Fig. 16.6). This organizing pneumonia imaging appearance is quite common in HSCT recipients and often necessitates a pulmonary consultation for bronchoscopy to rule out an underlying infection prior to instituting immunosuppressive therapy.

h. Acute interstitial pneumonitis (AIP)/DAD

i. AIP/DAD (or idiopathic pneumonia syndrome, IPS) is a diffuse lung injury. No identifiable cause is seen on pathology; it is a diagnosis of exclusion.
ii. Risk factors include high-dose total body radiation, alkylating agents (e.g., busulfan, carmustine, melphalan, cyclophosphamide), GVHD, and allogeneic HSCT.
iii. Most often occurs 1–2 months after HSCT with an incidence of approximately 12 % in allogeneic HSCT recipients.
iv. Clinical presentation includes nonproductive cough, hypoxemia, and dyspnea.
v. On radiography, there are patchy consolidative and ground-glass opacities that become more extensive and confluent over a period of days. The lung volumes decrease as lung compliance decreases.
vi. Chest CT may additionally demonstrate areas of architectural distortion, traction bronchiectasis, and reticulations of early fibrosis, characteristic for the severe underlying DAD reaction.

16.2 Abdomen

HSCT recipients are also at risk for abdominal complications such as infections (bacterial, fungal, and viral), hepatic sinusoidal obstructive syndrome (SOS), neutropenic colitis, GVHD, and hemorrhagic cystitis. Hemorrhagic cystitis is more common in pediatric population and will not be discussed here:

1. GI GVHD:

a. As discussed earlier, acute GVHD affects skin, liver, and GI tract prior to affecting lung parenchyma. GI manifestations of GVHD include inflammation of the colonic and small bowel walls.
b. On radiography, patients with gut GVHD show multiple dilated and fluid-filled loops of bowel. Air-fluid levels may also be seen. In more advanced cases, pneumatosis intestinalis and perforation may develop.

c. On contrast-enhanced CT, there is typically extensive lumenal dilation along with circumferential hyper-enhancing gut which represents mucosal injury/inflammation. Gallbladder and urinary bladder mucosal hyper-enhancement may also be seen. Mesenteric inflammatory stranding is often present, and hepatomegaly and ascites are frequently seen. Perforation and abscess formation develop in more severe cases.

2. Infections:

a. Abdominal infections are not uncommon during the post-HSCT period. The commonly identified organisms are *Clostridium difficile,* Candida, and CMV.
b. Neutropenic patients are at a higher risk for bacterial infections. Aggressive prophylaxis with broad-spectrum antimicrobial agents may lead to overgrowth of normal bowel flora, such as *C. difficile*:

i. Pseudomembranous colitis is the result of damaged colonic mucosa by toxins produced by *C. difficile* bacteria (Fig. 16.7).
ii. Patients usually develop copious watery diarrhea. Fever may or may not be present.
iii. On imaging, there is marked submucosal edema involving a long segment of colon, most frequently the entire colon (pancolitis):

- Thumbprinting may infrequently be seen signifying haustral thickening/edema.
- Occasionally, CT demonstrates the “accordion" sign: trapped enteric contrast between thickened colonic haustral folds. Adjacent inflammatory stranding is often present.

c. Abdominal Candidal infections usually manifest as multiple tiny hepatic, splenic, and renal microabscesses:

i. On sonography, microabscesses are usually seen as hypoechoic sub-centimeter nodules.
ii. On CT, microabscesses typically present as tiny hypo-dense nodules.

d. CMV is the leading viral pathogen causing early post-HSCT abdominal complications:

i. Abdominal pain, nausea, vomiting, diarrhea, fever, and/or GI bleeding are typical presenting symptoms. Hepatitis may also develop.
ii. On CT, there is typically wall thickening of colon, stomach, and small bowel (particularly, terminal ileum). Mesenteric stranding due to deep ulcers is often seen.

3. Hepatic SOS (see Chap. 21):

a. SOS is thought to develop secondary to injury to the hepatic venous endothelium from the conditioning regimen.

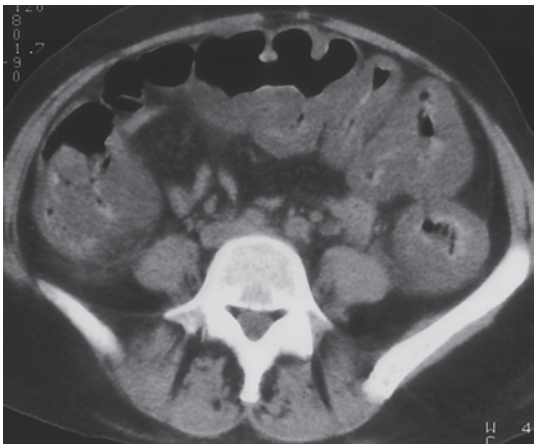

Fig. 16.7 CT scan obtained in a 28-year-old woman who developed pseudomembranous colitis following antibiotic therapy (borrowed from Kawamoto et al. 1999). *CT* computed tomography

b. Usually occurs within 2 weeks post HSCT.
c. Patients typically develop weight gain, tender hepatomegaly, ascites, and jaundice. Fever may be present.
d. Liver doppler ultrasound demonstrates increased phasicity of portal veins with subsequent development of portal flow reversal.
e. Increased hepatic arterial resistive index should raise a suspicion of developing SOS.
f. The liver is usually enlarged and demonstrates areas of periportal low attenuation.
g. Small caliber hepatic veins may be seen.
h. Liver biopsy may be required for a definitive diagnosis.

4. Neutropenic colitis:

a. Results from the pre-HSCT conditioning regimen together with immunosuppression in the pre-engraftment period.
b. It is an inflammatory process involving the cecum, ascending colon, and in rare instances distal ileum and appendix.
c. Patients typically present with abdominal pain and fever. Severe diarrhea is very common.
d. As shown in Fig. 16.8, abdominal CT demonstrates massive mural cecal thickening and hyper-enhancement with possible involvement of the ascending colon and distal ileum. Pericolic inflammation is often present. In more severe cases, perforation may develop.

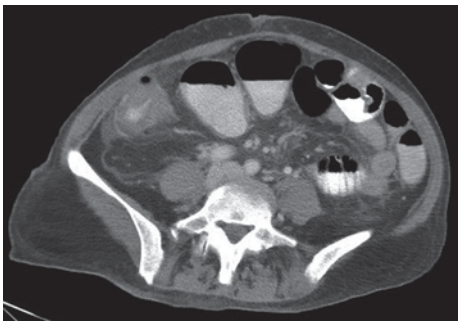

Fig. 16.8 Neutropenic colitis: Cecal wall thickening and adjacent inflammatory stranding

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Chapter 17
Infectious Complications

Lynne Strasfeld

Infections remain a cause of significant morbidity and mortality following hematopoietic stem cell transplantation (HSCT). The conditioning regimen (chemotherapy, radiation therapy), mucosal damage, type of transplant, immune suppressive therapy, and graft-versus-host disease (GVHD) all predispose the HSCT recipient to infection. Abnormal B- and T-lymphocyte function results in impaired humoral and cellular immunity, respectively. Neutrophil function is impaired by the use of corticosteroids and other medications. Hypogammaglobulinemia and functional asplenia are common. The occurrence of infections in an individual patient varies according to the phase of the transplant process and reflects the type(s) of immune defect(s), underlying disease, endogenous host flora, exposure history, and pre-treatment infections.

17.1 Temporal Sequence of Infections

1. First month post-transplant (pre-engraftment) (see Fig. 17.1):
   a. *Viral infections*: Herpes simplex virus (HSV), varicella zoster virus (VZV), community respiratory viruses, enteric viruses, human herpes virus-6 (HHV-6), etc.
   b. *Bacterial infections:* Gram-positive (*Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus* species, *Enterococcus* species) and gram-negative organisms (*Klebsiella* species, *Pseudomonas aeruginosa, Escherichia coli*), with resultant bacteremias as well as sinopulmonary, perirectal, gastrointestinal, and skin/soft tissue infections
   c. *Fungal infections:* Predominantly *Candida* and *Aspergillus* species

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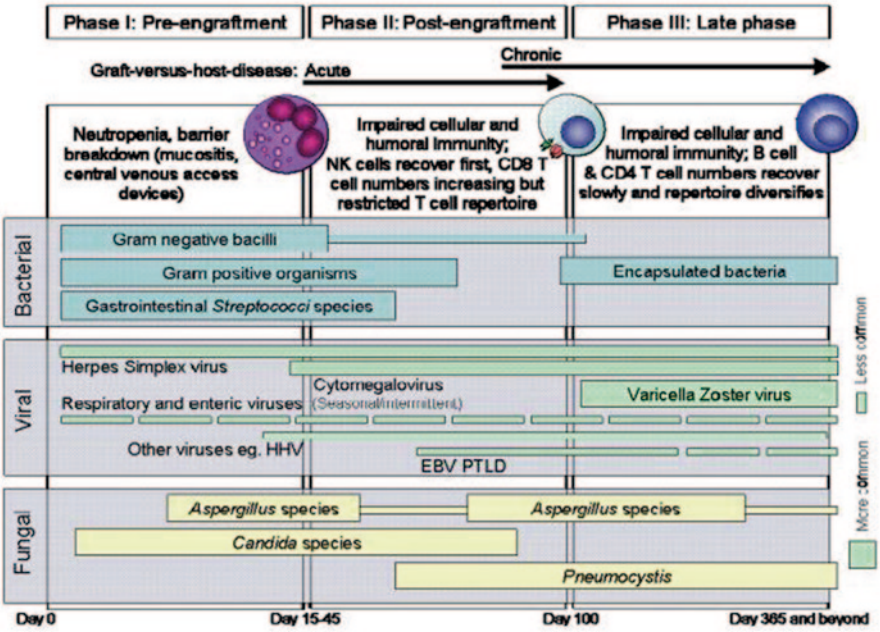

Fig. 17.1 Phases of opportunistic infections among allogeneic HSCT recipients. *EBV* Epstein–Barr virus, *HHV-6* human herpes virus 6, *PTLD* posttransplant lymphoproliferative disease. © Granted by Elsevier

2. One to four months post-transplant (early post-engraftment):
    a. *Viral infections*: Cytomegalovirus (CMV), HSV, VZV, community respiratory and enteric viruses, BK virus, and HHV-6, which can cause infection of the sinopulmonary, central nervous system, gastrointestinal, hepatic, and urogenital systems, depending on the causative organism
    b. *Bacterial infections*: Gram-positive and Gram-negative organisms, primarily arising from/involving the sinopulmonary system, the gastrointestinal tract, and skin/soft tissue
    c. *Fungal infections*: *Candida, Aspergillus,* and *Cryptococcus* species, Mucorales, reactivation of endemic fungi, typically involving the sinopulmonary, central nervous system, liver, spleen, mouth and/or skin/soft tissue; *Pneumocystis jirovecii* pneumonia (PCP) in patients on suboptimal PCP prophylaxis
    d. *Protozoal infections*: *Toxoplasma gondii,* which can affect the central nervous system or present in a disseminated fashion
3. Four to twelve months post-transplant (late post-engraftment):
    a. *Viral infections*: VZV, community-acquired respiratory and enteric infections, and CMV infection in patients with GVHD and prior history of early post-transplant CMV reactivation/infection

b. *Bacterial infections*: Encapsulated organisms (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*, etc.)
c. *Fungal infections*: Both yeasts and molds (e.g., *Candida, Aspergillus, Cryptococcus* species, Mucorales, etc.), particularly in those patients who remain on immunosuppressive therapy, have GVHD and/or CMV infection; *Pneumocystis* in patients on suboptimal prophylaxis
d. *Protozoal infections*: *T. gondii*, which can affect the central nervous system or present in a disseminated fashion

4. Greater than 12 months post-transplant:

a. *Viral infections*: VZV, community-acquired respiratory and enteric infections, and CMV infection in patients with chronic GVHD and prior history of CMV reactivation/infection.
b. *Bacterial infections*: Encapsulated organisms (e.g., *S. pneumoniae, H. influenzae,* etc.).
c. *Fungal infections*: Both yeasts and molds, particularly in those patients who remain on immunosuppressive therapy have GVHD and/or CMV infection.
d. *Protozoal infections* can occur late as well, again primarily in patients who remain on immunosuppressive therapy.

17.2 Empiric Antimicrobial Therapy and Evaluation of Neutropenic Fever

1. For the first neutropenic fever ($T \geq 38\,°C$):

a. Comprehensive fever workup to include the following, with additional testing as prompted by localizing signs/symptoms:

i. Blood cultures from peripheral blood draw as well as all lumens of central catheter
ii. Urine analysis (UA) dip/micro and urine culture
iii. Sputum culture if patient is coughing and able to expectorate sample
iv. Two-view chest X-ray (CXR) to evaluate for pulmonary infection

b. Discontinue prophylactic antibiotic and begin empiric parenteral antibiotic therapy as soon as possible, and always **within 1 h** of the initial fever:

i. Empiric antibiotic therapy should be sufficiently broad, providing coverage of *P. aeruginosa*, Enterobacteriaceae, and oral streptococci.
ii. Options include cefepime (fourth generation cephalosporin), piperacillin/tazobactam, or an antipseudomonal carbapenem (e g., meropenem or imipenem).
iii. Consideration of the local institutional antibiogram as well as any patient-specific history of prior drug-resistant bacteria is critically important in determining the empiric antibiotic selection.

iv. For septic/clinically unstable patients, consider broadening empiric regimen to include an aminoglycoside (e.g., tobramycin 5 mg/kg intravenous (IV) once daily, adjusted for renal function; once-daily dosing is preferred) as well as extended Gram-positive coverage (see Sect. 17.2).

c. For subsequent fevers:

i. Frequent (at least daily), thorough clinical evaluation for signs or symptoms of new or emergent infection is imperative.
ii. For T ≥ 38 °C, obtain blood cultures every 24 h for 2–3 days.
iii. If fevers persist, blood cultures should be obtained in the context of clinical worsening and/or prior to any change to the empiric antibiotic regimen.
iv. After initial defervescence with empiric antibiotics, recrudescent fever should be reevaluated with blood cultures and careful clinical assessment.

d. Adjustment of empiric antibiotic regimen:

i. If cultures are positive or if source of infection is defined, ensure regimen is appropriate based on pathogen susceptibility pattern and/or source.
ii. Discontinue empiric antibiotic therapy once absolute neutrophil count (ANC) > 500 cells/mm^3 if patient remains afebrile and provided there is no documented infection.

2. Indications for use of empiric extended Gram-positive coverage for neutropenic fever:

a. Add vancomycin for any patient with:

i. Sepsis/unstable clinical condition, particularly for those patients with an established history of methicillin-resistant *S. aureus* (MRSA) colonization or infection, and *not* previously known to be colonized/infected with vancomycin-resistant *Enterococcus* (VRE)
ii. Documented infection with a Gram-positive organism while awaiting results of identification and susceptibility testing (e.g., Gram-positive cocci in clusters or pairs/chains for patient *not* previously known to be VRE colonized/infected)
iii. Skin/soft tissue infection
iv. Suspected/established catheter-related infection
v. Healthcare-associated pneumonia, while awaiting data from respiratory culture

b. For patients known to be VRE colonized/infected, use daptomycin* as extended Gram-positive agent in the setting of sepsis and/or Gram-positive bacteremia (Gram-positive cocci in pairs and/or chains) while awaiting results of identification and susceptibility testing. Given the potential for myelosuppression with linezolid, daptomycin may be the preferred agent in this setting. *Note that daptomycin should *not* be used for the treatment of pneumonia, given its

ineffectiveness in this setting; in the setting of possible/proven MRSA pneumonia, consider the use of vancomycin or linezolid.

c. Blood as well as wound and sputum (when applicable) cultures should be obtained prior to adding vancomycin, daptomycin, or linezolid.
d. Discontinue vancomycin, daptomycin, or linezolid after 72 h if no Gram-positive organisms have been cultured and patient has no evidence of shock, pneumonia, skin/soft tissue, or central venous catheter source, regardless of the presence or absence of fever.

3. Management of persistent neutropenic fevers (> 72 h after initiation of empiric antibacterial therapy):

a. Frequent (at least daily), thorough clinical evaluation for signs or symptoms of new or emergent infection is imperative.
b. Strong consideration for computed tomography (CT) chest to evaluate for opportunistic pulmonary infection.
c. Consideration to broadening empiric antifungal coverage:

i. For patients who are receiving fluconazole prophylaxis, change therapy to voriconazole (see Chap. 10 for dosing guidelines), or to an echinocandin (e.g., micafungin 100 mg IV q24 h; caspofungin 70 mg IV × 1, then 50 mg IV q24 h; or anidulafungin 200 mg IV × 1, then 100 mg IV q24 h) if azole-resistant candidiasis is suspected/documented.
ii. If voriconazole is contraindicated (e.g., liver enzyme abnormalities, drug–drug interactions), alternatives include:

- Lipid-based amphotericin product (3–5 mg/kg IV q24 h)
- Echinocandin, though recognizing the inferiority of these agents for prophylaxis/treatment of mold infections

d. For patients who are receiving posaconazole prophylaxis, obtain a CT chest, check serum galactomannan, and send a posaconazole level (if not yet sent). If CT chest is suspicious for fungal infection or if the serum galactomannan is positive, consider switch to alternative agent (e.g., voriconazole or lipid-based amphotericin product) and consult pulmonary service for consideration of diagnostic bronchoscopy and/or other diagnostic testing.
e. If a patient is receiving voriconazole and there is clinical suspicion for invasive mold infection, entertain possibility of subtherapeutic voriconazole level or a voriconazole-resistant organism and consider empiric change to lipid-based amphotericin product (Ambisome® or Abelcet®). Voriconazole level should be checked prior to drug discontinuation (see Table 10.5).

4. Clinical criteria necessitating removal of central venous catheters include:

a. Septic patient with suspected line source
b. Tunnel tract infection
c. Failure of response (persistent bacteremia with positive blood cultures after 48 h of appropriate antibiotic therapy)

5. Central venous catheters should be removed for positive blood cultures with the following organisms:
    a. *S. aureus*
    b. *P. aeruginosa*
    c. *Candida* species
    d. Multidrug resistant Gram-negative organism
    e. Mycobacterial species

17.3 Treatment of Common Specific Infections in the HSCT Population

Of paramount importance in the treatment of infections in the HSCT recipient is the ability to obtain an accurate diagnosis. Symptoms of infection may be nonspecific or even attenuated in the heavily immune suppressed HSCT recipient. Diagnosis of infection may require culture of blood or other body fluid, molecular diagnostic testing (e.g., polymerase chain reaction, PCR), radiographic study, invasive diagnostics to obtain tissue or other material, as well as careful ongoing assessment for change in clinical status.

1. Herpes zoster (VZV) infection:
    a. Rate of occurrence is decreased with acyclovir (or a related congener) prophylaxis.
    b. Typically occurs 4–5 months post-transplant (or later in allogeneic recipients) and may be associated with visceral or central nervous system disease.
    c. May be localized to a single dermatome or disseminated (see Fig. 17.2). A thorough skin examination is recommended to evaluate for disseminated disease.
    d. Oral antiviral therapy with acyclovir 800 mg orally (po) five times daily (adjust dose for renal function) is standard of care for lesions confined to a single dermatome. Valacyclovir (Valtrex®) achieves better therapeutic plasma levels against VZV and may be used as preferred alternative to oral acyclovir if cost does not preclude use (dosed at 1000 mg po three times daily (TID), renal dose adjustment as indicted; see Table 10.2).
    e. For severe herpes zoster infections (>1 dermatome, trigeminal nerve involvement, visceral or disseminated disease), patients should be hospitalized and treated with intravenous acyclovir (10 mg/kg IV every 8 h, renal dose adjustment as indicated; see Table 10.2) until lesions have completely crusted and no new lesions are evident, then transitioned to an oral compound (acyclovir or valacyclovir) to complete the treatment course. Monitor for acute kidney injury and encephalopathy as possible adverse effects of high-dose, parenteral acyclovir.
    f. Acyclovir-resistant VZV is relatively unusual; if suspected, a viral culture should be obtained for phenotypic resistance testing, with consideration to

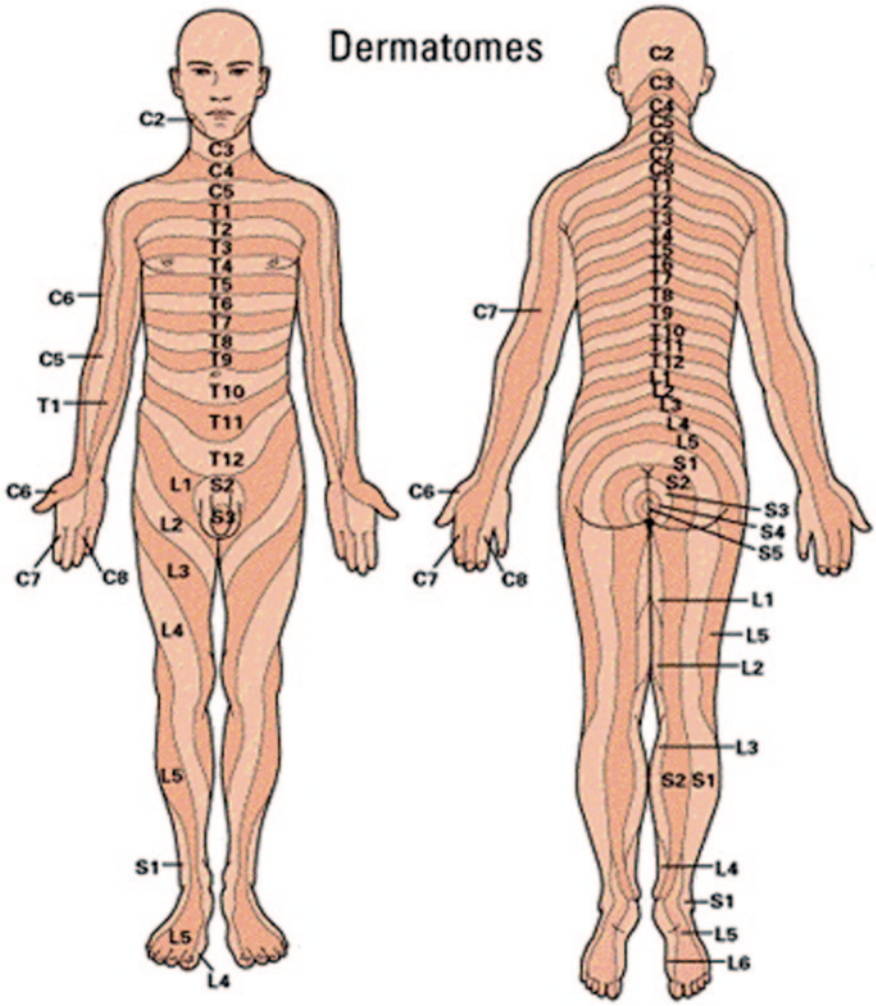

Fig. 17.2 Dermatome map for the determination of the extent of herpes zoster infection

use foscarnet (40 mg/kg IV every 8 h, renal dose adjustment as indicated) if resistance is proven or in the context of life-threatening infection while awaiting results of resistance testing, along with consultation to the infectious diseases service.

2. HSV infection:

   a. Infection is largely related to reactivation in the post-transplant setting, and absent prophylaxis, occurs early (within the first month post-transplant).
   b. Risk for infection is decreased with acyclovir (or a related congener) prophylaxis.

c. HSV-1 infections most often present as severe mucositis and occasionally esophagitis, and less often with secondary infection of various organs in the context of viremia. HSV-2 infections are less common and typically affect the genital/perineal/buttocks region.
d. For non-severe infection limited to the mucous membranes, oral antiviral therapy is usually adequate: acyclovir 400 mg po five times daily for approximately 7 days. If unable to tolerate oral medications, then use acyclovir 5 mg/kg IV every 8 h for approximately 7 days. Alternative therapy includes valacyclovir 500–1000 mg po two times daily (BID) for 5–10 days.
e. In the case of suspected/proven visceral dissemination (e.g., encephalitis, hepatitis, pneumonitis), acyclovir 10 mg/kg IV every 8 h should be used as initial therapy, with duration typically 14–21 days, depending on clinical syndrome and clinical course.
f. Select patients with frequently recurring outbreaks may require chronic antiviral suppression. Any of the following regimens is acceptable: acyclovir 400–800 mg po BID-TID or valacyclovir 500 mg po BID.
g. Drug doses should be renally adjusted as indicated (see Table 10.2).

3. HHV-6 infection:

a. Infection is almost universally related to reactivation and occurs in 30–50% of transplant recipients in the early post-HSCT period (2–4 weeks).
b. Viremia is often asymptomatic, though has been purported to be associated with a variety of nonspecific presentations (e.g., bone marrow suppression, delirium). A causal association with encephalitis is supported by numerous case reports and case series.
c. When encephalitis is suspected, HHV-6 PCR testing (cerebrospinal fluid (CSF), blood) should be performed; magnetic resonance imaging (MRI) of the brain may reveal abnormalities, often involving the temporal lobes.
d. Treatment is controversial, but for established encephalitis, foscarnet or ganciclovir should be used in therapeutic doses. Treatment decisions should be made on a case-by-case basis in consultation with the infectious diseases service.

4. CMV infection:

a. CMV infection can lead to end-organ disease in the HSCT recipient, manifesting as pneumonia, gastroenteritis, hepatitis, retinitis, encephalitis, etc.
b. While detection of CMV by PCR in blood in the context of clinical signs/symptoms consistent with CMV disease is suggestive, more certain diagnosis typically requires diagnostic bronchoscopy and/or tissue biopsy. Furthermore, CMV PCR detection in blood is not fully sensitive for the detection of end-organ disease, particularly gastrointestinal disease. If CMV disease is suspected, tissue biopsy (for histopathology and viral culture) should be obtained when feasible.
c. When CMV end-organ disease is suspected/proven, consultation with the infectious diseases service for patient-specific treatment recommendations is

advised. First-line therapy for CMV disease is generally IV ganciclovir, with foscarnet reserved for cases with intolerance to ganciclovir (e.g., refractory cytopenias) or if ganciclovir resistance is suspected (e.g., if CMV viral load increases while on therapy for more than 2 weeks) or documented.

d. Ganciclovir-resistant virus is an unusual occurrence in the HSCT population and most often occurs in patients who have had prolonged exposure to ganciclovir or valganciclovir.
e. Treatment duration should be determined on a case-by-case basis, taking into consideration the severity of CMV disease and the immune status of the host. Typically, induction dosing should be given for at least 3 weeks until the CMV viral load is undetectable and symptoms of end-organ disease have resolved, with several weeks of maintenance IV ganciclovir or oral valganciclovir dosing thereafter (see Tables 10.3 and 10.4 for dosing).
f. For CMV pneumonia, in addition to antiviral therapy, adjuvant immune globulin is generally recommended, largely based on small uncontrolled studies, though recent analyses have raised question about the value of this intervention:

    i. CMV-specific immune globulin has not been shown to be more effective than intravenous immunoglobulin (IVIG) and is more costly
    ii. The dose, frequency, and duration of IVIG for CMV pneumonia have not been well studied. Historically, IVIG dosing has been 500 mg/kg IV every other day for up to ten doses.

5. Adenovirus and BK virus infections of the genitourinary (GU) tract:

    a. Both adenovirus and BK virus can result in hemorrhagic cystitis post-transplant.
    b. For patients who develop BK viral cystitis, the initial approach should consist of supportive care:

        i. Begin with antispasmotics (e.g., oxybutinin) or urinary tract analgesics (e.g., phenazopyridine).
        ii. Consider reducing immune suppression if feasible and begin continuous bladder irrigation if symptoms are not controlled with antispasmotics.
        iii. For patients who develop fulminant hemorrhagic cystitis, consider therapy with cidofovir; a variety of cidofovir dosing protocols have been reported in case reports and small case series (e.g., 1 mg/kg weekly to three times weekly without probenecid), with the goal of minimizing drug toxicity. Important adverse drug effects associated with cidofovir administration include nephrotoxicity as well as hematologic and ocular toxicity, and so careful monitoring is recommended in this setting.
        iv. Viral load quantification does not correlate with symptoms, and the clinical significance of the viral load is unknown.

    c. Adenovirus infection can manifest as hemorrhagic cystitis, but is significantly more likely than BK virus to result in disseminated and potentially life-threatening disease:

i. Adenovirus can affect the lungs, gastrointestinal tract, liver, GU system and/or the central nervous system.
ii. Patients who have a positive culture or PCR for adenovirus from their urine should have blood sent for quantitative adenovirus PCR.
iii. For adenovirus viremic patients and/or in the setting of fulminant hemorrhagic cystitis, strong consideration should be given to systemic treatment, with cidofovir 5 mg/kg IV once weekly for 2 weeks and then every other week or 1 mg/kg three times weekly (renal dose adjustment as indicated). If systemic or disseminated disease (e.g., disease outside the GU tract) is suspected, add probenecid 2 g po 3 h prior to cidofovir dose, then 1 g po at 2 and 8 h after dose.

6. Community respiratory viral infections:
Community respiratory viral infections are common in HSCT recipients and can result in a spectrum of clinical findings, from upper respiratory tract infection (URI) to lower respiratory tract infection (LRTI), with often serious associated morbidity and even mortality. In addition to the "direct effects" of viral infection, there is increased risk for coinfection (e.g., with bacteria or fungi) in this setting, as well as risk for late airflow obstruction. While some of the community respiratory viruses have a distinct seasonality (e.g., influenza and respiratory syncytial virus, RSV), others occur year round (e.g., rhinovirus). Testing for community respiratory viral infections should be by molecular methods/multiplex PCR from nasopharyngeal sample or lower respiratory tract sample, as this methodology offers the highest sensitivity for diagnosis. Evaluation of suspected LRTI in patients with URI should include chest imaging (CXR and/or CT chest). Droplet and contact precautions should be initiated for hospitalized patients with either suspected or documented community respiratory viral infection, with the use of airborne precautions in the context of aerosol-generating procedures (e.g., bilevel positive airway pressure (BiPAP), suctioning, etc.); these precautions should continue until the patient is asymptomatic and repeat testing for viral infection is negative. If inhalational ribavirin is used, patient must be in a negative airflow room with airborne isolation.

a. RSV:

i. With RSV LRTI, patients should receive ribavirin 20 mg/ml (2 gm over 6 h every 8 h) × 7 days using a Viratek© small particle generator (SPAG-2) by face mask or endotracheal tube with adjuvant IVIG (500 mg/kg QOD × 5 doses).
ii. Consider inhalational ribavirin therapy along with IVIG administration, as above, for any allogeneic recipient with an absolute lymphocyte count (ALC) < 300 cells/mm^3 and/or steroid dose > 0.5 mg/kg/day (prednisone equivalent) presenting with RSV URI, with the goal of preventing progression to LRTI (acknowledging, however, the limited data on this approach).
iii. There are limited data from case series and uncontrolled studies on the use of systemic (oral or intravenous) ribavirin for treatment of RSV infection.

b. Influenza A and B:

   i. Initiate therapy with an appropriate antiviral agent as soon as possible. The two main classes of drugs are neuraminidase inhibitors (e.g., osteltamivir and zanamavir) and M2 inhibitors (e.g., amantadine and rimantadine). Antiviral therapy for influenza will vary depending on the drug resistance patterns of circulating strains. Duration of therapy with neuraminidase inhibitors is typically 5 days, though a longer duration of therapy (> 10 days) may be considered in hospitalized patients with severe influenza infection.
   ii. Unvaccinated caregivers and patients who have been exposed to a case of documented influenza should be referred for chemoprophylaxis as soon as possible and within 48 h of the exposure. Drug resistance patterns of the circulating influenza strain should guide the choice of antiviral prophylaxis.
   iii. In the context of a significant community outbreak or transmission on the transplant unit/transplant clinic, policies for chemoprophylaxis should be discussed with the infectious diseases service/infection control and considered based on drug resistance patterns of the circulating influenza strain.

c. Adenovirus:

   i. Systemic cidofovir should be strongly considered in the context of invasive adenovirus infection. While data on optimal dosing of cidofovir are not available, the usual practice is to use 5 mg/kg IV once weekly (renal dose adjustment as indicated) for 2 weeks and then every other week in the setting of life-threatening or disseminated disease, along with probenecid 2 g po 3 h prior to cidofovir dose, then 1 g po at 2 and 8 h after dose. Important adverse drug effects associated with cidofovir administration include nephrotoxicity as well as hematologic and ocular toxicity, and so careful monitoring is recommended in this setting.
   ii. When possible, immune suppression should be reduced in the setting of life-threatening or disseminated adenovirus disease.

a. Parainfluenza virus 1–4:

   i. Care is supportive.

b. Rhinovirus:

   i. Care is supportive.

c. Human coronavirus:

   i. Care is supportive.

d. Metapneumovirus:

   i. Care is supportive.

7. Epstein–Barr virus (EBV):
    a. EBV can result in post-transplant lymphoproliferative disease (PTLD), manifesting as fever, adenopathy, and/or extranodal disease.
    b. Quantitative EBV PCR from blood and/or other body fluids (e.g., CSF) may support the diagnosis, though certain diagnosis requires tissue biopsy with immunohistochemistry.
    c. EBV viral load monitoring has been recommended by some for certain high-risk HSCT recipients, though the threshold for preemptive intervention is not clear. Patients who have received T cell depleted, cord blood, or haplo-identical stem cell products, or who have been exposed to Anti-thymocyte globulin (ATG) should be considered for preemptive monitoring with quantitative EBV viral load monitoring.
    d. First-line therapy for established CD20-positive PTLD is the administration of anti-CD20 monoclonal antibody (rituximab). Infusion of EBV-specific cytotoxic T-lymphocytes has been used with success in various study protocols, though this requires significant time for in vitro generation. There is little evidence at this time to support the contribution of antiviral therapy for this indication.
8. *P. jirovecii* pneumonia:
    a. Infection is rare in patients compliant with first-line PCP prophylaxis (e.g., trimethoprim–sulfamethoxazole), but breakthrough infections are possible, in particular in patients on other than first-line agents.
    b. Radiographic studies of the chest (CT and CXR) typically reveal diffuse interstitial infiltrates with ground glass appearance, although appearance can be quite varied.
    c. Diagnosis is typically by visualization of the organism in respiratory specimens under microscopy with staining of induced sputum or bronchoalveolar lavage (BAL) specimens. While still considered investigational, PCR of BAL fluid or induced sputum can increase the diagnostic yield over conventional microscopy. At times, lung biopsy is required to make the diagnosis.
    d. First-line treatment is trimethoprim–sulfamethoxazole 20 mg/kg/day (renal dose adjustment as indicated) of trimethoprim equivalent divided into 3–4 daily doses for 21 days.
    e. In the case of significant sulfa allergy or intolerance, alternative therapies include pentamidine 4 mg/kg/day IV (renal dose adjustment as indicated) for 21 days for severe disease, or clindamycin 450 mg po every 6 h with primaquine 15 mg (base) po daily for mild to moderate disease. Unique side effects associated with daily pentamidine therapy include hypotension, hypo- or hyperglycemia, pancreatitis and/or cardiac arrhythmias.
    f. In the context of moderate to severe disease, adjunctive corticosteroids should be considered, though recognizing that direct data for this intervention in the HIV-negative population is lacking:

i. For patients with partial pressure of arterial oxygen (PaO_2) < 70 mmHg and/or an alveolar–arterial oxygen gradient > 35 mmHg and/or hypoxemia on pulse oximetry, prednisone 40 mg po BID days 1–5, then 40 mg po daily on days 6–10, and then 20 mg po daily on days 11–21 can be considered in combination with antimicrobial therapy, if patient is not already receiving steroids in comparable dosages.
ii. Patients who are on corticosteroids at the time of PCP diagnosis (e.g., for GVHD) should continue on their current regimen.

9. *T. gondii*:

a. The risk of toxoplasmosis following allogeneic HSCT depends on the seroprevalence in the population and on the conditioning regimen/degree of immune suppression. Seroprevalence studies indicate that 15–30 % of the US population has been previously infected with toxoplasmosis. Most toxoplasmosis in transplant HSCT recipients is reactivation disease.
b. Toxoplasmosis often affects the central nervous system, but can also present as disseminated infection in HSCT recipients. A CT or an MRI of the brain may reveal focal mass lesion(s) or less commonly, diffuse encephalitis.
c. If toxoplasmosis is suspected, a *Toxoplasma* PCR (CSF and/or blood) should be obtained. Tissue biopsy is often necessary to establish a certain diagnosis. Given the often nonspecific presentation of disseminated toxoplasmosis, a high index of suspicion for this diagnosis should be maintained, in particular in seropositive individuals.
d. Treatment of established disease due to toxoplasmosis includes:

i. Pyrimethamine 200 mg loading dose on day 1 then 50 mg po daily for patients < 60 kg or 75 mg po daily for patients > 60 kg
ii. Sulfadiazine 1000 mg po four times daily for patients < 60 kg or 1500 mg po four times daily for patients > 60 kg
iii. Folinic acid (10–25 mg po daily)

e. For patients who cannot tolerate sulfadiazine due to significant allergy or other contraindication, pyrimethamine and folinic acid plus clindamycin 600 mg po/IV four times daily (QID) or azithromycin 900–1200 mg po daily can be used.
f. For patients who cannot tolerate pyrimethamine, sulfadiazine plus atovaquone 1500 mg po BID can be used, with salvage single-agent atovaquone for those unable to tolerate either sulfadiazine or pyrimethamine.
g. Duration of therapy is typically 6 weeks followed by a course of suppressive therapy; however, this should be individualized based on clinical/radiographic response.
h. *Toxoplasma*-seropositive transplant candidates/recipients should receive trimethoprim–sulfamethoxazole as PCP prophylaxis given the protection this provides against toxoplasmosis, presuming no significant allergy or other strict contraindication.

10. *Clostridium difficile*:

    a. *C. difficile* is a frequent cause of infectious diarrhea among hospitalized patients, particularly HSCT recipients, owing to often long hospitalizations, receipt of broad-spectrum antibiotics, and chemotherapy-induced gut disruption. The 1-year incidence of *C. difficile* following transplantation was 9.2 % in a recent large single-center study by Alonso et al. There is a suggestion of a strong interaction between gastrointestinal GVHD and *C. difficile*.
    b. *C. difficile* should be considered in all HSCT recipients with new/worsening diarrhea, with the caveat that diarrhea is common post-HSCT, with a broad differential diagnosis.
    c. Laboratory diagnosis of *C. difficile* is typically by demonstration of *C. difficile* toxin(s). A number of tests are available for broad clinical use: PCR for toxins A and B, enzyme immunoassay (EIA) for *C. difficile* toxins A and B, and EIA for *C. difficile* glutamate dehydrogenase (GDH, an enzyme produced by toxigenic and nontoxigenic *C. difficile* strains):

        i. PCR is more sensitive than EIA for toxins A and B, but has potential for false positive results.
        ii. EIA for GDH is sensitive but not specific
        iii. Some laboratories favor the use of tiered screening, with EIA for GDH the first test, then reflexing to EIA and/or PCR for toxins A and B if the GDH test is positive.

    d. General principles of management include discontinuation or narrowing of antibacterials as able, fluid and electrolyte support, avoidance of antiperistaltic agents (e.g., loperimide, diphenoxylate/atropine), institution of appropriate infection control measures (contact precautions, strict hand hygiene with antibacterial soap and water, environmental cleaning with bleach, etc.), and antimicrobial therapy for *C. difficile*.
    e. The two main drugs used for treatment of *C. difficile* are oral metronidazole and oral vancomycin:

        i. Oral metronidazole (500 mg po/IV q 8 h) can be used for mild-to-moderate disease.
        ii. Oral vancomycin (125 mg po QID, and per rectum if ileus present) for severe disease.
        iii. With severe complicated *C. difficile* (ileus, megacolon, etc.), many providers use a combination of oral vancomycin (often at high dose, 500 mg QID) and intravenous metronidazole (500 mg IV q 8 h).
        iv. Duration of therapy is at least 14 days, and for patients who have an indication for other antibiotic therapy, providers often choose to extend the course of *C. difficile*-active therapy for a fixed period (e.g., 1 week) following the discontinuation of other antibacterials.
        v. The parameters are still being defined for the use of fidaxomicin, an antibiotic that is bactericidal against *C. difficile* and has been shown in a phase 3 study of patients with nonsevere *C. difficile* infection to have

lower recurrence rates than vancomycin; cost remains a major barrier to the use of this agent.

f. Early surgical evaluation should be obtained for patients with severe complicated *C. difficile*, with colectomy an aggressive but potentially life-saving intervention.
g. Recurrence after initial infection is not uncommon, affecting as many as 25 % of patients. Management of the first recurrence is guided by the same principles for first infection, with often prolonged/tapering courses of oral vancomycin for patients with multiple recurrences.
h. For patients with multiple *C. difficile* recurrences, fecal microbiota transplantation can be considered, though with the caveats that this should be avoided in patients who are neutropenic, early post-transplant (e.g., < 3 months), on high-dose immune suppression or with active GVHD or other gut mucosal disruption. Experience is limited to case reports, with data on long-term outcomes/sequnce lacking at this time.
i. "Secondary" prophylaxis, or the use of *C. difficile*-active therapy for patients with a history of *C. difficile* and subsequently requiring prophylactic or treatment antibiotics, is sometimes used by providers, though at this point there is no prospective data to support this practice. It should be noted that prolonged oral metronidazole is not advised, given risks for emergent drug toxicity (e.g., peripheral neuropathy, neutropenia) with protracted use.

11. *Candidiasis:*
Infections with *Candida* species can be classified as invasive (e.g., candidemia, hepatosplenic candidiasis, etc.) or superficial (e.g., mucosal). In the era of widespread use of azole prophylaxis, candidiasis occurs with relative infrequency in the HSCT population; however, fluconazole-resistant *Candida* species (*C. krusei* and *C. glabrata*) are of particular concern.

a. Candidemia:

i. An echinocandin (micafungin 100 mg IV daily or caspofungin 70 mg IV load then 50 mg IV daily, or anidulafungin 200 mg IV load then 100 mg IV daily) or an amphotericin B lipid-based product (dose 3–5 mg/kg IV daily) are recommended for empiric treatment of candidemia in neutropenic hosts while awaiting species-level identification which can guide further therapy. For patients who are not critically ill and without recent azole exposure, high-dose fluconazole (800 mg po/IV loading dose, followed by 400 mg po/IV daily) can be considered, or voriconazole (6 mg/kg po BID for two doses as load, followed by 4 mg/kg po BID) if mold coverage is also desired.
ii. Once species-level identification +/– antifungal susceptibility data are available, antifungal therapy should be adjusted:

- For infections due to *C. albicans* or *C. parapsilosis,* either fluconazole or an amphotericin-based product is acceptable, with fluconazole a less toxic and more convenient choice once the patient has stabilized.
- For infections due to *C. glabrata,* an echinocandin is often preferred, though acknowledging recent reports of emergence of echinocandin resistance, with amphotericin-based therapy a less attractive option in light of the potential for toxicity.
- For infections due *to C. krusei,* either an echinocandin, voriconazole, or a lipid formulation of amphotericin is generally acceptable.

iii. Duration of therapy for candidemia is 2 weeks from documented clearance of blood cultures and until resolution of neutropenia, providing there is no concern for deep-seated foci or persistent positive blood cultures.
iv. Removal of vascular catheter(s) should be strongly considered in the setting of candidemia, though acknowledging that gut translocation can be a source of infection.
v. An ophthalmology consultation should be obtained to evaluate for *Candida endophthalmitis*. A CT of the abdomen should be considered to evaluate for hepatosplenic candidiasis (see Sect. 17.11.b) in the appropriate clinical setting.
vi. With high-grade and persistent candidemia, an echocardiogram should be obtained to evaluate for endocarditis.

b. Chronic disseminated candidiasis:

i. This syndrome, also referred to as hepatosplenic candidiasis, is most often seen during or soon after recovery from neutropenia.
ii. *C. albicans* is most often the causative organism with other species seen far less often.
iii. Presenting signs/symptoms are often vague with malaise, fever, and/or nonspecific gastrointestinal complaints.
iv. Diagnosis is suggested by an elevation of the serum alkaline phosphatase and/or multiple hepatic hypodensities seen on abdominal CT. Blood cultures are often negative.
v. Definitive diagnosis is established by liver biopsy which classically demonstrates multiple granulomas with visualization of yeast and hyphal elements on special stains. More often than not, culture of tissue from liver biopsy is negative, particularly if the patient has received antifungal therapy.
vi. Molecular diagnostic studies (e.g., fungal PCR) can offer additional sensitivity and provide species-level information.
vii. Treatment considerations include azole therapy (frequently fluconazole, as *C. albicans* is the most common species implicated in this setting), an echinocandin, or a lipid-based amphotericin product. The bulk of available data is with amphotericin B deoxycholate and fluconazole. Treatment decisions should be based on previous antifungal therapy and, when available, microbiologic data.

viii. Duration of therapy is typically prolonged (many months) and is guided by clinical response and radiographic resolution or calcification.

c. *Candida cystitis*:

i. Consider whether a urine culture with *Candida* species represents colonization or infection based on whether the patient is displaying signs and/or symptoms of urinary tract infection (UTI).
ii. If the patient has an indwelling catheter, remove or, if it cannot be removed, exchange the catheter and repeat urine studies.
iii. Treatment of candiduria is indicated in neutropenic hosts, whether symptomatic or asymptomatic.
iv. Fluconazole 200 mg po/IV daily for 7–14 days is the treatment of choice for candidal cystitis due to fluconazole-sensitive organisms:

- For treatment of cystitis due to fluconazole-resistant organisms (e.g., *C. krusei* and *C. glabrata*), amphotericin B deoxycholate can be used, either systemically (at very low doses) or by bladder irrigation. One should note that urinary tract drug levels of lipid formulations of amphotericin B are not high enough to provide adequate treatment.
- Voriconazole is not an effective drug for candidal cystitis given that active drug is not excreted to the urine in a significant amount.
- Although echinocandins achieve low concentrations in the urine, there is limited data describing successful use of these antifungal agents for treatment of renal parenchymal infections.

v. In patients with recurrent or seemingly complicated *Candida* cystitis, a renal ultrasound should be performed to evaluate for a fungal mass which would entail systemic antifungal therapy as well as consideration of surgical approach.

d. Oropharyngeal candidiasis:

i. Topical therapy with nystatin suspension 5–10 mL (100,000 units/mL) swish and spit/swallow QID or clotrimazole troches 10 mg dissolved in mouth 4–5 times per day is first line, with use of systemic therapy with an azole, an echinocandin, or a low-dose amphotericin B lipid-based product for moderate to severe disease.

e. Esophageal candidiasis:

i. Fluconazole 200–400 mg po/IV daily for 14–21 days is first line in azole-inexperienced individuals:

- In patients with significant antecedent azole exposure, for infection with culture-documented fluconazole-resistant *Candida* species, or for fluconazole-refractory disease, an echinocandin (e.g., micafungin 150 mg IV daily) or an extended spectrum azole (e.g., posaconazole 400 mg po BID (suspension) or voriconazole 200 mg po BID) can be used.

- Low-dose amphotericin B lipid-based product is an alternative for patients refractory to other agents.

f. Vulvovaginal candidiasis:

i. Fluconazole 100–200 mg po/IV daily for 7–10 days or topical antifungal treatment (e.g., clotrimazole, miconazole, or nystatin) for 7–10 days can be used.
ii. If refractory or recurrent vulvovaginal candidiasis (>4 symptomatic episodes within a year) occurs, cultures may help to guide antifungal therapy and consultation with the infectious diseases service should be considered.

12. Invasive *aspergillosis:*

a. *Aspergillus fumigatus* is the most common *Aspergillus* species implicated as a cause of infection in immunocompromised hosts, though other species can also result in invasive infection.
b. Pulmonary infection is the most common presentation, with sinus disease and/or hematogenous dissemination with other organ involvement (e.g., central nervous system, sinuses, skin, etc.) seen on occasion.
c. The key to successful management is early consideration of this process, with imaging and appropriate diagnostic evaluation, along with prompt initiation of antifungal therapy.
d. Chest imaging can be suggestive in the appropriate context, but proven or probable diagnosis requires a mycologic diagnosis, either by culture or fungal biomarker.
e. Diagnosis of pulmonary infection can often be established with use of *Aspergillus* galactomannan testing on bronchoalveolar lavage fluid. When a diagnosis cannot be obtained by less invasive means, surgical biopsy should be considered.
f. Voriconazole is first-line therapy for invasive aspergillosis:

i. Voriconazole trough levels should be measured early in any patient with proven or probable invasive aspergillosis, or with a poor response to treatment, possible side effects of therapy, suspicion of poor oral absorption, or complex drug–drug interactions (see Table 10.5 for dosing guidelines and trough targets).

g. If a significant increase in serum transaminase levels is noted while on voriconazole therapy (>5 times the upper limit of normal), check a voriconazole level and consider change to a lipid-based amphotericin product or posaconazole (200 mg po QID x 1 week, then 400 mg po BID suspension) with careful monitoring. Posaconazole delayed-release tablets appear offer better oral bioavailability than suspension, with the convenience of once daily dosing after an initial load (300 mg po BID for 1 day, then 300 mg once daily); the tablet formulation and dosing schema has been studied and approved for prophylaxis, but is an approach that can be considered for treatment in

patients refractory or intolerant of conventional therapy for invasive fungal infection (e.g., amphotericin product, voriconazole, etc.). If the voriconazole level is supratherapeutic, reintroduction at a lower dose, with close monitoring, can be considered after normalization of serum transaminases.

h. Echinocandins are considered an inferior single-agent choice for management of invasive aspergillosis.
i. Preliminary results from a phase 4 clinical trial of combination therapy (voriconazole + anidulafungin or placebo) for invasive aspergillosis showed a trend toward improved outcome but did not meet statistical significance.
j. Reduction of immunosuppression is advised (especially taper or withdrawal of corticosteroids) when possible.
k. The use of recombinant human growth factors such as filgrastim or sargramostim may be helpful in this population, primarily in the neutropenic patient. A prospective study to determine the utility of granulocyte transfusions in this setting is ongoing.
l. Surgical resection should be considered when pulmonary lesions are in close proximity to the great vessels or pericardium, or in patients with persistent hemoptysis from a single cavitary lesion, pericardial infection or chest wall invasion.
m. Patients with a history of invasive aspergillosis prior to transplant should receive at least 6 weeks of antifungal therapy and have a documented partial or complete response to therapy before proceeding to conditioning. Strong consideration should be made for nonmyeloablative conditioning in patients with history of invasive aspergillosis:

    i. Secondary prophylaxis with an *Aspergillus*-active azole antifungal (voriconazole or posaconazole) should be given to patients in the post-transplant setting.
    ii. If significant drug–drug interaction or drug toxicity limits azole use, a lipid-based amphotericin product or an echinocandin can be used as a second-line approach in this setting.

13. Other fungal infections

While *Aspergillus* and *Candida* species are the most common fungal infections encountered in HSCT recipients, there are other fungi to consider in this patient population:

a. Mucormycosis (or zygomycosis) is increasingly recognized in highly immune suppressed HSCT recipients:

    i. In addition to intensive immune suppressive regimens, iron overload and chelation with deferoxamine predispose patients to infection.
    ii. Clinical presentation may include angioinvasive infection of the lungs, skin, brain, and/or widespread visceral involvement in the setting of disseminated disease.

iii. Diagnosis often requires tissue biopsy, though bronchoscopy with bronchoalveolar lavage can sometimes be informative in the setting of pulmonary infection.
iv. Management of this infection should include antifungal therapy, reversal of underlying defects in host defense when possible including tapering of immune suppression and restoration of euglycemia, and surgical debridement where applicable.
v. Liposomal amphotericin 5–7.5 mg/kg IV daily is first-line antifungal therapy. Posaconazole can be considered as salvage therapy for patients intolerant of first-line therapy or for secondary prophylaxis. Voriconazole does not have activity against mucormycosis.
vi. Despite aggressive management of this infection, mortality rates remain very high. Consultation with the infectious diseases service is recommended.

b. Disseminated fusariosis can be seen in highly immunosuppressed HSCT recipients and is often characterized by cutaneous lesions and positive blood cultures, with or without visceral involvement:

i. Antifungal susceptibility varies by species. Treatment of disseminated infection is with either voriconazole or liposomal amphotericin (indicated for *Fusarium solani* or *F. verticillioides*).
ii. In addition to antifungal treatment, management should include surgical debridement when applicable and manuevers to improve host immune response. Growth factor support and/or granulocyte transfusions can be considered as adjuvants to care in persistently neutropenic individuals.
iii. Prognosis for disseminated diseases is generally poor and is largely determined by the degree of immune suppression.
iv. Consultation with the infectious diseases service is recommended.

c. Cryptococcosis is reported uncommonly in the HSCT population. This may well relate to widespread use of azole prophylaxis in this patient population:

i. Cryptococcal infection may result in pulmonary, central nervous system, cutaneous, or widely disseminated infection.
ii. Common diagnostic modalities include culture (from blood and/or other body fluids/tissue) and antigen-based testing (serum or CSF cryptococcal antigen). Diagnostic workup should include lumbar puncture when this entity is considered.
iii. Management is with liposomal amphotericin or fluconazole, along with serial lumbar punctures for management of elevated intracranial pressure in the context of cryptococcal meningitis.
iv. Although a mainstay of combination therapy with an amphotericin B formulation for HIV-positive patients with cryptococcal meningitis, concurrent use of flucytosine is often poorly tolerated in HSCT recipients given the potential for marrow suppression.
v. Consultation with the infectious diseases service is recommended.

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Chapter 18
Acute Graft-Versus-Host Disease (GVHD)

Susan Schubach Slater

Despite advances in human leukocyte antigen (HLA) typing, acute graft-versus-host disease (aGVHD) remains a leading cause of morbidity and mortality among allogeneic hematopoietic stem cell transplant (HSCT) recipients. It is estimated that 30–50% of patients who receive stem cell products from HLA-identical siblings will develop grades 2–4 aGVHD while rates of aGVHD associated with matched unrelated donor transplants are estimated to be between 50 and 70%.

Acute GVHD has historically been defined as occurring prior to day +100 and chronic GVHD as occurring after day +100. However, recently there has been a move to define GVHD based on the clinical symptoms and pathologic findings rather than by an arbitrary timeline. Two main categories of aGVHD are now recognized:

1. Classic aGVHD which occurs within the first 100 days post-transplant and results in an erythematous maculopapular rash, nausea, vomiting or diarrhea, and/or hyperbilirubinemia.
2. Persistent, recurrent, or late aGVHD which occurs after day +100.

Additionally, a composite overlap GVHD syndrome has been identified in patients with chronic GVHD that has clinical findings of aGVHD during chronic GVHD flares.

The overall outcome of aGVHD is dependent on the overall grade of GVHD and the patient's response to initial treatment.

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18.1 Pathophysiology

Three conditions are considered to contribute to the development of acute GVHD:

1. The patient must receive an infusion of immune competent donor cells.
2. There must be an immunologic disparity between the recipient and donor cells.
3. The recipient must be unable to mount an appropriate immune response to these "foreign" cells, at least long enough for the donor cells to engraft and mount an anti-host immunologic response.

The development of GVHD is described as a three-part process:

1. Tissue damage occurs as a consequence of the patient's malignancy, prior therapies and/or the transplant conditioning regimen. This injury results in the release of inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-2 leading to activation of the recipient's antigen presenting cells (APCs).
2. These inflammatory cytokines and both patient and donor APCs interact with donor T cells leading to T cell expansion and release of additional inflammatory cytokines.
3. These activated T cells produce inflammatory cytokines and cellular mediators resulting in apoptosis in the target host cells, typically within the skin, gut, and liver target tissues.

More recent studies have identified the role of regulatory mechanisms, including regulatory T cells (Tregs), dendritic cells, natural killer T cells and B cells in the development of aGVHD.

18.2 Risk Factors

1. Stem cell source:
   a. When analyzed independently, peripheral blood stem cell (PBSC) = marrow > cord blood
   b. Higher risk of GVHD is associated with the combination of:
      i. PBSCs + total body irradiation (TBI) + myeloablative conditioning + matched sibling donor
      ii. PBSCs + myeloablative conditioning + unrelated donor
2. Regimen intensity (myeloablative > reduced intensity)
3. Female donor → male recipient
4. HLA disparity of donor and recipient
5. Immune suppressive regimen for GVHD prophylaxis (cyclosporine A (CSA) > tacrolimus)
6. Diagnosis of chronic myeloid leukemia (CML; possibly related to better functioning APCs due to minimal prior therapy)

Historically, risk factors for GVHD have also included increased recipient age, cytomegalovirus (CMV) positivity, and allosensitized donors (heavily transfused, prior pregnancy). However, more recent studies have found these etiologic factors not statistically significant.

18.3 Incidence

1. The median time to onset for symptoms of aGVHD is approximately 3 weeks, with a range of 1–14 weeks.
2. An estimated 30–50% of sibling-donor recipients and 50–70% of unrelated-donor recipients will develop grades 2–4 aGVHD:
   a. Skin is usually the first organ involved and often coincides with engraftment
   b. Of patients who develop aGVHD, approximately 80% will have skin involvement, 50% gut involvement, and 50% liver involvement.
3. For patients alive at 60 days post myeloablative HSCT, only 5–8% will subsequently develop aGVHD; the advent of reduced intensity regimens has contributed to a change in the natural history with more frequent late presentation.

18.4 Clinical Presentation

Onset of symptoms typically occurs 2–3 weeks after transplant. The primary organs affected by aGVHD are the skin, liver, and gastrointestinal (GI) tract (See Table 18.1).

1. *Skin*: Classically manifests as an erythematous, maculopapular rash +/− pruritus involving the pinnae, palms, and soles. This rash often spreads to involve the neck and trunk with later involvement of the extremities. Severity is determined by the percentage of body surface area (BSA) involved (see Fig. 18.1) and may range from a mild, nonpruritic rash to bullous formation and desquamation reminiscent of toxic epidermal necrolysis.
2. *Liver*: An elevated serum bilirubin is the typical manifestation of liver involvement, although elevated alkaline phosphatase may also be an indicator of impending disease. A variant of liver aGVHD has also been described that manifests as hepatitis with transaminitis and elevated alkaline phosphatase; however, these are not classic findings and are not specific.
3. *GI*: Manifestations include anorexia, nausea, vomiting, diarrhea, and/or abdominal cramping. However, these are relatively nonspecific findings and may be attributed to the conditioning regimen, immune suppressive medications or infections.

Table 18.1 Findings associated with aGVHD

Organ	Clinical manifestations	Histologic findings	Alternate diagnoses
Skin	Erythematous maculopapular rash involving the palms, soles, pinnae, spreading to the trunk and later extremities. +/− pruritis. Bullae/desquamation in severe cases	Basal vacuolization, necrotic epidermal cells, lymphocytes in dermis, exocytosis in epithelium	Chemotherapy/radiation effect Drug eruption Viral exanthem Infection
Liver	Hyperbilirubinemia, jaundice. Possible hepatitis with transaminitis, elevated alkaline phosphatase	Bile duct damage, bile duct lymphocytic infiltration, endothelialitis	Sinusoidal obstructive syndrome Medication effect Extra-hepatic obstruction TPN Infection Iron overload
GI	Anorexia, nausea, vomiting, diarrhea, abdominal pain/ileus, GI bleeding	Apoptosis, crypt cell necrosis and drop out, epithelial denudation	Chemotherapy/radiation effect GI tract infection (*Clostridium difficile*, CMV, etc.) Drug reaction

GVHD graft-versus-host disease, *GI* gastrointestinal, *TPN* total parenteral nutrition, *CMV* cytomegalovirus

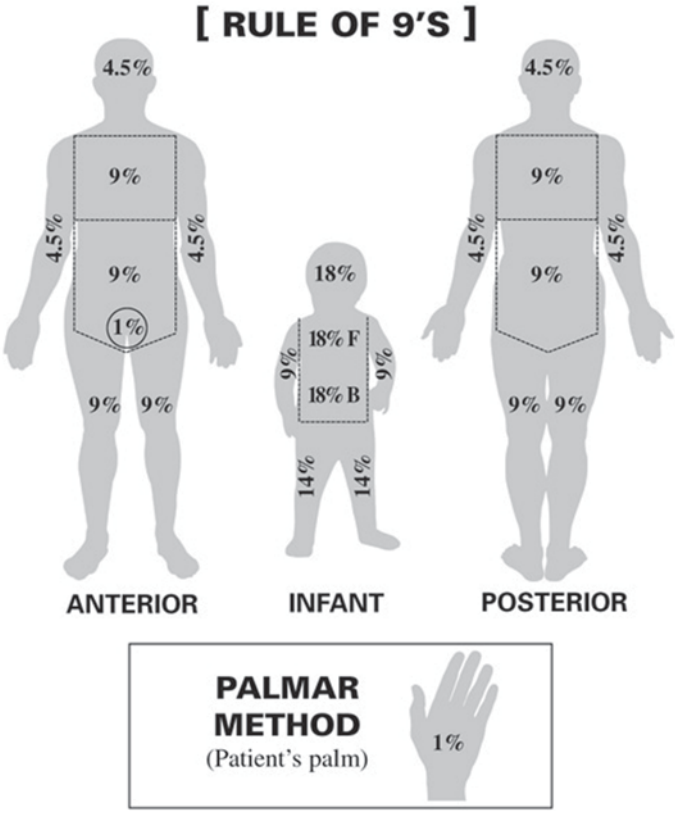

Fig. 18.1 *Rule of nines (Body surface area)*. (In adults, the "rule of nines" can be used to determine the total percentage of area affected for each major section of the body)

18.5 Evaluation and Diagnosis

Tissue pathology is the gold standard for diagnosis of GVHD; however, the sensitivity of biopsy testing is ~60%. Therefore, clinical correlation is necessary as many non-GVHD causes (tissue damage from the conditioning regimen, infection, medications, drug eruptions, viral exanthems) may mimic the pathologic findings of GVHD.

Efforts are under way to identify potential peripheral blood biomarkers to diagnose and guide the management of GVHD. Small retrospective studies have proposed multiple biomarkers including IL-2 and TNF-α which are markers of generalized inflammation and new lymphoid surface expression molecules such as CD30. Newer methods, including proteomics (study of complete sets of protein molecules), have identified several molecules, such as elafin, which are secreted as a result of end-organ damage and have been shown in early studies to correlate with prognosis.

1. Skin:
    a. Dermatology consult for skin biopsy. Criteria for diagnosis of aGVHD include evidence of basal vacuolization, necrotic epidermal cells, lymphocytes in the dermis, and exocytosis in the epidermis.
2. Liver:
    a. Liver ultrasound to rule out (r/o) sinusoidal obstructive syndrome (SOS), cholelithiasis, and/or biliary sludge.
    b. Consider liver biopsy for tissue diagnosis, either ultrasound-guided percutaneous or transjugular if patient is thrombocytopenic.
3. GI:
    a. Stools to r/o *Clostridium difficile* and other enteral pathogens.
    b. GI consult for endoscopy. There is no clear correlation between endoscopic findings and aGVHD stage.
    c. To make the diagnosis of aGVHD, apoptosis must be present on pathology review. However, this finding is not exclusive to aGVHD.
        i. A small study of GI pathology identified a combination of lamina propria eosinophia (>15/10 HPF), combined with a lack of endocrine cell aggregates and apoptotic microabscesses as indicators of mycophenolate colitis rather than gut aGVHD.

18.6 Staging/Grading

Standardized staging of aGVHD is critical to evaluating extent of disease, response to therapy and prognosis. The most widely used Glucksberg staging criteria, developed in 1974, are organ-specific and based on percentage of BSA involved, volume of diarrhea and/or total bilirubin (see Table 18.2). These stages are then evaluated together, in combination with performance status, to determine an overall grade of aGVHD (see Table 18.3).

There have been attempts to modify the Glucksberg system to identify a correlation of patterns of organ involvement with treatment-related morbidity and treatment failure. In 1994, following a consensus conference on aGVHD grading, the Minnesota group devised a system based on the Glucksberg criteria for organ staging, modified to include upper GI symptoms. In 1997, the Center for International Blood and Marrow Transplant Research (CIBMTR) developed a severity index (see Table 18.4) which grades GVHD based on organ involvement alone and grouping patients with similar risks of treatment-related morbidity and treatment failure.

More recently, standard clinical findings have been evaluated in the context of newly identified biomarkers in an attempt to classify patients into low-, intermediate-, and high-risk groups. This would allow for risk stratification to better

Table 18.2 Glucksberg organ staging

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No rash	<2 mg/dL	<500 mL/day or persistent nausea
1	Maculopapular rash ≤25% BSA	2–3 mg/dL	>500 mL/day
2	Maculopapular rash 25–50% BSA	3.1–6 mg/dL	>1000 mL/day
3	Generalized erythroderma	6.1−15 mg/dL	>1500 mL/day
4	Generalized erythroderma + bullous formation	>15 mg/dL	Severe abd pain, +/− ileus, +/− bleeding

BSA body surface area

Table 18.3 Glucksberg overall grading

Grade	Skin	Liver	Gut	ECOG performance
I	Stages 1–2	Stage 0	Stage 0	0
II	Stages 1–3	Stage 1 and/or	Stage 1	0–1
III	Stages 2–3	Stages 2–3 and/or	Stages 2–3	2–3
IV	Stages 2–4	Stages 2–4 and/or	Stages 2–4	3–4

ECOG Eastern Cooperative Oncology Group

Table 18.4 CIBMTR severity index

	Skin		Liver		GI	
Index	Stage (Max)	Extent of rash	Stage (Max)	Bilibrubin (μmol/L)	Stage (Max)	Diarrhea (mL/d)
A	1	<25%	0	<34	0	<500
B	2	25–50% or	1–2	34–102 or	1–2	500–1500
C	3	>50% or	3	103–255 or	3	>1500
D	4	Bullae or	4	>255 or	4	Pain, ileus

CIBMTR Center for International Blood and Marrow Transplant Research, *GI* gastrointestinal

customize initial and secondary treatments, predict prognosis, and allow for more meaningful interpretation of clinical trial results due to greater homogeneity in the enrolled patient population. For patients receiving therapy on a study protocol, one should become familiar with the staging system associated with that protocol to ensure accurate and consistent measurements of aGVHD.

Patients who develop grade 1 or 2 aGVHD have an 80% probability of long-term survival. Survivorship falls to 30% for patients with grade 3 disease and 5% for patients with grade 4 disease.

18.7 Treatment (See Chap. 11 for discussion of GVHD Prophylaxis)

The standard mainstay of treatment for aGVHD is corticosteroids; however, not all patients achieve durable responses to steroids alone. Two recent multicenter trials were conducted through the Bone Marrow Transplant Clinical Trials Network (BMT CTN) to evaluate initial therapeutic options for newly diagnosed GVHD.

1. BMT CTN 0302: Phase II trial randomizing patients with newly diagnosed aGVHD between four drugs, all given in combination with steroids: etanercept, mycophenolate (mycophenolate mofetil, MMF), denileukin diftitox, and pentostatin:
    a. Efficacy, survival, and toxicity all favored MMF
    b. Approximately 50% of patients receiving MMF did not achieve target drug levels; patients with drug levels >0.5 mcg/mL at weeks 1 and 2 had a significantly greater proportion of complete and partial responses at days 28 and 56, suggesting an MMF dose higher than 1 gm BID as prescribed in the trial is necessary to achieve a response.
    c. These data supported further study of MMF as primary therapy.
2. BMT CTN 0802: Phase III, double-blinded, randomized trial comparing steroids + MMF versus placebo:
    a. MMF dosing was increased to 1 gm q8 h based on data from CTN 0302.
    b. Study participation was terminated at interim analysis when no difference was observed between the two groups with regards to rates of GVHD, GVHD-free survival, overall survival, development of chronic GVHD, rate of Epstein–Barr virus (EBV) reactivation, and cumulative incidence of grade 3 infections.
    c. Benefit of adding MMF to corticosteroid therapy for new diagnosis aGVHD was not confirmed.
3. General treatment guidelines:
    a. There is no consensus on initial corticosteroid dosing or tapering schedule:
        i. Should patient's rash progress to >50% of BSA or patient develop aGVHD involving the gut or liver, systemic steroids should be dosed at 1–2 mg/kg/day depending on the current and potential predicted severity of aGVHD.
        ii. For patients with stage 1 and 2 disease, there is no evidence that beginning with 1 mg/kg/day of steroid results in worse patient outcomes overall. Additionally, no benefit has been shown with steroid doses >2 mg/kg/day.
    b. Maximize benefit of calcineurin inhibitors (CNIs) in combination with steroids by maintaining therapeutic drug levels (cyclosporin A (CSA) ~200 ng/ml, tacrolimus ~8–10 ng/ml)
    c. To avoid potential side effects of protracted high-dose steroids, tapering should begin after 7 days of therapy regardless of response:

i. There are no clear guidelines for steroid tapering.
ii. One could consider a step-wise decrease by 0.25 mg/kg/day every 5–7 days to a dose of 1 mg/kg/day, then continue to decrease by 10 % every 7 days as tolerated.

d. The most important predictor of long-term survival is response to high-dose steroids.

i. Response at day 28 of therapy is considered to be the best predictor of 2-year transplant-related mortality (TRM):

- A study from Minnesota evaluated the response of 864 patients with aGVHD to high-dose steroids (60 mg/m^2/day):
  - Complete response rate was 53 % and complete/partial response rate of 65 % at day 28.
  - Additional data suggested that most patients who would respond to therapy would do so by day 28.
  - Patients with no response by day 28 were 2.78 times more likely to experience TRM at 2 years than those who responded to therapy.

ii. Due to infection and organ failure, steroid refractory disease is associated with a high rate of morbidity and mortality.

e. Ensure adequate antifungal and antiviral prophylactics are in place (see Chap. 10 for monitoring and prophylaxis guidelines). Change to intravenous (IV) formulation if absorption is questionable due to diarrhea:

i. Acyclovir 800 mg po BID or 250 mg/m^2 IV daily
ii. Weekly monitoring of CMV PCRs remains critical as aGVHD often accompanies CMV reactivation
iii. Maximize fungal coverage:

- Posaconazole (Noxifil®) 200 mg po TID (suspension) or 300 mg po daily (tablet); however, therapeutic drug levels may be difficult to achieve in patients with GI aGVHD due to absorption issues
- Voriconazole (VFend®) 4 mg/kg po/IV BID
- If patient is unable to tolerate azoles due to transaminitis, consider low-dose liposomal amphotericin 1 mg/kg IV daily or 3 mg/kg IV three times weekly

f. Consider surveillance for EBV, adenovirus and human herpes virus 6 due to profound T cell suppression associated with GVHD therapy.

4. Organ specific:

a. Skin:

i. Stage 1 and 2 skin GVHD can be treated with topical steroids such as triamcinolone 0.1 % or betamethasone 0.1 % cream or ointment. These moderate-dose topical steroids should be used only on the trunk and

extremities. Hydrocortisone 1 % is safe for application to the face, neck, and groin. If possible, wrap affected areas after application to provide occlusion to increase absorption.

ii. Emollients to prevent breakdown of dry and fissured skin areas.
iii. Keep skin clean and dry, using gentle hypoallergenic soaps.
iv. Antipruritic agents (diphenhydramine 12.5–50 mg po q6 h, hydroxyzine 25 mg po QID)

b. Liver:

i. Hold medications which may contribute to hyperbilirubinemia (particularly azoles)
ii. Consider ursodeoxycholic acid (ursodiol, Actigall®) 300 mg po BID to increase water solubility of bile salts and protect liver cells from toxic bile acids

c. GI:

i. Nothing by mouth (NPO) or stage I GVHD diet (see Appendix) depending on symptoms
ii. IV hydration. Consider total parenteral nutrition (TPN) early depending on severity of symptoms
iii. Change all immune suppression to IV formulation to ensure absorption
iv. Supportive care with antiemetics and antidiarrheals
v. Consider gram-negative prophylaxis or anaerobic protection in light of compromised mucosal integrity:

- Ciprofloxacin (Cipro®) 500 mg po BID or 400 mg IV BID
- Levofloxacin (Levaquin®) 400 mg po/IV daily
- Imipenem (Primaxin®) 500 mg IV q6 h

vi. Oral nonabsorbable steroids may be considered as an adjunct to systemic therapy

- Beclomethasone (OrBEC®)
- Budesonide (Entocort®)

18.8 Steroid Refractory Disease

There is no standard definition of steroid refractory aGVHD. However, failure of therapy has been defined as progression of symptoms after 3 days of high-dose steroids or no improvement after 7 days of therapy. Approximately 40 % of sibling-donor and 25 % of unrelated-donor transplant patients will respond to therapy; 60–75 % of patients will require additional therapy. The addition of second-line therapy is associated with a 1-year survival rate of 20–30 %.

There is also no consensus on the best salvage therapy for steroid refractory disease. Multiple agents have been utilized with varying degrees of success.

However, in the past 30 years, no products have been approved by the Food and Drug Administration for the systemic treatment of aGVHD. The choice of second-line therapy should be based on the effects of prior treatment, potential for drug interactions, toxicity profile, and provider/patient preference (see Table 18.5):

1. Antithymocyte globulin (ATG):
   a. ATGAM® (equine):
      i. *Mechanism of action:* Affects cell-mediated immunity by selectively destroying lymphocytes
      ii. *Dosing and administration:*
         - Despite the fact that historically, ATG is the most commonly used second-line therapy, no standard regimen has been identified. ATG preparations should not be used interchangeably as their potency differs. Dosing examples: 10–15 mg/kg IV QOD × 6–7 doses; 15 mg IV BID × 8–10 doses; 30 mg/kg IV QOD × 6 doses; 15 mg/kg IV daily × 12 doses; or 40 mg/kg IV daily × 4 days.
         - A test dose is recommended prior to the first dose of ATG. Inject 0.1 mL of a 1:1000 dilution intradermally into one arm with a control of 0.1 mL NS into the contralateral arm. A systemic reaction including rash, tachycardia, dyspnea, hypotension, or anaphylaxis is a contraindication for administration of the drug. If a wheal and/or erythema > 10 mm occurs, consider an alternative therapy.
         - Premedicate for all doses (excluding test dose) with acetaminophen 650 mg po, diphenhydramine 50 mg IV and methylprednisolone (or equivalent) 50–100 mg IV.
         - Meperidine 12.5– 25 mg IV q1 h prn rigors.
      iii. *Adverse effects*:
         - Sepsis
         - Anaphylaxis
         - Serum sickness
         - Dyspnea, pulmonary edema
         - Chest/back pain
         - Leukopenia, thrombocytopenia
         - Rash, urticaria
         - Fever, rigors
         - N/V/D
         - Renal function abnormalities
         - Extravasation may result in tissue necrosis and nerve damage
   b. Thymoglobulin® (rabbit):
      i. *Mechanism of action:* Affects cell-mediated immunity by selectively destroying lymphocytes
      ii. *Dose and administration:*

Table 18.5 Agents for salvage therapy in steroid refractory GVHD

Drug	Class	Dose/route	Preferred use	Current FDA approval
Alemtuzumab (Campath®)	MAB	10 mg IV/day × 5 doses	Skin, liver	B cell CLL
ATG—equine (ATGAM®)	Immune serum	No defined standard dosing	Skin, GI, liver	Aplastic anemia; prevention/treatment of renal transplant rejection
ATG—rabbit (Thymoglobulin®)	Immune suppressant	2.5 mg/kg IV × 4–6 days or 2.5 mg/kg QOD on days 1, 3, 5, and 7	Skin, GI, liver	Renal transplant rejection
Basiliximab (Simulect®)	MAB	No defined standard dosing	Skin	Prevention/treatment of renal transplant rejection
Beclomethasone (orBec®)	Adrenal glucocorticoid	2 mg po q6 h of both immediate release & enteric coated capsules	GI only	Orphan drug status
Budesonide (Entocort®)	Adrenal glucocorticoid	3 mg po TID or 9 mg po daily	GI only	Crohn's disease
Etanercept (Enbrel®)	TNF inhibitor	25 mg SQ twice weekly × 4–8 weeks	GI	Ankylosing spondylitis, chronic plaque psoriasis, RA, juvenile idiopathic arthritis
Extracorporeal photopheresis	n/a	n/a	Skin, liver	Cutaneous T cell lymphoma
Infliximab Remicade®	TNF inhibitor	10 mg/kg/day IV weekly × 1–4 weeks	GI	Ankylosing spondylitis, chronic plaque psoriasis, RA, Crohn's disease, ulcerative colitis
Inolimobab	MAB	11 mg/day × 3 days or 5.5 mg/day IV × 7 days, then 5.5 mg IV QOD × 5 doses	Skin, liver	Investigational
Mesenchymal stromal cells	Biologic	$1–10 \times 10^6$/kg recipient body weight, dosing schedule varies	GI, liver	Orphan drug status

Table 18.5 (continued)

Drug	Class	Dose/route	Preferred use	Current FDA approval
Mycophenolate mofetil (Cellcept®)	Immune suppressant	1.5–3 g po daily in two divided doses	Skin, liver	Prevention/treatment of rejection in cardiac, renal and liver transplant
Pentostatin (Nipent®)	Antimetabolite, antineoplastic	1.5 mg/m^2 on days 1–3 and 15–17	Skin, GI, liver	Hairy cell leukemia
Sirolimus (Rapamune®)	Bacterial macrolide antibiotic	15 mg/m^2 po load on day 1, then 5 mg/m^2 po daily x 13 days or 4-5 mg/m^2 po daily × 14 days without a loading dose; adjust dose to maintain a trough level of 4–12 ng/mL	Skin, GI, liver	Prevention/treatment of rejection in renal transplant
Tocilizumab (Actemra®)	MAB	8 mg/kg IV every 3–4 weeks until CR, then 4 mg/kg IV every 3–4 weeks	Skin, GI	Juvenile idiopathic arthritis, polyarticular juvenile RA, moderate to severe RA

MAB monoclonal antibody, *CLL* chronic lymphocytic leukemia, *RA* rheumatoid arthritis, *IL-2* interleukin 2, *TNF* tumor necrosis factor, *CR* complete response, *FDA* Food and Drug Administration, *GVHD* graft-versus-host disease, *ATG* antithymocyte globulin, *GI* gastrointestinal

- No standardized dosing has been established: 2.5 mg/kg IV daily × 4–6 days; 2.5 mg/kg IV on days 1, 3, 5 and 7 are included within the various schedules that have been reported.
- No test dose is required
- Premedicate for all doses with acetaminophen 650 mg po, diphenhydramine 50 mg IV and methylprednisolone (or equivalent) 50–100 mg IV.
- Meperidine 12.5–25 mg IV q1 h prn rigors.

iii. *Adverse effects*:

- CMV reactivation, sepsis
- Abdominal pain, N/V/D
- Hypertension, tachyarrhythmias
- Fever, rigors
- Leukopenia, thrombocytopenia
- Myalgias
- Dyspnea
- Dizziness, headaches

2. Etanercept (Enbrel®):

a. *Mechanism of action:* Dimeric soluble TNF receptor that inactivates TNF-α and TNF-β.
b. *Dose and administration:* 25 mg SQ twice weekly for 4–8 weeks
c. *Adverse effects:* Increased risk for serious infections, including bacterial sepsis, invasive fungal and other opportunistic infections:

i. Abdominal pain, N/V
ii. Headache
iii. Injection site reaction
iv. Rhinitis/upper respiratory tract infection (URI)
v. Rare complications include: cytopenias, aplastic anemia, Stevens–Johnson syndrome, autoimmune hepatitis, malignant lymphoma (children > adults)

3. Extracorporeal photopheresis (ECP)

a. *Mechanism of action:* The definitive mechanism of action is not completely understood. The leading hypothesis involves induction of cellular apoptosis which results in modulation of APC activation inducing immune tolerance and increased production of Tregs.
b. *Procedure:*

i. Through leukopheresis, a patient's blood is removed then centrifuged. 8-Methoxypsoralen is added to the buffy coat/plasma which is then exposed to an ultraviolet A (UVA) light source prior to being returned to the patient.
ii. ECP is administered in multiple schedules. One typical schedule is that ECP is performed on two consecutive days, every 1–4 weeks for varying lengths of time depending on patient's response.

c. *Adverse effects*:

i. Vasovagal syncope/hypotension
ii. Anemia/thrombocytopenia
iii. Bleeding secondary to procedure-related anticoagulant
iv. Central venous catheter-associated bacterial infections/sepsis
v. Constitutional symptoms of nausea, fever/chills, headache

4. Mesenchymal stromal cells (MSC)

a. *Mechanism of action:* Not clearly defined; however, proposed mechanisms include T cell immune suppression, polarization of macrophage and monocyte population, induction of Tregs, and secretion of soluble factors that enhance tissue repair.
b. *Dose and administration:* $1–10 \times 10^6$ MSCs per kilogram recipient body weight with variable dosing schedules per specific clinical trial
c. *Adverse effects:*

i. No infusion-related toxicities have been reported with either cryopreserved or fresh product. However, there remains the possibility for infusional toxicity comparable to other cryopreserved products (see Chap. 12)
ii. No long-term adverse events have been reported
iii. Costs of goods and manufacturing are higher than with other biologic or pharmacologic therapies

5. Monoclonal antibodies

a. Alemtuzumab (Campath®):

i. *Mechanism of action:* Binds to cell surface CD52 which is present on all B and T lymphocytes, resulting in cell lysis.
ii. *Dose and administration*: 10 mg/day IV × 5 doses
iii. *Adverse effects*:

- Increased risk of infection, specifically CMV reactivation/infection, EBV, and sepsis
- EBV-associated lymphoproliferative disorder, tumor lysis syndrome or progressive multifocal leukoencephalopathy
- Autoimmune hemolytic anemia/thrombocytopenia
- Cardiomyopathy, chronic heart failure (CHF), cardiac dysrhythmia
- Pancytopenia
- Guillain–Barre syndrome
- Toxic optic neuropathy
- Goodpasture's syndrome (rapidly progressive glomerulonephritis with pulmonary hemorrhage)
- Rash, urticaria
- N/V/D
- Bronchospasm, dyspnea

iv. As of 9/4/12, alemtuzumab is available only through compassionate use through the Campath Distribution Program of Genzyme

b. Basiliximab (Simulect®):

i. *Mechanism of action:* An IL-2 receptor antagonist that inhibits IL-2 binding, preventing IL-2 mediated activation of lymphocytes and impairing immune response
ii. *Dose and administration:* No standardized dose has yet been defined. In trials, various doses have been utilized with varied response. Additional studies are required to determine optimal dosing.
iii. *Adverse effect*s:

- Acute allergic reaction
- CMV reactivation/infection
- Candidiasis
- Dysuria
- Cough, dyspnea
- Edema
- Hypertension
- Abdominal pain, vomiting
- Dizziness, weakness

c. Infliximab (Remicade®):

i. *Mechanism of action:* Binds to soluble and transmembrane forms of TNF-α, neutralizing its activity and causing cell lysis.
ii. *Dose and administration:* 10 mg/kg/day IV weekly for 1–4 weeks
iii. *Adverse effects:* Increased risk for serious infections, including bacterial sepsis, invasive fungal and other opportunistic infections. Rare cases of hepatosplenic T cell lymphoma, usually fatal, have been reported in patients with Crohn's disease and ulcerative colitis treated with infliximab and who were concurrently receiving treatment with azathioprine or 6-mercaptopurine:

- Acute coronary syndrome
- Erythema multiforme, Stevens–Johnson syndrome
- Pancytopenia
- Demyelinating disease of the CNS
- Abdominal pain, nausea
- Headache
- Fatigue
- Rare complications include: hepatotoxicity, drug-induced lupus erythematosis, immune hypersensitivity reaction.

d. Inolimomab:

i. *Mechanism of action:* A murine anti-IL-2 receptor which blocks activation of the alpha-chain of the IL-2 receptor (CD25): this may inhibit IL-2-mediated T cell activation
ii. *Dose and administration:* 11 mg/day IV × 3 days, 5.5 mg/day IV × 7 days, then 5.5 mg QOD × 5 doses per manufacturer's instructions. Alternatively,

0.3 mg/kg/day IV × 8 days, then 0.4 mg/kg 3 times per week × 3 weeks. The optimum dose and duration of therapy have yet to be determined.

iii. *Adverse effects*:

- Human antimouse antibody response occurs frequently (allergic reaction to the mouse antibodies ranging from a mild rash to acute renal failure). There is no clear evidence of decreased effectiveness of the drug.
- Rates of infection are comparable to standard immune suppression alone.

e. Tocilizumab (Actemra®):

i. *Mechanism of action:* Humanized anti-IL-6 receptor antibody that blocks IL-6 signaling

ii. *Dose and administration:* 8 mg/kg IV weekly every 3–4 weeks, dose reduced to 4 mg/kg IV every 3–4 weeks once a complete remission was achieved

iii. *Adverse effects:* Increased risk for infections, including bacterial sepsis, invasive fungal and other opportunistic infections. Evaluate for latent tuberculosis and treat if necessary prior to initiation of therapy. Monitor patients for signs and symptoms of infection, including tuberculosis, even if initial latent tuberculosis test is negative:

- Cytopenias
- Hypersensitivity reaction, anaphylaxis
- Upper respiratory infection, nasopharyngitis
- GI perforation
- Hypertension
- Transaminitis
- Dizziness, headache

6. Mycophenolate Mofetil (MMF, Cellcept®)

a. *Mechanism of action:* The active metabolite, mycophenolic acid, inhibits the synthesis pathway of guanosine nucleotides resulting in selective suppression of B and T cell proliferation and possibly preventing the recruitment of leukocytes to sites of inflammation.

b. *Dose and administration:* 1.5–3 gm po or IV daily in two divided doses. IV and po dosing are equivalent.

c. *Adverse effects:*

i. Hypertension, peripheral edema
ii. Hyperlipidemia
iii. Electrolyte abnormalities
iv. Increased risk of opportunistic infection
v. Abdominal pain, N/V/D/C
vi. Weakness, headache, insomnia

vii. Increased frequency of urinary tract infections (UTIs), renal function abnormalities
viii. Dyspnea, cough, pleural effusions, pulmonary fibrosis
ix. Pancytopenia
x. Progressive multifocal leukoencephalopathy
xi. Rare complications include gastric ulceration/perforation

7. Nonabsorbable corticosteroids

a. Beclomethasone (orBec®):

i. *Mechanism of action:* A synthetic corticosteroid with potent glucocorticoid but weak mineralocorticoid activity. The mechanism of its anti-inflammatory effects has not been clearly established.
ii. *Dose and administration:* 2 mg po q6 h of both immediate release and enteric coated capsules
iii. *Adver*se effects: Minimal adverse effects reported with oral dosing. Systemic absorption is similar to oral prednisone 2.5 mg po daily and < 1 mg IV dexamethasone daily.

b. Budesonide (Entocort EC®):

i. *Mechanism of action:* An anti-inflammatory corticosteroid with high affinity for the glucocorticoid receptor and low systemic bioavailability due to rapid first-pass metabolism in the liver.
ii. *Dose and administration:* 3 mg po TID or 9 mg po daily
iii. *Adverse effects*:

- Nausea, diarrhea
- Arthralgias
- Headache
- Sinusitis, respiratory tract infection
- Cushing's syndrome
- Rare complications include: immune hypersensitivity reaction, glaucoma, cataracts, increased risk of developing basal cell/squamous cell carcinoma or malignant melanoma

8. Pentostatin (Nipent®):

a. *Mechanism of action:* A nucleoside analog that inhibits adenosine deaminase, leading to increased levels of 2'-deoxyadenosine 5'- triphosphate (dATP) resulting in lymphocyte apoptosis
b. *Dose and administration:* 1.5 mg/m^2 IV over 15–30 min on days 1–3 and 15–17. Reduce dose by 50 % for absolute neutrophil count (ANC) < 1000 and/or CrCl of 30–50 mL/min, hold for ANC < 500 and/or CrCl < 30 mL/min.
c. *Adverse effects:*

i. Increased risk of infection
ii. Cytopenias
iii. Abdominal pain, N/V/D, anorexia

iv. Stomatitis
v. Headache, weakness
vi. Transaminitis
vii. Constitutional symptoms of fever/chills, fatigue
viii. Rash/pruritus
ix. Hyponatremia
x. Acute renal failure
xi. Microangiopathic hemolytic anemia/thrombotic thrombocytopenia purpura
xii. Immune hypersensitivity reaction

9. Sirolimus (Rapamune®)

a. *Mechanism of action:* Inhibits IL-2, IL-4, and IL-15 stimulated T cell activation and proliferation, as well as inhibiting antibody production.
b. *Dose and administration:* Load with 15 mg/m^2 po on day 1, then 5 mg/m^2 po daily × 13 days or 4–5 mg/m^2 po daily × 14 days without a loading dose; adjust dose to maintain a trough level of 4–12 ng/mL.
c. *Adverse effects:*

i. Hemolytic uremic syndrome (HUS), nephrotic syndrome, renal insufficiency
ii. Thrombotic thrombocytopenia purpura
iii. Thromboembolism, deep vein thrombosis
iv. Interstitial lung disease/pneumonia, pulmonary hemorrhage
v. Hyperlipidemia
vi. Hypertension
vii. Rash
viii. Abdominal pain, nausea, diarrhea, constipation
ix. Pancytopenia
x. Increased risk of urinary tract infections
xi. Increased risk of developing basal cell/squamous cell carcinoma or malignant melanoma

18.9 Autologous GvHD

While GvHD is typically considered to be a complication of allogeneic transplant alone, an acute GvHD-like syndrome is recognized to occur in approximately 5–20% of autologous and syngeneic HSCT recipients. It is thought that the incidence of autologous/syngeneic GvHD is underreported as symptoms mimic those of regimen-related toxicity.

The pathophysiology is not well understood but is thought to be related to a failure of self-tolerance through the thymic depletion of regulatory T cells following the conditioning regimen.

Target organs include the skin, GI tract and liver; clinical symptoms and histopathologic findings are identical to those of allogeneic GvHD. Autologous/

syngeneic GvHD most commonly affects the skin, is usually milder than allogeneic GvHD, and is often self-limiting, burning out in 1–3 weeks. Some patients, however, may require systemic steroids, and deaths have been reported, most commonly from complications of prolonged immune suppressive therapy.

18.10 Conclusions

Only 20–40 % of patients with acute GvHD will experience long-term responses to therapy, and the likelihood of response decreases as the severity of the disease increases. Of those patients with steroid-refractory disease, overall long-term survival rates fall to < 20 %. Patients with grade IV disease typically have < 5 % long-term survival.

Minimal improvement has been made in the past 15 years despite multiple new agents. Most studies have been small, and patient responses have been variable. Clinical practice relies mainly on institutional bias and provider experience. The emergence of the BMT CTN with focused multicenter clinical trials targeting GVHD will guide future therapies. Treating providers are encouraged to enroll patients on clinical trials to aid in identifying superior agents and determining standard, effective second-line therapy. Future trials should be multicenter studies with clearly defined response criteria and end points to "standardize" responses across institutions.

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Chapter 19
Chronic Graft-Versus-Host Disease

Jonathan Brammer and Shernan Holtan

Chronic graft-versus-host disease (cGVHD) is a multisystem immunologic disorder that impacts long-term outcomes, including risk of relapse, transplant-related mortality, and the quality of life after allogeneic hematopoietic stem cell transplantation (HSCT). cGVHD is an alloimmune process (donor versus recipient) that results in anti-host T cell responses, as well as alloantibody formation, and may involve single or multiple organ systems. The incidence of cGVHD is approximately 30–70 %, depending on various patient and donor factors. Despite improvements in the care of allogeneic HSCT recipients, management of cGVHD remains a significant challenge.

The management of cGVHD can be similar to autoimmune disorders such as scleroderma or Sjogren's syndrome. Steroids have been the mainstay of treatment for over 30 years. Protracted steroid tapers of 2–3 years or longer are often required to avoid flares of the disease. Steroid-sparing agents, such as tacrolimus, cyclosporine, mycophenolate mofetil, sirolimus, and other systemic immune suppressants have been used to treat established cGVHD with variable success.

19.1 Pathophysiology

Chronic GVHD is a heterogeneous immunologic disorder:

1. The pathophysiology of cGVHD is incompletely understood, but involves disruptions in T- and B-cell homeostasis including impaired T regulatory cell function.

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2. cGVHD is closely linked to the graft-versus-leukemia (GVL) effect:
   a. Development of cGVHD and its correlation with the GVL effect was first demonstrated in 1980, when decreased rates of relapse were noted in patients who experienced cGVHD compared to patients who did not experience cGVHD after HSCT for leukemia.
   b. Patients with cGVHD have a strong GVL effect as demonstrated by a decreased incidence of relapse, suggesting that similar mechanisms underlie the immunologic biology of both processes.

19.2 Incidence

The incidence of cGVHD ranges from 30 to 70%, depending on the conditioning regimen utilized, stem cell source, and multiple host and donor factors.

19.3 Risk Factors

1. Previous acute GVHD
2. Age of recipient (GVHD increases with recipient's age)
3. Parous female donor
4. Use of a multiply transfused donor
5. Use of allogeneic peripheral blood stem cells instead of bone marrow
6. Human leukocyte antigen (HLA) mismatched donor graft
7. History of acute inflammation (sunburn, Stevens–Johnson syndrome, colitis, pneumonia, etc.)
8. Cytomegalovirus (CMV) seropositivity
9. Sex-mismatched donor graft
10. Donor leukocyte infusion (DLI)
11. Unrelated donor HSCT

19.4 Factors Associated with Decreased Survival

The Centers for International Blood and Marrow Transplant Research (CIBMTR) evaluated 5343 patients with cGVHD. They were able to stratify risk factors and develop a tool to determine the probability of 5-year overall survival and the cumulative incidence of 5-year nonrelapse mortality.

This calculator can be found at: www.ohsuknightcancer.com/bmt-calculator:

1. Age
2. History of aGVHD
3. Onset of cGVHD < 5 months after HSCT

4. Bilirubin > 2 g/dL at onset of cGVHD
5. Advanced disease status at transplant
6. Impaired performance status (Karnofsky performance status, KPS < 80)
7. Platelet count < 100,000 at diagnosis of cGVHD
8. Mismatched unrelated donor product
9. GVHD prophylaxis utilized (cyclosporine > tacrolimus-containing regimen or T cell depletion)
10. Gender mismatch (female donor → male recipient)

19.5 Diagnosis of cGVHD

1. Chronic GVHD may involve either a single organ or multiple organ systems and can range in severity from mild disease, not requiring systemic treatment, to severe and life-threatening disease.
2. Signs typical of cGVHD may include:

   a. Skin, mucosal, or genital lichenification
   b. Bronchiolitis obliterans (BO)
   c. Ocular dryness, irritation, corneal keratitis
   d. Sclerosis of skin and joints.

3. Disease stage was originally defined as "limited" versus "extensive," based on a series from the Fred Hutchinson Cancer Research Center:

   a. Limited disease was characterized as localized skin involvement, hepatic dysfunction or both, and found to have a more favorable prognosis.
   b. Extensive disease was characterized by generalized skin involvement, or localized skin involvement and hepatic dysfunction/ocular/salivary gland involvement or involvement of any other target organ:

i. Patients with extensive cGVHD had a worse prognosis.

   c. In 2005, a National Institutes of Health (NIH) consensus project sought to develop more specific clinical and pathologic criteria for the diagnosis of cGVHD given inconsistent and incomplete staging using the limited/extensive system:

ii. These new guidelines recognized two main categories of cGVHD:

   - Classic cGVHD without features of acute GVHD (see Chap. 18)
   - Overlap syndrome in which features of cGVHD and acute GVHD are both present

iii. Historically, cGVHD was described as occurring beyond post-HSCT day 100; however, it increasingly has been seen that aGVHD and cGVHD are part of a continuum, and an overlap variant of GVHD has been described.

4. The diagnosis of cGVHD requires the following criteria:
   a. Exclusion of aGVHD
   b. Presence of at least one diagnostic clinical sign of cGVHD, or presence of at least one distinctive manifestation confirmed by biopsy or other testing (Table 19.1)
   c. Exclusion of other diagnoses

19.6 Grading of cGVHD

1. According to the 2005 NIH consensus guidelines, cGVHD is graded on a scale of mild, moderate, or severe (Table 19.2):
   a. The multicenter Chronic GVHD Consortium was organized to prospectively validate these guidelines and initiate novel trials.
   b. A retrospective analysis by the Consortion revealed 2-year overall survival correlated with grade of cGVHD:
      i. Sixty-two percent in patients with severe cGVHD
      ii. Eighty-six percent in patients with moderate cGVHD
      iii. Ninety-seven percent in patients with mild cGVHD
   c. These data led to the adoption of this scale as the standard for the study and management of cGVHD

19.7 Treatment of cGVHD

1. The goals of cGVHD therapy are to relieve symptoms and prevent progression while waiting for the establishment of immune tolerance:
   a. Once treatment is initiated, the median duration of treatment is typically 2–3 years.
   b. About 85 % of patients who survive 5 years after development of cGVHD are able to discontinue systemic therapy.
   c. A paucity of randomized clinical trial data regarding the treatment of cGVHD exists.
2. Mild, cutaneous involvement of cGVHD can be managed by topical steroids alone and tapered based on symptomatology:
   a. Topical therapy alone has the benefit of minimal systemic immune suppression, particularly in patients who are at higher risk of relapse.
   b. A summary of topical agents is provided in Table 19.3.

Table 19.1 Stigmata and clinical features of cGVHD

Organ or site	Diagnostic (adequate for the diagnosis of cGvHD)	Distinctive (seen in cGvHD but not aGvHD; insufficient to establish cGvHD diagnosis)	Other features (cannot be used to establish a diagnosis)	Common (seen with aGvHD and cGvHD)
Skin	Poikilodermia Lichen-type features Sclerotic features Morphea-like features Lichen sclerosis	Vitiligo	Sweat impairment Ichtyosis Keratosis pilaris Decreased pigmentation Increased pigmentation	Erythema maculopapular rash Puritus
Nails		Dystrophy Longitudinal ridging, splitting, brittleness Onycholysis Pterygium Destruction (usually symmetric, affects most nails)		
Scalp and body hair		New alopecia (after recovery from chemoradiotherapy), scarring and nonscarring alopecia; scaling, papulosquamous lesions Loss of body hair, typically patchy (including eyelashes, eyebrows)	Thinning scalp hair, coarse or dull (not due to endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Sclerosis with decreased range of motion	Xerostomia Mucocele Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Corneal ulceration	Excessive aqueous tearing Photophobia Periorbital hyperpigmentation Blepharitis	
Genitalia	Lichen-type features Vaginal strictures or stenosis	Ulcers Fissures Erosion		

Table 19.1 (continued)

GI tract	Esophageal webbing Strictures or stenosis in the upper third of the esophagus		Pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive
Liver				Total bilirubin, alk phos 2x ULN ALT or AST 2x ULN
Lung	Bronchiolitis obiterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology		BOOP
Muscles *Fascia* *Joints*	Fasciitis Joint stiffness of contractures secondary to sclerosis	Myositis or polymyositis (proximal muscle weakness; myalgia is uncommon)	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Auto-antibodies (also AIHA, ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

cGVHD chronic graft-versus-host disease, *aGVHD* acute graft-versus-host disease, *GI* gastrointestinal, *ULN* upper limit of normal, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *GI* gastrointestinal, *PFT* pulmonary function test, *BOOP* bronchiolitis obliterans organizing pneumonia, *AIHA* autoimmune hemolytic anemia, *ITP* idiopathic thrombocytopenia purpura

Table 19.2 NIH cGHVD organ-specific staging form. (Source: Filopovich et al., BBMT 2005)

	Score 0	Score 1	Score 2	Score 3
Performance score _____ KPS ECOG LPS	□ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	□ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80–90%)	□ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60–70%)	□ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN	□ No symptoms with no or minimal distinct signs	□< 18% BSA with disease signs but *no* sclerotic features	□ 19–50% BSA *or* superficial sclerotic features "not hidebound" (able to pinch)	□> 50% BSA OR deep sclerotic features "hidebound" (unable to pinch) *or* interference with ADL due to impaired mobility, ulceration or severe pruritis
Clinical features				
□ Maculopapular rash				
□ Lichen-type features				
□ Papulosquamous or icthyosis				
□ Hyperpigmentation				
□ Hypopigmentation				
□ Keratosis pilaris				
□ Erythema				
□ Erythroderma				
□ Polikiloderma				
□ Sclerotic features				
□ Pruritis				
□ Hair				
□ Nails				

Table 19.2 (continued)

	Score 0	Score 1	Score 2	Score 3
%BSA involved _____				
MOUTH	□ No symptoms with no or minimal distinct signs	□ Mild symptoms with disease signs but not limiting oral intake significantly	□ Moderate symptoms with signs with partial limitation of oral intake	□ Severe symptoms with disease signs on examination with major limitation of oral intake
EYES	□ No symptoms	□ Mild dry eye symptoms not affecting ADL (requiring eye drops ≤3 x per day) *or* symptomatic signs of sicca keratitis	□ Moderate dry eye symptoms partially a affecting ADL (requiring drops >3 x per day or punctal plugs), WITHOUT vision impairment	□ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) *or* unable to work due to ocular symptoms *or* loss of vision caused by pseudomembranes or corneal ulceration
Mean tear test (mm):				
□>10				
□6–10				
□≤5				
□Not done				
GI TRACT	□ No symptoms	□ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	□ Symptoms associated with mild to moderate weight loss (5–15%)	□ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs *or* esophageal dilation
LIVER	□ Normal LFTs	□ Bilirubin, AP, AST or ALT <2 × ULN	□ Bilirubin > 3 mg/dl or bili, enzymes 2–5 × ULN	□ Bili or enzymes >5 x ULN
LUNGS	□ No symptoms	□ Mild symptoms (dyspnea with stair climbing)	□ Moderate symptoms (dyspnea with level walking)	□ Severe symptoms (dyspnea at rest; requiring 02)

Table 19.2 (continued)

	Score 0	Score 1	Score 2	Score 3
	□ FEV_1/FVC ratio <0.75 OR FEV_1 of 51–75%, without distinct findings of bronchiolitis obliterans (BO) on HRCT	□ FEV_1/FVC ratio <0.75 *or* FEV_1 of 51–75% *with* mild distinct findings of BO on HRCT	□ FEV_1/FVC ratio <0.75 *or* FEV_1 of 35–50% *with* distinct findings of BO on HRCT	□ FEV_1/FVC ratio of <0.75% *or* $FEV_1 \leq 34\%$ *with* distinct findings of BO on HRCT
JOINTS AND FASCIA	□ No symptoms	□ Mild tightness of arms or legs, normal or mild decreased ROM *and* not affecting ADL	□ Tightness of arms or legs or joint contractures erythema thought due to fasciitis, moderate decrease ROM *and* mild to moderate limitation of ADL	□ Contractures *with* significant decrease of ROM *and* significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
GENITAL TRACT	□ No symptoms with no or minimal distinct signs on examination	□ Symptomatic with mild distinct signs on exam *and* no effect on coitus and minimal discomfort with GYN exam	□ Symptomatic with distinct signs on exam *and* with mild dyspareunia or discomfort with GYN exam	□ Symptomatic *with* advanced signs (stricture, labia agglutination or severe ulceration) *and* severe pain with coitus or inability to insert vaginal speculum
□ Weight loss	□ Eosinophilia ≥500/μl	□ Progressive onset		
□ BO (lungs)	□ Fasciitis	□ Disabling contractures		
□ Malabsorption	□ Plts <100,000μl	□ None		
□ BOOP (lungs)	□ Myositis			
□ Esophageal stricture or web	□ Serositis			

KPS Karnofsky performance status, *ECOG* Eastern Cooperative Oncology Group, *LPS* Lansky performance status, *NIH* National Institutes of Health, *cGVHD* chronic graft-versus-host disease, *BSA body surface area*, *ADL* activity of daily living, *LFT* liver function test, *AST* aspartate aminotransferase, *AP* alkaline phosphatase, *ULN* upper limit of normal, *FEV* forced expiratory volume, *FVC* forced vital capacity, *HRCT* high-resolution computed tomography, *ROM* range of motion, *GYN* gynecological

Table 19.3 Common agents used for the treatment and supportive care of cGVHD

First line agents		
Agent	Typical starting dosage	Notes
Prednisone	1 mg/kg po daily	Dose usually continued for a minimum of 4–8 weeks prior to taper May be used as a single agent and at lower doses for mild disease May use up to 2 mg/kg daily for severe disease Side effects include osteoporosis, avascular necrosis, diabetes
Tacrolimus	0.075–0.15 mg/kg po every 12 h	Adjust dose as necessary to maintain therapeutic drug level of 5–10 ug/L May be used in combination with prednisone as a steroid-sparing agent Side effects include magnesium wasting, renal toxicity, hypertension. Higher doses need if patient is on azole such as fluconazole
Cyclosporine	2–3 mg/kg po BID	Adjust dosage to maintain a therapeutic target level of 100–150 ng/mL. May be used in combination with prednisone as a steroid-sparing agent Side effects include magnesium wasting, renal toxicity, hypertension
Second line agents		
Sirolimus	Loading dose 4 mg po × 1 followed by 1–2 mg po once daily	Adjust dose as necessary to maintain therapeutic drug level of 6–12. Administration with voriconazole with extreme caution (lower sirolimus dose by ~90%, typically starting at 0.2 mg daily). Monitor for transplant-associated microangiopathy and sinusoidal obstruction when given with tacrolimus
Mycophenolate-mofetil	0.5–1.5 gm po BID	Associated with cytopenias and gastrointestinal side effects No benefit when added in triple combination in the first line setting Risk of viral infections and relapse
Extracorporeal Photopheresis	Schedules vary, but one strategy is twice weekly sessions × 4 weeks, followed by twice weekly sessions QO week × 4–6 months, followed by further tapering	Most effective for sclerodermatous skin changes and pulmonary GVHD Requires venous access Spares steroid dose Risk of infections due to central venous access, photosensitivity
Rituximab	375 mg/m2 IV weekly × 4 weeks	Risk of infusion reaction, neutropenia, infection
Imatinib mesylate	100 mg po daily	Risk of cytopenias and fluid retention Benefit predominantly observed in sclerodermoid cutaneous involvement
Acitretin	Starting dose of 10 mg po daily.	Increase gradually to a maximum dosing of 40 mg po daily for cutaneous cGVHD until skin peeling Risk of skin toxicity and hyperlipidemia

Table 19.3 (continued)

First line agents		
Agent	Typical starting dosage	Notes
Hydroxychloroquine	3.5–5.0 mg/kg/day po in 2–3 divided doses (do not exceed 400 mg/day)	Risk of gastrointestinal side effects Need baseline and periodic ophthalmology examinations
Other agents	Etanercept, infliximab, thalidomide, clofazimine, pentostatin, thoracoabdominal radiation can be considered for refractory disease.	
Topical agents and organ-specific treatment considerations		
Cutaneous	Topical corticosteroids Topical CNI UVA/UVB	Referral to dermatology for moderate to severe disease recommended Nonhealing lesions should be referred to dermatology Annual skin examination due to increased risk of cutaneous malignancy Massage and physical therapy for sclerodermoid manifestations
Ocular	Artificial tears Topical corticosteroids Topical CNI Autologous serum eye drops Topical antibiotics	Referral to ophthalmology recommended.
Oral	Steroid mouthwashes Artificial saliva Sialogogues	Referral to oral medicine recommended. Annual oral examination due to increased risk of oral malignancy.
Pulmonary	Systemic treatment Inhaled corticosteroids Bronchodilators Azithromycin	All patients with chronic GVHD should be screened for pulmonary manifestations with PFTs regardless of symptoms. Supportive care, including vaccinations, and appropriate antimicrobial prophylaxis encouraged
Liver	Ursodiol	All patients should be assessed for iron overload contributing to hepatic dysfunction
Gastrointestinal	Steroids with low systemic absorption (beclomethasone, budesonide) Pancreatic enzymes	Referral to gastroenterologist should be considered Referral to dietician with experience in managing patients with GVHD should be considered
Genital	Topical steroids, especially mucoadherent formulations Topical CNI	Referral to gynecology should be considered Consideration of hormone supplementation for those with premature menopause or signs/symptoms of hypogonadism
Infections	Prophylaxis against encapsulated bacteria, viruses (HSV/VZV), fungal infections, and PCP should be considered	Vaccinations against influenzae, pneumococcus, and *Haemophilus influenza* should be provided Live virus vaccines should not be administered IVIG can be supplemented if significant hypogammaglobulinemia and recurrent infections

cGVHD chronic graft-versus-host disease, *IV* intravenous, *CNI* calcineurin inhibitors, *UV* ultra violet, *PFT* pulmonary function tests, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *IVIG* intravenous immunoglobulin, *PCP* **Pneumocystis carinii pneumonia**

3. Mild fasciitis and internal organ manifestations should be managed with systemic corticosteroids, with the lowest effective dose possible:
    a. Typically, patients should remain on systemic steroids for 4–8 weeks, with tapering doses based on clinical symptomatology.
4. Mild liver dysfunction can be managed with ursodiol (Actigall®).
5. Moderate and severe cGVHD require systemic immunosuppression:
    a. The standard first-line therapy is corticosteroids with a dose of 1–2 mg/kg/day of prednisone or equivalent as the standard of care.
    b. Tapering schedules vary widely and are often employed on an empiric basis. One management strategy is shown below:
        i. If the patient achieves resolution of symptoms, initiation of a taper is recommended at 4–8 weeks with a reduction of steroids to 1 mg/kg every other day by 6–8 weeks, followed by 10–20 % taper per week thereafter.
        ii. If symptoms recur, an increase in steroids may yield a response, and slower taper thereafter is recommended.
        iii. If no response is achieved after 2–3 months of therapy, alternative treatments should be considered.
    c. In patients on high-dose steroids (>25 mg/day of prednisone or equivalent), mold-active anti-fungal agents are recommended (voriconazole, Vfend® or posoconazole, [Noxafil®]).
    d. Additionally, CMV polymerase chain reaction (PCR) and Aspergillus galactomannan monitoring can be useful to detect reactivation or infection.
6. Steroid-refractory cGVHD.
    a. Some patients may have persistence of cGVHD despite adequate therapy with corticosteroids.
    b. Limited data exists for the management of these patients, but the addition of tacrolimus, cyclosporine, or sirolimus as ‘steroid sparing agents’ may decrease the side effects of long-term steroid use while controlling cGVHD

19.8 Response Assessment

Clinically, response to therapy is measured by evaluating the organ(s) affected by cGVHD using the NIH consensus grading:

1. Baseline and serial NIH cGVHD scale surveys should be completed to chart the course of the disease.
2. Quality of life measurements also have been validated as an end point in cGVHD:
    a. In particular, the Lee symptom score which correlates to the 2005 consensus guidelines, rates GVHD-related symptoms on a five-point scale and can be

used to assess a patient's overall quality of life and to judge the effectiveness of therapy.
   b. While these tools may help guide therapy, they have not correlated to overall survival or improved quality of life in randomized studies.
3. As with all of cGVHD management, treatment is administered and response evaluated on a personalized, empiric basis.
4. Patients must be monitored frequently and closely, preferably by a consistent evaluator, to determine treatment benefit.

19.9 Follow-up

1. Serial monitoring of all organ systems for signs/symptoms of cGVHD is recommended and should be performed at least annually for up to 5 years post-HSCT.
2. Evaluation should include medical, psychosocial, nutritional, and developmental assessments including Tanner scoring in children and adolescents. These measures allow for instituting preventative and early treatment measures.
3. Suggested monitoring and follow-up:
   a. Follow-up with consistent evaluator weekly initially, then monthly thereafter until stabilization of symptoms.
   b. Complete blood counts with differential and complete metabolic panel every 1–6 months.
   c. Therapeutic drug monitoring weekly initially, then every 1–3 months after stable levels are achieved.
   d. IgG levels every 1–6 months until normalization (>400).

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Chapter 20
Oral Complications

Kimberly Brennan Tyler

Mucositis is reported as the side effect that most negatively affects quality of life in patients receiving cancer treatment. It is also associated with increased rates of infection and increases the demand for health-care resources. Mucositis is a consequence of chemotherapy that results in tissue damage manifested by erythema, edema, and ulceration of the gastrointestinal mucosa that disrupts the protective barrier. It is typically noted post-HSCT and lasts until the healing effects of engraftment, although one may also see similar mucosal changes associated with graft-versus-host disease (GVHD) or certain infections. Up until this point, treatment for OM has primarily focused on management (see Table 20.2).

20.1 Pathophysiology

Mucositis is the consequence of a variety of pathophysiologic processes occurring in conjunction with multiple cytokine releases with resulting damage of the epithelial surfaces and subsequent disruption of the integrity of the epithelial layer. Due to the direct chemotherapeutic effect on epithelial tissues, there can be significant delay in repair of the damaged tissues which further potentiates the effects of the inflammatory process. The epithelial lining is then at a greater risk for colonization of an invasion by various microorganisms. In hematopoietic stem cell transplant (HSCT) recipients, as a consequence of dose escalation of chemoradiotherapy, increased tissue damage is anticipated.

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20.2 Risk Factors

1. Conditioning regimen (total body irradiation (TBI), melphalan)
2. Medications that result in xerostomia and decreased saliva production (e.g., opiates, diuretics, antiemetics, etc.)
3. Prolonged antimicrobial usage
4. Prolonged hospitalization
5. Prolonged myelosuppression
6. History of mucositis with previous treatment cycles
7. Body mass index >25 increases risk of oral mucositis (OM)
8. Graft-versus-host disease (GVHD) prophylaxis (calcineurin inhibitor, methotrexate)
9. Emesis
10. Poor oral health and hygiene
11. Poor nutritional status
12. Tobacco and alcohol use
13. Infectious disease exposures (e.g., herpes simplex)
14. GVHD
15. Mouth breathing

20.3 Prophylaxis

1. Oral hygiene prior to admission
    a. Brushing with fluoride toothpaste BID and flossing daily.
    b. Use foam toothbrush if painful mucositis precludes use of a regular toothbrush, or once platelet count falls below 50,000/μl. Daily flossing if atraumatic and platelet count is >50,000/μl.
    c. Chlorhexidine gluconate 0.12 % (Peridex®) contains alcohol and should only be used to minimize bacterial colonization prior to signs of OM. Chlorhexidine 0.12 % aqueous alcohol-free solution (GUM® Paroex™) is available by prescription through a dentist's office.
    d. Pre-transplant dental evaluation and cleaning by a dentist with experience working with HSCT patients.
        i. All sources of dental infection should be preferentially corrected prior to conditioning. Badly decayed teeth/dental caries may require extraction.
        ii. Patients receiving intravenous (IV) bisphosphonates require special consideration and conservative management of dental problems to reduce the risk of osteonecrosis of the jaw.
        iii. Conditioning regimen may begin 10–14 days after mucosa has healed.
        iv. Patients should be educated on the importance of good oral care during HSCT with ongoing reinforcement throughout the HSCT course.

e. Low-level laser therapy to reduce plaques before HSCT, if available.
f. Orthodontic bands should be removed.
g. Avoid the use of other dental appliances unless they have been evaluated and approved prior to HSCT.
h. Avoid alcohol and tobacco.

2. Oral hygiene during transplant

a. Ongoing oral assessment using validated staging tool (Tables 20.1).
b. Ongoing oral assessment from a specialized oral management group.
c. Encourage the patient to communicate symptoms in a timely manner for prompt initiation of therapy.
d. Palifermin (Kepivance®) 60 mcg/kg/day on 3 consecutive days, with the last dose given no less than 24 h prior to initiation of the conditioning regimen, then on days +1, +2, and +3 post-HSCT. This growth factor has been approved for use in autologous HSCT recipients only and is used primarily with TBI-based regimens.
e. Oral cryotherapy during and for 1 h after the administration of high-dose melphalan.
f. Artificial saliva (Caphosol®) oral rinse solutions: One ampule each of sodium phosphate and calcium chloride, combined, at least four times and up to ten times daily. Patient will rinse with half of solution for one full minute and spit.

Table 20.1 Stomatitis evaluation scales

Grade	WHO[a]	NCI-CTC[b]	Bearman
Grade 0	No oral abnormalities	No oral abnormalities	No oral abnormalities
Grade 1	Oral soreness +/− erythema without ulceration; able to tolerate regular diet	Erythema	Pain and/or ulceration not requiring a continuous IV narcotic drug
Grade 2	Oral soreness with erythema and ulcerations; able to tolerate solid food	Patchy ulcerations or pseudomembranes	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)
Grade 3	Oral soreness with erythema and ulcerations; able to tolerate liquids only	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Severe ulceration and/or mucositis requiring preventative intubation; or resulting in documented aspiration pneumonia with or without intubation
Grade 4	Oral soreness with erythema and ulcerations; unable to tolerate anything by mouth	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Grade 5		Death	

IV intravenous
[a] World Health Organization
[b] National Cancer Institute-Common toxicity criteria

Repeat with remaining half of solution. Patient should refrain from oral intake for 15 min after each dose.

g. Denture use should be minimized; dentures should be immersed in antimicrobial solution when stored with change in solution on a daily basis.

Avoid use if dentures are ill-fitting, abrasive to mucosa, or if there is active mucositis.

h. Avoid hot, abrasive, sharp, or hard foods. Moisten food with sauces or gravies. Avoid hot, acidic, or carbonated liquids. Avoid artificial flavoring, especially pungent compounds such as mint and cinnamon.
i. Maintain adequate hydration.
    i. Keep lips moist using ointment and lip moisturizers containing aloe. Avoid petroleum products.
    ii. Sucralfate (Carafate®) 1 g dissolved in solution, swish and swallow every 6 h beginning on admission has been used in some centers. Not to be used with radiation-induced OM.
j. Maintain and promote saliva production.

Table 20.2 Management of oral complications

Symptom	Severity	Treatment
Pain	Mild	Use of bland oral rinses to maintain moisture Normal saline swish and spit every 2 h Sodium bicarbonate solution every 2 h Sodium chloride rinses Sponge swab Ice chips Use of sialagogues Artificial saliva Sugarless hard candies or sugarless gum Pilocarpine (Salagen®) 5–10 mg po TID Cevimeline (Evoxac®)30 mg po TID Bethanechol 25 mg po TID Topical fluoride treatments Biotene® mouthwash or toothpaste Reduce oral challenges such as converting all medications to IV formula, providing IV fluid and/or parenteral nutrition
	Moderate	Topical analgesia Compounded mouthwashes (Maalox®: Benadryl elixir: Viscous Lidocaine 1:1:1) 10–15 mL swish and spit every hour PRN Benzocaine gel apply topically to oral lesions QID PRN Doxepin (Sinequan®, Adapin®) 5 mg/mL, 5 mL po held in the mouth for 5 min PRN Systemic opiates Scheduled opiate administration
	Severe	Parenteral narcotics Use of narcotic patches and IV administration Patient-controlled analgesia

Table 20.2 (continued)

Symptom	Severity	Treatment
Xerostomia and hyposalivation		Use of bland oral rinses to maintain moisture Normal saline swish and spit PRN Sodium bicarbonate solution every 2 h Sponge swab Half-strength hydrogen peroxide swish and spit PRN Use of sialagogues Artificial saliva Sugarless hard candies or sugarless gum Pilocarpine (Salogen®) 5–10 mg po TID Cevimeline (Evoxac®) 30 mg po TID Bethanechol 25 mg po TID Topical fluoride treatments Biotene® mouthwash or toothpaste Caphosol® swish and spit 4–10 times daily PRN
Thick secretions		Use mucolytic drying agents Scopolamine patch (Transderm Scop®) TD behind ear apply every 72 h Dimenhydrinate (Dramamine®) 25–50 mg po every 4 h PRN Diphenhydramine 25–50 mg po or 12.5–25 mg IV every 6 h PRN Lorazepam 0.5–1 mg po/IV every 6 h PRN (gag reflex) Utilize suction to alleviate secretions Utilize blow by humidified air
Emesis		Antiemetics scheduled around the clock
Bleeding		Transfuse to maintain platelets > 20,000 for mild gingival bleeding Transfuse to maintain platelets > 50,000 for severe gingival bleeding
Airway protection		Utilize blow-by humidified air Short course of IV steroids ENT consult for preemptive intubation for airway protection

TID three times a day, *IV* intravenous, *PRN* as needed, *QID* four times a day, *ENT* ear, nose, and throat

20.4 Infections

1. Most common pathogens causing infection in patients with OM undergoing HSCT.
    a. *Streptococcus viridans*
    b. *Coagulase negative Staphylococci*
    c. *Gram-negative bacteria*
    d. *Herpes simplex*
    e. *Candida albicans*
    f. *Cytomegalovirus*

2. Swab and culture all oral lesions.
3. Candidal infections.
    a. Topical treatments
        i. Nystatin liquid 10 mL swish and spit/swallow every 6 h
        ii. Clotrimazole (Mycelex®) troches one by mouth five times daily
        iii. Amphotericin mouthwash: 50 mg amphotericin B mixed in 200 mL sterile water 5–10 mL swish and spit/swallow every 6 h
    b. Systemic antifungals
        i. Fluconazole (Diflucan®) 400 mg po or IV daily if oral involvement
        ii. Micafungin (Mycamine®) 150 mg IV once daily if esophageal involvement and fluconazole intolerance
4. Viral infections
    a. Systemic antivirals
        i. Acyclovir (Zovirax®) 800 mg po daily or 250 mg/m^2 IV twice daily
        ii. Valacyclovir (Valtrex®) 500 mg po twice daily
5. Bacterial
    a. Systemic antibacterials
        i. Fluoroquinolone through engraftment or for periods of neutropenia >7 days
        ii. Ciprofloxacin (Cipro®) 500 mg po BID
        iii. Levofloxacin (Levaquin®) 400 mg po daily

20.5 Dental Procedures

The American Dental Association does not recommend prophylaxis for dental procedures for immunocompromised hosts; however, it continues to be standard practice at some institutions. Common regimens:

1. Amoxicillin 2 g po once, 1 h prior to procedure
2. Clindamycin (Cleocin®) 600 mg po once, 1 h prior to procedure or QID for 10 days post-procedure
3. Azithromycin (Zithromax®) 500 mg po once, 1 h prior to procedure or once daily for 10 days post procedure

20.6 Taste Alterations

1. Dysgeusia (distorted taste), hypogeusia (loss of taste), or ageusia (absence of taste)
    a. Most affected are sweet and salty tastes
    b. Maintain good oral hygiene
    c. Use artificial sialagogues
    d. Season foods
    e. Eat small portions

20.7 Discharge Instructions

1. Patients may begin flossing once platelet count is > 50,000.
2. Patients should be encouraged to use saline rinses for 3–6 months post-HSCT as recommended by their medical provider.
3. Patients with GVHD should:
    a. Undergo oral evaluation every 3–6 months
    b. Practice meticulous dental hygiene with use of toothbrush TID, flossing daily providing platelets are > 50,000, dental fluoride treatments, and use of sialagogues as needed
4. Sugar-free candy or gum should be encouraged particularly in patients with xerostomia.
5. Return to routine professional dental care in 6–12 months if blood counts are normal. Delay elective oral procedures for 12 months.

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Chapter 21
Gastrointestinal Complications

Eneida R. Nemecek

Gastrointestinal (GI) and hepatic complications are common in the hematopoietic stem cell transplant (HSCT) patient. The agents used in the conditioning regimen induce direct disruption of the intestinal barrier as well as indirect damage from cytokine release and a generalized inflammatory state. These events lead to permeation of bacteria and endotoxins through the bowel wall with subsequent organ damage and increased risk for infection. Similarly, HSCT conditioning can directly affect the hepatic parenchyma or hepatic sinusoids. The immunosuppressed state of the HSCT patient also increases the risk for opportunistic infections of the GI tract and liver.

21.1 Upper Gastrointestinal

1. Anorexia
   a. Etiology and pathogenesis
      Usual onset during conditioning and first week post-transplant; may last longer in patients with mucositis, infection, or graft-versus-host disease (GVHD). May result from:
      i. Direct emetogenic effect from conditioning therapy
      ii. Delayed gastric emptying
      iii. Circulating inflammatory cytokines directly affecting appetite centers
      iv. Mucositis-related pain and dysphagia
      v. GVHD
      vi. Infection
      vii. Medications

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b. Diagnosis
Most cases are identified by clinical presentation and do not require additional workup. Endoscopic evaluation (i.e., esophagogastroduodenoscopy) with biopsies to identify potential underlying causes is recommended for cases of protracted or prolonged nausea, vomiting, or anorexia after mucositis has resolved.

c. Treatment

i. Conditioning regimens for HSCT include highly emetogenic therapy. Antiemetic prophylaxis during conditioning therapy (see Chap. 6) should aim at minimizing nausea and vomiting and preserving enteral nutrition for as long as possible.
ii. Daily calorie count to determine:

- If adequate nutritional goals are achieved
- If there is a need for enteral or parenteral supplementation (see Chap. 7)

iii. The efficacy of appetite stimulants in the post-transplant setting has not been determined and is generally not recommended. However, if anorexia becomes chronic, one could consider a trial of megestrol (Megace®) acetate oral solution 800 mg po daily or dronabinol (Marinol®) 2.5–5 mg po before lunch and dinner daily. The safety and efficacy of these agents in children have not been established although empiric use has been reported. Consultation with a pediatric pharmacist prior to their use is recommended.

2. Esophagitis/Gastritis

a. Etiology and pathogenesis
Usually presents during conditioning and period of mucositis but may last longer in patients with GVHD. Potential etiologies include:

i. Mucositis
ii. Medications
iii. Poor oral intake
iv. Altered gastric pH
v. "True" peptic ulcer disease

b. Diagnosis
Diagnosis is clinical. Symptoms typically include heartburn and/or epigastric pain.

c. Treatment

i. First line of therapy is elevation of the head of bed and administration of antacids (calcium carbonate, magnesium, or aluminum hydroxide).
ii. H2 blockers (ranitidine, cimetidine, famotidine) should be avoided in the first 100 days post-HSCT due to their myelosuppressive potential.

iii. Proton pump inhibitors may be of utility in patients with gastritis symptoms. However, their use should be reserved for patients failing first-line treatment and limited to 7–10 days, as prolonged use may inhibit the natural antimicrobial barrier and increase the risk for infection.

- Lansoprazole (Prevacid®) 30–60 mg po daily to BID
- Omeprazole (Prilosec®) 20–40 mg po daily to BID
- Pantoprazole (Protonix®) 40–80 mg po daily

iv. Gastric acid blockade therapy can impact the absorption of concurrent oral azole antifungal therapy.

3. Nausea

a. Etiology and pathogenesis
b. Diagnosis
c. Treatment

i. Patients with persistent nausea despite prn antiemetics should receive scheduled antiemetics.
ii. Schedule a dopamine antagonist + a short acting benzodiazepine, e.g., lorazepam (Ativan®) ± diphenhydramine (Benadryl®).
iii. Lorazepam should not be used alone as a scheduled antiemetic unless for anticipatory nausea.
iv. Examples of dopamine antagonists include:

- Prochlorperazine (Compazine®) 5–10 mg po/IV q 6 h
- Metoclopramide (Reglan®) 20 to 30 mg po/IV or qAC and HS
- Droperidol (Inapsine®) 0.625 mg IV q 6 h
- Haloperidol (Haldol®) 0.5–2 mg po/IV q 4–6 h
- Promethazine (Phenergan®) 12.5 mg po/IV q 4–6 h

v. Motion-induced nausea should be treated with either a scopalomine patch (Transderm Scop®) 1.5 mg changed every 3 days, or meclizine (Bonine®, Antivert®) 12.5–25 mg po q 8 h.
vi. These medications have been proven effective for acute nausea, however not in the setting of delayed nausea.
vii. Anticipatory nausea should be treated with lorazepam (Ativan®) or alprazolam (Xanax®) prior to the aggravating factor (e.g., medications, meals, etc.).

21.2 Lower Gastrointestinal

1. Diarrhea (see Table 21.1)

a. Etiology and pathogenesis
May present any time during conditioning or post-HSCT. The time of onset may assist in identifying potential etiologies, including:

i. Direct side effect from conditioning and other medications
ii. Mucositis and intestinal epithelial sloughing
iii. Infection
iv. GVHD
v. Pancreatic insufficiency
vi. Brush border disaccharidase deficiency
vii. Malabsorption
viii. Intestinal thrombotic microangiopathy
ix. Mycophenolate mofetil (CellCept®) is a very common inciting agent (through direct mucosal toxicity) and may be very difficult to distinguish from GVHD.

b. Diagnosis
Rule out infection with stool cultures for enteric pathogens. For patients in which diarrhea does not improve after resolution of oral mucositis, consider rectosigmoidoscopy to perform visual inspection and obtain tissue biopsies.

c. Treatment

i. Identify and treat the underlying cause.
ii. Supportive care should focus on hydration and prevention/treatment of electrolyte imbalances.
iii. Bowel rest/restricted diet (low roughage, low residue; low or no lactose (see Appendix 7).
iv. Calculate and replace enteral volume losses with isotonic fluid.
v. Monitor and replace protein losses (albumin, gamma globulin).
vi. Vitamin K depletion associated with chronic diarrhea is common. If the prothrombin time is elevated, vitamin K should be replaced. The dose is 2.5–25 mg IV or SQ (max 10 mg for children); if prothrombin time is not satisfactory within 6–8 h, the dose may be repeated.
vii. Loperamide (Imodium®) 2–4 mg po every 6 h or octreotide (Sandostatin®) may be effective to treat or relieve diarrhea associated with conditioning regimen and GVHD. The recommended octreotide regi-

Table 21.1 Diarrhea associated with chemotherapy (not GVHD)

Grade	Diarrhea
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4–6 stools per day over baseline; IV fluid indicated < 24 h; moderate increase in ostomy output compared to baseline; not interfering with ADL
3	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 h; severe increase in ostomy output compared to baseline; interfering with ADLs
4	Life-threatening consequences (i.e., hemodynamic collapse)
5	Death

GVHD graft-versus-host disease, *IV* intravenous, *ADL* activities of daily living

men varies. A fixed dose of 500 mcg IV every 8 h for 7 days or 50 mcg (2 mcg/kg) IV TID escalated to continuous infusion at 15 mcg/h (1 mcg/kg/hr) have been reported to have some success in control of diarrhea in the HSCT setting.

viii. Denatured tincture of opium (DTO) has also been used in settings of high-volume diarrhea but should be used with caution as opiate-induced ileus can be observed.

ix. Antidiarrheal agents should not be used in patients with infectious diarrhea; negative C. difficile toxin assay should be ascertained prior to the addition of antimotility agents

2. Gastrointestinal Bleeding

a. Etiology and pathogenesis
Most cases have diffuse areas of bleeding as opposed to a localized site. Causes of GI bleeding include:

i. Thrombocytopenia
ii. Esophageal trauma (from retching)
iii. Esophagitis
iv. Colitis
v. Anal fissures or hemorrhoids
vi. Viral infections
vii. GVHD

b. Diagnosis
Diagnosis is clinical. An esophagogastroduodenoscopy with rectosigmoidoscopy/colonoscopy may aid in identifying the cause of and controlling localized bleeding.

c. Treatment
If possible, treatment of the underlying disorder should be initiated. Symptom control may be achieved with:

i. Platelet support to maintain platelets $\geq 50{,}000/mm^3$.
ii. Packed red blood cells (PRBC) transfusion to maintain hematocrit > 28 %.
iii. Octreotide may provide short-term control.
iv. Control of localized bleeding with endoscopic cautery or embolization.
v. If large-volume acute blood loss occurs, consider desmopressin (DDAVP®) ± aminocaproic acid (Amicar®) or tranexamic acid (Lysteda®), providing the patient has no evidence of hematuria.
vi. The use of recombinant factor VII (NovoSeven®) 90 mcg IV q 2 h to control bleeding in the HSCT setting has not been studied and its routine use is not recommended.
vii. Consider radiologic assessment with angiography or a red cell nuclear scan to identify areas of active bleeding.

21.3 Hepatobiliary Diseases

1. Sinusoidal Obstruction Syndrome or Veno-Occlusive Disease (SOS/VOD) of the Liver

   a. Epidemiology
   Incidence is reported at approximately 5–10 %. Severe SOS/VOD frequently leads to multiorgan failure and is associated with day 100 mortality of > 90 %.

   b. Etiology and pathogenesis
   Usually presents during the first weeks following conditioning, prior to engraftment, and results from direct injury to sinusoidal endothelial cells and hepatocytes. Pre-transplant risk factors include:

      i. Older age (or younger age for children)
      ii. Poor performance status
      iii. Female gender
      iv. Advanced malignancy or patients with inherited disorders of metabolism
      v. Reduced pulmonary diffusion capacity (diffusing capacity of carbon monoxide (DLCO))
      vi. Prior hepatic disease (elevated bilirubin or aspartate transaminase (AST), preexisting cirrhosis)
      vii. Prior abdominal radiation
      viii. Use of gemtuzumab ozogamicin (Mylotarg®) within 3 months of conditioning

   c. Transplant risk factors include:

      i. Myeloablative conditioning
      ii. Second HSCT
      iii. Use of high-dose alkylating chemotherapy or total body irradiation (TBI)
      iv. Use of methotrexate for GVHD prophylaxis.

   d. Diagnosis

      i. Clinical picture includes

         - Total bilirubin > 2 mg/dL
         - Weight gain > 5 % from baseline
         - Right upper quadrant tenderness (tender hepatomegaly) ± ascites.

      ii. Abdominal ultrasound with liver Doppler usually shows hepatomegaly, ascites, and, in more advanced cases, reversal of portal flow.
      iii. Liver biopsy is not necessary for diagnosis. If needed to rule out other causes, a transjugular liver biopsy with measurement of hepatic venous pressure gradient should be obtained. More invasive procedures (percutaneous or open biopsy) carry higher risk due to high pressures and potential coagulopathy associated with hepatic synthetic dysfunction.
      iv. Differential diagnoses include sepsis-related cholestasis, other cholestatic liver disease, and GVHD.

e. Treatment

i. Prevention of SOS/VOD is the best "treatment" by recognizing patients who are at risk and, when possible, avoiding exposure to known risk factors (i.e., selection of transplant conditioning regimen).
ii. Ursodeoxycholic acid (Ursodiol®) 300 mg po TID from start of conditioning until approximately 1 week after engraftment has been shown in small randomized studies of prophylaxis to provide benefit in decreasing the severity of SOS/VOD.
iii. Prompt treatment is crucial as the severe form of this disease results in very high rates of mortality.
iv. Supportive care is the treatment of choice, including:

- Maintaining careful fluid (water and sodium) balance
- Providing aggressive diuresis
- Discontinuing/avoiding agents that may exacerbate hepatotoxicity when possible
- Preserving renal blood flow (renal dose dopamine 2–5 mcg/kg/min), if needed

v. Defibrotide is a potent antithrombotic and profibrinolytic agent. A historical-controlled phase III study demonstrated a survival advantage for patients with severe SOS/VOD who receive this drug early in their course. This agent is not commercially available in the USA as of this printing. However, it can be procured under compassionate, emergency use.

2. Acute Hepatitis (also see Chap. 17)

a. Etiology and pathogenesis
May present anytime during conditioning or post-HSCT. The time of onset may assist in identifying potential etiologies which includes:

i. Infection/sepsis
ii. Acute biliary obstruction
iii. Drug-induced toxicity
iv. GVHD

b. Diagnosis

i. Sudden elevation of serum transaminases (AST, alanine transaminase (ALT)).
ii. Blood tests for viral DNA (herpes viruses, adenovirus, hepatitis B, hepatitis C).
iii. Imaging (computed tomography (CT) or ultrasound) may be used to identify fungal abscesses in the setting of disseminated infection.
iv. Liver biopsy may aid in identifying a cause.

c. Treatment
Supportive care, removal of inciting agents when possible (if drug-related), treatment of infection.

i. A prolonged course of antibiotics or antifungals may be required for bacterial or fungal infections.
ii. Acute viral hepatitis may lead to fulminant hepatic failure if not treated promptly. Possible viruses include herpes simplex, varicella, cytomegalovirus, and human herpes viruses (HHV-6 and HHV-8). If the patient is not receiving acyclovir prophylaxis, initiation of empiric treatment is recommended.
iii. Hepatitis B can also present with fulminant hepatic failure. Patients with a previous history of hepatitis B or exposure to a donor with a previous history of hepatitis B are at higher risk. Antiviral therapy should be initiated promptly (lamivudine [Epivir], tenofovir [Viread], or similar). The initiation and further dosing for these agents should be determined with the assistance of the gastroenterologist/hepatologist).

3. Gallbladder Disease and Pancreatitis

a. Etiology and pathogenesis
Biliary sludging is very common in transplant patients and is usually asymptomatic, but may also cause acute acalculous cholecystitis, pancreatitis, or cholangitis. Sludging may result from:

i. Chemotherapy.
ii. Parenteral alimentation with prolonged absence of oral intake.
iii. Antibiotics.
iv. Hyperlipidemia.
v. GVHD.
vi. Infection/sepsis. Consider adenoviral infection, especially in children.

b. Diagnosis
Abdominal ultrasound may reveal gallbladder disease (thickening of gallbladder wall, stones, etc.). Hepatobiliary iminodiacetic acid (HIDA) scan may reveal gallbladder obstruction.

c. Treatment

i. Bowel rest.
ii. Removal of parenteral alimentation, if inciting agent.
iii. Cholecystectomy is infrequently needed.
iv. Endoscopic retrograde cholangiopancreatography (ERCP) is only needed in the case of obstructive cholangitis.

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Chapter 22
Pulmonary Complications

Bart Moulton and Alan F. Barker

22.1 Pulmonary Function Tests

1. Spirometry is used to aid in the diagnosis of obstructive versus restrictive lung disease. Two-year mortality after hematopoietic stem cell transplant (HSCT) has been estimated using a pre-transplantation assessment of mortality (PAM) score which incorporates spirometry and diffusing capacity variables in combination with the presence of renal and hepatic dysfunction, conditioning regimen, and disease risk.
    a. Obstructive lung disease is diagnosed with a forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio < 70 % and FEV1 < 80 %. If plethysmography (measurement of changes in lung volumes) is performed, increased residual volume (RV) indicates air trapping as seen in bronchiolitis obliterans syndrome (BOS).
    b. Low FVC with normal FEV1/FVC ratio indicates restriction. Lung volumes will help confirm restriction as seen in idiopathic pneumonia syndrome (IPS) or usual interstitial pneumonia. All lung volumes, including RV, will be reduced with restriction.
2. DLCO
    a. Diffusion capacity of carbon monoxide (DLCO) corrected for hemoglobin should be used (DLCOadj)
    b. > 80 % normal, 60–80 % mild, 40–60 % moderate, < 40 % severe impairment

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22.2 Bronchoscopy

1. Bronchoalveolar lavage (BAL) via bronchoscopy should be pursued once pneumonia is considered.
2. Pre-procedure stabilization with supplemental oxygen is key.
   a. Depressed mental status may increase the risk of the procedure.
   b. The presence of severe hypoxia and depressed mental status may require endotracheal intubation to safely perform the procedure.
   c. Conscious sedation with fentanyl and/or midazolam is often used for comfort and amnesia.
3. Unless there is active bleeding, correction of coagulopathy is not required, and there is no absolute platelet level required for safety with BAL alone.
   a. If transbronchial biopsy will be attempted, a pre-procedure platelet count of $\geq 30{,}000/mm^3$ and international normalized ratio (INR) of < 1.5 is recommended.
4. Complications of bronchoscopy include worsening hypoxemia, airway hemorrhage, and respiratory failure.
5. The risks with transbronchial biopsy are much higher, including pneumothorax, respiratory failure, and difficult to control airway bleeding.
6. Electromagnetic navigational bronchoscopy with BAL and biopsy may improve rates of diagnosis.
7. Appropriately stained BAL smears may suggest a pathogen in a matter of hours while cytology, culture, and genetic results are pending. BAL fluid should routinely be sent for:
   a. Cytology, including stains for organisms (fungi, *Pneumocystis jiroveci* pneumonia (PCP)) and hemosiderin-laden macrophages
   b. Bacterial cultures (including *Nocardia*) and sensitivity
   c. Fungal smear and culture
   d. Mycobacterium smear and culture
   e. Cell count and differential
   f. Galactomannan antigen (Aspergillus)
   g. Polymerase chain reaction (PCR) for respiratory viral panels
   h. PCR for legionella
   i. Direct fluorescent antibody (DFA) staining for PCP

22.3 Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a subset of pulmonary hemorrhage that can develop in up to 5% of all post-HSCT recipients with mortality rates ranging between 50 and 80% based on the two largest case series. About 87% of the cases develop in the first 3 weeks post-HSCT.

1. Risk factors
    a. Advanced age
    b. Grade 3–4 acute graft-versus-host disease (aGVHD)
    c. Allogeneic transplant
    d. Pre-HSCT myeloablative conditioning regimen
    e. Thrombocytopenia
    f. Renal insufficiency
    g. Coagulopathy
2. Clinical findings
    a. Subjective Findings
        i. Shortness of breath
        ii. Cough
        iii. Rarely hemoptysis
    b. Objective Findings
        i. Fever
        ii. Tachypnea
        iii. Acrocyanosis
        iv. Crackles heard on lung auscultation
3. Diagnostic tests
    a. Chest X-ray often shows bilateral diffuse alveolar opacities which could be confirmed by CT scan imaging (Fig. 22.1) as ground glass opacities. These findings are not specific and may be seen in many other conditions.
    b. Pulmonary function tests (PFTs) show increased DLCO; however, often these patients cannot participate in such testing.
    c. Bronchoscopy with BAL is the confirmatory diagnostic method. BAL shows progressive bloody return. Cytology with Prussian blue staining should show >20% hemosiderin-laden macrophages. This test is limited if alveolar hemorrhage occurred <48–72 h before the procedure, as duration of time may be too short for red blood cells (RBC) phagocytosis by pulmonary macrophages.
4. Pathogenesis of DAH
   There is no clear etiology for DAH post-HSCT. The development of DAH around the engraftment period suggests an inflammatory cascade involving the alveoli. Pre-HSCT conditioning regimens (including total body irradiation (TBI)) may initiate the inflammatory process.
5. Management
   Patients with suspected DAH should be transferred to the medical intensive care unit, given that respiratory failure may develop rapidly. Some patients require high-flow oxygen and subsequent mechanical ventilation for acute respiratory distress syndrome (ARDS). Supportive management and high-dose systemic steroids are the key elements of DAH treatment.

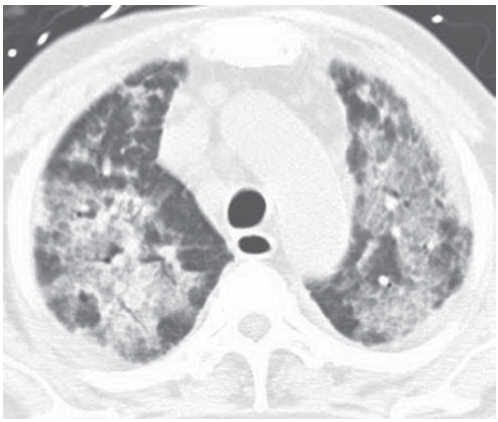

Fig. 22.1 Diffuse ground glass opacities in diffuse alveolar hemorrhage, confirmed by BAL. *BAL* bronchoalveolar lavage

a. Mechanical ventilation should be tailored to each individual, reflecting the ARDS mechanical ventilation protocol/low tidal volume for management of acute lung injury. This practice has not been validated in DAH, but the pathological pattern of DAH is similar to acute lung injury/ARDS. Similarly, prone positioning may be of benefit in refractory cases.
b. Immunosuppressive therapy with high-dose corticosteroids is the mainstay of therapy based on case reports and retrospective series. Doses of up to 1 g of methylprednisolone daily divided into 2–4 doses should be given daily for 3–5 days, followed by a slow taper over 1–3 months. Alternate dosing schedules have been suggested, beginning at 2 mg/kg daily in divided doses, tapering over a 2-month period.
c. Correction of underlying coagulopathy by maintaining platelet count > 50,000/mm^3 and INR < 2.
d. BAL to rule out a concomitant infectious pathogen.
e. Recombinant factor VIIa (NovoSeven®) has been used; however, no benefit has been demonstrated.
f. Aminocaproic acid (Amicar®) has been used less frequently with limited supporting data.

22.4 Idiopathic Pneumonia Syndrome

IPS is severe lung injury that develops after allogeneic HSCT with no evidence of an infectious process. The incidence ranges between 2 and 35 % with mortality rates ranging from 60 to 80 %. More recent studies report a lower incidence likely reflecting improved diagnosis of viral infections with newer PCR tests. If mechanical ventilation becomes necessary, mortality approaches 95 %. IPS typically occurs within the first 2 months post-HSCT. However, delayed onset has been reported.

Delayed pulmonary toxicity syndrome (DPTS) is considered distinct from IPS per the American Thoracic Society official statement due to its relationship with a specific conditioning regimen. DPTS occurs in up to 64% in patients who receive a conditioning regimen containing bis-chloroethylnitrosourea (BCNU), cyclophosphamide, and cisplatin.

1. Risk factors

   a. Grade 3–4 aGVHD
   b. Donor cytomegalovirus (CMV) positivity
   c. Conditioning regimens containing TBI
   d. Older age
   e. Certain malignancies (acute leukemia, myelodysplastic syndrome)
   f. Drug toxicity has been implicated; however, there is no method to discriminate between drug-induced lung damage and IPS.

2. Clinical findings

   Findings are indistinguishable from pneumonia which include fever, cough usually productive of scant or no phlegm, shortness of breath, and hypoxia.

3. Diagnostic tests

   All patients with suspected IPS should undergo chest imaging and bronchoscopy with BAL to rule out infection. Occasionally, chest X-ray does not show obvious infiltrates and CT scan of the chest is warranted. The criteria for diagnosis of IPS proposed by the National Heart Lung and Blood Institute in 1993 include:

   a. Radiologic imaging evidence of multilobar diffuse alveolar infiltrates.
   b. Hypoxia or elevated alveolar–arterial gradient.
   c. Negative BAL for blood and cultures for bacterial, fungal, and viral pathogens.
   d. Negative infectious studies from the blood, specifically for CMV.

4. Pathogenesis of IPS

   Evaluation of BAL fluid from IPS patients shows elevated inflammatory cytokine markers compared to negative or healthy controls. IPS is likely a complex cytotoxic and immune-mediated attack of the lung.

5. Management

   a. Corticosteroids should be started early in the disease course. Historically, patients who developed IPS around engraftment responded better to steroids. A reasonable starting dose is 2 mg/kg daily of methylprednisolone (or equivalent) for the first week followed by a slow taper over the course of 2–3 months.
   b. PCP and fungal prophylaxis are recommended.
   c. Etanercept (Enbrel®) 25 mg SQ twice weekly for 8 weeks has been used in conjunction with corticosteroids; however in small case series, no additional benefit was seen when compared with placebo.

22.5 Bronchiolitis Obliterans Syndrome

The most common late pulmonary complication following allogeneic HSCT is BOS. The reported incidence varies from 2 to 6% with estimate as high as 20%. However, recent studies suggest the incidence is more prevalent than previously reported. The median time to onset is 1 year post-HSCT. However, the onset varies from 3 months to >10 years post-HSCT. BOS is rarely reported after autologous HSCT or umbilical cord blood HSCT. Most investigators consider BOS to be GVHD of the lung. It is also important to recognize BOS as a separate clinical entity from cryptogenic organizing pneumonia (COP).

1. Risk factors reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) include:

    a. Blood-derived stem cells
    b. Busulfan-based conditioning regimen
    c. Degree of human leukocyte antigen (HLA) mismatch
    d. Presence of gastroesophageal reflux
    e. Prior interstitial pneumonitis
    f. An episode of grade 3–4 aGVHD

Additional risk factors include:

a. Personal tobacco use
b. Older age
c. Preexisting airflow obstruction
d. Previous respiratory viral infection (CMV, respiratory syncytial virus (RSV), or parainfluenzae)
e. Immunoglobulin G (IgG) level <400 results in a two- to threefold risk of developing BOS

2. Definition
   The National Institutes of Health (NIH) diagnosis and staging working group prepared a consensus definition for BOS to provide uniform inclusion criteria for future studies. To make the diagnosis of BOS, these four criteria must be present along with active chronic GVHD in at least one organ other than the lung:

    a. FEV1 <75% of predicted normal
    b. Evidence of airway obstruction with a ratio of FEV1/FVC <0.7
    c. Expiratory high-resolution chest CT that reveals air trapping, small airway thickening, or bronchiectasis or RV >120% of predicted normal
    d. Absence of active infection or pathologic confirmation

        i. Lung biopsy typically shows cicatricial bronchial obliterans (i.e., obliteration of airways by dense fibrous scar tissues)

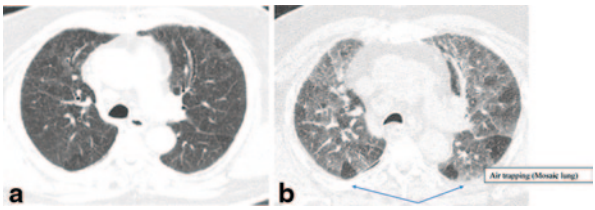

Fig. 22.2 **a** Inspiratory CT scan of the chest. **b** Expiratory phase CT scan chest in a patient with BOS. *CT* computed tomography, *BOS* bronchiolitis obliterans syndrome

3. Clinical findings

   Insidious course manifested by nonproductive cough, wheezing, and dyspnea. Early in BOS, pulmonary exam may be normal; however, later stages are manifested by wheezing, prolonged expiratory phase, and inspiratory crackles.

4. Diagnostic tests

   a. Chest imaging should be carried out in all patients undergoing workup for BOS. Chest X-rays may be normal early in BOS. As the disease progresses, hyperinflation may be present.
   b. High-resolution CT (HRCT) of the chest is more specific (see Fig. 22.2). Inspiratory and expiratory phases should be included to evaluate for air trapping or "mosaic lung appearance" which indicates regional airflow obstruction during the expiratory phase.
   c. PFTs are obtained as part of every patient's pre-HSCT baseline evaluation.

      i. The definition of airflow obstruction includes FEV1 $<75\%$, FEV1/FVC <0.70, or a decline in FEV1 $>10\%$ in 1 year.
      ii. Also noted is air trapping or increased RV and RV to total lung capacity (RV:TLC) ratio.
      iii. DLCO is not expected to be reduced but is often low pre-transplant and/or after induction chemotherapy.

   d. Bronchoscopy is not routinely performed during the workup of BOS unless imaging is suspicious for an infectious process.
   e. Transbronchial biopsy is often nondiagnostic as the disease process is patchy.
   f. Surgical lung biopsy has higher chance of demonstrating constrictive bronchiolitis, the pathology seen in BOS.

i. With the introduction of HRCT, surgical lung biopsy is often not required to confirm a diagnosis of BOS.

5. Pathogenesis of BOS

   BOS may be a manifestation of primarily chronic GVHD with the etiology related to recognition of disparate antigens present in the context of HLA class I and class II major histocompatibility complex (MHC) molecules. It begins with

fibroproliferative disease of the small airways, which results in inflammation, epithelial metaplasia, and denudification. Submucosal/mucosal fibrosis then develops, resulting in obliteration of the airways. Allogenic inflammatory conditions such as viral infections may also contribute to the development of BOS.

6. Management

   Management of BOS mainly involves intensifying immunosuppressive therapy and supportive care. There are no specific recommendations associated with treatment of BOS. The management of BOS mimics that of chronic GVHD.

   a. Response to bronchodilators is often minimal but nevertheless should be considered because of presence of airflow obstruction.
   b. Corticosteroids 1–1.5 mg/kg prednisone per day for 2–6 weeks, then tapered over 6–12 months if there is a response. This regimen is based on case series and expert opinions.
   c. Other immunosuppressive medications maybe effective as steroid-sparing agents, including calcineurin inhibitors. Tacrolimus may reduce the incidence of BOS as compared to cyclosporine.
   d. Macrolides have been used post-transplant to prevent BOS. Small case series have reported stabilization of FEV1. Azithromycin 250 mgpo three times each week is a suggested regimen.
   e. Leukotrienes have been reported to be elevated in BAL fluid of patients with BOS. Trials of montelukast (Singulair®), a leukotriene inhibitor, are underway.
   f. A small phase II trial etanercept (Enbrel®) in patients with subacute lung injury showed improvement in lung function with a 5-year overall survival of 67%, and 90% in patients who responded to therapy.
   g. Patients should be assessed for oxygen needs using 6-min walk test and/or nocturnal O_2 monitor study.
   h. Echocardiogram can screen for pulmonary hypertension and left ventricular dysfunction, both accompanied by dyspnea.
   i. Lung transplant may be considered for very selected patients with severe respiratory impairment.

The management of BOS is complicated and requires a multispecialty approach (bone marrow, pulmonary, and radiology specialists). Prognosis of progressive BOS (>10% FEV1 decline per year) is poor. Two-year overall survival has been reported at 45% with a 5-year survival rate of only 13%. The majority of patients die of respiratory failure triggered by infection. Attention to dyspnea and early and frequent PFTs may allow for earlier identification of BOS before permanent (fibrotic) airway changes, respiratory insufficiency, and pneumonia occur.

22.6 Cryptogenic Organizing Pneumonia

COP, previously known as bronchiolitis obliterans organizing pneumonia (BOOP), is a disease process of unknown etiology that differs from BOS in clinical findings, response to treatment, and prognosis. One case series of open-lung biopsies done in patients who underwent HSCT found that COP was the most common inflammatory pathology (52 %).

1. Risk factors

   a. No risk factors have been identified. However, a correlation has been demonstrated between the development of COP and viruses, radiation exposure, connective tissue disease, inhalational drugs (cocaine), amiodarone, and inflammatory bowel disease.

2. Clinical findings

   The presentation of COP is similar to many respiratory disorders; most commonly, dyspnea is accompanied by nonproductive cough and fever. Physical exam is primarily notable for the presence of crackles and the absence of wheezing.

3. Diagnostic tests

   a. Chest X-ray may show patchy consolidation with ground glass or nodular infiltrates.
   b. CT scan of the chest is typically required to demonstrate areas of bilateral organizing pneumonia and consolidation in subpleural or peribronchial distribution associated with areas of ground glass opacities. Migratory opacities on CT scan chest have been described in 25 % of patients with COP.
   c. PFTs typically show a restrictive pattern with decreased FVC, FEV1/FVC >70%, and decreased DLCO; airflow obstruction (decreased FEV1/FVC) is generally absent.
   d. Bronchoscopy with BAL may be helpful in determining the diagnosis. BAL fluid demonstrates lymphocytes with a decreased CD4/CD8 ratio.
   e. Lung biopsy, either by transbronchial biopsy or by video-assisted thoracic surgery (VATS), is occasionally required to confirm the diagnosis. Typical pathology shows granulation tissue plugs in the bronchioles and alveolar ducts associated with surrounding chronic interstitial inflammation.

4. Management

   a. Prognosis of COP is favorable; 80 % of patients can be expected to recover.
   b. Bronchoscopy with BAL is often required to rule out infectious processes.
   c. Corticosteroids have been used with great efficacy. However, relapses may occur if steroids are tapered too rapidly.

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Chapter 23
Cardiovascular Complications

Stephen B. Heitner and Stanley Chou

The antecedent assessment and attention to the cardiovascular system of patients undergoing hematopoietic stem cell transplant (HSCT), as well as an awareness of the treatment's potential long-term cardiac effects, are critical in the overall care of these complex and often very ill patients. The issues facing patients and their treating providers are primarily centered in three arenas: (1) cardiovascular comorbidities and the overall cardiovascular reserve, (2) chemotherapy and radiation associated cardiovascular toxicities, and (3) long-term effects of HSCT.

Patients with hematologic malignancies may have preexisting cardiovascular comorbidities that interfere with the successful delivery of high-dose chemotherapy and most effective cell-based treatments. Awareness of these comorbidities allows the treatment team to address these issues actively and improve the outcomes for patients from an oncology perspective. Early identification and treatment of cardiotoxicities, as well as the potential prediction of at-risk patients, will allow the treating hematologists to ensure that the most appropriate therapies are delivered at the most efficacious doses.

Lastly, the monitoring of patients for long-term effects of HSCT may prevent the success of cancer therapy from being overshadowed by cardiovascular morbidity and mortality.

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23.1 Baseline Cardiac Evaluation

1. History and physical examination
    a. Risk factors for post-transplant cardiac complications
        i. Advanced age (> 70 years old)
        ii. Prior anthracycline use
        iii. Cyclophosphamide-based conditioning regimens

Adequate blood pressure control in hypertensive patients is important as post-transplant immunosuppressive medications (cyclosporine, tacrolimus) can worsen hypertension (HTN).

2. Twelve-lead electrocardiogram (EKG)
    a. QT-interval prolongation is an independent risk factor for developing acute heart failure post-transplantation.
        i. Normal QTc is 390–450 ms for men and 390–460 ms for women.
    b. QT-interval dispersion (difference between the maximum and minimum QT intervals) has also been suggested as a risk factor for developing acute heart failure post-transplantation.
        i. Normal QT-interval dispersion is 40–50 ms.
    c. Conduction or rhythm abnormalities should be documented (hematopoietic cell transplant-comorbidity index (HCT-CI) risk assessment, see Chap. 4). Patients are at risk of supraventricular tachyarrhythmias (and less commonly ventricular arrhythmias) during the immediate post-transplant period.
3. Chest X-ray
    a. Presence of cardiomegaly (increased cardiothoracic ratio) suggests cardiomyopathy.
    b. Pulmonary edema and pleural effusions suggest congestive heart failure (CHF).
4. Assessment of left ventricular ejection fraction (LVEF)
    a. LVEF ≥45–50 % is arbitrarily chosen as an eligibility criterion for HSCT by most centers.
    b. Transthoracic echocardiography (TTE) and multigated radionuclide angiography (MUGA) are commonly available and validated diagnostic modalities.
        i. MUGA when compared to TTE
            ii. Higher specificity
            iii. Less interobserver variability
            iv. More expensive
            v. Radiation risk

ii. TTE
    i. Provides additional information such as valvular function, diastolic function, and global strain when compared to MUGA.
    ii. With the added benefit of objective measurement of global longitudinal strain (early indicator of myocardial dysfunction with the potential to predict future systolic dysfunction), TTE becomes a more attractive method to assess left ventricle (LV) function in experienced centers.

5. Noninvasive stress testing

   a. No conclusive data to suggest that stress testing improves the ability to predict risk of post-transplant cardiac complications. However, some centers routinely perform noninvasive stress testing as part of the pre-transplant evaluation.
   b. If pre-transplant evaluation reveals an indication to perform noninvasive stress testing independent of the HSCT, stress testing should be performed.
      i. Current indications for stress testing include, but are not limited to, patients with a history or physical examination findings that are suggestive of ischemic heart disease
      ii. Newly diagnosed cardiomyopathy
      iii. Valvular heart disease
      iv. Certain arrhythmias
      v. Significant risks for coronary artery disease in patients who are undergoing non-cardiac surgery.
   c. Further cardiac evaluation and management should be pursued if indicated based on the results of the stress test.

23.2 Systolic Heart Failure

1. Etiologic considerations in HSCT patients

   a. Cyclophosphamide cardiotoxicity
      i. Heart failure associated with cyclophosphamide therapy occurs in 7–28 % of patients.
      ii. Dose-related risk (> 150 mg/kg and 1.5 g/m2/day).
      iii. Occurs within 1–10 days after administration of the first dose.
   b. Other risk factors include prior anthracycline therapy and mediastinal irradiation.
   c. Hypoalbuminemia, fluid shifts, tachyarrhythmias, ischemia, and renal failure may exacerbate acute decompensated heart failure in patients with preexisting cardiomyopathies.

2. Symptoms
    a. Low output
        i. Fatigue
        ii. Weakness
        iii. Altered mental status
    b. Congestion
        i. Dyspnea
        ii. Orthopnea
        iii. Paroxysmal nocturnal dyspnea
        iv. Peripheral edema
3. Physical exam
    a. Elevated jugular venous pressure (JVP)
    b. Positive hepatojugular reflux with right upper quadrant (RUQ) abdominal pressure (4 cm increase in JVP; suggests pulmonary artery wedge pressure >15 mmHg)
    c. Presence of S3 on cardiac auscultation
    d. Rales and/or crackles
    e. Decreased breath sounds at bases due to pleural effusion
    f. Peripheral edema and ascites
4. Diagnostic studies
    a. Lab studies
        i. Increased SCr and BUN
        ii. Decreased Na
        iii. Abnormal LFTs
        iv. Elevated BNP or NT-proBNP
    b. Chest x-ray
        i. Pulmonary edema
        ii. Pleural effusions
        iii. Cardiomegaly as evidenced by increased cardiothoracic ratio
    c. Echocardiogram
        i. Decreased LVEF
        ii. Increased LV chamber size
        iii. Valvular abnormalities
        iv. Pericardial abnormalities
    d. Pulmonary artery catheterization
        i. Increased pulmonary capillary wedge pressure
        ii. Decreased cardiac output or cardiac index
        iii. Increased systemic vascular resistance

5. Management
   a. Treatment of acute pulmonary edema (LMNOP)
      i. Lasix® (furosemide) or other diuretics such as bumetanide (Bumex) or torsemide
      ii. Morphine
      iii. Nitrates
      iv. Oxygen
      v. Position (sit patient up)
   b. Treatment of advanced heart failure
      i. Consider pulmonary artery catheter-guided therapy
      ii. Intravenous vasodilators
      iii. Inotropes
      iv. Ultrafiltration
      v. Mechanical circulatory support in consultation with cardiology
   c. Treatment of chronic heart failure
      i. Treatment of CHF in HSCT patients is generally consistent with treatment of CHF in the general population as outlined in the American College of Cardiology/American Heart Association Guidelines.
         • Use of an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin receptor blocker (ARB), beta-blocker (carvedilol or metoprolol succinate), and aldosterone antagonists
      ii. Prophylactic use combination therapy with enalapril and carvedilol has been shown to reduce the risk of chemotherapy-induced cardiomyopathy.

23.3 Atrial Fibrillation

1. Common complication in HSCT patients.
2. Risk factors, independent of transplantation
   a. Advanced age (> 70 years)
   b. HTN
   c. Obesity
   d. Underlying cardiac disease
3. Possible precipitants
   a. Direct effects from the chemotherapy agents
      i. Melphalan
      ii. Etoposide
      iii. High-dose corticosteroids

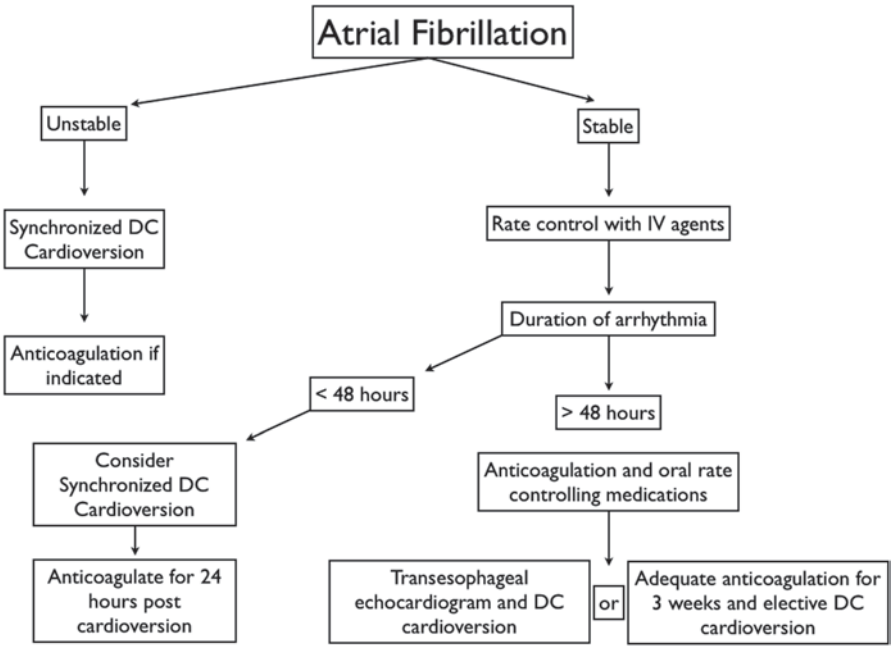

Fig. 23.1 Standard approaches to acute atrial fibrillation

b. Cardiac
   i. CHF
   ii. Pericarditis
   iii. Ischemia
c. Pulmonary
   i. Hypoxia
   ii. Pulmonary embolism
d. Metabolic
   i. High catecholamine state
   ii. Infections
   iii. Electrolyte disturbances

4. DMSO.
5. Symptoms may include palpitations or light-headedness. Many patients are also asymptomatic.
6. Diagnosis is made by capturing the rhythm on telemetry or EKG.
7. Management
   a. Standard approach to acute atrial fibrillation (see Fig. 23.1)
   b. Rate controlling agents (all can cause hypotension and bradycardia and should be administered in a monitored setting)

i. Metoprolol 5 mg intravenous (IV), every 5 min × 3, 25–200 mg/day po in divided doses
ii. Diltiazem 0.25 mg/kg IV, may repeat after 15 min, 120–360 mg/day po in divided doses (caution with decreased LVEF)
iii. Digoxin 1 g IV or po load in three divided doses every 4–8 h given as 50 % initially and then 25 % × 2, then 0.125–0.375 mg po daily (need to adjust for creatinine clearance)
iv. Amiodarone 150 mg IV over 10 min, and then 0.5–1 mg/min IV

23.4 Cardiac Ischemia

1. Etiologic considerations in HSCT recipients
   a. Etoposide has been associated with vasospastic angina and myocardial infarction (MI).
   b. Patients with underlying CAD are at risk for cardiac ischemia and MI due to physiologic stresses associated with transplantation.
2. Management of cardiac ischemia and acute coronary syndrome is often complicated by limitations in the use of antithrombotic and anticoagulant therapies due to thrombocytopenia from HSCT conditioning therapy or from the underlying hematologic disease.
3. If percutaneous coronary intervention is indicated, strongly consider the use of bare-metal stents or balloon angioplasty alone over drug-eluting stents depending on the clinical scenario due to shorter duration of required dual antiplatelet therapy (see Chap. 13).
4. Oncology and cardiology should work closely together in managing HSCT patients with active cardiac ischemia.

23.5 Hypertension

1. Chronic immunosuppression with calcineurin inhibitors (CNIs (cyclosporine, tacrolimus)) is the mainstay of therapy for prevention of graft-versus-host disease (GVHD).
2. CNI-associated HTN occurs in 15–50 % of patients and typically develops within a month of starting therapy.
3. The treatment of choice is calcium channel blockade which reduces peripheral vascular resistance (including the renal arteriolar constriction associated with CNIs) and lowers blood pressure by causing direct vasodilation in the peripheral arteries of the vascular smooth muscle.
   a. Nifedipine XL (Adalat CL) 30–60 mg po daily
   b. Amlodipine (Nirvase) 2.5–10 mg po daily

4. Posterior reversible encephalopathy syndrome (PRES) is a neurologic complication seen occasionally in patients with CNI-associated HTN.
    a. The clinical syndrome includes headache, mental status changes, and seizures with specific radiologic features.
    b. Management includes withdrawal of the drug and aggressive blood pressure control.

23.6 Pericarditis

1. Pericarditis and accompanying pericardial effusion with or without cardiac tamponade are associated with cyclophosphamide and cytarabine therapy.
2. Chronic GVHD can involve the pericardium with resultant pericardial effusion, cardiac tamponade, constrictive pericarditis, or effusive–constrictive pericarditis.
3. Cardiac tamponade
    a. Increased intrapericardial pressure results in cardiac chamber compression and decreased venous return, resulting in decreased cardiac output.
    b. Clinically presents as cardiogenic shock without pulmonary edema.
    c. Beck's triad
        i. Distant heart sounds
        ii. Increased JVP
        iii. Hypotension
    d. Pulsus paradoxus is present with a decrease in systolic pressure ≥10 mmHg with inspiration.
        i. Exaggeration of normal physiology with inspiration causing a decrease in intrapericardial and right atrial pressures, increasing right-sided venous return and right ventricular size.
        ii. Due to increased ventricular interdependence, increased right-sided filling is at the expense of decreased left ventricular filling, resulting in decreased left ventricular stroke volume and blood pressure.
    e. Diagnosis is made by clinical manifestations and presence of pulsus paradoxus.
    f. Echocardiographic findings include
        i. Pericardial effusion.
        ii. Dilated inferior vena cava (IVC).
        iii. Diastolic collapse of the right-sided cardiac chambers.
        iv. Respirophasic changes in transvalvular velocities are supportive.
    g. Treatment
        i. Intravascular volume

   ii. Inotropes
   iii. Pericardiocentesis

4. Constrictive pericarditis

   a. Stiff pericardium limits diastolic filling.
   b. Clinically presents as right-sided > left-sided heart failure.
   c. Physical exam

      i. Increased JVP with a prominent y descent
      ii. Pericardial knock
      iii. Kussmaul's sign (increased JVP with inspiration)

   d. Diagnosis

      i. Suggested by clinical manifestations and echocardiographic findings of a "septal bounce."
      ii. Thickened pericardium can also be seen on echocardiogram, computed tomography (CT), or magnetic resonance imaging (MRI).
      iii. Definitive diagnosis is established by cardiac catheterization.

   e. Primary treatment is with diuretics to manage volume status.
   f. Surgical pericardiectomy is reserved for cases that have failed conservative management, although outcomes are generally poor.
   g. Effusive–constrictive pericarditis is an uncommon pericardial syndrome with features of both pericardial effusion with cardiac tamponade and constrictive pericarditis.

23.7 Effects of Radiation Therapy

1. Radiation therapy can lead to the accelerated development of CAD.

   a. Both endovascular proliferation and accelerated atherosclerosis appear to be involved in the disease process.
   b. Ostial lesions are common, with the left anterior descending artery most frequently involved due to its location.
   c. Management of radiation-associated CAD is similar to conventional treatment for ischemic heart disease, although coronary artery bypass surgery may be more difficult because of prior irradiation to the surgical field.

2. Radiation therapy can cause fibrotic changes to the heart valves and valvular heart disease.

   a. Regurgitant lesions are more common than stenotic lesions.
   b. Left-sided valves are more commonly affected.

3. Mediastinal irradiation can cause acute pericarditis, subacute and chronic pericardial effusions, constrictive pericarditis, and, rarely, cardiac tamponade.

   a. The right side of the heart is more frequently involved.

4. Radiation therapy can cause myocardial fibrosis and small-vessel ischemic disease, leading to a spectrum of sequelae ranging from diastolic dysfunction to restrictive cardiomyopathy.
5. In restrictive cardiomyopathy, decreased myocardial compliance leads to increased end-diastolic pressures despite normal end-diastolic volumes. This causes increased systemic and pulmonary venous pressures.

    a. Clinically, restrictive cardiomyopathy presents as right-sided > left-sided heart failure with more peripheral edema and less dyspnea. Patients can be "refractory" to diuresis.
    b. Physical exam findings can include increased JVP, Kussmaul's sign, S3 and S4, hepatomegaly, ascites, and peripheral edema.
    c. Echocardiographic findings of biatrial enlargement and abnormal diastolic parameters are suggestive.
    d. Definitive diagnosis is established by hemodynamics on cardiac catheterization.
    e. Management is with gentle diuresis, heart rate control, and maintenance of sinus rhythm.
    f. Tachyarrhythmias lead to significant decreases in ventricular filling and are poorly tolerated.

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Chapter 24
Kidney Disease in Hematopoietic Stem Cell Transplantation

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Kidney damage is a common complication of hematopoietic stem cell transplantation (HSCT); its severity may range from a transient and reversible rise in creatinine to a complete loss of kidney function with need for hemodialytic support. Acute kidney injury (AKI) requiring dialysis in critically ill HSCT recipients is associated with greater than 80 % mortality. Additionally, AKI of any degree of severity confers risk for the development of chronic kidney disease (CKD). Even in the absence of AKI in the immediate post-HSCT period, HSCT recipients are at high risk for CKD over the long term, and this complication is associated with decreased life expectancy. Thus, nephroprotective measures during the HSCT process are of utmost importance and should not be overlooked. Early diagnosis and treatment of AKI, and early nephrology consultation, should likewise be considered. Long-term follow-up of HSCT patients should include routine surveillance for the development of CKD.

24.1 Definitions of AKI and CKD

1. AKI: This entity was previously called acute renal failure (ARF). The definition is based on an acute rise in serum creatinine or a fall in urine output or both. There are several expert guidelines describing staging of AKI severity; the most recent is summarized in Table 24.1. In HSCT patients who are cachectic with low muscle mass, the baseline creatinine may be below the reference range for normal; in these patients, a rise in the serum creatinine to a normal level may indicate AKI.

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Table 24.1 Stages of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline or >/=0.3 mg/dL increase	<0.5 mL/kg/h × 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for >12 h
3	3.0 baseline or increase to >/+4.0 mg/dL or need for dialytic support	<0.3 mL/kg/h for >/=24 h or anuria for >/=12 h

AKI acute kidney injury

Table 24.2 Stages of CKD

Stage	GFR
1	>90 mL/min/1.73 m^2 and proteinuria or structural abnormality
2	60–89 mL/min/1.73 m^2
3	30–59 mL/min/1.73 m^2
3a	45–59 mL/min/1.73 m^2
3b	30–44 mL/min/1.73 m^2
4	15–29 mL/min/1.73 m^2
5	<15 mL/min/1.73 m^2

CKD chronic kidney disease, *GFR* glomerular filtration rate

2. CKD: Previously known as chronic renal insufficiency or failure (CRI or CRF), CKD is a structural or functional renal abnormality that persists for at least 3 months. Reduced glomerular filtration rate (GFR) and persistent albuminuria (proteinuria) are the most common manifestations of chronic kidney injury. Five stages of CKD are defined based on GFR (Table 24.2).

24.2 Kidney Disease in HSCT: Incidence and Risk

1. AKI:
   a. The incidence of AKI in the days to weeks following HSCT is likely >50%, though estimates in the literature range from 15 to 60%.
   b. Risk factors include:
      i. Pre-transplant CKD and/or hypertension
      ii. Post-HSCT complications
         - Sepsis

- Amphotericin product exposure
- Hepatic sinusoidal obstructive syndrome (SOS)
- Acute graft-versus-host disease (GVHD)

iii. The type of HSCT performed influences the risk for SOS and GVHD, and the need for calcineurin inhibitor (CNI) therapy, and therefore the risk of severe AKI.

- Myeloablative regimens, with their more intensive conditioning and higher risk for SOS compared with nonmyeloablative regiments, are associated with the highest risk of AKI (estimates range from 36 to 78%; 20–33% may require dialysis).
- Autologous HSCT patients enjoy the lowest risk for severe AKI, given lack of need for CNIs and decreased incidence of GVHD (incidence of AKI approximately 20%, with roughly 7% requiring dialysis).

2. CKD: Survivorship has improved among HSCT recipients; as a result, long-term complications are becoming more widely recognized.

   a. CKD occurs in about 20% of patients post-HSCT, a rate more than double that in the general population.
   b. Risk factors

      i. AKI at the time of HSCT
      ii. Total body irradiation as a part of the conditioning regimen
      iii. Certain chemotherapeutic agents (see Table 24.3)
      iv. Chronic GVHD
      v. Long-term CNI exposure

24.3 General Classification of Causes of AKI and Basic Evaluation

It is useful to consider causes as *prerenal* (or reduced blood flow to the kidneys), *intrinsic* renal, and *postrenal* in order to have a systematic approach to evaluating a patient with AKI.

1. Prerenal

   a. Causes

      i. Hypotension
      ii. Volume depletion secondary to vomiting, diarrhea, poor fluid intake, etc.
      iii. Hypercalcemia
      iv. Hepatic SOS

Table 24.3 Drug-induced AKI

Mechanism of injury	Drug	Typical urinary findings
Prerenal state	ACE inhibitors, angiotensin receptor blockers, NSAIDs, diuretics, calcineurin inhibitors, IV contrast	Urine Na < 10 mmol/L; FeNa < 1 %; Urine sediment w/ hyaline casts
Ischemic ATN	All of the above if other prerenal factors present, such as hypotension	Urine Na > 20 mmol/L; FeNa > 1 %; Urine sediment w/ granular or "muddy brown" casts
Nephrotoxic ATN	Vancomycin, aminoglycosides, IVIG, platins	As for ischemic ATN
AIN	Penicillins, cephalosporins, quinolones, sulfa drugs, furosemide, allopurinol, NSAIDs, rifampin, proton pump inhibitors	Peripheral eosinophilia possible; Eosinophiluria possible; Sterile pyuria common; proteinuria often present
Crystal formation/obstruction	Acyclovir, methotrexate, foscarnet, ganciclovir	Crystalluria present
Thrombotic microangiopathy	Calcineurin inhibitors	Hematuria, proteinuria likely

ACE angiotensin converting enzyme, *IV* intravenous, *NSAID* nonsteroidal anti-inflammatory drugs, *ATN* acute tubular necrosis, *IVIG* intravenous immunoglobulin

v. Medications (CNIs, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics)
vi. Hypoalbuminemia

b. If the kidney is otherwise functioning normally, reduced renal blood flow will result in a sodium-avid state. The laboratory hallmark is a low spot urine sodium value (< 10–20 mmol/L) or a FeNa of < 1 %. Patients exposed to diuretics, however, may be volume-depleted with a high urine sodium concentration.

2. Intrinsic renal

a. Causes

i. Acute tubular necrosis (ATN) due to prolonged prerenal state (see above)
ii. Sepsis or drug toxicity
iii. Intravenous (IV) contrast-induced nephropathy
iv. Thrombotic microangiopathy (TM)
v. Allergic interstitial nephritis (acute interstitial nephritis (AIN), drug reaction)

b. Urinalysis is often abnormal when there is intrinsic renal damage.

   i. Muddy brown casts are seen in ATN.
   ii. Sterile pyuria with or without white blood cell (WBC) casts is typical for AIN.
   iii. Hematuria and proteinuria can be seen with TM

3. Postrenal

   a. Causes

      i. Intrarenal obstruction from uric acid, phosphate, or drug crystals
      ii. Extrarenal obstruction from bladder outlet obstruction (prostatic hypertrophy or clot from hemorrhagic cystitis)

4. Initial evaluation

   a. History, including potential nephrotoxin exposures, and careful physical examination with attention to trends in the vital signs, urine output, and estimated intravascular volume status
   b. Basic chemistries, including calcium, phosphate, and uric acid
   c. Complete blood count (CBC)
   d. Urinalysis and microscopy
   e. Spot urine for sodium, creatinine, and protein
   f. Bladder scan for post-void residual
   g. Renal ultrasound

24.4 Timing and Cause of Renal Injury

1. Conditioning regimen (AKI)

   a. Tumor lysis syndrome (TLS)
   b. Stem cell infusion toxicity

2. Days–weeks post-HSCT (AKI)

   a. Volume depletion
   b. ATN
   c. SOS
   d. Medications (e.g., CNIs, antibiotics, antivirals, amphotericin products)
   e. Hemorrhagic cystitis with urinary obstruction
   f. TM

3. Months post-HSCT (CKD)

   a. CNI toxicity
   b. TM
   c. Chronic GVHD

24.5 Evaluation and Management of Common Causes of AKI

1. General recommendations

   It is important to prevent renal injury, given the high rate of mortality associated with severe AKI and the risk for the development of CKD over the long term. Close monitoring of renal function, avoidance of nephrotoxic agents when feasible, maintenance of adequate intravascular volume (as is standard with chemotherapy protocols), and avoidance of hypotension are all important nephroprotective strategies. Nephrology consultation early in the course of AKI, rather than waiting until dialysis is imminent, is recommended. When AKI is diagnosed, the following points should be considered in management:

   a. Diagnosis and treatment of the underlying cause (see sections 24.5.2-8),
   b. Maintenance of intravascular euvolemia
   c. Adjustment of dietary intake to limit potassium and phosphorus
   d. Sodium and fluid restriction should also be instituted if hypervolemia is present (a typical hospital "renal diet" includes sodium, potassium, and phosphorus restrictions)
   e. Avoidance of nephrotoxins as possible (including IV contrast, ACE inhibitors, angiotensin receptor blockers, CNIs, and NSAIDs)
   f. Adjustment in medication dosing for estimated GFR
      i. Accurate assessment of GFR is not possible when creatinine is not at steady state
      ii. A rise in creatinine of 0.5–1.0 mg/dL over 24 h may correlate with a GFR of < 10 mL/min)

2. TLS

   a. TLS is caused by rapid massive tumor cell necrosis with release of intracellular contents into the blood. High lactate dehydrogenase (LDH), hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia are hallmark signs.
   b. Elevated urinary levels of uric acid and phosphate lead to formation of uric acid and calcium phosphate crystals, both toxic to kidney tubule cells and can cause obstruction, and, thus, AKI.
   c. In the context of AKI, hyperkalemia may be life threatening via induction of cardiac dysrhythmias.
   d. Prophylaxis
      i. IV fluids: Aggressive IV hydration (up to 3 L/m^2/day for up to 2 days prior to therapy) establishes high urine output to prevent precipitation of uric acid and phosphorus in the renal tubules, and should be given to those patients at intermediate and high risk for the development of TLS.

ii. Allopurinol: Decreases formation of new uric acid by blocking the metabolism of xanthine to uric acid.

- The usual dose in adults is 100 mg/m^2 po every 8 h, dose adjusted for renal function
- The maximum dose is 800 mg/day
- Ideally, begin 1–2 days prior to induction chemotherapy and continue for up to 7 days after the resolution of tumor lysis.

iii. Recombinant urate oxidase (Rasburicase®): Lowers uric acid by increasing the conversion of uric acid to water-soluble allantoin. It can be used for both prevention and treatment of hyperuricemia.

- Food and Drug Administration (FDA)-labeled dose is 0.15–0.2 mg/kg in 50 mL of isotonic saline IV over 30 min daily for 5 days, but lower doses may be effective in some patients.
- Dosing should be adjusted for renal function
- Specific institutional guidelines are often established for administration of Rasburicase, often fixed-dose administration based on vial size.

e. Management

i. Hyperuricemia

- Administer Rasburicase if not already given.

ii. Hyperkalemia

- If the plasma potassium level is >5.5:
  - Obtain an EKG; if there are changes consistent with hyperkalemia, give 1 ampule of calcium gluconate IV to (transiently) decrease risk of dysrhythmia
  - Give insulin 10 units IV and D_{50} 1 ampule IV to (transiently) shift potassium into the intracellular compartment
  - Remove potassium from the body by giving a loop diuretic (e.g., furosemide IV bolus), (Kayexalate®), or via dialysis.
  - For all patients with hyperkalemia, ensure the patient is on a low potassium diet, IV fluids are potassium-free, and medications do not include potassium supplements or drugs that impair the renal excretion of potassium (e.g., ACE inhibitors, angiotensin receptor blockers, or NSAIDs).

iii. Hyperphosphatemia

- Initiate a low phosphate diet, and add an oral phosphate binder with meals. Examples of phosphate binders:
  - Aluminum hydroxide (Amphojel®, etc.) 300–600 mg, or 5–15 mL with each meal; well-tolerated and most efficacious binder, but use is limited by risk for aluminum toxicity with long-term exposure; limit use to 1–2 weeks.

- Calcium-containing formulations (calcium carbonate and calcium acetate, 1–3 tabs/capsules with each meal); use should be avoided until plasma phosphorus level is < 7 mg/dL to avoid calcium phosphate precipitation and urinary crystal formation.
- Sevelamer hydroxide (Renagel®) 800–2400 po mg with each meal
- Lanthanum carbonate (Fosrenol®) 500–1000 po mg with each meal; must be chewed, so not appropriate choice for edentulous patients unless crushed and sprinkled on food.

iv. Hypocalcemia

- In the presence of concomitant hyperphosphatemia (> 7 mg/dL), avoid repletion of calcium unless symptoms or EKG signs of hypocalcemia are present.

v. AKI

- Supportive care is described in Section 24.5.1.
- Nephrology should be consulted for persistent AKI and/or electrolyte abnormalities (especially hyperkalemia), hyperuricemia unresponsive to medical management, or oliguria.
- Hemodialysis or continuous renal replacement therapy may be required for uric acid, phosphate, potassium, and volume removal.

3. Stem cell product infusional toxicity

a. May occur in patients undergoing autologous HSCT.
b. Dimethyl sulfoxide (DMSO), a cryopreservative, can cause hemolysis, leading to pigment nephropathy and AKI.
c. Because of changes in stem cell preservation and thawing/washing techniques, this complication is now uncommon.

4. Volume depletion

a. Results from vomiting, diarrhea, increased insensible losses (e.g., with fever), poor oral intake, or excessive diuretic use.
b. May cause a transient prerenal state with reversible rise in creatinine upon rehydration.
c. Because this is a very sodium-avid state, a spot urine sodium (or FeNa) will be low, as described in Sect. 24.3.1.b.
d. Prolonged prerenal state may result in necrosis of highly metabolic renal tubular cells and the development of ATN.
e. Concomitant use of certain medications (ACE inhibitors, angiotensin receptor blockers, NSAIDs) interferes with autoregulation of renal blood flow and increases risk of conversion of prerenal azotemia to ischemic ATN.

5. Sepsis
    a. Common cause of AKI, particularly in neutropenic patients.
    b. Systemic cytokine release results in renal hypoperfusion via vasodilation and capillary leak, as well as local renal vasoconstriction; cytokines may also be directly toxic to renal tubular cells.
    c. ATN is the usual renal pattern of injury due to sepsis, and muddy brown casts are commonly seen in the urine sediment.
    d. Antibiotics may also cause AKI, either via direct renal tubular toxicity (e.g., aminoglycosides or amphotericin products), or via an idiosyncratic hypersensitivity reaction (allergic interstitial nephritis (AIN)).
    e. Supportive care is required if AKI develops, along with treatment of the underlying infection.
    f. Consult to the Transplant Infectious Disease service can be helpful in choosing appropriate drugs that may be less nephrotoxic.
6. SOS (see Chap. 21)
    a. SOS occurs in approximately 5–10 % of allogeneic HSCT recipients.
    b. Myeloablative conditioning therapy may cause injury to the endothelial cells of hepatic venules, resulting in thrombosis of small vessels and subsequent sinusoidal and portal hypertension.
    c. The clinical triad of painful hepatomegaly, anasarca, and jaundice usually occurs in the first weeks following conditioning.
    d. There is intense vasoconstriction in the kidney which results in a prerenal, sodium-avid state.
        i. Weight gain, peripheral edema, and very low urinary sodium concentrations (< 10 mmol/L) result
        ii. These features may be observed even with the use of diuretics
        iii. Hemodialysis may be required to manage volume overload in these diuretic-resistant patients.
    e. Severe SOS is associated with ~90 % mortality at 100 days
        i. Tissue plasminogen activator (TPA) and defibrotide have been used with variable success to treat this condition.
7. Drug-induced AKI
    a. A common occurrence, as many drugs used in HSCT are nephrotoxic.
    b. AIN, a drug-induced renal hypersensitivity reaction may also occur, particularly with antibiotics.
    c. Typical drugs that are associated with AKI include chemotherapy agents (methotrexate), antimicrobial agents (amphotericin products, aminoglycosides) and immunosuppressants (CNIs).
        i. Some liposomal formulations of amphotericin are less nephrotoxic.

ii. Aminoglycoside and vancomycin trough levels should be monitored to reduce toxicity.
iii. CNIs are vasoconstricting and nephrotoxic; high levels may contribute to development of a prerenal AKI.

- Trough drug levels should be monitored, and doses should be reduced or drug temporarily held if a patient develops AKI.

8. TM

a. May occur early (within 3 months) or late (6–12 months) after HSCT, and may result in AKI, CKD, or both.
b. Early TM with AKI is often caused by drugs (especially CNIs), complement deficiency, or infection.
c. Treatment should be directed towards the underlying etiology.

24.6 Evaluation and Management of Common Causes of CKD

1. General considerations:

a. Given the high prevalence of CKD in the post-HSCT population, annual surveillance of renal function, including estimated GFR and urinalysis, with evaluation for proteinuria is recommended.
b. When CKD is diagnosed, referral to nephrology should be considered.
c. CKD is an independent risk factor for cardiovascular disease and mortality; therefore, aggressive management of modifiable cardiovascular risks should be considered as well.

2. Chronic CNI toxicity

a. Common cause of CKD in HSCT patients, even in the setting of therapeutic levels.
b. Chronic vasoconstriction and ischemia are the likely mechanism.

i. CNIs are nearly always continued even when chronic nephrotoxicity is suspected.

c. CNIs are also implicated in both acute and chronic TM as an idiosyncratic reaction.

i. CNI-associated TM may involve the kidneys only with lack of usual systemic signs.
ii. Withdrawal of CNI should strongly be considered for any patient who develops TM.

3. TM
    a. TM that develops 6–12 months after HSCT is usually the result of the myeloablative process, GVHD, or infection, any of which cause endothelial cell damage.
    b. Pre-HSCT total body irradiation is strongly associated with the later development of TM; concomitant use of conditioning chemotherapeutic agents such as high-dose cyclophosphamide, busulfan, carmustine, or cisplatin further increase risk.
    c. Presentation includes hematuria, proteinuria, hypertension, and renal failure. Patients have microangiopathic anemia with elevated LDH, decreased haptoglobin and thrombocytopenia.
    d. Both the TM and resultant hemoglobinuria cause ATN.
    e. TM-related kidney injury requires supportive therapy.
        i. Plasma exchange in HSCT-related TM may not have the same success rates as in renal failure due to TM from other causes.
    f. Some patients have renal recovery but most develop CKD.
4. Nephrotic syndrome
    a. Defined by heavy proteinuria (>3 g/24 h), hypoalbuminemia, and edema.
    b. This is a rare, late complication of HSCT, and most commonly associated with chronic GVHD of the kidney after nonmyeloablative HSCT.
    c. The usual pattern of injury on renal biopsy is membranous nephropathy; however, minimal change disease, immunoglobulin A (IgA) nephropathy, focal segmental glomerulosclerosis (FSGS), and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis have also been reported.
    d. Treatment includes high-dose steroids, cyclosporine, and other immunosuppressive agents to achieve resolution of the nephrotic syndrome.

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Chapter 25
Neurologic Complications

Jennie W. Taylor and David Schiff

25.1 Chemotherapy-Induced CNS Toxicities

Several chemotherapeutic agents given over the course of the hematopoietic stem cell transplant (HSCT) process can be neurotoxic (Tables 25.1 and 25.2).

1. High-dose cytarabine
    a. Neurotoxicity generally occurs in doses ≥2 g/m2 every 12 h
    b. Acute cerebellar syndrome, manifesting as dysarthria and ataxia, is the most common neurotoxic event from high-dose cytarabine
    c. Incidence is ~10 %
    d. First signs include nystagmus and ataxia with concurrent cerebral dysfunction (encephalopathy) and altered mental status
    e. Neuroimaging with magnetic resonance imaging (MRI) is initially unrevealing; however, imaging later in the course reveals cerebellar atrophy
    f. Risk factors may include
        i. Age ≥50
        ii. Total cumulative doses ≥48 g/m2
        iii. Prior central nervous system (CNS) disease
        iv. Renal dysfunction, both prior to initiation of chemotherapy or development of acute kidney injury during the chemotherapy administration

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Table 25.1 Risk factors for neurologic complications

Older age (>60)
Renal dysfunction
Type of transplant: allogeneic>autologous
Pre-transplant CNS disease
Total body irradiation
High-dose conditioning regimen
Acute myeloid malignancy
GVHD>grade II
Calcineurin inhibitor use

CNS central nervous system, *GVHD* graft-versus-host disease

Table 25.2 Drug-induced neurotoxicity

Drug	Symptoms	Timing	Treatment
HiDAC (high dose ara-C)	Cerebellar syndrome, polyneuropathy	Conditioning: acute, during administration	Discontinue infusion
Fludarabine	Peripheral neuropathy, visual changes, delayed leukoencephalopathy	Conditioning	Discontinue drug
Calcineurin inhibitors—tacrolimus, cyclosporine	PRES	Chronic	Discontinue drug
Sirolimus	PRES	Chronic	Discontinue drug
Busulfan	Seizures, encephalopathy, myoclonus, hallucinations	Conditioning	Prophylactic antiepileptics—phenytoin, klonipin, or levetiracetam
Ifosfamide	Encephalopathy, myoclonus, hallucinations, seizures	Conditioning	Discontinue drug

PRES posterior reversible encephalopathy syndrome

g. Mechanism of injury is likely related to accumulation of metabolites in the cerebrospinal fluid (CSF) leading to selective injury of the cerebellar Purkinje cells.
h. Treatment includes discontinuing cytarabine (though symptoms onset may not become apparent until therapy completed). Steroids are often administered; however, benefit has not been proven.
i. Daily monitoring for nystagmus, dysmetria on finger-to-nose, and unsteady gait should be performed and the infusion halted with detection of any sign.
j. Though most symptoms resolve over 2 weeks, a small minority of patients have permanent deficits.

2. Fludarabine
   a. Generally associated with doses higher than 50 mg/m2/day. At lower doses, this severe complication is less common.
   b. Risk factors may include
      i. Age ≥ 60
      ii. Renal dysfunction
      iii. Prior CNS disease
      iv. Dose
   c. Neurotoxicity may be delayed, potentially severe, and sometimes irreversible
   d. Symptoms, including cognitive changes, altered mental status, and visual changes, may evolve to coma and death
   e. MRI reveals nonenhancing periventricular white matter changes with restricted diffusion
3. Calcineurin inhibitors (CNIs)
   a. CNIs are immunosuppressants used as graft-versus-host disease (GVHD) prophylaxis in allogeneic HSCT recipients and are notorious for instigating neurotoxicity
   b. Neurotoxicity with Cyclosporine is quoted at 4–30 %
      i. Less common with tacrolimus and newer generation CNIs
      ii. CNI levels should be monitored closely. However, there may not be a significant correlation between drug levels and the development of neurotoxicity
   c. Symptoms range from tremor (see Sect. 25.2) and mild changes in mental status to more significant visual changes, including cortical blindness, seizures, and coma.
   d. Posterior reversible leukoencephalopathy or posterior reversible encephalopathy syndrome (PRES) is the most common manifestation of CNIs (described in Sect. 25.D).
4. Busulfan
   a. Administered as part of many reduced-intensity and myeloablative conditioning regimens: high CNS penetration leads to cortical irritability and seizures (~ 10 %), which are usually generalized
   b. Antiepileptic prophylaxis is widely used.
      i. Phenytoin and phenobarbital are potent cytochrome P450 inducers leading to many drug interactions, variable plasma levels, and effect on busulfan metabolism.
      ii. New antiepileptics, such as levetiracetam (Keppra®), are better tolerated with fewer drug interactions and are becoming more widely used.
      iii. A typical seizure prophylaxis regimen combines levetiracetam 500 mg po BID and clonazepam 0.5 mg po BID, beginning 12 h prior to the first dose of busulfan and continuing for 24 h after the last dose.

5. Ifosfamide
    a. Encephalopathy occurs during or shortly after infusion and manifests as confusion, hallucinations, and/or seizures; progression to coma and death is rare.
    b. Treatment includes discontinuation of the infusion.
        i. Use of methylene blue 50 mg q4 intravenous (IV) is anecdotally reported to be beneficial.
        ii. Metabolites can be removed with hemodialysis.
    c. Symptoms typically resolve within 7 days.
6. Intrathecal methotrexate
    a. Neurotoxicity includes aseptic meningitis, occurring in ~10% of cases and manifesting with fever and signs of increased intracranial pressure with headache, nausea/vomiting, and lethargy
    b. CSF shows increased protein and monocytic or lymphocytic pleocytosis; while infectious etiologies should be ruled out, the timing usually points to drug effect.
    c. Acute encephalopathy similar to PRES has been reported.
    d. Protracted use of intrathecal methotrexate, especially in patients treated with whole-brain radiation, may produce a chronic diffuse leukoencephalopathy.
        i. Symptoms typically present 6 months after treatment with progressive neurocognitive decline.
        ii. MRI reveals diffuse subcortical white matter T2/fluid attenuated inversion recovery (FLAIR) hyperintensity and cerebral atrophy.
    e. Patients treated via lumbar puncture (LP; rather than via Ommaya reservoir) may develop radicular symptoms and imaging suggestive of myeloradiculopathy.

25.2 Tremors

1. Most common neurologic toxicity from CNIs, seen in up to 40%, and may be associated with chronic GVHD
2. Manifests as postural tremor with high frequency and low amplitude affecting both upper extremities
3. Symptoms insidiously progress during 2–4 weeks after starting CNI
4. Treatment
    a. Propranolol (Inderal®) 10 mg po QID. Recommend titrating to 20 mg po QID if no response. Total daily dose ≤120–320 mg po daily in divided doses.
    b. Propranolol LA (Inderal LA®) 60–120 mg po daily can be substituted for patient convenience.
    c. Gabapentin (Neurontin®) 400 mg po TID. Recommend starting at 400 mg po QHS and titrating up by 400 mg daily to TID as tolerated.

Table 25.3 Opportunistic CNS infections

Timing	Pathogens	Mechanism
Prior to engraftment	Bacterial	Impaired mucosal barrier
	Candida	
	HSV	
	Aspergillus	Prolonged neutropenia
Early post-engraftment	Gram-positive bacteria (*Nocardia*)	Impaired cellular immunity
	Fungal (*Candida, Aspergillus*)	
	CMV	
	HHV-6	
Late post-engraftment	HSV	Chronic immunosuppression
	Toxoplasmosis	
	Encapsulated bacteria	

CNS central nervous system, *HSV* herpes simplex virus, *HHV* human herpesvirus, *CMV* cytomegalovirus

25.3 Infectious Complications (see also Chap. 17)

Infectious complications involving the CNS occur in 3–8 % of HSCT patients, are more common in allogeneic recipients, and vary depending on timing post-HSCT (Table 25.3).

1. Fungal
   a. Aspergillus
      i. Most common fungal CNS infection in transplant patients with an incidence of 3–40 %.
      ii. Infection occurs via septic emboli from the lung and may lead to ischemia or hemorrhage from focal invasion or mycotic aneurysm rupture.
      iii. Neuroimaging reveals multiple, non- or minimally enhancing lesions (Fig. 25.1).
      iv. Definitive diagnosis with biopsy is often difficult given patient's medical condition, and empiric antifungals are recommended.
      v. Treatment with voriconazole is recommended given its superior CNS penetration.
   b. *Candida* and *Mucorales* species may also cause fungal brain abscesses
      i. Patients present with focal deficits with or without encephalopathy.
      ii. Imaging reveals multiple lesions that may or may not contrast enhance.
      iii. Definitive diagnosis may be difficult.

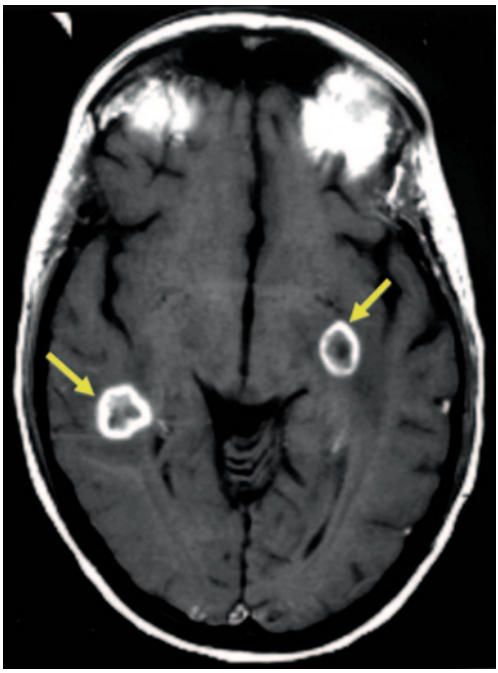

Fig. 25.1 Axial MRI image of CNS aspergillosis depicted by two T1 post-contrast ring-enhancing areas lesions (*arrows*) in a 39-year-old man with headaches after allogenic HSCT with unrelated donor and found to have disseminated aspergillosis

2. Toxoplasmosis
    a. *Toxoplasma gondii* is the most common parasitic infection of the CNS, with the highest incidence in allogeneic HSCT recipients on chronic immunosuppression for GVHD
    b. Prevalence is highly variable and depends on the institution's seroprevalence
    c. Imaging reveals multiple mass lesions, with predilection for the basal ganglia that may or may not enhance
    d. Polymerase chain reaction (PCR) on CSF can be diagnostic
    e. Therapeutic strategies include
        i. Prophylaxis with trimethoprim/sulfamethoxazole (Bactrim®).
        ii. Treatment with pyrimethamine (Daraprim®) plus either sulfadiazine and folinic acid or clindamycin, or high-dose trimethoprim/sulfamethoxazole (Bactrim®).
3. Viral
    a. Human herpes virus-6 (HHV-6) encephalitis
        i. HHV-6 is a member of the β-herpes virus subfamily that is ubiquitous and reactivates in 40–50 % of immunocompromised hosts
        ii. Risk factors as defined by isolation of virus or DNA in blood
            - Allogeneic, unrelated or mismatched related, or cord blood HSCT
            - Prior treatment with anti-T cell antibodies or steroids

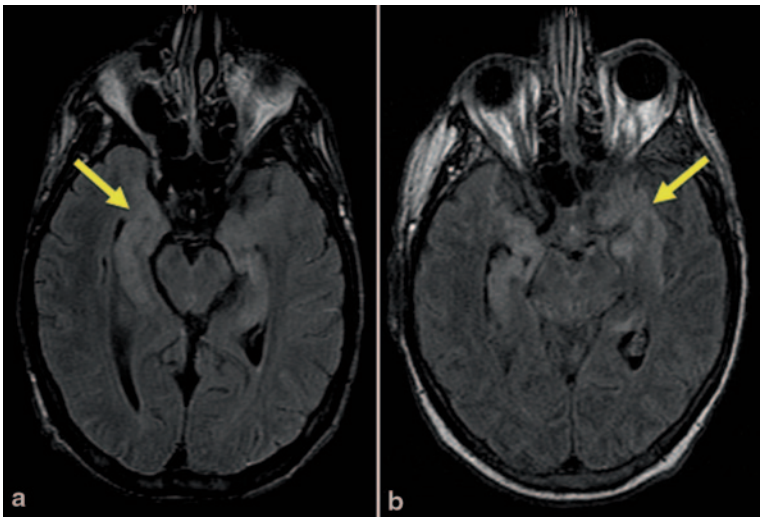

Fig. 25.2 Axial MRI images from two patients with HHV-6 limbic encephalitis demonstrating T2/FLAIR hyperintensities of bilateral medial temporal lobes (*arrows*) (Hill et al. 6). (Reprinted with permission from: Hill et al. 2012)

iii. Reactivation is a risk factor for CNS involvement, particularly with high plasma DNA levels, though data is conflicting and clinical suspicion should guide evaluation and treatment
iv. Clinical presentation is often within first month post-HSCT and similar to other encephalitides with altered level of consciousness, confusion/disorientation, fever, short-term memory impairment, and seizures. Subclinical seizures are common
v. MRI reveals T2/FLAIR hyperintensity of the medial temporal lobe, with or without contrast enhancement (Fig. 25.2)
vi. HHV-6 DNA PCR on the CSF is highly sensitive; CSF may otherwise be normal
vii. EEG frequently demonstrates abnormalities involving the temporal lobe and possibly subclinical seizures
viii. Treatment includes ganciclovir and/or foscarnet and is highly effective
ix. Many patients return to their baseline, although a subset have persistent neurologic deficits, and others progressive disease

b. Use of prophylactic acyclovir has significantly reduced viral encephalitidies from herpes simplex virus type-I, varicella zoster, and cytomegalovirus

4. *Nocardia asteroides, Listeria monocytogenes, Mycobacterium tuberculosis,* and Cryptococcus neoformans are opportunistic infections that may form abscesses or lead to cerebritis or meningitis.

25.4 Cerebrovascular Events

1. Hemorrhage
   a. Subdural hematomas are the most common intracranial hemorrhage encountered after HSCT.
   b. Risk factors include:
      i. Thrombocytopenia
      ii. History of myeloid leukemia
      iii. GVHD
      iv. Recent LP
      v. Risk is independent of transplant type
   c. Intraparenchymal hemorrhages (Fig. 25.3) are more common in allogeneic HSCT
   d. PRES may rarely result in intraparenchymal or subarachnoid hemorrhage.
   e. Treatment for any intracranial hemorrhage
      i. Platelet transfusions to maintain platelets > 50,000/ml and close monitoring
      ii. Neurosurgery should be consulted for consideration of drainage
      iii. Patients can often be managed conservatively
      iv. In emergent cases, recombinant factor VII, antifibrolytic amino acids such as aminocaproic acid and tranexamic acid, and/or DDAVP (1-deamino-8-D-arginine vasopressin) are also considered, though data are very limited
   f. When present, ischemic infarcts should prompt an evaluation for a source of septic emboli, which is most often fungal.
   g. Similarly, subarachnoid hemorrhage warrants evaluation for mycotic aneurysms.

25.5 Posterior Reversible Encephalopathy Syndrome

1. PRES is a clinicoradiographic diagnosis.
2. Results from reversible capillary endothelial injury leading to vasogenic edema due to increased microvascular permeability.
3. Predilection for posterior localization may result from susceptibility of the vertebrobasilar system to cerebral vascular autoregulation.
4. PRES is often associated with acute hypertension.
5. In HSCT recipients, PRES is most often a consequence of CNIs and other medications used for GVHD prophylaxis.
6. Risk is highest in the first months after HSCT when doses are higher and varies by CNI.

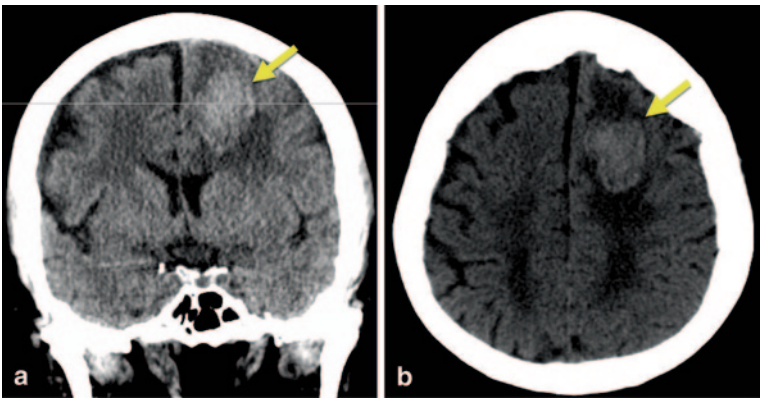

Fig. 25.3 Coronal (**a**) and axial (**b**) noncontrast CT demonstrating a left frontal intraparenchymal hemorrhage (*arrow*) in a 52-year-old woman with confusion and inability to follow directions, 22 days after matched-unrelated HSCT for acute lymphoblastic leukemia with platelets 18,000/microL

   a. Higher neurotoxicity rates are reported with cyclosporine, lower rates with tacrolimus.
   b. However, cases of PRES are reported for all these drugs and at therapeutic or subtherapeutic levels.

7. Presents with constellation of encephalopathy, seizures, and visual disturbances.
8. MRI (in the presence of an offending drug) is diagnostic with multiple white matter T2/FLAIR hyperintensities, usually involving the occipital lobes (Fig. 25.4), although other portions of the brain may be involved.
9. Treatment is supportive and includes discontinuation of the offending drug and changing to a different GVHD prophylactic.
10. Despite having "reversible" in the name, HSCT patients who develop PRES have inferior outcomes.

25.6 GVHD of the Central Nervous System

1. Usually manifests as a polymyositis
   a. Rare instances of myasthenia gravis or demyelinating polyneuropathy may occur
2. GVHD of the brain or spinal cord is a more controversial entity
   a. Case reports exist of perivascular and intraparenchymal lymphocytic and histiocytic inflammation of the CNS that are otherwise unexplained and are classic of GVHD in other organs.

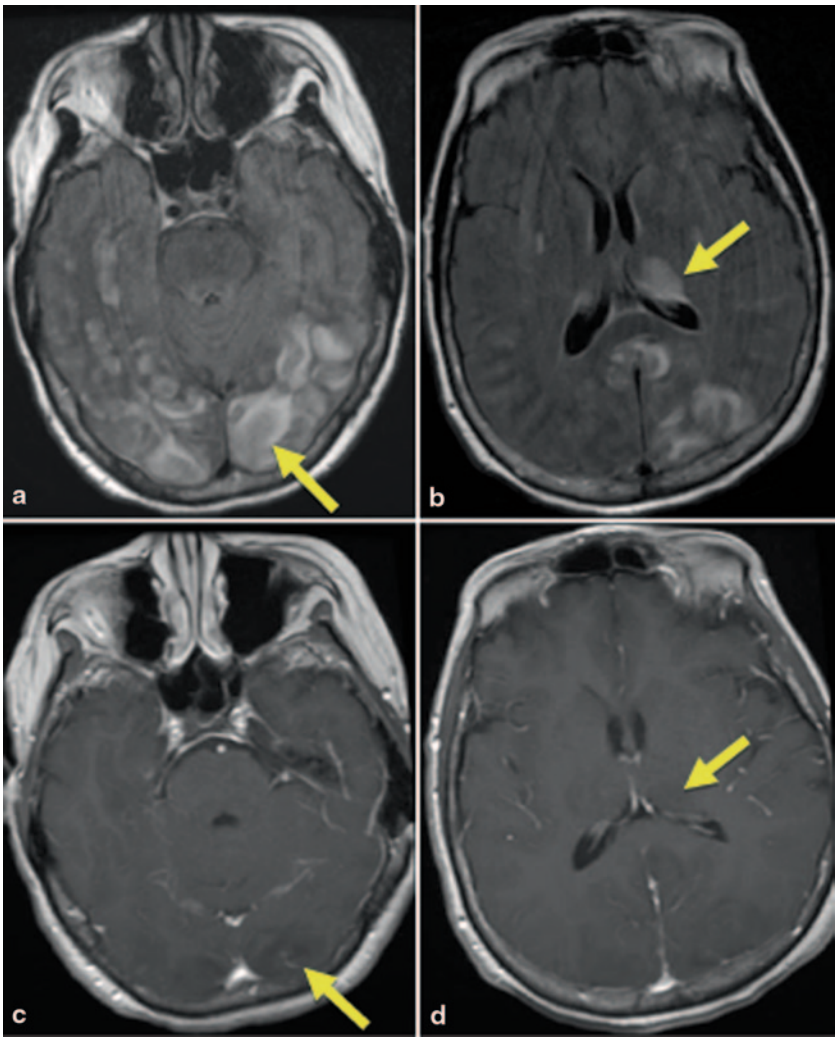

Fig. 25.4 Axial MRI images of PRES with multiple areas of T2/FLAIR (**a, b**) hyperintensity involving the white matter of the occipital lobes and thalamus (*arrows*) and correlating minimal T1-contrast enhancing (*arrows*) (**c, d**) in a 60-year-old woman with depressed consciousness, hypertension, fever, day 216 after reduced intensity allogeneic HSCT

b. Multifocal arteriolar and capillary vasculitis and perivascular lymphocytic invasion lead to ischemia, leukoencephalopathy, or hemorrhage.
c. Presents with encephalopathy, seizures, or focal deficits.
d. MRI reveals nonenhancing T2 white matter lesions and diffuse atrophy.
e. May occur late post-HSCT and in conjunction with GVHD of other organs.
f. Treatment includes steroids and CNIs.

Summary

Neurologic complications post-HSCT are common, difficult to identify early in the treatment course, and portend a worse outcome. Clinicians caring for this population should have a low clinical suspicion for thoroughly investigating any neurologic symptoms even up to a year after transplant and regardless of risk factors. Though deficits are often reversible, early detection and discontinuing the offending agent (if drug induced) and appropriate treatment are critical.

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Chapter 26
Endocrine Complications in Childhood Cancer Survivors

Kevin C. J. Yuen

26.1 Introduction

Although childhood cancers are relatively rare, improvements in therapy have resulted in increased survival rates. The overall 5-year survival rate now exceeds 80%. However, many of these survivors are susceptible to long-term health complications of cancer therapy. Endocrine complications are among the most commonly reported, affecting between 20 and 50% of individuals, particularly in those individuals exposed to radiotherapy and high doses of chemotherapeutic alkylating agents (Table 26.1), as well as survivors of central nervous system tumors and Hodgkin's lymphoma. Such treatments can cause direct damage to the hypothalamic–pituitary axis, thyroid gland, and gonads, decrease bone mineral density (BMD), and alter body composition and glucose homeostasis.

Primary factors associated with late endocrine complications are as follows:

1. Radiotherapy: the involved field, cumulative dose, and the greater duration of exposure
2. Chemotherapy: type and dose
3. Surgery: degree and number of surgeries

These are treatment and not disease specific. Therefore, knowledge of current and past therapies is critical in understanding their risk and for selection of the appropriate diagnostic evaluations required to screen for those risks. Treatment exposures can be modified by a number of factors:

1. Age: In some cases, younger age is protective, whereas in other cases, younger age is associated with increased endocrine dysfunction.

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Table 26.1 Chemotherapeutic agents associated with endocrine complications

Alkylating agents
Busulfan
Cisplatin
Cyclophosphamide
Ifosfamide
Mechlorethamine
Melphalan
Nitrosureas
BCNU (carmustine)
CCNU (lomustine)
Procarbazine
Thiotepa

2. Gender: For unclear reasons, females are at slightly higher risk for many of these endocrine disorders.
3. Genetics: hereditary predisposition.
4. Social: health and lifestyle practices, e.g., smoking, alcohol, and obesity.

26.2 Disorders of the Hypothalamic–Pituitary Axis

Childhood cancer survivors are at risk for multiple pituitary hormone deficiencies (Table 26.2).

1. Growth Hormone Deficiency (GHD)
    a. Impaired linear growth resulting in adult short stature occurs frequently, particularly in individuals treated before puberty.
    b. Results from the direct insult to pituitary somatotropes due to tumor expansion in the pituitary gland, surgical resection, or cranial radiotherapy.
    c. The most common anterior pituitary deficit to develop after cranial radiotherapy.
    d. GHD following irradiation of the hypothalamic–pituitary region occurs in a time- and dose-dependent fashion, i.e., greater risk is associated with higher doses of radiation (>30 Gy) and longer interval from treatment.
    e. Radiation-induced GHD is usually permanent.
        i. Patients should be retested after the completion of linear growth before considering treatment with growth hormone (GH) through adulthood.
    f. Diagnosis requires failing of at least one of the two stimulation tests, e.g., insulin tolerance and glucagon stimulation tests.

Table 26.2 Therapy-related complications affecting the hypothalamic–pituitary axis

Complication	Therapy-related risks	Relationship to time, dose, and available cumulative incidence data
GH deficiency	Surgery	Immediate effect
	Radiation to the hypothalamic–pituitary region	Doses > 30Gy: effect by 5 years after exposure. Cumulative evidence ~ 90% over 4 years
		Doses 18–24 Gy: effect only > 10 years after exposure
Precocious puberty	Radiation to the hypothalamic–pituitary region	Doses > 18 Gy
		Increased risk for girls < 5 years with incidence 10–20%
Hypogonadotropic hypogonadism	Radiation to the hypothalamic–pituitary region	Doses > 30 Gy
		Incidence 10–20% with doses > 50 Gy
ACTH deficiency	Surgery	Immediate effect
	Radiation to the hypothalamic–pituitary region	Doses > 30 Gy: possible cumulative incidence 38% over 4 years
	Glucocorticoids	Effect dose and duration dependent
TSH deficiency	Radiation to the hypothalamic–pituitary region	Doses > 30 Gy
		Cumulative incidence 23% over 4 years with doses > 40 Gy

GH growth hormone, *ACTH* adrenocorticotropic hormone, *TSH* thyroid-stimulating hormone

g. Safety of GH therapy

   i. No increased risk of primary tumor recurrence in patients treated with GH (primarily brain tumor survivors).
   ii. Treatment with GH may slightly increase the risk of a secondary solid tumor, such as meningiomas.

h. Benefits of GH therapy

   i. Positive effects on quality of life.
   ii. Modest improvements in metabolic parameters, e.g., body composition, lipids, and cardiovascular risk markers.

2. Disorders of Luteinizing Hormone/Follicle-Stimulating Hormone

   a. Central precocious puberty (CPP)

      Cranial irradiation at both lower doses (18–35 Gy) and higher doses (> 35 Gy) is associated with the development of CPP by disrupting inhibitory cortical influences.

i. Risk factors following cranial irradiation

- Female sex
- Young age at treatment (i.e., before puberty)
- Body mass index (BMI) > 30 kg/m^2

ii. Risk factors for early menarche

- Radiation before the age of 5 years
- Radiation with doses > 50 Gy

iii. Definition

- In girls, the onset of sustained breast development < 8 years of age
- In boys, testicular volume that is inappropriately small for a given stage of puberty

iv. Assessment

- Skeletal maturation assessed using the standard bone age (X-ray examination of the left wrist and hand) to estimate the individual's skeletal age.
- Advancement of the bone age > 2 standard deviations for chronological age is consistent with CPP.
- In girls, uterine growth on pelvic ultrasound is a sign of estrogen stimulation.
- Gonadotropin secretion is best assessed using the gonadotropin-releasing hormone (GnRH) or GnRH agonist stimulation tests. Ample luteinizing hormone (LH) response, greater than the follicle-stimulating hormone (FSH) response, indicates a pubertal pattern.
- Plasma estradiol levels in girls and testosterone levels in boys are important indicators of pubertal development.

v. Treatment

- Delaying the progression of puberty by using long-acting formulations of GnRH agonists stabilizes the advancement of bone age and improves statural outcome.

b. Hypogonadotropic hypogonadism

i. Deficits of LH and FSH secretion following cranial irradiation occur less often than GHD, and generally only occur following doses to the sellar region, from 30 to 40 Gy.

ii. Late menarche (onset of menstrual cycles > 16 years of age) is associated with doses of radiation > 50 Gy, treatment after 10 years of age, and the diagnosis of medulloblastoma.

iii. In female acute lymphoblastic leukemia (ALL) survivors, "subtle" defects of gonadotropin secretion following radiation doses in the 18–24 Gy range have been described.

c. Adrenocorticotropic hormone (ACTH) deficiency

   i. Apart from transient ACTH deficiency resulting from chronic suppression due to the prolonged use of high doses of glucocorticoids, ACTH deficiency is relatively uncommon.
   ii. May be observed either as a result of direct tumoral impingement on the hypothalamic–pituitary axis and surgery in that region, or following high-dose (>30 Gy) radiation.

d. Thyroid-stimulating hormone (TSH) deficiency

   i. TSH deficiency is rare following cranial irradiation, but has been reported following doses >30 Gy.
   ii. In contrast, doses <30 Gy does not induce central hypothyroidism.

26.3 Disorders of the Thyroid Gland

Thyroid dysfunction is among the most frequent endocrine complications in childhood cancer survivors (Table 26.3).

1. Therapy-induced primary hypothyroidism

   a. The most frequently observed thyroid disorder following radiation exposure of the gland to the following types of radiation:

      i. Neck/mantle irradiation for Hodgkin's lymphoma
      ii. Craniospinal irradiation for brain tumors
      iii. Total body irradiation (TBI) for cytoreduction before *hematopoietic stem cell transplantation* (HSCT)

   b. Risk factors for developing hypothyroidism

      i. Total dose of radiation to the thyroid
      ii. Increased duration of exposure

Table 26.3 Therapy-related complications relating to the thyroid

Complication	Therapy-related risks	Relationship to time, dose, and available cumulative incidence data
Hypothyroidism	Radiation to the neck	Hodgkin's lymphoma survivors: cumulative incidence 28%, reaches 50% with doses >45 Gy over 20 years
Hyperthyroidism	Radiation to the neck	Doses >35 Gy, cumulative incidence 5% over 25 years
Autoimmune disease	Hematopoietic stem cell transplantation	By transfer of abnormal clones of B or T cells from donor to host
Cancer	Radiation to the neck	Doses >20 Gy: cumulative incidence 18% Patients treated <10 years of age higher risk Median latency >20 years

iii. Female gender
iv. Caucasian race
v. Age > 15 years

2. Therapy-induced primary hyperthyroidism

   a. Occurs less frequently than primary hypothyroidism, and is diagnosed most often following external beam radiation to the neck for Hodgkin's lymphoma.
   b. A risk factor is exposure to radiation doses > 35 Gy to the thyroid.
   c. In ALL survivors, the cumulative incidence of primary hyperthyroidism was 0.6 %, which is much lower than the incidence of primary hypothyroidism but still higher than the incidence of hyperthyroidism observed in a sibling control population.

3. Autoimmune thyroid disease

   a. May occur in allogeneic HSCT recipients by the adoptive transfer of abnormal clones of T or B cells from donor to recipient.
   b. Hypothyroidism with or without a preceding hyperthyroid phase may be observed in subjects with positive thyroglobulin autoantibody.
   c. Hyperthyroidism with positive TSH receptor autoantibodies has also been reported following allogeneic HSCT.

4. Thyroid neoplasms

   a. Risk factors

      i. Exposure of the thyroid to either direct or scatter radiation.
      ii. Children < 10 years of age treated with radiation doses in the range of 20–29 Gy.
      iii. Survivors of Hodgkin's lymphoma (majority of cancers are differentiated carcinomas, i.e., papillary and follicular).

   b. The association between thyroid irradiation and thyroid neoplasms is linear at low doses of radiation. With doses > 30 Gy, neoplasms are less likely to develop and tend to have a more indolent natural history.

26.4 Gonadal Dysfunction

Gonadal dysfunction is due to the derangements to gonadotropin secretion and to the direct insult to the testes or ovaries (Table 26.4).

1. Males

   a. Leydig cell failure

      i. Results in delayed/arrested puberty and lack of secondary sexual characteristics if it occurs before the onset of puberty.
      ii. If Leydig cell failure occurs after normal pubertal development, it may result in low libido, erectile dysfunction, decreased BMD, decreased muscle mass, and other metabolic disturbances.

iii. Raised plasma concentrations of LH combined with low levels of testosterone are characteristic of Leydig cell dysfunction, but these changes may not become apparent until mid-adolescence.
iv. Leydig cells are more vulnerable to radiation-induced damage, but may also sustain damage following treatment with alkylating agents.
v. Occurs at doses of radiation >24 Gy, higher than those associated with germ cell dysfunction.
vi. The likelihood of sustaining radiation-induced Leydig cell failure is directly related to the dose delivered and inversely related to age at treatment.

b. Sperm-producing cells are more vulnerable to cancer treatments than Leydig cells and are frequently impaired by radiotherapy and chemotherapy.
c. Germ cell dysfunction with resultant infertility is often associated with decreased testicular volume, increased FSH, and decreased inhibin B and sperm count.
d. The chemotherapeutic agents most commonly associated with impaired male fertility are alkylating agents (Table 26.1).
e. Impaired sperm production

i. Can occur at doses of radiation as low as 0.15 Gy.
ii. If the dose is < 1–2 Gy, recovery can be anticipated.
iii. Recovery is not expected at doses >2 Gy.
iv. TBI commonly induces germ cell dysfunction.
v. Recovery of germ cell function has occurred rarely, primarily following single-dose irradiation.

f. Sperm banking should be offered to all adolescent males prior to the initiation of cancer therapy.

2. Females

a. The sex steroid-producing cells and oocytes are functionally and structurally interdependent within the ovarian follicle.

i. When ovarian failure occurs, both sex hormone production and fertility are disrupted.
ii. Older age is an important risk factor for ovarian failure.

- If ovarian function is lost prior to the onset of puberty, it will result in delayed puberty and primary amenorrhea.
  - Due to a greater follicular reserve, the ovaries of prepubertal girls are more resistant to chemotherapy-induced damage compared with the ovaries of adults.
- If ovarian function is lost during or after pubertal maturation, arrested puberty, secondary amenorrhea, and menopausal symptoms (e.g., hot flashes and vaginal dryness) may be observed.
  - These women are then predisposed to developing osteoporosis and coronary artery disease.

iii. Increased FSH and decreased estradiol are typical findings.
iv. Loss of ovarian function owing to exposure to cancer treatments can occur either early (during or immediately after treatment), or many years after the completion of cancer therapy.
v. Certain chemotherapeutic agents, especially alkylating agents (Table 26.1), when given at high doses can cause ovarian failure, even in younger subjects.

b. Risk factors for acute ovarian failure

i. Older age at treatment
ii. Exposure to procarbazine at any age and to cyclophosphamide at ages 13–20 years
iii. High-dose alkylating agents such as busulfan, melphalan, and thiotepa in preparation for HSCT

c. Most prepubertal girls and adolescents receiving standard chemotherapy will maintain or recover ovarian function during the immediate post-treatment period.

i. In a subset of prepubertal and postpubertal girls treated for solid tumors or leukemia, histologic examination of the ovarian tissue revealed a decreased number of ovarian follicles and inhibition of follicular growth that predisposes them to premature menopause at ages 20s and 30s.

d. If pregnancy is achieved in female cancer survivors treated with chemotherapy, no adverse pregnancy outcomes are known.
e. Risk factors for chronic ovarian failure

i. Abdominal, pelvic, or spinal irradiation with doses >20 Gy
ii. Irradiation given in combination with alkylating agent chemotherapy
iii. TBI
iv. Older age at the time of irradiation

f. Recovery of ovarian function can be observed in a small number of women who have received TBI, but these women have an increased risk of miscarriage and premature delivery of low-birth weight infants.

26.5 Bone Health

1. Childhood cancer survivors are at an increased risk for osteopenia, osteoporosis, and fractures due to

a. Primary disease exposure to glucocorticoids and chemotherapeutic agents such as methotrexate
b. Pituitary hormonal deficiencies associated with cancer and treatments
c. Vitamin D deficiency and poor nutrition
d. Decreased weight-bearing exercise

2. Genetic predisposition (such as corticotropin-releasing hormone receptor 1 (CRHR1) polymorphisms) may increase the risk of decreased BMD, especially following exposure to glucocorticoids or methotrexate.
3. For high-risk individuals
    a. Periodic dual-energy X-ray absorptiometry (DEXA) scans should be performed.
    b. Preventive measures, such as supplementation with calcium and vitamin D, smoking cessation, and weight-bearing exercise, should be encouraged.
4. In addition, sex hormone replacement therapy and GH replacement are useful in improving BMD in subjects with known deficiencies.

26.6 Obesity and Disorders of Glucose Homeostasis

1. Risk factors for developing obesity
    a. Cranial irradiation at doses >20 Gy, especially in females treated at a young age (<4 years)
    b. Female gender
    c. Exposure to high doses of glucocorticoids
    d. Genetic susceptibility
    e. GHD
    f. Hypothalamic tumors and its treatments (e.g., surgery and radiation)
2. Risk factors for diabetes mellitus:
    a. TBI
    b. Abdominal radiation
    c. Alkylating agents (Table 26.1)
3. The primary abnormality is increased insulin resistance and decreased pancreatic β-cell insulin secretion.

26.7 Recommended Tests for Screening for Late Endocrine Complications

1. GH deficiency
    a. Initiated only when GH therapy is considered safe from inducing secondary neoplasm (>2–3 years after completion of treatment)
    b. Insulin-like growth factor 1 (IGF-1) annually
    c. Consider GH stimulation testing

2. Gonadal deficiency
   a. Basal LH, FSH, and estradiol or AM testosterone annually
3. Precocious puberty
   a. Height, weight, testicular volume
   b. Basal LH, FSH, and estradiol or AM testosterone prn
4. ACTH deficiency
   a. Morning ACTH and morning cortisol annually
   b. Consider ACTH stimulation test if morning cortisol < 13 μg/dL
5. TSH deficiency
   a. TSH and free T4 annually
6. Thyroid nodule
   a. Thyroid examination annually
   b. Consider thyroid ultrasound and fine needle aspiration
7. Other laboratories/tests
   a. Prolactin, fasting glucose, hemoglobin A1c, fasting lipids, calcium, and vitamin D annually
   b. Consider DEXA scan to assess BMD

26.8 Summary

1. Endocrine complications are highly prevalent in childhood cancer survivors (Table 26.4)
2. Risk for late effects is determined largely by the individual's therapeutic exposures
3. Risk for late effects increases over time
4. Adult survivors treated with radiation to the hypothalamic–pituitary axis remain at risk for the development of anterior pituitary deficits
   a. Risk is time and dose dependent
   b. GHD is the most common pituitary hormone deficit
5. Long-term GH replacement may improve quality of life and several metabolic parameters
6. Data on long-term safety of GH in adult survivors is limited and inconsistent
7. Lifelong surveillance and appropriate consideration for hormone replacement therapy is required to improve the quality of life of childhood cancer survivors

Table 26.4 Summary of the endocrine late effects of childhood cancer therapy

	GHD	Hypothyroid	Hyperthyroid	Thyroid nodule/ cancer	ACTH deficiency	Low BMD	Precocious puberty	Hypogonadism/ infertility	Obesity/ hyperlipidemia	MBS
Cranial irradiation[a]	+	+	–	+	+	–	+	+	+	+
TBI	+	+	–	+	–	–	–	+	+	+
Target organ irradiation Thyroid[b] Gonadal[c]	–	+	+	+	–	–	–	+	–	–
Alkylating agents	–	–	–	–	–			+	–	–
GCs	–	–	–	–	–	+	–	+	–	–
HSCT	–	–	–	–	–	+	–		–	–

ACTH adrenocorticotropic hormone, *GCs* glucocorticoids, *GHD* growth hormone deficiency, *HSCT* hematopoietic stem cell transplantation, *MBS* metabolic syndrome, *TBI* total body irradiation

[a] Includes cranial, orbital, eye, ear, and nasopharyngeal

[b] Includes thyroid, neck, cervical spine, oropharyngeal, supraclavicular, mantle, and mini–mantle

[c] Includes lumbosacral spine, abdomen, pelvis, and testicular

8. The interval at which pituitary function tests is conducted depends on factors that relate to the dose and radiation schedule, time since radiation, patient characteristics, and clinical needs
9. Important for clinicians and investigators with expertise in this field to recognize endocrine complications early and to refer to endocrinologists for future management of these complications in childhood cancer survivors

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Chapter 27
Thrombotic Microangiopathies

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27.1 Clinical Presentation

The basic problem in all thrombotic microangiopathies (TMs) is occlusion of the vasculature by platelet aggregates. This event restricts blood flow which leads to areas of high shear that damage red cells resulting in fragmentation. This is the origin of the "helmet cells" or "schistocytes" part of the diagnostic criteria (microangiopathic hemolytic anemia). This vascular occlusion leads to tissue ischemia and end-organ damage. In classic hemolytic uremic syndrome (HUS), this pathophysiology is restricted to the kidney leading to renal failure while in thrombotic thrombocytopenic purpura (TTP), it can occur in any organ. The high lactate dehydrogenase (LDH) that is seen in TMs is due to both red cell destruction and tissue ischemia. In transplant patients, the onset of the TM is often gradual with slowly rising LDH and deteriorating renal function. Often, hypertension develops and can be an early clue to the diagnosis. In TMs associated with agents such as calcineurin inhibitors (CNI), the onset can be more rapid. As the TM progresses, renal insufficiency and neurological symptoms are the most common findings, in many patients running a relentless course until the patient expires.

27.2 Risk Factors

Many risk factors for TM have been proposed. One difficulty with these risk factors is that any widespread disease process such as severe infection or graft-versus-host disease (GVHD) can lead to a clinical syndrome similar to TM. This lack of clarity

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in identification of etiologic events results in the extreme variations in reported incidence rates ranging from 0 to 93 % of patients!

Risk factors include:

1. Older age
2. Female gender
3. Advanced disease
4. Unrelated donor transplant
5. Radiation-containing conditioning regimens
6. Calcineurin inhibitors
7. Infection
8. GVHD

27.3 Classification

Pettitt and Clark (1994) proposed a classification which still provides a useful schema for thinking about transplant-related TM.

1. One group is the "multiorgan fulminant" which occurs early (day +20–60), has multiorgan system involvement, and is often fatal.
2. A second type of TTP/HUS is similar to CNI-associated HUS.
3. A third type described as "conditioning" TTP/HUS occurs 6 months or more after total body irradiation and is associated with primary renal involvement.
4. Finally, patients with systemic cytomegaloviral (CMV) infections may present with a TTP/HUS syndrome related to vascular endothelial cell CMV infection.

27.4 Etiology

In classic TTP, most patients have very low levels of ADAMTS-13 (< 5 %) which is thought to lead to spontaneous platelet aggregation via the failure to cleave the ultra-high molecular weight multimers of von Willebrand protein. In patients with transplant related TM, most reports show reduced but not extremely low levels of ADAMTS-13. The underlying factor in most transplant-associated TMs is endothelial damage, either by GVHD, medications, radiation, or infection. This endothelial damage leads to platelet aggregation, microangiopathic hemolytic anemia, and end-organ damage. Over-activation of complement has been reported, similar to genetic atypical HUS, suggesting inhibition of complement may be a future therapeutic target. This premise that endothelial injury is the main trigger for transplant TM would explain why vascular damage is a shared component of many of the risk factors for TM.

27.5 Diagnosis

Given that the diagnosis of any TM is a clinical one and that transplant patients are prone to have many complications that can mimic a TM, it is easy to appreciate and understand the great center-to-center variation in describing the incidence. Recently, two groups have proposed diagnostic consensus criteria that share the common features of evidence of a microangiopathic hemolytic anemia and elevated LDH. However, applying these criteria to an individual patient still requires clinical judgment.

1. Blood and Marrow Transplant Clinical Trial Network (BMT-CTN) Criteria
    a. RBC fragmentation and ≥ 2 schistocytes per high-powered field
    b. Concurrent increase in LDH from institutional baseline
    c. Concurrent renal and/or neurological dysfunction with no other explanation
    d. Negative Coombs test
2. International Working Group Criteria
    a. Increased percentage (> 4 %) of schistocytes in the blood
    b. New, prolonged or progressive thrombocytopenia (< 50,000/uL or > 50 % decrease from previous counts)
    c. Sudden and persistent increase in LDH
    d. Decreased hemoglobin or increased transfusion requirements
    e. Decrease in serum haptoglobin

27.6 Treatment

1. Calcineurin inhibitor TM: This disorder often occurs either days after the introduction of these medications or with an increase in blood levels of these agents. The renal and neurological manifestation can be rapid and severe including malignant hypertension, seizures, and cortical blindness. Therapy is discontinuation of the medications and to manage the closely associated hypertension. In patients with mild TM and high serum levels, one can lower the dose to see if the symptoms abate.
2. Conditioning TM: This subtype is rare and may be a manifestation of radiation damage to the vasculature. Usually, the course is progressive with no specific therapy available.
3. Systemic CMV TM: CMV is trophic to the endothelium and aggressive therapy of CMV is the cornerstone of therapy.
4. Multiorgan fulminant: Therapy remains unsatisfactory. The first step is to maximize treatment of any process that may be aggravating the TM (GVHD, infections, etc.).

a. Unlike classic TTP, the role of plasma exchange remains controversial.
    i. Most series report very poor response rates with poor outcomes and high rates of complications.
    ii. It is common that the patient may respond for a few days but then relapse.
    iii. A practical approach would be to use one plasma volume/day exchange daily in patients with TM until it is clear that they are not responding to therapy.
    iv. For patients who respond, the frequency of plasma exchange can be tapered once renal function and LDH returns to normal.

b. Based on the findings of over-activation of complement, there are anecdotes of successful use of eculizumab (Soliris®), the monoclonal inhibitor of C5a, in patients who have failed plasma exchange, but more research is needed before widespread use of this agent can be recommended.

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Chapter 28
Women's Hormonal Health Issues

Leon Speroff

Women's health issues have often been treated by gynecologist specialists as opposed to internal medicine specialists or subspecialists. Concerns of osteoporosis, menopause, and estrogen replacement therapy, as well as complications of hematopoietic stem cell transplantation (HSCT) including chronic graft-versus-host disease of the female genital tract, are routine for gynecologists. This chapter provides a women's health specialist's perspective on issues of hormonal health in the female HSCT recipient, drawing from observations made in the healthy female population.

28.1 Amenorrhea

Commonly seen after hematopoietic stem cell transplantation (HSCT) as a result of prior chemotherapy and/or the HSCT conditioning regimens

1. Diagnostic Procedures
    a. In women who have menstruated previously, amenorrhea is defined as no menses for an interval equivalent to at least 3 cycles or 6 months.
2. Consequences of premature amenorrhea
    a. Reproductive-age women with amenorrhea have increased risks of coronary heart disease and osteoporosis.
    b. Genitourinary and breast atrophy can be especially disturbing, both emotionally and physically.

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3. Postmenopausal hormones
    a. No guard against spontaneous recovery and an unwanted pregnancy. For this reason, oral contraceptive (OC) treatment is the preferred choice.

28.2 Contraception

1. Contraception and pregnancy are rare events post-HSCT but may occur more frequently if reduced-intensity allogeneic HSCT become more widely used in premenopausal women.
2. If ovarian function is demonstrated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH), consider birth control to prevent pregnancy in the first 2 years post-HSCT.
3. Oral contraception
    a. The commonly used birth control pills are combinations of estrogen and progestin, now limited to what are called low-dose OCs, containing < 50 μg estrogen.
    b. Twenty-four-day regimens are preferred, providing a lower risk of "escape" ovulation and less fluctuation in endogenous estrogen levels.
        i. Results in a more quiescent and stable endometrium associated with reduced uterine bleeding.
    c. OCs can be 99.7% effective, but because of patient errors, the typical failure rate is 8.7% during the first year of use in fertile women.
    d. The risk of venous thromboembolism (VTE) is increased about twofold, but the risk is manifested primarily in the first year of use and concentrated in overweight women.
        i. This risk is dose-related to the estrogen content within the pill.
        ii. Estrogen-progestin contraception is contraindicated in women who have a history of idiopathic VTE and in women who have a close family history of idiopathic VTE.
        iii. Progestin-only methods can be used for high-risk women and for women who are anticoagulated.
        iv. OCs containing less than 50 μg ethynyl estradiol *do not* increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, *regardless of age*.
            − This conclusion probably also applies to the transdermal and vaginal methods of steroid contraception.
        v. A former smoker must have stopped smoking for at least 6 consecutive months and preferably 12 months to be regarded as a nonsmoker. Women who use nicotine patches or gum should be regarded as smokers.

vi. Women over the age of 35 who have cardiovascular high-risk factors, especially smoking and hypertension, should not use estrogen-progestin steroid contraception. Progestin-only methods can be used by these patients.

e. Women on medications that affect liver metabolism should not use oral steroid contraception.
f. Noncontraceptive benefits of OCs reported in healthy female subjects include

i. Decreased incidence of endometrial cancer
ii. Decreased incidence of ovarian cancer
iii. Decreased incidence of colorectal cancer
iv. More regular menses with less flow
v. Decreased dysmenorrhea
vi. Decreased incidence of anemia
vii. Decreased incidence of salpingitis
viii. Decreased benign breast disease
ix. Increased bone density
x. Probable decreased incidence of endometriosis
xi. Possible decreased incidence of rheumatoid arthritis
xii. Possible protection against atherosclerosis
xiii. Possible decreased incidence of fibroids
xiv. Possible decreased incidence of ovarian cysts

4. Injectable Contraception

a. Depot-medroxyprogesterone acetate 150 mg every 3 months.

i. A newer formulation allows self-administration of 104 mg subcutaneously every 3 months.

b. Contraceptive efficacy > 99 %.
c. The following are good indications for this contraceptive method based on observations in healthy women

i. At least 1 year of birth spacing desired
ii. Highly effective long-acting contraception not linked to coitus
iii. No serious side effects
iv. Private, coitally independent method desired
v. Estrogen-free method is required due to estrogen-associated risk factors
vi. Breast-feeding (lactation is enhanced)
vii. Sickle-cell disease
viii. Seizure disorder

5. Intrauterine contraception

a. The copper intrauterine device (IUD) and the levonorgestrel-releasing IUD both provide highly effective protection (> 99 %).
b. Noncontraceptive benefits of the levonorgestrel-releasing IUD

i. Reduction of heavy menstrual bleeding and improvement in anemia
ii. Treatment of dysmenorrhea
iii. Reduction of fibroid prevalence as well as uterine volume and bleeding associated with fibroids
iv. Decrease in uterine volume and pain associated with adenomyosis
v. Reduction of menstrual bleeding in women with hemostatic disorders and in anticoagulated women
vi. Protection against pelvic inflammatory disease
vii. Treatment and suppression of endometriosis
viii. Protection against endometrial hyperplasia and polyps associated with postmenopausal estrogen therapy or tamoxifen treatment
ix. Prevention of ectopic pregnancy
x. Reduction of endometrial cancer risk

c. Women at risk for bacterial endocarditis should receive prophylactic antibiotics at insertion and removal.
d. The following truthful statements counteract commonly held myths regarding IUDs

i. IUDs are *not* abortifacients.
ii. An increased risk of infection is related only to the technique of insertion.
iii. IUD use *does not* increase the risk of pelvic inflammatory disease or infertility.
iv. IUDs *do not* increase the risk of ectopic pregnancy and can be used by women with a previous ectopic.
v. IUDs *can* be used by nulliparous women.
vi. IUDs *can* be inserted immediately postpartum, including after first- and second-trimester abortions.
vii. IUDs *can* be inserted in HIV-positive women.
viii. The modern IUD has *not* exposed clinicians to litigation.

28.3 Perimenopausal Transition and Menopause

Menopause is that point in time when permanent cessation of menstruation occurs following loss of ovarian activity.

1. Hormonal Changes

a. Even irregular cycles can be ovulatory, meaning that late perimenopausal women can be at risk for pregnancy.
b. Postmenopausal levels of FSH (>20 IU/L) can be seen despite menstrual bleeding.
c. Several months of amenorrhea together with an FSH level of ≥40 IU/L are reliable signals that menopause is either near or already passed.

2. Preventive health screening (see also Chap. 34)
   a. Annual visits should include a
      i. Breast and pelvic examination, including a rectal examination.
      ii. Recording of the body mass index (BMI).
      iii. Screening for sexually transmitted infections when appropriate.
   b. Annual screening mammography should begin at age 40.
   c. Colon cancer screening should begin at age 50.
   d. At each visit, appropriate testing is scheduled for specific chronic conditions, including abnormal lipids.
   e. Appropriate immunizations.
   f. Counseling regarding changing nutritional needs, physical activities, injury prevention, occupational, sexual, marital, and parental problems, urinary function, and use of tobacco, alcohol, and drugs.

3. Sexuality and menopause
   a. Approximately 60 % of women 55–64 years old are sexually active, and 26 % of individuals age 75–85 are still sexually active. However, only a small percentage of postmenopausal women will complain of sexual problems. *It pays to ask!* The lack of questions does not indicate an absence of problems.
   b. Given the availability of a partner, the same general high or low rate of sexual activity can be maintained throughout life.
   c. A significant component of a decline in sexual activity around menopause is due to symptoms associated with decreasing estrogen levels.
   d. The two main physiologic changes in postmenopausal women impacting sexual activity are a reduction in the production of vaginal lubricating fluid and the loss of vaginal elasticity and increased thickness of the epithelium.
   e. Dyspareunia associated with postmenopausal urogenital atrophy includes a feeling of dryness and tightness, vaginal irritation and burning with coitus, and postcoital spotting and soreness.
   f. HSCT may result in fatigue and changes in body image that affect sexuality.
      i. Consider individual and/or couples counseling both before and after HSCT.
   g. Drugs may also affect sexual function.
      i. Antihypertensive agents may cause vaginal dryness.
      ii. Adrenergic blocking agents may depress libido.
      iii. Psychotropic drugs of all categories may inhibit sexual function.
         − One should always consider alcoholism when patients complain of sexual dysfunction.

4. Menopausal signs and symptoms
   a. Disturbances of menstruation include anovulation and reduced fertility, decreased or increased menstrual flow, irregular frequency of menses, and, ultimately, amenorrhea.

b. Vasomotor instability produces hot flushes and sweats.
c. Atrophic conditions include atrophy of vaginal epithelium; formation of urethral carbuncles; dyspareunia and pruritus due to vulvar, introital, and vaginal atrophy; general skin atrophy; urinary difficulties such as urgency and abacterial urethritis and cystitis.
d. Health problems secondary to long-term deprivation of estrogen, particularly osteoporosis and cardiovascular disease.

5. Problems associated with relative estrogen excess
   a. Excess estrogen can be caused by several conditions
      i. Anovulation.
      ii. Increased aromatization of androgens as seen with obesity, hyperthyroidism, and liver disease.
      iii. Increased precursor androgens from functional endocrine tumors, liver disease, or even stress.
      iv. Increased direct secretion of estrogen from ovarian tumors.
      v. Decreased levels of sex hormone-binding globulin with liver disease leading to increased levels of unbound estrogen.

   b. Dysfunctional uterine bleeding is common in the perimenopausal years because of anovulation; however, specific organic causes, such as neoplasia (especially uterine fibroids), complications of unexpected pregnancy, or bleeding disorders, must be ruled out.
      i. Requires endometrial evaluation
      ii. Transvaginal ultrasonography measurement of endometrial thickness can avoid unnecessary biopsies.
      iii. Uterine biopsy
         - Unnecessary in perimenopausal women when endometrial thickness is less than 5 mm.
         - Indicated when history suggests long-term unopposed estrogen exposure even when the thickness is normal, 5–12 mm.
         - Should be performed when thickness is > 12 mm even when clinical suspicion of disease is low.
         - Approximately 10% of patients who have benign findings at the initial evaluation subsequently develop pathology. The persistence of abnormal bleeding demands repeated evaluation.
      iv. In the absence of disease, treatment of uterine bleeding consists of periodic oral progestin administration to prevent endometrial cancer.
         - Medroxyprogesterone acetate 5–10 mg or micronized progesterone 200 mg PO daily for the first 14 days of each month.
         - If endometrial hyperplasia is present, follow-up biopsy after 3–4 months is required.
         - Monthly progestin therapy reverses simple hyperplasia in 95–98% of cases, and treatment should be continued. When withdrawal bleeding ceases, this is a reliable sign of menopause.

- If contraception is required, the healthy, nonsmoking patient with normal blood pressure should consider the use of hormonal contraception. A postmenopausal hormone regimen does *not* inhibit ovulation.

6. Problems associated with estrogen deprivation
   a. The hot flush
      i. 10–25 % of premenopausal women
      ii. 60 % of perimenopausal women
      iii. Postmenopausal:
         - No flushes 15–25 %
         - Daily flushing 15–20 %
      iv. Duration
         - Average 1–2 years
         - 5 or more years: 25 %
      v. Other causes
         - Psychosomatic
         - Stress
         - Thyroid disease
         - Subacute, chronic infections
         - Pheochromocytoma
         - Carcinoid
         - Malignancy
   b. Atrophic changes
      i. Vaginal atrophy can be accompanied by vaginitis, pruritus, dyspareunia, and stenosis.
      ii. A vaginal pH > 4.5 is almost always observed with estrogen deficiency.
      iii. There is no convincing support for a beneficial impact of estrogen treatment on incontinence.
      iv. A decline in skin collagen content, elasticity, and skin thickness that occurs with aging can be considerably avoided by estrogen therapy.
   c. Psychophysiologic effects
      i. The concept of a specific menopause-induced psychiatric disorder has been abandoned.
      ii. A negative view of mental health at the time of menopause is not justified; many of the problems reported are due to life events.
      iii. Approximately 85 % of women experience the perimenopausal transition without mood difficulties.
         - Some vulnerable women with underlying psychological problems are at greater risk for new onset depressive symptoms, perhaps enhanced by hormonal variations and vasomotor symptoms.

- The most common cause of perimenopausal mood problems is preexisting depression.

iv. Estrogen therapy improves the quality of sleep.
v. The overall "quality of life" is improved by better sleep and alleviation of hot flushing.

d. Cognition and Alzheimer's disease

i. Evidence of beneficial effects of estrogen on cognition can be found, especially on verbal memory, but the effects are not impressive.
ii. Evidence supports a primary preventive effect on the risk of Alzheimer's disease and an absence of effect in secondary prevention trials.

e. Cardiovascular disease

i. Women with premature ovarian failure are at increased risk for cardiovascular disease. These observations are important for long-term survivor counseling.
ii. There are multiple mechanisms favorably influenced by estrogen that inhibit the development of atherosclerosis.
iii. When indicated, appropriate estrogen treatment can reduce the risk of cardiovascular disease later in life.

- Evidence indicates that adequate estrogen exposure at the onset of clinical events, such as hormone therapy in the early postmenopausal years, provides primary prevention of clinical coronary disease.

f. Osteoporosis

i. Characterized by low bone mass and increased bone fragility.
ii. The subsequent risk of fracture in women depends on bone mass at the time of menopause and the rate of bone loss following menopause.

- 75% or more of the bone loss that occurs during the first 15 years after menopause is due to estrogen deficiency rather than to aging itself.

iii. Interventions and treatments to prevent future osteoporosis are not necessary in perimenopausal women who have adequate estrogen levels and who are eating normally.
iv. Factors for increased fracture risk

- Aging: risk doubles every 7–8 years after age 50
- Previous history of a fragility fracture
- Family history of a fragility fracture in close relatives
- Smoking
- Thin and small-framed body habitus
- Family history of osteoporosis
- Amenorrhea (hypoestrogenism)
- Lifelong calcium and vitamin D intake deficiency

- Use of bone-resorption medications (e.g., steroids)
- Sedentary lifestyle
- Excessive use of alcohol
- Rheumatoid arthritis

v. Reasons to measure bone density

- To help patients make decisions regarding therapy
- To assess response to therapy in selected patients, e.g., smokers and women with eating disorders
- Patients treated long term with glucocorticoids, thyroid hormone, anticonvulsants, or heparin
- Postmenopausal women who present with fractures, who have one or more risk factors for osteoporosis, or > age 65

vi. Postmenopausal hormone therapy effectively reduces the number of all osteoporotic fractures
- Primarily seen in women who have taken estrogen for > 5 years.
- Maximal protection requires lifelong therapy.

vii. Raloxifene (Evista®), an oral selective estrogen receptor modulator, is an option for women reluctant to use hormone therapy, but it requires periodic evaluation of bone density in the hip.

viii. Women not receiving estrogen replacement require a calcium supplementation of at least 1000 mg daily; women receiving estrogen require at least 500 mg daily.

ix. Clinicians should measure serum vitamin D 25-OH levels at least annually.

- A value < 30 ng/mL is below normal.
- Vitamin D 50,000 units PO weekly × 8–12 weeks is indicated if deficiency is identified with additional serum monitoring after completion of therapy.

x. Bisphosphonate treatment is best in older postmenopausal women.

- Duration of treatment is limited to 5 years, followed by monitoring of the bone density.
- Onset of severe pain at any site is an indication to discontinue treatment.
- Estrogen and bisphosphonates should *not* be used together.

28.4 Postmenopausal Hormone Replacement Therapy

1. The daily dose of estrogen effective for most women is comparable to 0.5–1.0 mg estradiol.
2. Transdermal estrogen therapy is the method of choice for

a. Women at high risk for VTE.
b. Women with spontaneous or estrogen-induced hypertriglyceridemia.
c. Obese women with metabolic syndrome.
d. *Probably* in smokers and women with hypertension.

3. Vaginal atrophy can be treated with local vaginal administration; however, treatment longer than 6–12 months requires endometrial surveillance.
4. In women with a uterus, estrogen must be administered along with a progestin to protect against endometrial cancer.

   a. Long-term use of a sequential regimen is associated with an increased risk of endometrial cancer.
   b. The most effective oral method is a daily, continuous, combined regimen with progestins in the following comparable doses:

      i. Medroxyprogesterone acetate 1.5 or 2.5 mg, or
      ii. Norethindrone 0.35 mg, or
      iii. Norethindrone acetate 0.5 or 1 mg, or
      iv. Micronized progesterone 100 mg, or
      v. Drospirenone 2 mg, or
      vi. Dienogest 2 mg

         − *Note*: Micronized progesterone is a less potent progestin, and there is evidence that treatment for several years or more is associated with an increased risk of endometrial cancer. Transdermal progesterone will not protect against endometrial hyperplasia and cancer.

5. The contraceptive levonorgestrel-releasing IUD effectively protects against endometrial cancer.
6. Special conditions warrant the use of a combined regimen in hysterectomized women with

   a. History of pelvic endometriosis.
   b. Residual endometrium, e.g., after a supracervical hysterectomy or an endometrial ablation.
   c. History of treatment for endometrial cancer.
   d. History of treatment for endometrioid tumors of the ovary.

7. Custom-compounded formulations of “bioidentical” hormones have not been proven to be safer or more effective and should be regarded as having similar risks and benefits as commercial products in comparable doses.

   a. Salivary sex steroid levels vary widely, and tailor-making a hormone regimen according to salivary testing has never been tested in appropriate clinical studies.

8. Many women seek alternative medicine options. All phytoestrogen products, including soy and red clover, are no different than placebo in treating hot flushes. Black cohosh is not estrogenic and has no effect on symptoms.

9. Serotonin uptake inhibitors are the next most effective treatment for hot flushes, resulting in approximately a 60 % reduction in flushing compared to 90 % with estrogen.
10. The Women's Health Initiative (WHI)
    The WHI, initiated in 1991 by the US National Institutes of Health, consisted of three clinical trials and one observational study to address major health issues in postmenopausal women, particularly cardiovascular disease, cancer, and osteoporosis. More than 160,000 post menopausal women aged 50–79 years were followed over a period of 15 years, making it the largest US prevention study of its kind.

    a. The WHI concluded that hormone therapy should not be used for primary prevention of coronary heart disease. However, the WHI did not study the appropriate population in the appropriate time period. The average age of the participants in the WHI was 63, and they were an average of slightly > 12 years distant from menopause.
    b. In the last decade, evidence indicates that a healthy endothelium is needed to respond to estrogen, and the beneficial effects progressively diminish with increasing atherosclerosis.

        i. The optimal approach is to start treatment close to menopause.
        ii. Appropriately timed hormone therapy can yield primary prevention of coronary heart disease.

    c. The risk of VTE is increased twofold, about two cases per 10,000 women per year, concentrated in the first 1–2 years of treatment.

        i. In the WHI, the cases of VTE were mostly in the oldest women in the study and in the heaviest women.
        ii. Observational studies support the choice of transdermal administration for women who are at higher risk for VTE.

    d. Observational studies and the WHI have found an increased risk of breast cancer that is < 2.0 (compared to a 25-fold increased risk of lung cancer associated with smoking). However, it is not known whether this represents new breast cancers or whether the epidemiologic data reflect the impact of hormone treatment on preexisting tumors.

        i. The increased risk is observed sooner with the use of combined estrogen-progestin regimens, and is observed only in current users.
        ii. The increase risk is confined to estrogen receptor-positive tumors, mainly lobular cancers.
        iii. Women who develop breast cancer while using hormone therapy are diagnosed early in treatment, have lower grade and stage disease, and have a reduced risk of dying from breast cancer compared with never users.

    e. These observations support an effect on preexisting malignancy, diagnosed at a less aggressive stage, with better survival rates.

i. Contrary to common belief, estrogen-progestin exposure may cause greater differentiation and earlier detection of preexisting malignant disease, with better outcomes.
ii. A positive family history of breast cancer is *not* a contraindication for hormone therapy. Hormone therapy does *not* further increase risk.

11. Metabolic contraindications to estrogen therapy include *chronically* impaired liver function, acute vascular thrombosis, and neuro-ophthalmologic vascular disease.
12. Rather than causing body weight gain, hormone therapy reduces the increase in insulin resistance and abdominal fat usually seen with aging, with a beneficial impact on the risks of hypertension, diabetes mellitus, and dyslipidemia.
13. The guiding principle for hormonal treatment is the right dose for the appropriate duration according to an individual patient's needs.

28.5 Graft-Versus-Host Disease (see Chap. 19 for Diagnosis Criteria and Staging)

1. Graft-versus-host disease (GVHD) of the female genital tract affects a woman's quality of life, sexual function, and personal relationships.
2. Affects approximately 25% of female allogeneic HSCT recipients, typically within the first year post-HSCT
3. Signs and symptoms mimic those of vaginal atrophy secondary to ovarian failure, thereby making the diagnosis challenging and often overlooked.
   a. Vulvar and/or vaginal dryness or irritation, burning, dysuria, dyspareunia, discharge and postcoital bleeding
   b. If left untreated, may result in friable tissue with ulceration and tearing, introital stenosis, and vaginal adhesions
4. Treatment
   a. Nonhormonal vaginal moisturizers/lubricants
      i. Moisturizers
         - Replens®
         - Vagisil®
         - K-Y SILK-E®
      ii. Water-based lubricants
         - Astroglide® liquid/gel
         - K-Y Jelly®
      iii. Silicone-based lubricants

Table 28.1 Vaginal estrogen therapy products for postmenopausal use. (Reprinted with permission from Gass et al. 2013)

Composition	Product name	FDA-approved dosage
Vaginal creams		
17β-estradiol	Estrace vaginal cream®	Initial: 2–4 g/day for 1–2 weeks maintenance: 1 g/1–3 times/week
Conjugated estrogens	Premarin vaginal cream®	For VVA: 0.5–2 g/day for 21 day then off 7 d for dyspareunia: 0.5 g/d for 21 day then off 7 day, or twice/week
Estrone	Estragyn vaginal cream®	2–4 g/day; intended for short-term use; progestogen recommended
Vaginal rings		
17β-estradiol	Estring®	Device containing 2 mg releases approximately 7.5 μg/day for 90 day
Estradiol acetate	Femring®	Device containing 12.4 mg or 24.8 mg estradiol acetate releases 0.05 mg/day or 0.1 mg/day estradiol for 90 days
Vaginal tablet		
Estradiol hemihydrate	Vagifem®	Initial: 1 tablet/day for 2 weeks maintenance: 1 tablet twice/week

VVA vulvovaginal atrophy, *FDA* Food and Drug Administration

- Astroglide X®
- K-Y Intrigue

iv. Oil-based lubricants

- Elegance Women's Lubricants
- Olive oil

b. Topical estrogen treatments (see Table 28.1)
c. Transdermal or oral hormone therapy
d. Topical steroid cream/ointment (e.g., triamcinolone or clobetasol propionate)
e. Topical calcineurin inhibitor ointment (i.e., tacrolimus (Protopic®) 0.03% or 0.1% applied twice daily)
f. Use of lubricated vaginal dilators of graduated sizes to gently stretch the vagina
g. Pelvic floor physical therapy
h. Systemic immune suppressive therapy
i. In severe cases, surgical lysis of adhesions may be required.

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Chapter 29
Psychiatric Complications

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Patients are generally counseled extensively regarding the medical impact of hematopoietic stem cell transplantation (HSCT). They attend educational visits with providers and transplant staff, supplemented by information available on the internet, from special interest groups such as the American Cancer Society or the Leukemia and Lymphoma Society, and from their referring physicians. A great deal of attention is focused on determining performance status and the potential risk of the procedure based upon the patient's preexisting comorbid medical conditions. However, little attention is often paid to the potential psychological and psychiatric complications of the HSCT procedure.

Patients undergoing intensive, life-threatening therapy, such as HSCT, can develop delirium, drug-induced psychosis, paranoia, acute situational depression, and other psychiatric disorders. Catatonia has also been encountered. This chapter discusses the diagnosis and intervention of the most commonly encountered psychiatric complications of the HSCT patient.

29.1 Monitoring Mental Status

While HSCT patients undergo daily laboratory and physical evaluations, close attention must also be paid to mental status changes. Change in mental status is common in the acute hospital setting, especially in patients undergoing intensive medical

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or surgical interventions, and is often exacerbated by medications. Decreasing cognition, somnolence, lethargy, confusion, agitation, withdrawal, and other behavioral changes should trigger the need for a formal mental status evaluation.

1. Narcotics and benzodiazepines contribute to significant somnolence and lethargy in the hospitalized HSCT patient.
2. Patients with mucositis often require parenteral narcotic management. The use of patient-controlled analgesia (PCA) drug delivery systems is less likely to result in severe lethargy, somnolence, or obtundation, but may still be a major contributor to mental status changes.
3. Patients with chemotherapy-induced nausea and vomiting (CINV) receive medications that can contribute to depressed cognition.
4. Hospitalized patients may experience disrupted sleep patterns and may often be aggressively treated with hypnotics or anti-anxiolytics, also contributing to somnolence.
5. Assessment should include evaluations for orientation, inattention, cognition with particular assessment of logical flow of ideas, short- and long-term memory, and lability of emotions.
    a. Determining whether there is a significant change of mental status from baseline is essential.
    b. Fluctuations in mental status are commonly seen first and may be subtle in presentation.
6. Workup for change in mental status (see also Chap. 25)
    a. Evaluation for organic sources, such as CNS bleed or infection.
    b. Radiologic assessments and lumbar puncture for cerebral spinal fluid sampling is critical.
    c. Assessment of hepatic and renal function is necessary as impairment of clearance will lead to accumulation of medications that can contribute to change in mental status.
7. Transplant pharmacy specialists can also provide critical insights in identifying pharmacologic causes of change in mental status.

29.2 Delirium

Delirium is defined as a sudden state of confusion with observed fluctuations in mental status that can be associated with disorientation and withdrawal from personal interactions. Delirium is increasingly being recognized as a major medical complication of hospitalization, particularly in elderly and sicker patients and contributing to in-hospital mortality ranging from 20 to 76%, with 1-year mortality rates of the hospitalized patient of 35–40%. It has been reported in intensive care unit patients as high as 70–87% with reports of hospital incidence ranging from 6

to 56%. However, the great majority of patients with delirium are underrecognized by the provider and nursing staff.

1. Delirium may be a manifestation of underlying dementia, electrolyte disorders, infection, side effects of medications, reactions to stress and unfamiliar environments, or metabolic dysfunction.
2. Patients with a history of prior alcohol abuse are more likely to present with delirium, as are older patients with delirium affecting 20% of hospitalized patients over age 65.
3. Symptoms may persist as late as 6 months from the event in up to 30% of patients.
4. Medications associated with delirium include anticholinergics, (e.g., diphenhydramine), antipsychotics (e.g., chlorpromazine), corticosteroids, benzodiazepines, selected antihypertensive medications, diuretics, H2 blocking agents, and narcotics. Delirium has even been observed in the HSCT patient treated with scopolamine transdermal delivery patch used for emesis control.
5. Additionally, patients who experience withdrawal from alcohol or who discontinue selective serotonin reuptake inhibitors (SSRIs) are often at risk.
6. Frequent reorientation, maintaining mobility, utilizing supplemental glasses or hearing aids, and avoiding diphenhydramine or other drugs can assist in avoiding the development of delirium.
7. Pharmacologic treatment of delirium

    a. Evidence-based approach to the management of delirium has not yet been established
    b. Standard treatments:

        i. Haloperidol (Haldol®)

            - The mainstay of therapy and first-line therapy
            - Minimal anticholinergic side effects
            - No active metabolites
            - Lower extrapyramidal side effects when given intravenously
            - Lower sedation rates than compared to other neuroleptics or benzodiazepines
            - Can be associated with prolonged QT interval and requires cardiac monitoring
            - Dosing

                - For urgent need and breakthrough: 0.25–1 mg IV followed by 0.5–1 mg PO every 4 h
                - Can give as frequently as 1–2 mg PO every 1–2 h PRN
                - Maximum dosing up to 10 mg per day
                - For patients > age 65, a lower maximum dose of 4.5 mg per day is generally recommended

        ii. Quetiapine (Seroquel®)

            - 12.5–25 mg PO as frequently as every 4 h with maximum dose of 150 mg per day

iii. Risperidone (Risperdal®)

- 0.25–0.5 mg PO as frequently as every 4 h with maximum dose of 2 mg per day

iv. Olanzapine (Zyprexa®)

- 2.5–5 mg PO as frequently as every 4 h with maximum dose of 10 mg per day
  - Alternatively, 2.5–5 mg IM every 4–6 h may be used

v. Benzodiazepines

- Can be used in combination with neuroleptics
- Generally, lorazepam (Ativan®) 0.5–1 mg IV/PO can be given every 1–2 h
- Maximum dose of 10 mg per day

8. Steroid psychosis is a drug-induced delirium associated with corticosteroid exposure. Dramatic and rapid change of mental status with violent outbursts can be experienced.
   a. Haloperidol (Haldol®) may be required for dealing with the abrupt changes in personality.
   b. Olanzapine (Zyprexa®) can also be utilized for patients with lability of mood or with steroid-induced delirium.
   c. May be used as a prophylactic agent.
      i. At our institution, for example, multiple myeloma patients requiring multiple courses of dexamethasone may be concurrently treated with olanzapine 5–10 mg PO daily to prevent steroid-related psychosis.

29.3 Depression

Depression is a psychiatric disorder associated with persistent feelings of hopelessness, anorexia, lack of energy, anhedonia (inability to experience pleasure), insomnia, and recurrent thoughts of death. It has been estimated that nearly one in five Americans will have a major depressive episode during their lifetime. One event is highly predictive of future events with nearly 50% of patients having recurrent events. When depression is identified, the major goals of therapy are to minimize the depression symptoms and avoid side effects of medications that are prescribed to improve the quality of life. The need to focus on reduction of future recurrences is also critical.

1. There is a biochemical basis of depression which is thought to be dysregulation of neurotransmitters, with particular focus on serotonin, norepinephrine, and dopamine.

   a. Therapeutic interventions achieved by exogenous antidepressants target neurotransmitter levels at the synapse.

2. Selection of an antidepressant is based upon the rapidity of onset, concurrent medical conditions (see Table 29.1), side effect profile and potential contraindications, responses in patients with a prior history, and cost.
3. A general treatment approach is to begin at a lower dose and to dose escalate every 3–7 days based upon the agent utilized.
   a. Geriatric patients and HSCT patients with complicated medical histories should begin at 50% dose with slower increases.
   b. SSRIs should be initiated at therapeutic doses for most patients.
4. It may take up to 3–4 weeks before symptoms begin to improve.
   a. Patients with psychomotor retardation and neurovegetative symptoms such as anorexia, profound fatigue, and excess sleep may respond earlier.
   b. Partial response may indicate a need for dose escalation while no response suggests the need to change medications.

Table 29.1 Clinical applications for antidepressants

Patient condition	Suggested antidepressant drug of choice
Depression with anxiety or agitation	Paroxetine (Paxil®)
Depression with lethargy and amotivation	Fluoxetine (Prozac®), buproprion (Wellbutrin®), or venlafaxine (Effexor®)
Preexisting cardiac disease	
Congestive heart failure/coronary artery disease	SSRI, buproprion (Wellbutrin®)
Heart block	SSRI, buproprion (Wellbutrin®)
Hypertension	SSRI
Hypotension	Venlafaxine (Effexor®), desipramine (Norpramin®), nortriptyline (Pamelor®), SSRI, buproprion (Wellbutrin®)
Neurologic disease	
Parkinsonism	Buproprion (Wellbutrin®)
Cerebrovascular accident (stroke)	SSRI
Migraine headaches	Desipramine (Norpramin®), nortriptyline (Pamelor®)
Miscellaneous	
Prostatism	Buproprion (Wellbutrin®), SSRI (excluding paroxetine (Paxil®))
Irritable bowel syndrome	Desipramine (Norpramin®)
Diabetes	SSRI
HIV	Mirtazepine (Remeron®)
Thrombocytopenia or leukopenia	Citalopram (Celexa®), escitalopram (Lexapro®)

SSRI selective serotonin reuptake inhibitor

c. Efficacy can be equivalent across agents, but the need for multiple drug trials is justified as approximately 50 % of patients fail to respond to the first agent.

   i. When one chooses to exchange antidepressant agents, the washout period depends on the actual drug and its half-life as well as patient comorbidities.
   ii. 1–2-week washout is recommended for most agents, particularly with monoamine oxidase (MAO) inhibitors and up to 5 weeks for fluoxetine.
   iii. This can be managed with a lower dose of the new agent as the prior agent is cleared from the patient if it is felt clinically necessary to treat a patient more aggressively.

5. When responses are identified, drug administration should be maintained for a minimum of 6 months prior to initiating a slow taper.

   a. Most people require between 7 and 12 months of therapy for first depressive episode.
   b. For patients with recurrent or chronic depression, a minimum of a 12-month treatment course should be considered, as 50–80 % of patients will relapse without maintenance therapy.

6. For most patients, tapering is needed if they have been on any drug for over 2 months.

   a. Nearly one third of patients will have withdrawal symptom with abrupt cessation of the agent, including somatic complaints of flu-like symptoms, gastrointestinal distress, arrhythmias, and sensory and sleep disturbances.
   b. Psychiatric manifestations include anxiety, agitation, mania, panic attacks, irritability, labile emotions with excess crying, and possibly delirium.
   c. Risk factors for the development of abstinence symptoms include

      i. SSRIs with short half-life (e.g., paroxetine, fluvoxamine)
      ii. Prolonged therapy
      iii. Presentation with anxiety
      iv. History of withdrawal.

   d. When seen, abstinence symptoms typically develop within 1–3 days after cessation with episodes lasting 7–14 days.
   e. If symptoms are significant, the agent can be reinstituted with a more gradual taper or changed to an agent with a longer half-life prior to tapering the antidepressant.

7. Depression early in the post-HSCT period, which is often associated with hospitalization, may be hard to distinguish from the hypoactive/hypo-alert variant of delirium.

   a. Depression can be an acute situational response or can be chronic.
   b. SSRIs are often the first choice with the goal of utilizing a therapeutic dose from initiation of therapy (Table 29.2).

Table 29.2 Selected antidepressants and dosing (suggested starting at 50% dose if elderly or debilitated)

Drug	Starting dose (daily) (mg)	Dosing range (daily) (mg)	Comments
Selective serotonin reuptake inhibitors (SSRI)			
Citalopram (Celexa®)	10–20	20–60	QTc prolongation increased with doses >40 mg/day with minimal increase in benefit
Escitalopram (Lexapro®)	10	10–20	Doses above 20 mg may confer little additional benefit
Fluoxetine (Prozac®)	20	10–80	More activating than other SSRI
Paroxetine (Paxil®)	20	20–50	More anxiolytic than other SSRI but more delirium
Sertraline (Zoloft®)	50	50–200	–
Serotonin norepeinephrine reuptake inhibitors (SNRI)			
Duloxetine (Cymbalta®)	40	60–120	Dosed twice daily, best evidence for diminishing neuropathic pain as collateral benefit
Venlafaxine (Effexor®)	50–75	150–375	May cause hypertension over 300 mg daily, many dosing forms
Miscellaneous agents			
Buproprion (Wellbutrin®)	100–200	300–450	Many dosage forms, helps with tobacco addiction
Desipramine (Norpramin®)	50–75	150–300	No longer agent of first use in any patient group
Mirtazapine (Remeron®)	15	15–45	May diminish nausea and increase appetite
Nortriptyline (Pamelor®)	50–75	75–150	No longer agent of first use in any patient group

i. If side effects are encountered, they are most often gastrointestinal or central nervous system and occur within the first 2 weeks.
   - The gastrointestinal side effects may be diminished by twice daily dosing within the first month.

ii. Syndrome of inappropriate antidiuretic hormone (SIADH) has been seen but usually occurs late.

iii. For patients with hepatic dysfunction or for the elderly, initiating therapy at the lowest dose available with slow titration upward is recommended.

8. Psychomotor retardation or impairment involves a general slowdown of thought processes, emotional reactions, and physical movements.
   a. Manifests with speech abnormalities including changes in volume and intonation, fixed eye gaze or lack of eye contact, psychomotor slowing, slumped posture, and increased self-touching, particularly of the face.

b. Considered to be a key aspect of major depressive disorder or the depressed phase of bipolar disorder.
c. Can be associated with certain medications including benzodiazepines, cannabis, and antipsychotics, as well as calcineurin inhibitors, particularly in elderly patients.
d. Initially thought to be strictly a psychiatric illness, it may be associated with physical conditions such as Parkinson's disease.
e. Recommendations for the treatment vary with inconsistent reports of efficacy in the literature for SSRIs, tricyclics, and monoamine oxidase inhibitors.

29.4 Sleep Disorders

Insomnia, or trouble sleeping, is a common problem for patients with cancer. Several recent studies have reported an incidence of 30–50 % in cancer patients compared to 15 % in the general population. In addition, symptoms of insomnia were found in 23–44 % of patients 2–5 years after treatment for cancer. Despite this prevalence, one study found that only 16 % of patients with insomnia informed their health care provider about the problem, and many practitioners failed to ask about sleep. This likely occurs for one of the several reasons: insomnia may be viewed as a normal response to the cancer diagnosis and treatment; insomnia may be viewed as a lesser priority than the cancer treatment; and practitioners may lack the knowledge to diagnose and treat this problem.

1. Insomnia may present as difficulty falling asleep, multiple awakenings during the night, or early morning awakenings with the inability to get back to sleep. All of these can be heightened during the acute inpatient hospital stay and can contribute to development of delirium.
2. Criteria for insomnia syndrome, as defined by the international classification of sleep disorders.
    a. Difficulty sleeping characterized by 30 min or more to fall asleep and/or more than 30 min of nighttime awakenings, with a ratio of total sleep time to time spent in bed of less than 85 %.
    b. The sleep disturbance must occur at least three nights per week and cause significant impairment of daytime functioning or marked distress.
3. Many patients may not fit these specific criteria but suffer from the symptoms of insomnia nonetheless.
    a. Insomnia can lead to fatigue, memory and concentration problems, mood disturbances, and psychiatric disorders.
    b. Studies have suggested that insomnia may play a role in physical symptoms, shorter lifespan, and immunosuppression.
    c. For these reasons, and to improve quality of life, patients should seek and be offered treatment for insomnia.

4. The potential causes of insomnia are many.
    a. A personal or family history of insomnia
    b. The presence of a depression or an anxiety disorder
    c. Advanced age
    d. Female gender
5. Factors that may contribute to the development of insomnia
    a. Certain medications, most commonly steroids in the post-HSCT population
    b. Hospitalization
    c. Chemotherapy and/or radiation
    d. Hormonal therapy or hot flashes
    e. Pain
    f. Nausea and vomiting
    g. Several additional factors that can often be easily modified
        i. Irregular sleep schedule
        ii. Excessive amount of time spent in bed
        iii. Napping
        iv. Engaging in sleep-interfering activities in the bedroom such as watching TV, computer work, etc.
        v. Unrealistic sleep expectations
6. Interventions include
    a. Sleep hygiene (instructional videos or manuals)
    b. Simplify sleep medication regimens (Table 29.3)
    c. Provide patient with sleep diaries to document sleep:wake cycles
    d. Provide patient with relaxation techniques to help assist with falling asleep
    e. Consider adding a medication if nonpharmacologic interventions are not working
    f. Set realistic expectations about reversal of disordered sleep patterns
7. It should be noted that while medications are a frequent intervention to assist a patient in falling or staying asleep, they do not restore normal sleep architecture and most result in diminished levels of deep sleep and increased periods of REM sleep.
    a. Of the available agents, it appears that ramelteon (Rozerem®) has the greatest likelihood of providing a sleep cycle more near to that which occurs without medication assistance.

29.5 Drug Interactions

Many psychiatric agents have the potential for drug interactions. The best documentation involves the CYP450 families of enzymes. Individual agents' potential for interacting with agents metabolized via specific enzymes are listed in Table 29.4.

Table 29.3 Selected hypnotics and characteristics

Drug	Mechanism of action	Common dose	Half-life (h)	Food effect
Diphenhydramine (Benadryl®)	Antihistamine (sedative property)	25–50 mg HS	2–8 Elderly: 13.5	None
Eszopiclone (Lunesta®)	Non-BDZ; interacting with $GABA_A$ receptor	Adult: 2–3 mg HS Elderly: 1–2 mg HS	6	High-fat meal delays absorption
Ramelteon (Rozerem®)	Melatonin receptor agonist with high affinity for MT1 and MT2 receptors	8 mg HS	1–5, multiple receptor interactions	High-fat meal delays absorption
Temazepam (Restoril®)	BDZ, acting on benzodiazepine receptor	7.5–30 mg HS	8.8	Serum level may be increased by grapefruit juice
Zolpidem (Ambien®)	Non-BDZ; interacting with $GABA_A$ receptor	10 mg HS, 12.5 mg ER Elderly: 5–10 mg HS, 6.25 mg ER	2–3	Food may delay absorption

GABA γ-aminobutyric acid, BDZ = benzodiazepine, HS = at beditme, ER = extended release

Table 29.4 Drug interactions involving the CYP450 families of enzymes

Drug	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
Buproprion (Wellbutrin®)	–	–	–	–	–	–	W	–	–
Citalopram (Celexa®)	W	–	W	–	–	W	W	–	–
Desipramine (Norpramin®)	–	M	M	–	–	–	M	W	M
Diphenhydramine (Benadryl®)	–	–	–	–	–	–	M	–	–
Duloxetine (Cymbalta®)	–	–	–	–	–	–	M	–	–
Escitalopram (Lexapro®)	–	–	–	–	–	–	W	–	–
Eszopiclone (Lunesta®)	–	–	–	–	–	–	–	–	–
Fluoxetine (Prozac®)	M	–	W	–	W	M	S	–	W
Haloperidol (Haldol®)	–	–	–	–	–	–	M	–	M
Mirtazapine (Remeron®)	W	–	–	–	–	–	–	–	W
Olanzapine (Zyprexa®)	W	–	–	–	W	W	W	–	W
Paroxetine (Paxil®)	W	–	M	–	W	W	S	–	W
Quetiapine (Seroquel®)	–	–	–	–	–	–	–	–	–
Ramelteon (Rozerem®)	–	–	–	–	–	–	–	–	–
Risperidone (Riseridol®)	–	–	–	–	–	–	W	–	W
Sertraline (Zoloft®)	W	–	M	W	W	M	M	–	M
Temazepam (Restoril®)	–	–	–	–	–	–	–	–	–
Venlefaxine (Effexor®)	–	–	W	–	–	–	W	–	W
Zolpidem (Ambien®)	–	–	–	–	–	–	–	–	–

W weak, *M* moderate, *S* strong

Weak (W) interactions are not clinically relevant, while moderate (M) and strong (S) interactions should be discussed with a pharmacist for potential dose changes.

29.6 Dose Adjustments for Renal or Hepatic Impairment

The intent in medication dosing in patients with organ dysfunction is to reduce the dose to one that achieves a similar whole body or receptor-targeted dose, similar to that seen in individuals with normal organ function. Once the agent is initiated, dose titration should occur at slower intervals (approximately 1.5–2 times longer) to allow the individual to reach a steady state blood concentration and allow clinical effects and side effects to be assessed prior to further dose titration (see Table 29.5).

Table 29.5 Suggested dose adjustments for estimated renal function (mL/min) and degree of hepatic dysfunction

	Renal dysfunction (estimated creatinine clearance in mL/min)			Hepatic dysfunction		
Drug	30–50	10–30	<10 and dialysis	Mild	Moderate	Severe
Buprioprion (Wellbutrin®)	None	None	50%	None	Consider ↓ 25%	75 mg maximum
Citalopram(Celexa®)	None	None	None	None	↓ 25%	↓ 50%
Desipramine (Norpramin®)	None	↓ 25%	↓ 50%	None	None	None
Diphenhydramine (Benadryl®)	None	↓ 25%	↓ 50%	None	↓ 25%	↓ 50%
Duloxetine (Cymbalta®)	60 mg maximum	Do not use	Do not use	None	Do not use	Do not use
Escitalopram (Lexapro®)	None	None	None	None	↓ 25%	50%
Eszopiclone (Lunesta®)	None	None	None	None	None	1 mg, max dose 2 mg
Fluoxetine (Prozac®)	None	None	None	None	↓ 25%	↓ 50%
Haloperidol (Haldol®)	None	None	None	None	None	↓ 50%
Mirtazapine (Remeron®)	None	↓ 30%	↓ 50%	None	None	↓ 30%
Olanzapine (Zyprexa®)	None	None	None	None	None	None
Paroxetine (Paxil®)	None	None	None	None	↓ 25%	↓ 50%
Quetiapine (Seroquel®)	None	None	None	None	↓ 30%	↓ 50%
Ramelteon (Rozerem®)	None	None	None	None	None	Do not use
Risperidone (Riseridol®)	None	↓ 25%	↓ 50%	None	None	↓ 40%
Sertraline (Zoloft®)	None	None	None	None	↓ 25%	↓ 50%
Temazepam (Restoril®)	↓ 25%	↓ 50%	↓ 90%	None	None	None
Venlefaxine (Effexor®)	↓ 25%	↓ 50%	↓ 75%	None	↓ 30%	↓ 90%
Zolpidem (Ambien®)	None	None	↓ 50%	None	None	↓ 50%

↓ decrease dose by

Clinically, adjustments of these medications are often overlooked and may contribute to mental status changes in HSCT patients.

29.7 Competence

Legal competence is not a grey area—a patient is either lawfully entitled or not entitled to make decisions about their health care. This requires the mental capacity to

1. Reason and weigh the risks/benefits
2. Recognize the significance of the current circumstance
3. Understand the information provided
4. Convey a decision

Multiple formalized tools are available to evaluate a patient's legal competence for decision making. However, this evaluation is often best completed by a psychiatry or clinical psychology professional. Sometimes, circumstances will demand that competence declarations be obtained in conjunction with institutional ethics committees.

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Chapter 30
Graft Failure

Gabrielle Meyers

Despite excellent supportive care and enhanced infection prophylaxis and treatment, engraftment failure remains a devastating complication of both autologous and allogeneic hematopoietic stem cell transplantation (HSCT). Early or primary graft failure, defined as failure to recover from neutropenia, has the highest mortality compared to secondary graft failure, in which patients lose donor cells after initial engraftment. Numerous factors are associated with an increased risk of graft failure, and recognizing and modifying these risks, as possible, are of utmost importance.

In the setting of autologous HSCT, definition of clear minimum stem cell doses to proceed with the procedure, coupled with newer agents to enhance mobilization of stem cells, has decreased the risk. However, in the allogeneic HSCT setting, numerous factors have made graft failure a continued concern, in particular the increasing use of nonmyeloablative conditioning regimens, transplantation for nonmalignant disorders, and alternative graft sources. Testing for anti-HLA antibodies of donors and recipients prior to HSCT, choice of product source and dose, and enhanced use of immunosuppressive agents as part of the conditioning regimen are approaches that may minimize the risk of graft failure. In addition, prompt recognition of those at highest risk of graft failure and rapid steps to collect additional hematopoietic stem cell progenitor cells, provide the best chance of reversing the complications of prolonged and profound pancytopenia.

30.1 Autologous HSCT

1. Failure of engraftment is defined as a failure to achieve an absolute neutrophil count $\geq 200/mm^3$ by day +21. Hematopoietic recovery may be transient, partial, or absent.

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2. May be the consequence of
   a. Infusion of an inadequate number of stem cells
   b. A damaged marrow microenvironment
   c. Concomitant infections, e.g., cytomegalovirus (CMV)
   d. Cryopreservation techniques that may damage stem cells
   e. Post-HSCT medications, e.g., trimethoprim/sulfamethoxazole or ganciclovir.

30.2 Allogeneic HSCT

1. It is critical to differentiate between graft failure and graft rejection.
   a. Primary engraftment failure is defined as a complete lack of engraftment (absolute neutrophil count $<500/mm^3$ without evidence of relapse) at day +28 post-HSCT, irrespective of source of stem cells.
   b. Secondary graft failure is defined as development of pancytopenia and marrow aplasia in the setting of previously established donor-derived hematopoiesis.
      i. The systemic presentation of graft-versus-host-disease (GVHD) can lead to suppressed hematopoiesis and failure to maintain the stem cell graft.
   c. Graft rejection is best defined by the demonstration of donor chimerism that decreases over time in parallel with development of peripheral cytopenias.
      i. This can best be monitored by following donor lymphocyte pools.
      ii. Persistence and/or expansion of host-derived cytotoxic T cells or NK cells can be seen.
2. HLA antibody screening pre-HSCT is a highly useful tool to assess for donor-directed HLA-specific alloantibodies, which are known to markedly increase the risk of graft failure, particularly in the setting of partially matched or mismatched transplants.
   a. Determination of a positive panel reactive antibody (PRA) requires further investigation to determine alloreactive HLA specificities.
   b. The finding of donor-directed HLA-specific alloantibodies markedly increases the risk of graft failure and must be strongly considered in donor selection.

30.3 Donor Leukocyte Infusion

1. Donor leukocyte infusions (DLI) are frequently used as a salvage therapy for patients who relapse after T cell replete allogeneic HSCT or as a preemptive strategy in T cell depleted and T cell replete HSCT.

2. DLI can be either a nonstimulated or growth-factor stimulated peripheral blood product.
3. DLI may result in a significant degree of myelosuppression and even aplasia. It is hypothesized that aplasia is due to T cells that are transfused in the donor leukocyte product recognizing and destroying residual host marrow cells and other components of the host microenvironment.
4. If the patient has severe chronic GVHD or minimal residual donor cells are detected in the pre-DLI chimerism studies, hematopoiesis may not recover without the infusion of donor hematopoietic stem cells in the donor leukocyte product.
5. Studies regarding manipulation of DLI product are early, and the impact on the risk of marrow aplasia is not defined.

30.4 Risk Factors for Graft Failure

1. HLA incompatible graft
2. Matched unrelated donor graft
3. Alternative donor graft (cord blood and haploidentical donors)
4. Aplastic anemia (especially patients who were heavily transfused pre-HSCT)
5. Nonmalignant disorders (e.g., thalassemia)
6. Inadequate host immune suppression achieved with pre-HSCT conditioning regimen
7. T cell depletion or ex vivo purging
8. Infections (e.g., CMV reactivation)
9. Inadequate cell dose (See Table 30.1) based on choice of donor and/or product source.
10. Myelotoxin exposure (ganciclovir, ACE inhibitors, trimethoprim/sulfamethoxazole, vancomycin, linezolid, H_2 blockers, etc.)
11. Damaged marrow microenvironment
12. Allosensitization

Table 30.1 Recommended cell dose based on product type

Type of product	TNC/kg body weight of recipient	CD34+ cell/kg body weight of recipient
Bone marrow	$>2\times10^8$	
Peripheral blood stem cells	$>2\times10^8$	$>3\times10^6$
Double cord blood—each unit	$>2\times10^7$	
Single cord blood—5/6 match	$>2.5\times10^7$	
Single cord blood—4/6 match	$>5\times10^7$	
T cell depleted		$>5\times10^6$
Haploidentical		$>5\times10^6$

30.5 Diagnosis

1. Peripheral blood cell counts. Previous studies have shown that a leukocyte count of $< 200/mm^3$ on day + 16 post-HSCT is a strong predictor of subsequent primary graft failure.
2. Bone marrow aspirate and biopsy
    a. In both autologous and allogeneic recipients, bone marrow studies demonstrate a hypocellular marrow with no identifiable myeloid, erythroid, or megakaryocytic precursors.
3. Chimerism studies
    a. Fluorescent in situ hybridization (FISH)/cytogenetics for sex-mismatched recipient/donor
    b. Variable number of tandem repeats (VNTR) for sex-matched recipient/donor. These studies require pre-HSCT storage of DNA material (blood) from both donor and recipient.
4. Disease-specific double-fusion products (i.e., BCR/abl PCR)
5. CMV PCR, HHV6 PCR, Parvovirus PCR
6. Ensure nutrients important to hematopoiesis are adequate
    a. Methylmalonic acid, homocysteine, and copper levels
    b. Thyroid function studies

30.6 Treatment

1. Autologous HSCT recipients
    a. Hematopoietic growth factors (e.g., filgrastim +/− sargramostim) are more successful in treating hematopoietic failure than graft rejection.
    b. Consider dose escalated filgrastim at doses of 10 mcg/kg/day or 5 mcg/kg BID.
    c. Stem cell boost without additional conditioning provided the patient has additional stem cells cryopreserved.
    d. Consider agents that may stimulate hematopoietic stem cells.
        i. Trilineage hematopoietic responses were demonstrated in patients receiving eltrombopag (Promacta®), a thrombopoietin receptor agonist, for severe aplastic anemia.
        ii. Androgenic steroids (i.e., danazol) are early in studies in post-HSCT marrow failure.

2. Allogeneic HSCT recipients
    a. Hematopoietic growth factors (e.g., filgrastim +/− sargramostim) are more successful in treating hematopoietic failure than graft rejection.
        i. Consider dose escalated filgrastim 10 mcg/kg/day versus 5 mcg/kg BID.
    b. Stem cell boost +/− additional pre-infusion conditioning agents based on availability of original donor/product and assessment of the degree of host versus donor CD33 + and CD3 + chimerisms.
    c. Utilization of a different donor (i.e., cord blood or haploidentical donor) after fludarabine-based conditioning +/− TBI for engraftment failure shows promise.
    d. Augmentation of immunosuppression can be considered, particularly in the setting of decreasing donor chimerism.
    e. Pharmacist's review to identify myelotoxins for potential change in therapy.
    f. Treatment of active infections.
    g. Folic acid, vitamin B 12, and copper supplementation if deficiency is identified.

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Chapter 31
Secondary Malignancies

Ashley Manning

Approximately 50,000 patients undergo hematopoietic stem cell transplantation (HSCT) worldwide each year. Advancements in the field have led to increased survival rates for these patients. Long-term HSCT survivors are at risk for developing secondary malignancies, representing the fourth leading cause of nonrelapse-related death in patients who survive more than 2–5 years after HSCT. Although relatively rare, secondary malignancies are often associated with significant morbidity and mortality. The incidence of secondary malignancies continues to increase across the survivor's lifespan requiring heightened awareness and ongoing surveillance for the duration of the transplant recipient's life.

31.1 General Risk Factors

1. Total body irradiation (TBI)
   a. Induces double-strand DNA breaks leading to genomic instability and molecular alterations
   b. Increased risk with higher total cumulative doses
   c. Decreased risk with fractionated dosing
2. Chemotherapy agents (see Table 31.1)
   a. Alkylating agents
      i. Latency period of 3–8 years.
      ii. Commonly associated cytogenetic abnormalities include 5-, 7-, 5q-, and 7q-.
      iii. May present with myelodysplasia.

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Table 31.1 Characteristics of tAML/MDS

	Alkylating agents	Topoisomerase II inhibitors
Latency	3–8 years	2–3 years
Incidence	2–20%	2–12%
Myelodysplastic phase	Present	Absent
FAB type	M1, M2	M4, M5
Cytogenetics	5-, 7-, 5q-, 7q-	11q23 deletion and translocation
Pathogenesis	Tumor suppressor genes, RAS mutations	Translocations

b. Topoisomerase inhibitors

   i. Latency period of 2–3 years.
   ii. Commonly associated cytogenetic abnormalities include 11q23 deletion and translocation.
   iii. Does not typically present with myelodysplasia.

c. Lenalidomide maintenance therapy post-autologous HSCT for myeloma

   i. Increasing utilization given studies which have shown a benefit in both progression-free and overall survival.
   ii. Randomized trials have shown an increased numerical incidence of secondary primary malignancies of 8% in patients receiving lenalidomide maintenance compared to 3–4% of those patients not receiving maintenance therapy. This observation was not statistically significant.
   iii. Cause is likely multifactorial.
   iv. Additional long-term follow-up will be required for confirmation of these findings.
   v. In a recently published trial of approximately 2500 multiple myeloma patients who received lenalidomide as primary therapy, the cumulative incidence of second malignancies at 5 years was 6.9%, compared to 4.8% in patients who did not receive lenalidomide.

      - 3.8% incidence of solid malignancy
      - 3.1% incidence of hematologic malignancy
      - Significantly increased risk of secondary hematologic malignancy in patients who received lenalidomide + melphalan compared with patients who received melphalan alone (HR 4.86)

3. Chronic graft-versus-host disease (cGVHD) following allogeneic HSCT

   a. Genomic alterations have been identified, especially in the epithelium of the oral cavity.
   b. Frequency of these events exceeds the incidence of secondary malignancies suggesting additional factors play a role in the pathogenesis.

      i. Complex immune defect associated with cGVHD

4. Oncogenic viruses including human papilloma virus (HPV) and Epstein Barr virus (EBV)
5. Predisposition to carcinogenesis
    a. Age
    b. Gender
    c. Lifestyle choices

31.2 Incidence

1. Reported cumulative incidence of secondary malignancies remains low
    a. Post-allogeneic HSCT
        i. 1.2–1.6 % at 5 years
        ii. 2.2–6.1 % at 10 years
        iii. 3.8–14.9 % at 15 years
    b. Post-autologous HSCT for lymphoma
        i. 2.54 % at 5 years
        ii. 6.79 % at 10 years
        iii. 9.14 % at 15 years
    c. Post-autologous HSCT for myeloma
        i. 5.3 % at 5 years
        ii. 11.2 % at 10 years

31.3 Onset

1. Typically, there is a latency period of 3–5 years preceding the development of secondary malignancies following HSCT but cases occurring earlier have been reported.

31.4 Types of Secondary Malignancies

1. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) following **autologous** HSCT

a. Estimates of incidence of *therapy-related* MDS and AML (tMDS/AML) vary widely between 1 and 14 % at 3–15 years after autologous HSCT for lymphoma

   i. 3.1 % at 5 years
   ii. 4.5 % at 10 years
   iii. 6.8 % at 15 years

b. tMDS/AML is felt to be a consequence of the initial cytotoxic therapy for the primary malignancy rather than of the HSCT procedure and may represent a mutated stem cell pool that is transferred within the thawed cryopreserved product.

c. Risk factors

   i. Age
   ii. Extent of pre-HSCT therapy
   iii. Exposure to alkylating agents and TBI
   iv. Stresses imposed on stem cells during mobilization therapy and engraftment

      - Priming chemotherapy induces genotoxic damage in hematopoietic stem cells which are later infused during autologous HSCT
      - Proliferative stress during engraftment with many replication cycles has been proposed to contribute to genomic instability through telomere shortening

d. Prognosis

   i. Median overall survival of therapy related MDS/AML after autologous HSCT is 6–12 months although data regarding survival after salvage treatment with allogeneic HSCT are limited.

2. MDS and AML following **allogeneic** HSCT.

   a. Limited data are available regarding tMDS/AML following allogeneic HSCT, however case reports have been documented.

3. *Donor-derived* MDS/AML following allogeneic HSCT

   a. Incidence has been reported at < 1 %
   b. A European Group for Blood and Marrow Transplant (EBMT) study demonstrated median time to onset of 17 months with no specific risk factors identified

4. Posttransplant lymphoproliferative disorder (PTLD)

   a. A heterogeneous group of abnormal B-lymphoid proliferations that typically occurs in the setting of profound immunosuppression after allogeneic HSCT and presents as clinically aggressive and frequently fatal lymphomas

b. Vast majority are associated with EBV

   i. After allogeneic HSCT, PTLD is identified in the marrow derived, or adoptively transferred donor cells, differing from PTLD occurring in solid organ transplantation where it is of recipient origin

c. Incidence

   i. Cumulative incidence is 1–2% but may be as high as 8–10% among patients with multiple risk factors.
   ii. PTLD is rare following autologous HSCT and most commonly occurs in those patients requiring immunosuppressive therapy (i.e., steroids). However, there has been an increase in reported cases with use of CD34+ selected autologous HSCT in both adult and pediatric patients.

      − 80% of PTLD occur within 6 months to 1 year post-HSCT and incidence declines among survivors > 1 year post-HSCT.

d. Frequently presents with fever, lymphadenopathy, and hepatopslenomegaly
e. The two strongest risk factors are exposure to EBV and degree of immunosuppression, particularly T cell depleted allografts. Active surveillance, often weekly, for EBV reactivation using quantitative PCR is being increasingly advocated in high-risk patients.

   i. In vivo T cell depletion with antithimocyteglobulin (ATG) or alemtuzumab
   ii. Ex vivo T cell depletion
   iii. Alternative donor transplants such as haploidentical donors or cord blood

f. Preemptive therapy with CD20-active agents such as rituximab is being studied
g. Treatment requires restoration of immune response against EBV and elimination of EBV and neoplastic B cells.

   i. Withdrawal of immunosuppression if possible
   ii. Infusion of nonspecific donor T cells although the risk of GVHD is high
   iii. Infusion of EBV-specific T cells is under investigation

5. Secondary solid malignancies
   a. Skin/oral

      i. Occur in both autologous and allogeneic HSCT recipients
      ii. A large cohort of patients studied at The Fred Hutchinson Cancer Research Center (FHCRC) found the incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) to be 6.5% and 3.4% at 20 years, respectively, after allogeneic HSCT.
      iii. Total body irradiation (TBI) was a significant risk factor for BCC with higher incidence in younger and light-skinned patients.

iv. Acute GVHD increased risk of SCC whereas chronic GVHD increased the risk of both BCC and SCC.
v. Squamous cell carcinoma of the head and neck can arise from the buccal mucosa, salivary glands, gingiva, lip or tongue.
vi. Risk factors for oral cancer include oral cGVHD and underlying Fanconi anemia.

b. Lung

i. Recent study of patients receiving busulfan-cyclophosphamide conditioning reported an increased risk of lung cancer, especially among those with a prior history of smoking.

c. Hepatic

i. Long-term survivors with chronic Hepatitis C (HCV) represent a particularly high-risk cohort for cirrhosis and subsequent hepatocellular carcinoma.
ii. Incidence

- One historical retrospective analysis of patients infected with HCV during the HSCT period showed the incidence of cirrhosis to be 11 and 24% at 15 and 20 years, respectively
- Incidence of secondary cancer has been shown to reach 16% in HCV positive patients at 20 years.

d. Thyroid

i. Large cohort studied by the EBMT showed an increased incidence of thyroid cancer in patients who had undergone HSCT.

- The standardized incidence ratio of thyroid cancers in the population who underwent HSCT was 3.26 in comparison with the general population.

ii. Risk factors

- Younger age (<20) at HSCT was the strongest risk factor.
- Irradiation
- Female sex
- Chronic GVHD

e. Breast cancer

i. A retrospective analysis of 3337 female allogeneic HSCT survivors >5 years post-HSCT (FHCRC and EMBT registries) showed the cumulative incidence of breast cancer to be 11% at 25 years. This is compared to the overall incidence of 12% over a woman's lifespan.
ii. Risk factors

- Exposure of the breast tissue to radiation
- Disruption of ovarian function by alkylating agents
- Younger age (<18) at transplant

Table 31.2 Guidelines for screening for secondary solid cancers in allogeneic HSCT recipients

Site	Screening recommendations
Breast	Mammogram annually starting at age 40 years; begin at age 25 years or 8 years after radiation, whichever occurs later, in women who have received >20 Gy to chest region
Cervix	Papanicolaou (PAP) smear every year (for regular PAP test) or every 2 years (for liquid based PAP test); after age 30, if patient has had three consecutive normal tests, may screen every 2–3 years
Colorectal	Beginning at age 50, fecal occult blood annually and or flexible sigmoidoscopy every 5 years, or double-contrast barium enema every 5 years, or colonoscopy every 10 years; certain high-risk groups (i.e., patients with inflammatory bowel disease) may need earlier and more frequent screening
Lung	Yearly pulmonary examination with imaging as appropriate
Oral	Yearly oral cavity examination
Thyroid	Yearly thyroid examination
Skin	Skin examination as part of annual periodic health examination

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31.5 Screening and Preventive Practices

1. All HSCT recipients should be advised to reduce UV skin exposure through the use of high SPF sunscreen and/or skin coverage.
2. Patients should be advised of the risks of secondary malignancies and encouraged to perform screening self-examination such as breast, testicular, and skin.
3. Avoidance of high-risk behaviors is recommended including tobacco use, exposure to passive tobacco, or excessive unprotected UV skin exposure.
4. History and physical examination should be performed yearly, including symptom review for secondary malignancies in all HSCT recipients and the guidelines for screening for secondary solid cancers in allogeneic HSCT recipients should be followed (see Table 31.2).
5. Particular attention should be given to the oral cavity examination in patients with history of severe oropharyngeal chronic GVHD.
6. HPV vaccination is currently considered optional post-HSCT. Follow recommendations for general population in each country.
   a. Per CDC guidelines, HPV vaccination is routinely recommended for all 11- and 12-year-old girls and boys.
   b. The vaccine series can be started beginning at age 9.
   c. Vaccination is also recommended for 13- through 26-year-old females and 13- through 21-year-old males who have not completed the vaccination series.
   d. No data exist regarding the time after HSCT when vaccination can be expected to induce an immune response.

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Chapter 32
Posttransplant Relapse

Marlise R. Luskin and David L. Porter

Outcomes after autologous and allogeneic hematopoietic stem cell transplant (HSCT) have improved substantially as advances in supportive care and conditioning regimens, such as the introduction of reduced-intensity allogeneic transplants, have dramatically reduced treatment-related morbidity and mortality. Unfortunately, disease relapse remains a major cause of transplant failure and patient mortality. Center for International Blood and Marrow Transplant Research (CIBMTR) data identify relapse as the cause of 78% of autologous transplant-related deaths, 34% of related allogeneic transplant deaths, and 23% of unrelated transplant deaths. A lack of effective and well-tolerated therapeutic options for relapse after transplant is a major barrier in the care of these patients. To optimize outcomes, management of disease relapse after HSCT must be highly individualized and based on both patient and disease features.

32.1 Relapse After Autologous HSCT

1. Autologous HSCT is offered with either curative intent or with the goal of improving progression-free and overall survival. After relapse, further therapy may be pursued with either curative or noncurative intent and is guided by status and type of disease, prior therapies, and host factors.
2. In heavily pretreated patients, limited marrow reserve and patient comorbidities may limit eligibility for further cytotoxic chemotherapy including second transplant.

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3. Benefit of second autologous HSCT is predicted by underlying malignancy and, in some cases, history of durable response to first transplant (> 1 year), and continued presence of chemosensitive disease.
4. Allogeneic HSCT with reduced-intensity conditioning may be considered as a curative treatment option for select patients who relapse after autologous HSCT.
5. Targeted and other novel therapies play an expanding role in the management of patients who relapse.
6. Maintenance and consolidation strategies, generally using novel agents, are used with the goals of improving durability and rate of cure after transplant.

32.2 Relapse After Allogeneic HSCT

1. Allogeneic HSCT is offered to patients with high-risk hematologic malignancies with curative intent.
2. Management of relapse is influenced by status and type of disease, prior therapies, and host factors including performance status, comorbidities, presence of transplant-related complications (particularly the presence of active graft-versus-host disease (GVHD)), and timing and kinetics of disease relapse.
3. Allogeneic HSCT is successful in part due to the graft-versus-leukemia (GVL) effect. GVL effect is particularly potent against chronic myelogenous leukemia (CML), but has been identified to be active against acute myelogenous leukemia (AML), and acute lymphoblastic leukemia (ALL), as well as most other hematologic malignancies. Disease relapse may be addressed by manipulations that enhance the GVL effect; however, these approaches are limited in the setting of active GVHD.

    a. Withdrawal of immunosuppression

        i. Not effective in the majority of patients but there are anecdotal responses in relapsed leukemia. May be most effective to control some cases of low tumor-burden, indolent disease relapse.
        ii. High risk of GVHD.

    b. Donor lymphocyte infusions (DLI)

        i. Most successful in patients with relapsed chronic phase CML (durable remission rates of approximately 70%).
        ii. Less successful in relapsed AML (10–40% overall survival).
        iii. Although GVL activity is important to cure ALL with allogeneic HSCT, there is limited benefit for conventional DLI.
        iv. Patients who relapse early (within 6 months after transplant) are unlikely to benefit.
        v. Reasons for failure include rapid disease kinetics and ability of leukemia cells to evade immune recognition and blunt the immune response.

vi. Responses occur several weeks after infusion of donor lymphocytes necessitating administration of cytotoxic chemotherapy prior to DLI in settings of high kinetic relapse. It is unclear if pre-DLI chemotherapy improves outcome.
vii. DLI is more successful in the setting of minimal disease burden/complete remission.
viii. Low-dose DLI and subsequent dose escalation

- May minimize risk of GVHD and retain GVL activity in relapsed chronic phase CML.
- Is not practical for relapsed advanced phase CML or acute leukemia given the pace of disease progression.

ix. The use of growth factor mobilized DLI versus unstimulated DLI may speed hematopoietic recovery after cytotoxic chemotherapy, but unclear if this improves outcome.
x. Methods to improve DLI are being actively investigated (see 32.3.4.below).
xi. Toxicities are significant and include GVHD, marrow aplasia, and increased risk of infection.

c. Second allogeneic HSCT

i. Myeloablative approaches are limited by significant treatment-related morbidity and mortality. A minority of patients will be eligible.
ii. Reduced-intensity approaches may be considered in select patients

- Often considered after failed autologous HSCT for lymphoma and myeloma.

iii. Known to achieve long-term disease control (20–30 %) in groups of highly selected patients but with high risk of relapse and nonrelapse morbidity and mortality (40 % each). Optimal patient selection (identification of who is most likely to benefit), donor selection (same versus different donor), and conditioning regimens are not well defined.

d. Chemotherapy

i. Inadequate efficacy and durability in the relapse setting.
ii. Limited use in heavily pretreated and vulnerable patient populations.
iii. May be used as a bridge to DLI or second allogeneic HSCT.

e. Supportive care and palliation

1. Appropriate for patients unlikely to benefit from or unable to tolerate available therapy.

4. Disease-specific approaches
   a. CML
      i. Tyrosine kinase inhibitors (TKIs)
         - Imatinib, dasatinib, nilotinib, bosutinib, or ponatinib. Choice of agent determined by side-effect profile, previous exposure, and BCR/abl mutational analysis.
         - May be sufficient in chronic phase relapse.

      ii. DLI dramatically effective but associated with significant GVHD
         - In CML relapsed in chronic phase, low-dose DLI with subsequent dose escalation may minimize the risk of GVHD and retain GVL activity.
         - Not practical for advanced phase relapsed CML.

      iii. TKI versus DLI
         - Choice of therapy and decision to use a single approach or the two in combination depends on disease stage at relapse, prior treatment, BCR/abl mutational analysis and sensitivity of CML to TKI, and patient comorbidities.

      iv. Blast phase
         - TKI plus ALL regimens for lymphoid blast crisis.
         - TKI plus AML regimens for myeloid blast crisis.
         - Remission duration likely to be short and should be followed by TKI, DLI, or other novel therapies.

      v. Clinical trial preferred.

   b. AML
      i. DLI most effective for patients who relapse later (>6 months after transplant) and achieve remission prior to DLI. Role of pre-DLI chemotherapy uncertain.
      ii. Intensive cytotoxic regimens: Conventional regimens such as anthracycline plus cytarabine, high dose cytarabine, fludarabine/cytarabine/G-CSF (FLAG), clofarabine, or others depending on comorbidities and prior exposures.
      iii. Hypomethylating agents: 5-azacytidine, decitabine.
      iv. Targeted therapies: Sorafenib in FLT3-ITD+AML, other promising agents in clinical trials.
      v. Clinical trial preferred.

   c. ALL
      i. DLI of limited efficacy particularly in adults.
      ii. Conventional regimens: cyclophosphamide/adriamycin/vincristine/ dexamethasone (hyper-CVAD), high-dose cytarabine/mitoxantrone (HAM),

FLAG, nelarabine, clofarabine, or others depending on disease subtype, comorbidities and prior exposures.

iii. Novel therapies are promising and should be considered preferably in the context of a clinical trial

- TKIs if Philadephia chromosome positive (Ph+) depending on prior exposure and sensitivities.
- Blinitumumab or other antibody therapies.
- Chimeric antigen receptor modified T cells (CAR-T).

iv. Clinical trial preferred.

32.3 Areas of Active Research and Future Directions

Improvements are needed in our ability to prevent, detect, and treat disease relapse after HSCT. There have been few recent breakthroughs but many new approaches are in development. Proceedings from the second National Cancer Institute Workshop on Biology, Prevention, and Treatment of Relapse after Hematopoietic Stem Cell Transplantation ighlighted many of these strategies.

1. Relapse prevention
   a. Identification of patients at highest risk of relapse in whom potential toxicity of additional therapy (at any phase of the transplant process) is outweighed by benefit of improved disease control.
   b. Pretransplant
      i. Improve conditioning regimens to achieve better disease control prior to administration of autologous or allogeneic graft.
      ii. Incorporation of novel agents (e.g. monoclonal antibodies, small molecular inhibitors of signaling pathways, etc.) may allow for improved disease control and deeper remissions without added toxicity.
   c. Transplant modifications
      i. Improved donor selection (e.g., by incorporating KIR genotyping) and graft engineering (manipulations of the donor graft to promote antileukemia activity with less GVHD).
   d. Posttransplant prophylactic interventions
      i. Early withdrawal of immunosuppression, with or without prophylactic DLI.
      ii. Significant risk of GVHD.
2. Maintenance strategies to prevent relapse and support development of allogeneic immune response.
   a. In AML, maintenance low-dose azacitidine may improve event-free and overall survival.

b. In Ph+ ALL, TKI maintenance may improve long-term outcomes.
c. Post-transplant FLT3 inhibitors, monoclonal antibodies and other tumor-targeted immunotherapies may be effective in this setting and should be considered, preferably in the context of a clinical trial.
d. All maintenance strategies need to be evaluated for their impact on immune reconstitution.

3. Post-transplant monitoring and early intervention at preclinical relapse

a. Goal is to intervene before overt relapse when disease burden is minimal. Many therapeutic strategies may be more effective in this setting including targeted therapies and low-dose DLI.
b. Determine optimal methods and timing for monitoring minimal residual disease (MRD) and identify preclinical relapse.

i. For instance, the RELAZA trial showed that initiation of 5-azacytadine in the setting of decreasing CD34+ cell donor chimerism (suggesting imminent relapse) improved or stabilized chimerism and delayed time to overt AML relapse.

c. Identify most appropriate therapies, balancing efficacy and toxicity.

4. Clinical relapse

a. Enhancement of DLI

i. Unmodified DLI is most effective for chronic phase CML and indolent lymphomas.
ii. Limited efficacy for acute leukemias.
iii. Associated with substantial risk for GVHD-related morbidity.
iv. Due to rapid tumor growth after leukemia relapse, the administration of cytotoxic chemotherapy prior to DLI may provide disease control as GVL activity is delayed after DLI. Outcomes in AML and ALL despite pre-DLI chemotherapy are still poor.
v. Administration of cytokines (IFN-α, GM-CSF) could improve the success of DLI by enhancing tumor antigen presentation and T cell activation.
vi. IFN may increase the risk of GVHD, but is appropriate to study in combination with DLI.
vii. Ex-vivo activated DLI.
viii. Approaches to expand specific T cell and donor cell subsets are important for GVL induction and may improve the efficacy and specificity of DLI. For example, expansion of T cells that recognize hematopoietic-expressed minor HLA antigens or other tumor-associated antigens.

b. NK cells may provide important GVL activity in the setting of haploidentical transplantation.

1. Augmenting NK cell activity may be useful in treating relapse.

- Administration of IL-15 may enhance NK-cell mediated GVL activity.

c. Interruption of inhibitory effect on T cell activation via administration of anti-CTLA4 antibodies or anti-PD1/PDL1 antibodies (check point inhibitors) may enhance GVL with and without DLI though may result in GVHD.
d. Biologic and noncellular-targeted therapies
    i. Increasingly, novel therapies targeting specific molecular targets are being developed to control cancer cell proliferation at relapse.
    ii. FLT3 inhibitors, newer TKIs, monoclonal antibodies, bispecific antibodies such as blinitumumab, proteosome inhibitors, and IMiDs.
    iii. These drugs often have less systemic toxicity and therefore are tolerable in heavily pretreated patients. Some approaches that stimulate immune functions (lenalidomide, anti-CTLA4 therapy) may induce GVHD.
    iv. Use as monotherapy may be insufficient. Any of these interventions can be considered and tested in combination with or as a bridge to cellular therapy.
    v. Monitoring for unexpected effects and "targets" essential as drugs may have unique toxicity and unanticipated outcomes in the post-transplant setting.
e. Cellular-targeted therapies
    i. Isolation and expansion of tumor-specific T cells. This approach is technically difficult, patient specific, and hard to generalize.
    ii. Genetically modified T cells expressing specific novel T cell receptors or chimeric antigen receptors (CARs) are being developed to target tumor-expressed antigens
        − CAR-T can be generated against CD19 for CD19+ B cell malignancies.
        − CAR-T can kill in an antigen-specific but HLA-independent manner. Some studies show these cells are able to expand, persist in vivo, and provide long-term "vaccine-like" antitumor activity. They have been used successfully in refractory CLL and ALL.
        − Approach limited by the lack of tumor-specific targets in hematologic malignancies.

5. Future directions
a. Improved understanding of mechanisms of disease relapse and resistance will facilitate the development of new therapies and strategies for use in post-transplant setting.
b. Improved understanding of the significance of MRD test results may permit more appropriate early management when interventions are most likely to be successful.
c. Deeper understanding of the pathophysiology of GVL will facilitate our ability to deliver enhanced GVL with minimal GVHD.
d. Identification of new tumor antigens will allow development of targeted therapy that should be both safer and more effective than currently available approaches.

e. It is critical that a mechanism is developed to rapidly study new drugs and new approaches in prospective clinical trials. Ideally all patients who relapse after transplant should be treated on these clinical trials.

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Chapter 33
Palliative Care

Mary Denise Smith and Amy Guthrie

Patients and their families undergoing hematopoietic stem cell transplantation (HSCT) experience profound changes from diagnosis, during HSCT and through recovery, relapse, or death. Factors affecting their quality of life include pain and physical symptoms, emotional and psychological stresses, alterations in traditional roles and self-concept, and the social and economic impact of serious illness. Given the impact of HSCT on patients and their families, the prolonged period of decreased functional capacity, high symptom burden, and uncertainty of outcome, the integration of palliative care into the model of care for this patient population is indicated.

The benefits of early referral to palliative medicine have been demonstrated for patients with newly diagnosed advanced non-small cell lung cancer. Patients were randomly divided into two groups with one group receiving traditional oncologic care. The second group received traditional oncologic care and underwent evaluation by a palliative care specialist within 3 weeks of enrolment and then at least monthly thereafter. Patients who were seen by a palliative care specialist had improved pain and symptoms, improved mood, a more accurate perception of their prognosis, and improved median survival by 2.6 months. It is impossible to make a direct comparison to the patients undergoing HSCT. However, this randomized study confirms that there can be benefits to early referral to a palliative care specialist.

Three main concerns raised by hematologist–oncologists regarding referrals to palliative care specialists have been identified in the literature. These include:

1. Prognostication is difficult given the often rapid and unpredictability of change in a patient's status.

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2. Palliative care clinicians lack experience providing care to patients with hematologic malignancies.
3. There may be a perception of different goals between the two specialists.

The care of patients undergoing HSCT includes many issues approachable by palliative care. However, care experts may not agree regarding the appropriate timing of a palliative care consult. Many oncologists view a palliative care consult as appropriate when all treatment options have been exhausted, while palliative care specialists may view supportive interventions provided by oncology as nonbeneficial and burdensome. Patients with hematologic malignancies have an unpredictable trajectory associated with episodes of critical illness and recovery or rapid change in status and life-ending complications. The challenge is for the two specialties to reach a mutual understanding of what each can bring to enhance the quality of life of patients and their families.

The World Health Organization (WHO) defines palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems physical, psychological, and spiritual. It is applicable early in the course of an illness, in conjunction with other therapies that are intended to prolong life such as chemotherapy or radiation."

A common misconception is that palliative care and hospice are identical, while in reality, there are significant differences.

1. Palliative care can be provided while all other disease-modifying therapies are continued.
2. WHO recommends referral to palliative medicine be based on patient needs and be offered at any stage of treatments with a focus on supporting both the patient and their family members.
3. Referral to palliative medicine can be patient and purpose specific. The reason for a referral is based on the patient's needs and may consist of a single visit which is symptom specific, several visits to manage ongoing symptoms until a durable plan is created, or ongoing visits with both clinicians focusing on different patient needs.

33.1 Core Functions of Palliative Care Related to Direct Patient Care

The skill and knowledge required to provide expert palliative care are determined by the following core functions:

1. Prevention, assessment, and treatment of pain and other physical symptoms including dyspnea, nausea, insomnia, delirium, agitation, confusion, anorexia, vomiting, constipation, and fatigue.

2. Emotional, spiritual, and psychological support for patient and family.
3. Communication of the expected illness trajectory including prognosis while assisting the patient, or family, to clarify values and goals of care that support emotional well-being throughout the course of the disease.
4. Development of a safe plan for discharge connecting the patient and family with community resources that can provide adequate support.
5. Transition to hospice services when the patient is eligible and desires that level of support.

A referral to palliative care is appropriate when the patient's needs exceed the available skills or resources that the HSCT team can provide to address core functions of palliative care. Palliative care specialists work together with the HSCT team to develop a treatment plan with the focus of lessening patient and family suffering throughout the treatment course. The involvement of palliative care early in the treatment process establishes relationships which will ease the transition to hospice care and intensive symptom management if cure is not attainable.

The American Society of Clinical Oncology (ASCO) promotes and provides an evidenced-based quality of care framework that leads to outstanding treatment for oncology patients. Along with The National Quality Forum (NQF), ASCO has developed the Quality Oncology Practice Initiative (QOPI). This initiative has established quality standards in the domains of core practice, end-of-life care, symptom management, and disease-specific measures to guide optimal oncology treatment. Using QOPI measures as a guide, this chapter will discuss advance care planning, care of the caregiver, and the physical side effects that most commonly produce suffering in the HSCT recipient.

Even though HSCT may be the only option for survival, it is potentially life-altering or fatal; recipients may feel overwhelmed with these truths. The patient's perspective guides treatment choices throughout all phases of the HSCT process. For that reason, it is important to provide a balanced supportive treatment approach focusing on both physical and psychological well-being. If the multidimensional causes of suffering are addressed adequately, the treatment experience can be positive for everyone: patient, family, and care providers. Outcomes are enhanced when the patient receives holistic care, addressing the combination of physical, social, psychological, emotional, and spiritual stressors the patient and family may endure.

33.2 Advance Care Planning

An important task for patients and their families when diagnosed with a life-threatening illness is to plan for the potential of the patient not surviving their illness or for times when they may not be able to make important decisions. It is challenging for many patients, as well as clinicians, to discuss these issues due to the fear of not being optimistic, of taking away hope, or of causing the event by discussing

its possibility. In studies with patients and families, most report that even when the discussion is difficult, they are grateful for accurate information related to the risks associated with their illness.

1. Every patient should be given the opportunity to complete an Advance Directive for health care
    a. Identifies a surrogate decision maker and the scope of their authority, and insight into the patient's values and decisions they would make for themselves.
    b. Completion of this task frequently eases the burden on surviving family and friends, increases the chance that decisions are being made which are consistent with the patient's values, and are being made by the person of their choice.
    c. Frequently when patients become acutely ill in the hospital setting, there are regrets that this task was left undone.
2. Additional tasks to be addressed
    a. Financial power of attorney.
    b. Completion of wills.
    c. Sharing of information necessary to the smooth running of the household, employment process, and personal legacy work.
3. By providing guidance, encouragement, information, and support to our families to complete these tasks, future regrets and hardships may be avoided.

33.3 Support for Caregivers

HSCT recipients are dependent on caregivers during the treatment and recovery phases of their illness.

1. Fatigue is a major symptom leading to reliance on caregivers for completion of daily tasks, coordination of medical appointments, management of medications and ongoing medical tasks, monitoring for side effects, provision of emotional and psychological support, recognition of complications, and physical care.
2. Caregivers report a significant amount of stress associated with this role, disruption of their own life, stress on multiple family members, and financial burdens.
    a. The relationship between the patient and their caregivers influences the coping of both parties.
3. Palliative care interventions are focused on both the patient and the caregiver.
    a. The focus for the caregiver is on assessment of their strengths, resources, role enactment, degree of caregiver burden, and early interventions to reduce caregiver burdens, provision of support for the caregiver, and addressing ongoing concerns.

33.4 Common HSCT-Associated Side Effects

1. Suffering
    a. Invasive medical procedures, distressing physical symptoms, social isolation, uncertainty regarding outcomes, changes in body image, and a lost sense of control, all increase a patient's vulnerability and suffering.
    b. If these multidimensional features of suffering are improved, the experience of everyone concerned—patient, family, and the HSCT team—will improve.
    c. Relieving the suffering associated with HSCT begins with an understanding of the patient's unique perspective of the experience.
        i. Although it is important to know the diagnosis, pre-HSCT comorbidities, source of stem cells and degree of histocompatibility, conditioning regimens, and complications, it is equally important to remain aware of the patient's understanding throughout process.
        ii. This awareness will require obtaining feedback from the patient and the people that support them in their life.
2. Pain
    a. The first goals of pain management are to gain and sustain the patient's trust. To achieve those goals, one must work quickly and effectively to achieve relief.
        i. There are multiple reasons for the undertreatment of pain including malabsorption, underdosing of analgesics, and nausea/vomiting.
        ii. Understanding pharmacokinetics of the medications used and the different routes of administration will improve dosing efficacy.
        iii. The best approach is to involve an interdisciplinary team including a clinical social worker, psychologist, or psychiatrist.
            - Consider antidepressants and/or anxiolytics
            - Provide routine follow-up by a palliative care team provider
    b. The hospitalized HSCT patient's pain treatment differs from the standard approach to cancer pain management.
        i. These patients are frequently unable to take oral, subcutaneous, rectal, or transdermal opioids due to effects of therapy on the skin (GVHD) and lining of the GI tract (mucositis, infection, GVHD).
        ii. Thrombocytopenia may also lead to excessive bruising or bleeding if using the subcutaneous route.
        iii. Effective adjuvant therapy using acetaminophen and nonsteroidal anti-inflammatory drugs (NSAiDs) are often contraindicated and typically can only be dosed orally.
        iv. Opioid administration is often necessary and most effective in this patient population.

c. A common mistake is to choose a "standard" dose rather than a dose that is ideal for the patient.

   i. It is best to give an initial "standard" dose and observe the effect.
   ii. After a clear assessment of the change in pain level (e.g., using a 0–10 pain scale), consider doubling the dose if the pain remains severe (8−10 on the pain scale). Continue to double the dose until the patient experiences an improvement in the pain reported or experience dose-limiting side effects.
   iii. Continue to assess for intolerance of medications such as sedation, hallucinations, etc.
   iv. Consider continuous infusion narcotic dosing as indicated as this may provide more sustained pain relief than bolus or intermittent dosing.

d. To calculate appropriate continuous infusion narcotic dosing, total the amount of opioid required to achieve relief from the bolus doses administered during the dose-finding period. Divide the total by the amount of time to achieve relief; the product is the new basal rate.

   i. The most common mistake seen is the practice of incremental changes in the basal rate without dose finding of the appropriate bolus dose.

e. Frequently, patients may have physical symptoms enhanced by their emotional status and psychological coping strategies.

   i. Addressing fear, anxiety, depression, prior trauma, and drug abuse is necessary to adequately assess their pain.
   ii. Patients who chemically cope with stressful situations can be expected to continue this coping mechanism while hospitalized.
      − These patients may exhibit behaviors such as requesting specific opiates and dosing techniques and dosing more frequently than prescribed.
      − These patients may present a challenge to the treatment team due to clinician's fear of contributing to an addiction and resentment of being controlled by the patient's requests.
   iii. For optimal treatment, it is important to remember that this behavior may reflect undertreated pain rather than addiction. This is known as pseudoaddiction.
      − Pseudoaddiction is an iatrogenic collection of behaviors mimicking addiction that occurs as a result of undertreated pain.
      − The prevention of pseudoaddiction is accurate management of pain.

3. Nausea and vomiting (N/V) (see also Chap. 21)

a. Because nausea is highly subjective, a thorough assessment must be undertaken to identify all potential causes.
b. Effective treatment geared to the specific emetic pathways can be accomplished with a thorough and accurate history and physical examination.
c. An initial gastrointestinal (GI) assessment should include questions similar to:

i. Does N/V occur prior to or after meals?
ii. Does vomiting occur after nausea, or coughing, or without warning?
iii. Is the N/V associated with colicky pain, diarrhea, fever, or chills?
iv. Is there a pattern or specific times of the day that N/V occurs?
v. Is it intermittent or continuous?
vi. Any recent changes in bowel habits or medication regimen?
vii. Any pain or burning sensations related to N/V?
viii. Are there any other causes that you suspect are triggering the N/V?
ix. Include information regarding appetite, dysphagia, food intolerance, allergies, pain, bowel habits, characteristics of N/V, and past abdominal history (surgeries, liver disease, chemo or radiotherapy, etc.).
x. Additional information includes a current medication list, along with a history of headache, vertigo, and anxiety.

d. A physical examination should involve

i. Inspection of the mouth for oral candidiasis or other oral lesions.
ii. While auscultating the abdomen, high pitched or hyperactive bowel sounds may signify a partial or total obstruction.
iii. Hypoactive or absent bowel sounds suggest an ileus.

e. Laboratory tests should rule out fluid and electrolyte imbalances along with assessment of renal and liver function.
f. Treatment

i. The first line treatment is to reverse any underlying causes.

- The Education for Physicians on End-of-life Care (EPEC) Project simplifies the major causes of nausea and vomiting to "11 Ms of emesis". These causes include the following: metastases, meningeal irritation, movement, mentation, medications, mucosal irritation, mechanical obstruction, motility, metabolic, microbes, myocardial.

ii. Selection of the most effective antiemetic treatment involves identifying the suspected causes of N/V and identifying the pathway(s) causing N/V triggers.

- Choosing the antagonist most responsive to the identified receptor and the route of administration that will ensure the drug reaches the site of action are initial concerns.

iii. Routine administration of the antiemetic, symptom reassessment, and medication titration are important in optimal treatment.

g. Intractable N/V

i. Even with the identification of triggers and the implementation of receptor-specific antiemetics, a minority of patients develop intractable N/V.
ii. Younger patients with pelvic malignancies, patients experiencing anxiety due to treatment or disease unknowns, and those identified with autonomic failure are high incidence populations of intractable N/V.

iii. If symptoms persist and a single agent has been titrated to the maximum recommended dose, adding treatments that are specific to other receptors is frequently effective as more than one emetic pathway is often involved.

h. There are five classes of antiemetics drugs and a group of adjunctive drugs used to treat N/V (see Table 33.1).

i. Empiric treatment begins with a single medication targeting the presumed mechanism of N/V.
ii. Optimize the dose before adding a second medication with a different mechanism of action. Combination therapy may be required in some patients.

i. Chemotherapy-associated N/V

i. *Acute nausea/vomiting* occurs within the first 24 h after chemotherapy, typically within 1–2 h with peak occurring at 4–6 h.
ii. *Delayed nausea/vomiting* occurs > 24 h after chemotherapy.

- Cisplatin: N/V peaks 48–72 h after therapy and then gradually subsides over 2–3 days.
- This delay is also seen with carboplatin, cyclophosphamide, and the anthracyclines.
- The antineurokinin class is the first to show a definitive, yet small, effect.

iii. *Anticipatory nausea/vomiting* is a conditioned response to previous negative experiences. It is a learned response—it is not mediated by the usual emetic neurotransmitters, although benzodiapines have been used with some efficacy

j. Opioid-induced N/V

i. Acute nausea is a side effect of initial opiate therapy and is thought to be due to the direct effects in the chemoreceptor trigger zone and the vestibular apparatus.
ii. Antiemetic treatment should begin with opiate initiation anticipating this side effect.
iii. Patients normally develop a pharmacologic tolerance to this side effect within 5–7 days of initiating therapy, and antiemetics can then be discontinued.
iv. For some patients, changing to a different opioid is also effective.
v. Nausea that emerges after chronic use is most likely due to diminished gut motility and/or constipation, causing pseudo-obstruction. Management is then directed at increasing gut motility and relieving constipation.
vi. Combinations are required for patients with a variety of causes of nausea.
vii. Anti-nausea therapy should maximize the dose of a drug of a single class before combining it with maximized doses of other classes. Combining low doses of drugs of the same classes should be avoided.

Table 33.1 Antiemetic agents

Antiemetic agent	Action	Dosage	Side effects
Anticholinergics/ antimuscarinics	A direct depressant action on the VC. An antispasmodic action on the gut. *Useful for motion sickness and post-operative N/V (PONV)*	*Hyoscine* (scopolamine) SC, IV, IM 0.3–0.6 mg q4–8 h prn *Glycopyrolate* 1–2 mg q8–12 h. *Useful with colicky N/V associated with mechanical bowel obstruction*	'Central cholinergic syndrome' (confusion, disorientation, visual hallucinations) may occur in the elderly Pupil dilation, blurred vision, drowsiness, urinary retention, and dry mouth
Antihistamines	Antagonize the action of histamine at the H_1 receptor *Useful for treating nausea associated with motion sickness, mechanical bowel obstruction, or ↑ICP*	*Meclizine* 25–50 mg 3–4 times/day *Diphenhydramine* 25–50 mg PO 3–4 times/day Hydroxyzine 25 mg PO, IV 3–4 times/day	Drowsiness, blurred vision, confusion
Butrophenones/ Phenothiazines	Dopamine (D_2) antagonists act primarily in the CTZ. *First-line agents for most types of end-of-life N/V*	*Droperidol* IV, IM: 2.5–5 mg q3–4 h *Haloperidol* 0.5–5 mg q4–6 h prn or routinely. Ceiling dose at 30 mg/day *Prochlorperazine* IV, IM, PR, or PO: 5–20 mg q4–6 h prn or routinely (slow onset of action at 2–4 h after peak plasma concentrations) can go as high as 1–2 mg/kg with increased risk of restlessness, sedation, and dry mouth. *Effective in PONV* *Clorpromazine* IV, PR 25–50 mg q6–12 h. Also effective for hiccups *Promethazine* (H_1-receptor antagonist)—avoid use due to excessive sedation and minimal efficacy	Sedation, hypotension, anticholinergic effects, and EPS (dystonia and akathesia) May prolong QT interval, provoking ventricular arrhythmias (more so with Droperidol) *dexamethasone adds to efficacy of haloperidol and metoclopramide.* *Dronabinol adds to procholoperzine's efficacy for chemo induced N/V.* *Give metoclopramide with haloperidol only if haloperidol is a low dose and EPS s/e are not present*
Steroids	Action not clear; May involve ↓ serotonin turnover in the CNS and mediate the cerebral cortex pathway to the VC *Considered second line and can be adjuvant as mentioned above* *Will stimulate appetite and reduce somatic and visceral pain*	*Dexamethasone* IV and PO: 0.5–8 mg q6–12 h	Euphoria, insomnia, hyperglycemia, HTN, and immunosuppression in long-term use *Used as a prophylactic agent for acute and delayed nausea d/t chemotherapy* *Synergistic with serotonin antagonists, metoclpramide, and phenothiazines*

Table 33.1 (continued)

Antiemetic agent	Action	Dosage	Side effects
Hormone, anti-diarrheal	Globally decreases GI secretions. *Effective in refractory nausea, first line for bowel obstruction*	*Octreotide(Sandostatin®)—Must be given as an SQ injection 3 times/day. 50–100 mcg q8 × 48 h or 10 mcg/h continuous infusion SC or IV*	Minimal
Neuroleptic, Atypical neuroleptic		*Quetiapine* 25 mg PO BID and titrate *Olanzapine*: 2.5 mg PO QD. May advance to 5–10 mg QD. *Perphenazine*: 8–16 mg PO 2–4 times/day (ceiling dose: 64 mg/day; 24 mg in ambulatory patients)	Dizziness, hypotension, hyperkinesia, somnolence, nausea
Benzodiazepines	Amnesic and anxiolytic activity at the GABA receptors found in the cerebral cortex *Not to be used as a single agent for N/V* *Most effective for anticipatory N/V associated with chemotherapy, abdominal radiotherapy, and other noxious treatments*	*Midazolam* Inj: 1,5 mg/ml q3 hours prn or 0.5–5.0 mg/h sc continuous infusion *Lorazepam* SC, IV and PO: 1–4 mg q6–8 h	Drowsiness, confusion, somnolence
Cannabinoids	Depresses the higher cortical pathways that stimulate the VC *Considered 3rd line therapy* *Used instead of steroids in diabetic patients, or any other contraindication to steroids*	*Dronabinol* (Marinol®) PO: 2.5 q6–12 h and titrate. *Nabilone* PO: 1–2 mg BID started 1–3 h before chemotherapy (ceiling dose: 6 mg/day in three divided doses)	Sedation, euphoria, dysphoria, hallucinations, memory loss, and motor incoordination
Promotility Agent/ substituted Benzamide	*Metoclopramide*: At low doses -D_2 antagonist and $5HT_4$ agonist. At higher doses—$5HT_3$ antagonist. Also acts in the gut by increasing motility *First-line agent for most types of end-of-life N/V*	*Metoclopramide* IV and PO: 10–20 mg. Q6h (reduce to compensate for renal failure) 2 mg/kg (over 15 min. q2–3 h × 3–6 doses for greater efficacy in cisplatin chemotherapy *Dexamethasone adds to efficacy* *Give metoclopramide with haloperidol only if haloperidol is a low dose and EPS s/e are not present* *Trimethobenzamide* PO: 300 mg q8 h	Sedation, diarrhea, EPS EPS can be relieved by lorazepam or diphenhydramine

Table 33.1 (continued)

Antiemetic agent	Action	Dosage	Side effects
Serotonin antagonists	Block serotonin type 3 receptor on vagal afferent neurons in the GI tract Considered second and third line due to cost. Highly effective for chemo and radiotherapy. Considered first line in patients with altered mental status d/t least amount of CNS effects	*Dolasetron* (Anzemet®) IV and PO: 100 mg q24 h. Give 1 h before chemotherapy or 2 h before surgery. *Granisetron* (Kytril®) IV: 1 mg q24 h. PO: 1–2 mg q 24 h. Give 1 hour before chemotherapy and 12 h later. *Ondansetron* (Zofran®) IV, PO: 4–16 mg q8–12 h. *Palonosetron* PO: 5 mg 1 h before chemotherapy	H/A, constipation, occasional increases in liver transaminases
Substance P/Neurokinin 1 receptor antagonist		*Aprepitant* PO: with a corticosteroid. 125 mg 1 h before chemotherapy on day 1: 80 mg PO in am of days 2 and 3 *Fosaprepitant* IV: with a corticosteroid. 115 mg 30 min before chemotherapy on day 1. 115 mg infused IV over 15 min. on days 2 and 3, followed by 80 mg of aprepitant PO in the am	

4. Mucositis (see also Chap. 20)
    a. The most predictable symptom in patients undergoing HSCT.
    b. Usually observed within 5 days of beginning chemotherapy, with a peak in severity within 7–10 days post-therapy.
    c. Commonly occurs in patients receiving melphalan, cyclophosphamide, or total body irradiation.
    d. Prevention is considered the standard of care with adherence to oral evaluation and oral hygiene.
        i. Human keratinocyte growth factors such as palifermin (Kepivance®) were developed for mucositis prevention.
        ii. Currently, mucositis is managed with the use of topical oral formulations, such as equal parts of lidocaine and diphenhydramine (Benadryl®); plus aluminum sulfate, magnesium sulfate, or simethicone. Dexamethasone, ibuprofen, morphine, and other opioids can be added to the mixture.
        iii. Ketamine can improve pain from mucositis.
            − Based on current literature, dilute 20 mg of IV ketamine in 5 mL of artificial saliva substitute or normal saline; swish for 1 min and then spit every 3 h.
        iv. Gelclair® is a concentrated bioadherent oral gel indicated for the relief and management of pain. Initial results were promising with this agent, but cost did not outweigh the benefit.
        v. Rincinol®, an over-the-counter agent, has the same active ingredient as Gelclair® and is much less expensive.
        vi. It may be necessary to couple topical therapy with an opiate treatment administered by a Patient Controlled Analgesic (PCA) device.
        vii. Prevention of emesis also contributes to prevention/reduction of mucositis by avoiding local trauma.
    e. Mucositis typically resolves with recovery of neutrophils. Until then, rigorous oral hygiene is necessary as the patient remains at high risk for infectious complications.

5. Diarrhea (see also Chap. 21)
    a. HSCT recipients may experience multiple episodes of diarrhea post-HSCT.
    b. Management begins with an assessment of volume status and evaluation to identify the underlying cause.
        i. Diarrhea-associated infections may involve Salmonella, Shigella, Campylobacter, Yersinia, Clostridium difficile, Candida, Cryptosporidium, enteroviruses, adenovirus, rotavirus, or cytomegalovirus.
    c. Most HSCT recipients receive at least one course of antibiotics and are at a high risk of developing *C. difficile* infection.
        i. *C. difficile* continues to develop antibiotic resistance, substantially increasing the prevalence and virulence of this opportunistic pathogen.

d. Acute GVHD of the lower GI tract may also cause diarrhea resulting in depletion of protein stores.

   i. Management of intestinal acute GVHD consists of nutritional counseling, maintenance of fluid and electrolytes, corticosteroids and other immunosuppressive agents, and monitoring for secondary infectious complications.
   ii. Once infectious causes have been ruled out, patients may find relief from careful titration of loperamide (Imodium®) 2–4 mg po after each loose stool, maximum dose 16 mg po daily, or Octreotide (Sandostatin®) by subcutaneous or IV bolus or continuous infusion.

6. Anorexia

a. A decrease in appetite is common due to high-dose chemotherapy, pain, mucositis, N/V, constipation, diarrhea, and psychosocial issues.
b. Management must effectively improve the nutritional health of HSCT patients.
c. Treatment-related dietary restrictions render food preparation more difficult and less palatable.
d. Consider total enteral or parenteral nutrition to supply nutrients.
e. Corticosteroids are known to be effective appetite stimulants. However, this option is not ideal for HSCT patients as their effect is time-limited and they result in muscle weakness/loss.
f. Megastrol (Megace®) can be used at doses ranging from 100 mg to 1600 mg/day titrated as necessary. This drug should be used cautiously with patients with a known history of thromboembolic disease.
g. Dronabinol (Marinol®) 2.5–5 mg po daily or BID once or twice a day has been shown to increase appetite and stabilize body weight. However, this therapy is less effective than megestrol for improving appetite and weight gain.
h. There is some evidence that eicosapentaenoic acid (EPA) improves appetite and weight gain, however this remains under scrutiny.
i. Exercise has been shown to improve an overall sense of well-being, strength, endurance, and appetite. Aerobic exercise including weight training can be helpful to prevent deconditioning and aid in recovery.

7. Delirium (See also Chapter 29)

a. Delirium is considered a cognitive disorder with changing consciousness manifesting in inattention, disorganized thinking, disorientation, memory impairment, or hallucinations.
b. Presentation can be acute in onset with fluctuation related to an underlying medical cause.
c. Associated with longer hospital stays, decrease in activities of daily living, increase in medical complications, loss of physical strength or function, and even death.
d. Haloperidol (Haldol®), risperidone (Risperdal®), olanzapine (Zyprexa®), and quetiapine (Seroquel®) are commonly used with scheduled dosing and additional doses as needed for agitation.
e. If delirium persists despite treatment, titration of the dose of antipsychotic is preferred rather than switching to another agent.

33.5 Summary

Palliative medicine specialists are an important member of the HSCT treatment team, enhancing efforts to provide quality physical and emotional symptom management to transplant recipients and their family members. Many health care settings have palliative medicine consultation teams available for all complex medical treatment plans. Consultation should be considered upon the diagnosis of all life threatening illness, regardless of the treatment intention. Aggressive curative treatment deserves aggressive symptom management guided by specialists in the field of palliative medicine that focuses on the patient and their caregivers.

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Chapter 34
Long-Term Follow-Up and Survivorship

Lisa Hansen and Susan Schubach Slater

There are multiple definitions of a cancer survivor. Some define survivorship as beginning with initiation of therapy, while others suggest it begins at completion of therapy. Some define survivorship as beginning 5 years after diagnosis or at other points between initiation and completion of therapy.

In 2005, the Institute of Medicine released a report entitled *From Cancer Patient to Cancer Survivor: Lost in Translation*. It was recommended that on completion of therapy, cancer patients be provided with a summary of their care and a clear follow-up plan. The American College of Surgeon's (ACS) Commission on Cancer endorsed this recommendation. To maintain ACS accreditation, cancer programs must have a formal plan in place by 2015 to provide patients with comprehensive care plans at completion of their therapy. This care plan should include:

1. Diagnostic tests performed and results.
2. Important disease characteristics including site, stage and grade, cytogenetic or molecular markers.
3. Type and dates of therapies delivered including surgery (site), chemotherapy (agents used, total doses), radiation therapy (site, total dosage), hormonal or gene therapy and transplant details (conditioning regimen, graft-versus-host disease prophylaxis, donor match/source), as well as identifying data of clinical trials.
4. Psychosocial, nutritional, and other supportive services delivered.
5. Contact information for main providers and institutional details.
6. A clear follow-up plan with evidence-based standards when possible along with the identification of the coordinator for continuing care.

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Table 34.1 Resources for survivors and their caregivers

NCI office of Cancer Survivorship	http://cancercontrol.cancer.gov/ocs/
LiveStrong™ Foundation	http://www.livestrong.org
National Marrow Donor Program	http://www.bethematch.org
National Bone Marrow Transplant Link	http://www.nbmtlink.org

The field of cancer survivorship has matured over the past 15 years with the support of the National Cancer Institute's Office of Cancer Survivorship and the LiveStrong™ Foundation (http://www.livestrong.org). Efforts within the hematopoietic stem cell transplant (HSCT) field have been coordinated by the National Marrow Donor Program (NMDP), the American Society for Blood and Marrow Transplant (ASBMT), the European Group for Blood and Marrow Transplantation (EBMT), and the Center for International Blood and Marrow Transplant Research (BMT CTN), along with patient advocacy groups such as the National Bone Marrow Transplant Link (http://nBMTLink.org) (see Table 34.1).

HSCT survivors are faced with a significantly increased risk for chronic health conditions and premature death, even 10–15 years from their transplant procedure. The Bone Marrow Transplant Survivor Study (BMTSS) followed patients who survived at least 2 years post-HSCT and showed that the conditional survival probability at 15 years after allogeneic HSCT was 80 %, with mortality rates twice that of the general population after 15 years. For autologous HSCT recipients, the mortality rate is also higher for the first 10 years of survivorship before approaching that of the general population. Careful health surveillance, healthy lifestyle choices, and prompt management of medical conditions are essential to reduce nonrelapse mortality and improve quality of life. An international working group led by the NMDP recently updated the screening and preventive practice guidelines for patients who have undergone HSCT (see Table 34.2). The recommendations that follow will be focused on survivors who are alive more than 1 year post-HSCT.

34.1 Infection (See also Chaps. 10 and 17)

The risk of serious infection persists in HSCT recipients months to years after their procedure. Laboratory evidence of immune recovery generally occurs at 12 months for autologous patients but may be delayed in allogeneic recipients.

1. Risk factors for late infection
    a. The presence of chronic graft versus host disease (cGVHD)
    b. Ongoing immunosuppressive therapy (IST)
    c. Cord blood, human leukocyte antigen (HLA) mismatched or T cell depleted graft
    d. The presence of relapsed disease

Table 34.2 Recommended screening and preventive practices for post-HSCT patients. (Adapted from Majhail et al. 2012)

Recommended screening and prevention	Six months	One year	Annually
Liver			
Liver function testing	All	All	As indicated
Serum ferritin if patient received RBC transfusions		As indicated	As indicated
Respiratory			
Clinical pulmonary assessment	All	All	All
Smoking tobacco avoidance	All	All	All
Pulmonary function testing	cGVHD as indicated	Allo only	As indicated
Chest radiography	As Indicated	As Indicated	As indicated
Musculoskeletal			
Bone density testing (women, allo transplant, and patients with prolonged corticosteroid or calcineurin inhibitor use)		All	As indicated
Screen for corticosteroid-induced muscle weakness	cGvHD*	cGvHD*	cGvHD*
Physical therapy consultation as indicated	cGvHD*	cGvHD*	cGvHD*
Treatment of osteopenia with bisphosphonates		Those at risk	Those at risk
Kidney			
Blood pressure screening	All	All	All
Urine protein screening	All	All	As indicated
BUN/creatinine testing	All	All	All
Nervous system			
Neurological clinical evaluation		All	As indicated
Endocrine			
Thyroid function testing		All	All
Growth velocity in children		All	All
Gonadal function assessment (prepubertal boys and girls)	All	All	All
Gonadal function assessment (postpubertal women)		All	All
Vascular			
Cardiovascular risk factor assessment		All	All
Fasting lipid profile and blood glucose		All	All
Immune system			
Encapsulated organism prophylaxis	cGvHD*	cGvHD*	cGvHD*
PCP prophylaxis	All	cGvHD*	cGvHD*

Table 34.2 (continued)

Recommended screening and prevention	Six months	One year	Annually
CMV testing	cGvHD*	cGvHD*	As indicated
Consider antifungal prophylaxis	cGvHD*	cGvHD*	cGvHD*
Prophylaxis for VZV for those at risk	All	All	cGvHD*
Endocarditis prophylaxis with dental procedures—AHA guidelines	All	All	All
Immunizations—see Chap. 13	All	All	All
Second cancers			
Second cancer vigilance counseling		All	All
Breast/skin/testes self-exam		All	All
Clinical screening for second cancers		All	All
Pap smear, mammogram for women over the age of 40 (see text)		All	All
Psychosocial			
Psychosocial/QOL clinical assessment	All	All	All
Mental health counseling for recognized psychosocial problems	As Indicated	As Indicated	As indicated
Sexual function assessment	All	All	All
Oral complications			
Dental assessment, intraoral malignancy assessment	All	All	All
Ocular			
Ocular clinical symptom evaluation	All	All	All
Ophthalmologic exam of visual acuity and fundus		All	As indicated

All Allogeneic and autologous patients, *CGvHD** Recommended for any patient with ongoing chronic GvHD or immunosupression, *As Indic* reassessment recommended for abnormal testing in a previous time period or for new signs/symptoms, *QOL* quality of life, *RBC* red blood cells, *PCP* pneumocystis jiroveci pneumonia, *CMV* cytomegalovirus, *AHA* the American Heart Association, *VZV* varicella-zoster virus

2. Surveillance
    a. CBC at least annually
    b. Immune reconstitution assessment
        i. BMT CTN recommends post-allogeneic HSCT monitoring of T, NK, and B cell subsets (CD3, CD4, CD8, CD45RA/R0, CD56, CD16, CD19, CD20) and quantitative immunoglobulins at various milestones post-HSCT
    c. Cytomegalovirus (CMV) PCR based on risk factors including the intensity of IST regimen, the presence of cGVHD, post-HSCT maintenance therapy, etc.

3. Interventions
    a. Antimicrobial prophylaxis (see also Chap. 10)
        i. Encapsulated bacteria prophylaxis for HSCT recipients who require extended IST; consideration should be given for those patients who are surgically/functionally asplenic.
        ii. *Pneumocystis jiroveci* pneumonia prophylaxis for the first 6 months post-autologous HSCT; continue for the duration of IST in allogeneic HSCT recipients.
        iii. Varicella zoster virus prophylaxis should continue for at least 1 year post-HSCT, longer in those patients who require prolonged IST.
        iv. Fungal prophylaxis is indicated for high-risk patients, specifically those with cGVHD requiring prolonged IST.
        v. Post-HSCT vaccinations based on published guidelines (see Chap. 15).

34.2 Cardiovascular (See also Chap. 23)

HSCT survivors are twice as likely as the general population to die from cardiac conditions. Reduced carotid artery distensibility has been demonstrated in a cohort of pediatric HSCT survivors (see also Chap. 23). Precocious coronary arteriosclerosis develops when the radiation field encompasses the heart. Conduction system disturbances, valve defects, or restrictive cardiomyopathy are additional late effects.

1. Risk factors
    a. Cumulative anthracycline dose > 550/m^2 daunorubicin equivalent
    b. Thoracic radiotherapy with heart in the radiation field, either before or after HSCT
    c. Iron overload associated with multiple transfusions, especially those patients with iron stores documented by cardiac magnetic resonance imaging (MRI)
    d. Metabolic syndrome
        i. A constellation of hypertension, insulin resistance, abdominal obesity, elevated triglycerides, reduced high-density lipoprotein (HDL) → three of these five signs constitutes metabolic syndrome
        ii. Patients with metabolic syndrome have a 2–3 times higher risk of developing cardiovascular disease
        iii. Prevalence in HSCT survivors is 2 –3 times that of the general population
    e. Family history of cardiovascular disease
2. Surveillance
    a. Screening for hypertension and cardiovascular risk annually
    b. Fasting lipid panel annually
    c. Electrocardiogram (ECG) and/or echocardiogram as clinically indicated

3. Interventions
    a. Early intervention for identified risk factors (i.e., hypertension, dyslipidemia, etc.)
    b. Encourage healthy lifestyle choices including cardiac prudent diet, exercise, and smoking cessation
    c. Endocarditis prophylaxis per the American Heart Association (AHA) guidelines (see Chap. 23)
    d. Cardiology referral and evaluation as indicated

34.3 Pulmonary (also see Chap. 22)

Serious pulmonary complications generally develop during the first few weeks or months post-HSCT. However, pulmonary function can become compromised in long-term survivors as a consequence of late infection, obstructive, or restrictive disease.

1. Risk factors
    a. cGVHD
    b. Immunosuppressive medications
    c. CMV disease and other infections
    d. Conditioning regimens including busulfan, carmustine, or total body radiation
    e. Pre-HSCT pulmonary dysfunction
    f. Older age
2. Surveillance
    a. History and physical exam, including pulse oximetry.
    b. Pulmonary function testing (PFT) for allogeneic recipients at 1 year. However, as early presentation of bronchiolitis obliterans is asymptomatic and prognosis is poor for symptomatic disease, consider PFT monitoring as early as 3 months post-HSCT.
        i. More frequent PFT monitoring (every 3–6 months) may be indicated in patients with cGVHD, identified dysfunction, or new clinical symptoms of pulmonary dysfunction
    c. Appropriate imaging for symptomatic patients (CXR, high-resolution CT chest without contrast with expiratory views)
3. Prevention and intervention
    a. Annual inactivated influenza vaccination for patients and close contacts
    b. Smoking cessation
    c. Education of patient and family on infection control measures to reduce exposure to community respiratory viral infections
    d. Prompt treatment of respiratory infections

34.4 Neurologic

1. Cognitive dysfunction (see also Chap. 25)
   Pediatric HSCT survivors suffer the greatest burden of neurologic effects post-HSCT. Adult HSCT patients can be plagued by cognitive dysfunction. However, the majority recover normal function by 1 year.

   a. Risk factors

      i. Patient age
      ii. Unrelated donor > matched sibling > autologous
      iii. GVHD, calcineurin inhibitors (CNIs)
      iv. Prior cranial radiation or intrathecal therapy
      v. Possible genetic predisposition (E4 allele of apoliprotein)
      vi. Preexisting cognitive deficits

   b. Surveillance and diagnosis

      i. Annual neurologic exam

         • Careful history from patient and family of intellectual, social, and physical functioning

      ii. Serum electrolytes, renal and liver function tests
      iii. MRI of brain if indicated
      iv. Referral for neurologic consultation and neuropsychological testing as indicated

   c. Interventions

      i. Treatment is individualized, based on age, degree of cognitive disruption, and presumed etiology
      ii. Research suggests physical exercise improves cognitive function

2. Peripheral neuropathy
   Ten to twenty percent of patients treated for a malignant disease develop peripheral neuropathy which may impair mobility, increase fall risk, and may require chronic narcotic analgesia. Neuropathy symptoms may gradually improve.

   a. Risk factors

      i. History of treatment with neurotoxic chemotherapeutic agents (vinca alkyloids, platinum compounds, bortezomib, thalidomide, taxanes)
      ii. CNIs
      iii. Older age
      iv. Diabetes mellitus and liver disease can exacerbate preexisting symptoms

   b. Interventions

      i. Gamma aminobutyric acid for painful neuropathy

- Gabapentin (Neurontin®) beginning at 100–300 mg po qhs, increasing dose to 900–3600 mg daily in dose increments of 50–100 % every 3 days. Slower titration recommended for elderly or medically frail patients. Dose adjust for renal insufficiency.
- Pregabalin (Lyrica®) 50 mg po TID, may be increased to 100 mg po TID. Slower titration recommended for elderly or medically frail patients. Dose adjust for renal insufficiency.

ii. Antidepressants (e.g., duloxetine (Cymbalta®) 30–60 mg po daily) for burning pain
iii. Narcotic analgesics
iv. Topical application of compounded 2 % amitriptyline and 1 % ketamine
v. Lidocaine topical patches (Lidoderm®)
vi. Consider available clinical trials

3. Central nervous system complications

a. Includes vascular complications such as cerebrovascular accidents and CNI-induced neurotoxicity, infectious complications, leukoencephalopathy secondary to intrathecal chemotherapy and secondary brain tumors (see Chap. 25)
b. Risk factors

i. Infections
ii. Metabolic encephalopathy
iii. Intrathecal chemotherapy and/or cranial radiation
iv. History of CNS disease
v. Prolonged IST, especially with CNIs
vi. cGVHD

c. Surveillance

i. Neurologic exam at least annually to screen for neurologic complications
ii. Consider more specific testing in symptomatic patients

34.5 Hepatic

1. Hepatitis B virus (HBV) or hepatitis C virus (HCV) reactivation

a. A large multi-institutional retrospective study showed no significant difference in the incidence of treatment-related mortality, survival, GVHD, and hepatic toxicity in HBV and HCV HSCT recipients compared with controls with median follow-up of 5.9 years.
b. HBV in post-HSCT survivors typically manifests as mild to moderate disease
c. HCV

i. Often asymptomatic aside from fluctuating transaminases
ii. ~35% incidence of cirrhosis and end-stage liver disease related to chronic HCV among 40-year HSCT survivors with progression to cirrhosis more rapid than in non-HSCT patients.
    - 11% at 15 years
    - 24% at 20 years

d. Interventions
    i. Monitor LFTs at least annually
    ii. Liver biopsy 8–10 years post-HSCT to assess for cirrhosis may be considered

2. Iron overload
    a. Mainly transfusion related, however ineffective erythropoiesis or hereditary hemochromatosis may contribute to development
    b. Associated with increased incidence of infection and nonrelapse mortality
    c. Surveillance
        i. Serum ferritin is not a reliable predictor of tissue iron overload as ferritin is an acute phase reactant
        ii. Consider Ferriscan®, T2 MRI or superconducting quantum interference devise (SQUID) as these are noninvasive and sensitive/specific for quantifying liver iron concentration
        iii. Liver biopsy may be beneficial to rule out other potential etiologies of liver dysfunction
    d. Interventions
        i. Consider phlebotomy or chelation for patients with demonstrated liver iron concentration >5–7 mg/g dry weight liver iron and signs of liver dysfunction
            - Deferasirox (Exjade®) 20 mg/kg body weight, rounded to the nearest whole tablet (125, 250, or 500 mg) daily
            - Desferoxamine (Desferal®)
                - 20–40 mg/kg/day SQ over 8–24 h daily
                - 40–50 mg/kg/day IV over 8–12 h, 5–7 days/week

3. Chronic GVHD
    a. Main clinical finding is elevated liver function tests
    b. Consider liver biopsy to rule out alternative etiologies prior to initiation of immune suppression

34.6 Ocular

1. Keratoconjunctivitis sicca syndrome
   a. Typically a manifestation of cGVHD with signs/symptoms including
      i. Inflammatory destruction and fibrosis of the conjunctiva and lacrimal glands
      ii. Decreased goblet cell density
      iii. Decreased tear production with low tear turnover rate, high evaporation and osmolarity, and an unstable lipid layer
      iv. Patient symptoms include complaints of dry eye, photophobia, wind-intolerance, and/or foreign body sensation
      v. May progress to corneal ulceration or perforation
   b. Develops in 40–60 % of allogeneic HSCT recipients and 60–90 % of patients with GVHD
   c. Treatment Options
      i. Preservative-free saline drops, ointments or gels prn
      ii. Steroid eye drops (ensure patient has no signs of viral or bacterial keratitis before initiation)
      iii. Cyclosporine eye drops (Restasis®) although this medication is generally poorly tolerated due to burning with instillation
      iv. Punctual plugs
      v. Hyprolose (Lacrisert®)
      vi. Antibiotic drops
      vii. Scleral lenses (“bandage” lenses)
      viii. Autologous serum eye drops
2. Cataracts
   a. HSCT recipients who receive total body irradiation (TBI), regardless of fractionation, are likely to develop cataracts by 10 years post-HSCT
   b. Develop more rapidly in recipients who receive steroids for GVHD prophylaxis and treatment
3. Ischemic microvascular retinopathy
   a. Present with decreased visual acuity or visual field deficits or both
   b. Clinic examination may reveal cotton wool spots, telangectasias, microaneurysms, retinal hemorrhage, and/or optic disc edema
   c. TBI, steroid and/or cyclosporine use, and hypertension contribute to development
   d. Typically resolves within 2–4 months of presentation; therefore, aggressive intervention is not indicated

4. Surveillance
    a. Annual evaluation by an ophthalmologist experienced with post-HSCT complications beginning 1 year post HSCT or sooner as needed for symptoms

34.7 Oral

1. Risk factors for oral complications include
    a. Oral cGVHD
    b. History of radiation to the head/neck
    c. Underlying diagnosis of Fanconi anemia
    d. Age of the patient at the time of HSCT
2. cGVHD
    a. Signs/symptoms include oral ulcerations and erythema with formation of lichen planus, mucoceles, and pseudomembranes, oral pain or dry mouth, intolerance of spicy or acidic foods, and difficulty swallowing.
3. Xerostomia
    a. May result in increased incidence of dental caries, periodontal disease, and/or cancer of the oropharynx
4. Squamous cell carcinoma
    a. May arise from the buccal mucosa, salivary glands, gingiva, lip, or tongue
    b. Higher risk in patients with Fanconi anemia and those with history of cGVHD of the oral mucosa
5. Surveillance
    a. Close attention to oral mucosa at every visit with oral examination by a dental professional every 6 months for patients at high risk and every 12 months for lower-risk patients
    b. Encourage healthy behaviors including preventative oral health, avoidance of smoking and smokeless tobacco, avoidance of sugar-containing beverages and intraoral piercings
6. Interventions
    a. Fluoride-containing tooth paste and/or oral rinse for patients with decreased saliva production to decrease the incidence of dental caries
    b. Consider topical steroid preparations (dexamethasone mouth wash, beclomethasone ointment), systemic or intrabuccal steroid injections for treatment of oral GVHD
    c. Additionally, patients should follow the AHA recommendations for endocarditis prophylaxis with dental procedures.
    d. See Chap. 20 for additional treatment recommendations.

34.8 Endocrine

1. Hypothyroidism (see also Chap. 26)
   a. Hypothyroidism is a common late complication of HSCT, developing in 7–50% of HSCT recipients depending on their pre-HSCT treatment and the HSCT conditioning regimen.
   b. Less commonly, autoimmune thyroiditis and thyroid neoplasms may occur post-HSCT
   c. Risk factors
      i. Total body irradiation
      ii. Involved field radiotherapy to the neck region
      iii. High-dose alkylating agents in conditioning regimen (busulfan, cyclophosphamide)
      iv. Prolonged corticosteroid therapy
   d. Surveillance
      i. Annual thyroid function testing including thyroid stimulating hormone (TSH), T3 and free T4
   e. Interventions
      i. Thyroid hormone replacement as indicated
2. Hypogonadism
   a. Ovarian failure
      i. Affects ~99% of female HSCT recipients
         - Highest risk in patients who receive TBI or busulfan
         - Lower risk in patients who are treated with cyclophosphamide alone
      ii. Typically irreversible in adults
      iii. Surveillance
         - Annual gynecologic exams to evaluate for symptoms associated with early menopause and/or cGVHD such as vaginal atrophy
      iv. Interventions (see also Chap. 28)
         - Consider early hormone replacement therapy to increase libido, decrease vaginal atrophy, and prevent cardiovascular and osteoporotic complications of early menopause.
         - Vaginal lubrication, dilators
         - Individual and couples counseling
   b. Germ cell damage
      i. Affects ~92% of male HSCT recipients
         - Highest risk in patients who receive high-dose radiation or chemotherapy

ii. Surveillance

- Testosterone levels recommended based on symptoms

iii. Interventions

- Testosterone replacement therapy
- Injectable esters (Depotestosterone®, Delatestryl®)
- Implantable pellets (Testopel®)
- Patches (Testoderm®, Androderm®)
- Transdermal gel (AndroGel®, Testim®, Fortesta®, Axiron®)
- Buccal (Striant®)

3. Diabetes

a. Steroid-induced diabetes is common in allogeneic transplant patients requiring corticosteroids for control of GVHD.
b. Metabolic syndrome (see Sect. 34.2) predisposes patients to type II diabetes and cardiovascular disease.
c. Findings from the BMTSS revealed that allogeneic HSCT recipients were 3.7 times more likely to report a diagnosis of diabetes than their matched sibling cohort. Obesity and at least two components of metabolic syndrome were increased nearly threefold in childhood cancer survivors.
d. Risk factors

i. Corticosteroid therapy
ii. Obesity
iii. Family history of diabetes
iv. Physical inactivity

e. Surveillance

i. Annual fasting blood glucose and Hgb A1c levels
ii. Hypoglycemic agents
iii. Dietary modification
iv. Exercise program
v. Close monitoring for cardiovascular risk factors

34.9 Musculoskeletal Complications

1. Osteoporosis

a. May develop prematurely secondary to chronic corticosteroids or therapy-induced menopause (see Chaps. 15 and 28 for further recommendations)
b. Surveillance

i. Patients should be counseled regarding their risk for osteoporosis
ii. Bone densitometry scan (DEXA) at 1 year post-transplant, then as needed based on findings

c. Interventions

i. Calcium and vitamin D supplementation
ii. Regular weight-bearing exercise as tolerated
iii. Vitamin D supplementations if deficiency identified
iv. Oral or IV bisphosphonates; dental evaluation prior to initiation of therapy with frequent follow-up exams to evaluate for osteonecrosis of the jaw
v. Consider estrogen replacement for women after evaluation of risk-benefit ratio

2. Avascular necrosis (AVN)

a. AVN is a late complication with a reported incidence of 4–19%.
b. Commonly affects weight-bearing joints in a bilateral distribution.

i. Hips are most commonly affected; however, knees, ankles, and wrists may also be affected.

c. Risk factors

i. Corticosteroid therapy, typically with prolonged exposure, however, may occur with a short-course or low-dose therapy
ii. Total body radiation, particularly high total doses

d. Surveillance and diagnosis

i. Careful patient history, focusing on quality, intensity and duration of joint pain
ii. MRI of symptomatic joints

- Plain films do not show early changes of AVN

e. Interventions

i. Analgesia
ii. Orthopedic devices
iii. Core decompression to relieve pressure and create channels for new blood vessels to improve blood flow to the joint
iv. Definitive treatment requires total joint replacement

3. Myopathy

a. Proximal muscle weakness, typically affecting the quadriceps, is a frequent complication of protracted corticosteroid use.
b. Risk factors

i. Protracted corticosteroid therapy
ii. Inactivity

c. Surveillance and diagnosis

i. Patient history
ii. *Timed Get up and Go test* which measures the time it takes for a person to rise from a chair, walk 3 meters, turn around, walk back to the chair and sit down

d. Interventions

   i. Physical therapy consult with home safety evaluation as indicated
   ii. Durable medical equipment as indicated (e.g., cane, walker, bedside commode, shower chair)

34.10 Second Malignancies

1. Individuals diagnosed with a malignancy are twice as likely to develop a second cancer as age and gender-matched individuals who lack a cancer history (see Chap. 31). For HSCT survivors, the risk is magnified two to three times.
2. The incidence of secondary malignancies in HSCT survivors increases over time and varies among different studies (from 3 to >10%).
3. Risk factors
   a. Diagnosis of Hodgkin lymphoma
   b. Radiation therapy including total body irradiation
   c. ATG-containing preparative regimens
   d. Long-term IST
   e. cGVHD
4. Secondary malignancies in HSCT survivors
   a. Basal and squamous cell carcinomas
   b. Squamous cell carcinoma of the oral cavity with a higher incidence in patients with a history of oral cGVHD
   c. Solid tumors of the liver, cervix, thyroid, bone/connective tissue, breast
   d. Central nervous system tumors
   e. Non-Hodgkin lymphomas
   f. Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)
   g. Post-transplant lymphoproliferative disorder (PTLD)
5. Surveillance
   a. Physical exam with specific attention to signs and symptoms of secondary malignancies
   b. Annual dermatology evaluation
   c. CBC, comprehensive chemistry at least annually
   d. Routine cancer screenings per the American Cancer Society recommendations including mammography, cervical cancer screening, colonoscopy, etc. (http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer)
      i. For females who received TBI or chest radiation, screening mammography should begin at age 25, or no later than 8 years from radiation therapy, whichever comes first.

6. Counseling and interventions
   a. Survivor counseling regarding increased risk with instruction on self-monitoring for signs and symptoms
   b. Lifestyle modifications to reduce risk: smoking avoidance, heart healthy diet, exercise to maintain normal weight
   c. High sun protective factor sunscreen and sun-protective clothing
   d. PTLD may be effectively managed, as first line, with a reduction in immunosuppressive medications and administration of anti-B cell monoclonal antibody therapy (e.g., rituximab)
7. Outcome of secondary MDS/AML is generally poor despite aggressive therapy

34.11 Sexuality and Reproductive Issues (see Chap. 9)

1. Fertility
   a. Gonadal dysfunction and infertility are prevalent and distressing complications of HSCT.
   b. Estimated incidence of natural pregnancy in post-HSCT survivors is < 15 %
   c. Pre-treatment sperm donation, in vitro fertilization, and improved infertility drug regimens, as well as investigational treatments such ovarian and testicular tissue harvesting have contributed to increasing pregnancies in cancer survivors.
   d. Observational studies reveal rates of congenital abnormalities or miscarriages were comparable to those of the general population
   e. Miscarriages, premature births, and low birth weight infants were increased in women who received total body irradiation, possibly related to uterine vessel damage and/or reduced uterine volume
   f. Current NMDP guidelines recommend that pregnancy be delayed for at least 2 years post HSCT as this is the timeframe of highest risk for relapse.
      i. All patients and their partners of childbearing potential should be counseled to use adequate contraception during this interval.
   g. Risk factors
      i. Age < 15 > 30
      ii. Female sex
      iii. Total body irradiation
      iv. Alkylating agents
      v. Heavily pretreated HSCT recipients
      vi. Myeloablative conditioning > nonmyeloablative conditioning (theorized however there is insufficient long-term follow-up of nonmyeloablative recipients to sustain this)

h. Diagnosis

i. Females

- Amenorrhea
- Follicle stimulating hormone (FSH) in menopausal range on two consecutive tests, at least 1 month apart
- Low estradiol levels

ii. Males

- Elevated FSH
- Azoospermia

i. Interventions and education

i. Fertility preservation maneuvers should be addressed prior to initiation of therapy
ii. Referral to a reproductive endocrinologist
iii. Counseling regarding alternative parenthood options including in vitro fertilization, surrogacy, and adoption

2. Sexual dysfunction

a. A recent longitudinal study revealed that nearly 50% of men and 80% of women report long-term sexual problems after HSCT.

i. While most males recover pre-HSCT function, most females do not.
ii. Both male and female survivors report inferior sexual function when compared with healthy controls, even 5 years post-HSCT. Sexual activity and satisfaction are both adversely affected.

b. Possible mechanisms

i. Females

- Ovarian failure
- Pituitary axis damage from alkylating agents, total body irradiation
- Hypothyroidism
- Radiation-induced vaginal stenosis
- Vaginal mucosal changes associated with cGVHD, early menopause
- Depression and other psychosocial factors

ii. Males

- Hypogonadism
- Pituitary axis damage from alkylating agents, total body radiation
- Cavernosal arterial insufficiency
- Hypothyroidism
- Depression and other psychosocial factors

c. Evaluation and Interventions

i. Encourage discussion of sexual concerns with consideration for individual and/or couples counseling, sex therapy

ii. Females

- Gynecologic referral and exam
- Thyroid function tests; FSH and estradiol
- Vaginal lubricants, dilators, or vibrator
- Consider hormone replacement therapy after careful consideration of risks/benefits

iii. Males

- Thyroid function tests; testosterone level
- Trial of phosphodiesterase 5 inhibitor if not contraindicated
  - Sildenafil citrate (Viagra®) 25–100 mg po 1 h prior to sexual activity; maximum once daily.
  - Tadalafil (Cialis®) 2.5 mg po daily, may increase to 5 mg po daily as tolerated; or for intermittent use, 10 mg po prior to sexual activity, may increase or 20 mg po prior to sexual activity as tolerated.
- Referral to urologist for management of erectile dysfunction, hypogonadism.

34.12 Psychosocial Concerns

1. Depression, anxiety, and post-traumatic stress disorder (PTSD) compound the physical challenges associated with long-term recovery from HSCT.
2. Astute clinicians will include a careful history to screen for depression and psychosocial adjustment disorders during follow-up visits.

   a. Formal quality of life (QOL) studies indicate that autologous HSCT recipients enjoy excellent QOL at 1 year post HSCT.
   b. Allogeneic survivors report good to excellent QOL at 1 year; however, the presence of cGvHD negatively affects physical functioning scores in most patients at 1 year.
   c. Persistent concerns include physical functioning, sexual satisfaction, difficulties with health and life insurance, and returning to work or school.

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Appendices

Appendix 1

The Vocabulary of Transplant

Allele	Molecular variants of a single gene.
Allogeneic	Cells derived or obtained from another individual.
Antigen	Any molecule that is recognized and bound by immunoglobulin or T-cell receptors; in immunogenetics, this term is often interchangeably used to describe a particular HLA molecule.
Antigenic determinant/epitope	The specific part of an antigen bound by immunoglobulin or T-cell receptor.
ASBMT	American Society for Blood and Marrow Transplantation. An international professional association that promotes the blood and marrow transplantation field.
Autologous	Cells derived or obtained from the afflicted individual.
BMT CTN	Blood and Marrow Transplant Clinical Trial Network. National Heart, Lung, and Blood Institute (NHLBI) and National Cancer Institute (NCI)-sponsored intergroup focused on the development of clinical trials in the hematopoietic stem cell transplantation arena.
Bone marrow harvest	The procedure through which donor stem cells are collected directly from the bone marrow cavity.
CD34	A surface marker of the earliest progenitors and stem cell pools. Clinical exploitation has been achieved using this molecule in determining if adequate numbers of transplantable stem cells are obtained prior to a procedure.
Chimerism	The establishment of donor cells within another recipient; can be partial or complete.

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CIBMTR	Center for International Blood and Marrow Transplant Research, the registry of >400 transplant centers worldwide that contribute outcomes data to a central data repository for analysis.
Conditioning	The euphemistic term for the chemotherapy or radiation-based preparation of the host prior to the transplant, the goals of which include immune suppression and myelosuppression.
EBMT	The European Group for Blood and Marrow Transplantation. An organization based in Europe that promotes cooperative studies and collects transplant outcome data from multiple European and Eurasian countries.
Haplotype	The location of a linked set of polymorphic HLA genes on a single chromosome; all cells, other than the germ cells of an individual, express two haplotypes, each inherited from a single parent.
Haploidentical	The circumstance in transplantation in which there is a partial or complete mismatch at a single HLA locus between two individuals.
Hematopoietic stem cell	A bone marrow derived stem cell with the capacity for self-renewal and the ability to generate downstream mature products of red cells, white blood cells, and platelets. By definition, a transplantable product.
HLA	Human leukocyte antigen.
HLA Class I	Gene products of HLA A, B, and C universally expressed on the surface of all cells of an individual (with some specific exceptions, e.g., trophoblast tissue); the class of histocompatibility molecules that present cellular peptides to CD8 T-cell effectors.
HLA Class II	Gene products of HLA DR, DP, and DQ limited cell surface expression on lymphohematopoietic tissues; inducible cell surface expression on many tissues after inflammatory cytokine exposure; the class of histocompatibility molecules that present cellular peptides to CD4 T-cell effectors.
MHC	Major histocompatibility complex. The collection of genes located on human chromosome 6 that encode the polymorphic proteins involved in antigen presentation to T-cells; the regulators of the cellular immune response.
Mobilization	The act of enhancing the movement of stem cells from their microenvironment niche into circulation; usually performed with growth factor or growth factor plus chemotherapy exposure.
Myeloablative	Conditioning regimens designed to eliminate all host stem cells.
NCI CTC	National Cancer Institute Common Toxicity Criteria. A widely accepted criterion for assessing severity of adverse events. Its utilization allows for overcoming institutional variation in reporting and for comparative outcomes research to be performed.
NMDP	National Marrow Donor Program. An American organization focused on facilitating unrelated donor and cord blood transplant procedures.

Non-myeloablative	Conditioning focused on immune suppression and establishment of donor chimerism without dose intensity enough to destroy all residual host stem cells.
Peripheral blood stem cell collection (apheresis)	The procedure by which stem cells mobilized directly into the blood of the donor are harvested by leukapheresis.
Reduced intensity transplantation	A blanket term for any degree of conditioning that is less intense than traditionally defined maximal myeloablative conditioning.
Syngeneic	Cells derived or obtained from an identical twin.
WMDA	The World Marrow Donor Foundation. An international organization focused on donor safety, stem cell accessibility, and generation of standard practices for the exchange of hematopoietic stem cells for clinical transplantation worldwide.

Appendix 2

Procedure: Bone Marrow Aspirate and Biopsy

Indication Evaluate marrow for disease involvement; restaging; evaluate cytopenias.

Procedure

1. Contact the Bone Marrow Bench to schedule a technician for the procedure.
2. Complete all appropriate requisitions or electronic orders as outlined below.
3. Identify the patient and complete TEAM PAUSE documentation.
4. Obtain written consent. If patient requests medication for anxiolysis, indicate this on the consent form and ascertain that the patient *is accompanied by a driver*.
5. Obtain a bone marrow biopsy tray. This should contain an 11 g 4″ aspirate needle and a 11 g 4″ biopsy needle, a 30 ml luer lock syringe, a 10 ml syringe with 21, 20, and 25 g needles, 10 ml lidocaine 1 %, scalpel, paper drapes, Betadine swabsticks, 4 × 4 gauze sponges and an adhesive bandage. Also obtain sterile gloves.
6. Position the patient in the prone position and prepare your supplies.
7. Identify the iliac crest. Prepare the biopsy site with Betadine, put on your sterile gloves and drape the area.

8. Administer local anesthesia using lidocaine 1 %. Begin by forming a wheal on the skin. Continue to numb the area with lidocaine through the fatty layer down to the bone. Administer lidocaine in a widening circular area over the surface of the bone completely infiltrating the periosteum.
9. Prepare your syringes to obtain aspirate specimens. The bone marrow technician will provide additional sterile syringes and sodium heparin to use during the procedure.
10. Using the scalpel, make a single cutaneous incision to the hub of the scalpel to allow easy passage of the aspirate needle.
11. Insert the aspirate needle through the skin incision until contact with the bone is made. Using gentle, steady, rotating pressure, continue until the needle is firmly seated in the marrow space.

    a. The first aspirate should be a quick pull into an unheparinized syringe (1–2 ml). Slides should be made from this specimen if spicules are present. The remainder of the specimen should be sent for morphology.
    b. Specimens which should be sent in a heparinized syringe include flow cytometry, cytogenetics and FISH studies along with samples for appropriate research studies.
    c. If same-sex chimerisms are required, aspirate should be sent for VNTR in an unheparinized syringe.
    d. Any additional specimens should be sent per lab guidelines.
    e. Please keep in mind that collection methods and sample collection varies from institution to institution. Your institution's guidelines should be followed to ensure adequate interpretation of the sample.

12. Once the aspirates have been collected, remove the aspirate needle. Insert the biopsy needle through the skin incision until contact with the bone is made. Using gentle, steady, rotating pressure, introduce the needle through the cortex slightly into the marrow space. Remove the trochar and continue to advance the needle further into the marrow space to obtain a core biopsy. Using the trochar, measure the approximate length of the core by inserting it back through the biopsy needle. Once the core measures at least 2 cm, break the core biopsy off by rotating the biopsy needle multiple times.
13. Remove the biopsy needle and attach the needle guard to the bottom of the biopsy needle. Insert the shepherd's hook through the bottom of the needle to dislodge the core onto a sterile gauze or slide provided by the bone marrow technician.
14. Once adequate specimens have been obtained, hold pressure to the biopsy site until bleeding has stopped and apply a clean bandage.
15. Assist the patient to the supine position and observe for 10–15 min for signs of bleeding. The patient may require longer observation if anxiolysis was used.
16. Instruct the patient to keep the bandage clean and dry for 24 h. The bandage may then be removed. Also instruct the patient to call should any signs of infection develop.
17. Document the procedure in the patient's medical record.

Standard Tests for Marrow Studies

1. Acute myeloid leukemia (AML)
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH studies pending MD input, e.g., t(15;17), t(9;21)
      5. FLT-3, NPM-1, c-kit, CEBPA
      6. Leukemia mutation panel
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics (not indicated on day 14 marrow studies)
      4. FISH for previous abnormalities, if applicable
      5. Additional molecular markers depending on findings at diagnosis
2. Acute lymphoid leukemia
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH for BCR/abl, MLL locus
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics (not indicated on day 14 marrow studies)
      4. FISH for previous abnormalities, if applicable
3. Chronic myeloid leukemia
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH for BCR/abl
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry (only required if accelerated phase or blast crisis is suspected)
      3. Cytogenetics

4. FISH for previous abnormalities, if applicable
5. Polymerase chain reaction(PCR) for BCR/abl is *not indicated*—this is done on peripheral blood only

4. Chronic lymphoid leukemia
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH for CLL panel (chromosome 11, 13, 17 abnormalities)
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH for CLL panel
5. Myelodysplastic syndrome
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH for 5q and deletion 7
      5. Mutational analyses
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH for previous abnormalities, if applicable
      5. Mutational analyses
6. Myelofibrosis
   a. At diagnosis
      1. Morphology
      2. Flow cytometry (if AML is suspected)
      3. Cytogenetics
      4. JAK-2 mutation
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry (if suspect progression to AML)
      3. Cytogenetics

4. FISH for previous abnormalities, if applicable
5. JAK-2 mutation if previously identified

7. Non-Hodgkin lymphoma
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
      3. If mantle cell lymphoma, FISH for t(11;14)
      4. If follicular lymphoma, PCR for t(14;18)
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry
      3. If marrow is done to assess disease status prior to stem cell mobilization, cytogenetics are indicated
8. Hodgkin lymphoma
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry
9. Multiple myeloma
   a. At diagnosis
      1. Morphology
      2. Flow cytometry
      3. Cytogenetics
      4. FISH for myeloma panel [chromosome 1, t(11;14), t(4;14), t(14;16), 17p, 13, ploidy]
      5. Congo red stain to r/o amyloid
   b. Subsequent marrow studies
      1. Morphology
      2. Flow cytometry
      3. FISH for previous abnormalities, if applicable
10. Post-tranplant marrow studies
    a. Follow above parameters for diagnosis
    b. FISH for XY for opposite-sex donors or VNTR for same-sex donors to assess chimerisms

Appendix 3

Procedure: Lumbar Puncture

Indications

- Diagnostic: r/o CNS leukemia/lymphoma, r/o infection
- Therapeutic: instillation of intrathecal chemotherapy

Procedure

1. Review lab studies to verify patient's platelet count is > 50,000/mm^3. If platelet count is < 50,000/mm^3, transfuse one single-donor irradiated platelet product and check a post-platelet count. Continue to transfuse single-donor irradiated platelet products to achieve a platelet count > 50,000/mm^3.
2. If chemotherapy will be administered during the procedure, submit the orders to pharmacy for mixing. All intrathecal chemotherapy should be mixed in preservative free normal saline only. Chemotherapy should be checked prior to administration according to institutional policy.
3. Place the orders for CSF studies in the patient's chart or electronic medical record. These typically include:
    a. Tube 1—protein, glucose.
    b. Tube 2—cell count and differential
    c. Tube 3—flow cytometry and cytology
    d. Tube 4—cultures for diagnostic studies, if indicated
4. Identify the patient and complete TEAM PAUSE documentation.
5. Obtain written consent. If patient requests medication for anxiolysis, indicate this on the consent form and ascertain that the patient *is accompanied by a driver*.
6. Obtain lumbar puncture tray. This should contain a 20 g 31/2 needle with stylet, a 3 ml syringe with 25 and 22 g needles, 2 ml lidocaine 1%, four numbered specimen vials, gauze pads, Betadine swabsticks, paper drapes and an adhesive bandage. Also obtain sterile gloves.
7. Place the patient in the lateral decubitus position, curled into the fetal position or supported in the upright position and prepare your supplies.
8. Locate the sacral promontory. The end of this structure coincides with the L5–S1 interspace. Use this reference to locate the L4–L5 interspace.
9. Using sterile technique, prep the skin over L4–L5 with betadine and drape the area.
10. Administer local anesthesia using lidocaine 1%. Begin by forming a wheal on the skin. Continue to numb the deeper tissue with lidocaine, positioning the needle towards the umbilicus.
11. Insert the spinal needle bevel up through the skin and into the deeper tissue. Aim the needle towards the umbilicus. A slight pop will be felt when the dura is punctured. If you hit bone, partially withdraw the needle, reposition and attempt again.

12. Once inside the dura, remove the stylet. If fluid does not flow, reinsert the stylet and attempt to enter the dura again. This may require slight advancement or partial withdrawal and repositioning.
13. Once CSF flows, collect the appropriate specimens in the numbered tubes.
14. If chemotherapy is to be administered during the procedure, attach the chemotherapy syringe to the hub of the spinal needle once fluid collection is completed, keeping one hand sterile.
15. Slowly inject the chemotherapy over a period of 2–3 min, checking for flow every 2–3 ml.
16. Once fluid collection and chemotherapy administration are completed, withdraw the needle and apply gentle pressure to the insertion site. Apply a clean bandage.
17. Instruct the patient to lie flat for 1–4 h to avoid postprocedure headache.
18. Label all specimens appropriately and transport specimens to the lab for processing.
19. Document the procedure in the patient's medical record.

Appendix 4

Procedure: Ommaya Reservoir Tap

Indications

- Diagnostic: r/o CNS leukemia/lymphoma, r/o infection
- Therapeutic: instillation of intrathecal chemotherapy

Procedure

1. If chemotherapy will be administered during the procedure, submit the orders to pharmacy for mixing. All intra-ommaya chemotherapy should be mixed in preservative free normal saline only. Chemotherapy should be checked prior to administration per institutional policy.
2. Place the orders for CSF studies in the patient's chart or electronic medical record. These typically include:
    a. Tube 1—protein, glucose
    b. Tube 2—cell count and differential
    c. Tube 3—flow cytometry and cytology
    d. Tube 4—cultures for diagnostic studies, if indicated.
3. Identify the patient and complete TEAM PAUSE documentation.
4. Obtain written consent. If patient requests medication for anxiolysis, indicate this on the consent form and ascertain that the patient *is accompanied by a driver*.
5. Obtain supplies including: 10 ml luer-lock syringe, 25 g butterfly needle, Betadine swabsticks, sterile 2 × 2 gauze pads, and an adhesive bandage. Also obtain sterile gloves.

6. Place the patient in the supine position with the head of bed elevated approximately 30°. Locate the Ommaya reservoir and pump the port gently three times to ensure flow.
7. Using sterile technique, prep the skin over the port.
8. Insert the needle into the center of the port until the needle strikes the back of the port. Observe for flow of CSF.
9. Attach the sterile syringe to the butterfly needle and slowly withdraw 6 ml of CSF.
10. Once the specimen has been collected, attach the syringe containing chemotherapy and slowly inject the chemotherapy over a period of 2–3 min, checking for flow after every 2–3 ml.
11. Remove the needle from the Ommaya and hold gentle pressure to the site until the bleeding has stopped. Apply a clean bandage.
12. Instruct the patient to lie flat for 1–4 h to avoid postprocedural headache.
13. Cap and label the syringe and transport specimen to the lab for processing.
14. Document the procedure in the patient's medical record.

Appendix 5

Procedure: Skin Biopsy

Indication Evaluation of rash or other skin lesion; r/o GvHD, infection, etc.

Procedure

1. Identify the patient's affected areas of skin to be biopsied and mark those areas.
2. Obtain topical anesthetic, either topical anesthetic spray (e.g., Flori-Methane) or Elamax cream. If using Elamax cream, apply 2.5 g (approximately 1/2 of a 5 g tube) in a thick layer over the site to be biopsied. Cover with an occlusive dressing (Op-Site/Tegaderm). Note the time of application on the dressing. A minimum of 1 h is necessary to obtain analgesic effect. If using anesthetic spray, spray area to be biopsied for 3–5 s at a distance of approximately 12 in. Do not frost the skin. Note: intradermal injections of lidocaine may distort the histologic architecture.
3. Obtain skin biopsy tray which should contain 3 or 4 mm punch biopsy needle, scalpel, scissors, forceps, needle driver, cloth/paper drapes, betadine swabsticks, alcohol wipes, 4 × 4 gauze sponges, 5–0 nylon suture material and a specimen container with formalin. A syringe, 1 % lidocaine, and sterile gloves should also be available. A suture removal kit may be used to obtain some of the supplies.
4. After a minimum of 1 h application of the Elamax cream, remove the occlusive dressing and wipe off the Elamax cream. Prepare and lay out required supplies. Using sterile technique, prepare the biopsy sites with Betadine, put on gloves, and apply drape if necessary. Apply anesthetic spray, if using.

5. Place the punch biopsy needle on the skin and exert moderate downward pressure. Rotate the punch biopsy needle until the entire blade is within the skin, then remove the biopsy needle.
6. Using forceps, gently pull the punch from the skin which will leave the base of tissue attached to the subcutaneous layer of tissue. Using scissors, cut the base of the biopsy and lift it free from the surrounding tissue.
7. Place the specimen in the formalin solution and label the container with the patient's identifying data.
8. Blot or apply pressure briefly to the biopsy site with gauze, then suture or steristrip site as needed. If the patient experiences discomfort at the biopsy site during suturing, intradermal lidocaine should be used at this time.
9. Apply a small amount antibacterial ointment to biopsy site and cover with occlusive dressing. Instruct patient to leave dressing in place for 24 h. After 24 h, remove the dressing. Apply small amount of antibacterial ointment to biopsy site twice a day. Instruct the patient/caregiver to notify the nursing staff if redness, swelling, persistent or colored drainage, or discomfort occurs at the biopsy site.
10. Complete an appropriate requisition and send specimen to dermatopathology per institutional guidelines.
11. Remove the sutures in 7–10 days.
12. Document the procedure in the patient's medical record.

Appendix 6

OHSU Low Bacteria Diet

Below is the low bacteria diet currently in use at Oregon Health & Science University. It is intended to be an example of one institution's practice.

Inpatient

Certain whole, undamaged fresh fruit and vegetables are allowed as long as they are thoroughly washed with water by a staff or family member.

Allowed Items That Must Be Washed and Peeled

[a]Apple	Melons	Lime	Cucumber
[a]Orange	Peach	Pineapple	Carrot
[a]Banana	Kiwi	Mango	Onion
Grapefruit	Avocado	Papaya	Squash
Cantaloupe	Lemon	Pear	Garlic

[a] Provided by the dietary service

May Be Eaten Unpeeled After Stems and Greens Removed and Washed

Plum	[a]Tomato	Cherry
Apricot	Celery	Green beans
Blueberry	Bell pepper	Grapes
Prunes	Radish	Raisins

[a] Provided by the dietary service

Other packaged dried fruits.

Not Allowed Unless Cooked or Processed

Strawberry	Broccoli	Spinach
Raspberry	Cauliflower	Leafy greens
Marionberry	Mushroom	Lettuce
Blackberry	Cabbage	Bulk dried fruits

General Guidelines

- Pasteurized yogurt is allowed at all times. Avoid Nancy's, Stoneyfield, Dannon, Activia, etc.
- No unpasterized milk products; no aged cheeses (brie, bleu, sharp cheddar, etc.)
- Sodas should be in cans or bottles
- Nuts allowed in cans or packets, no "bulk" foods
- Meats should be cooked until well done; no smoked fish
- No miso or tempeh
- No moldy or out-dated foods.
- No "fresh" salsa or salad dressings
- No home canned foods or homemade freezer jams.

Outpatient

Above diet should be followed until:

Day +60 for autologous, day +100 for allogeneic (except those with active GvHD)

May go to restaurants at:

Day +30 for autologous, day +60 for allogeneic

Appendix 7

OHSU Graft-Versus-Host Disease (GVHD) Diet

Description This diet is low in fiber, low fat, and low lactose.

Indication This diet is intended for hematopoietic stem cell transplant (HSCT) patients who suffer from GVHD of the gut. Patients are typically placed on TPN to allow for gut rest, and then transition to this diet when symptoms (pain and ileus) subside and stool volume decreases to < 1 L/day. Fat and lactose tolerance is individual, and some patients may need to restrict certain foods longer than others.

Adequacy In the liquid and early solids phase, this diet dose not meet the Recommended Daily Dietary Allowances.

1. Initiate oral diet with isotonic, low residue, low lactose beverages.

Include	Avoid
Gatorade	Milk
Diluted juices (1/2 juice and 1/2 ice)	Commercial milkshakes
Chicken broth	Commercial supplements (i.e., Ensure and Boost)
Diluted soda (1/2 soda and 1/2 ice)	Regular soda

2. As tolerated, advance to low fiber, low fat, low lactose solids.

Include	Avoid
Plain starches (rice, pasta, and bread)	Starches with gravy, butter, or fried starches
Canned fruit (applesauce and peaches)	Fresh fruit
Pureed vegetables (squash and carrots)	Raw vegetables
Soups (broth and chicken noodle)	Cream soups
Isotonic beverages (lactose-free milk)	Milk, milkshakes, and regular soda

3. When above tolerated well, add:

- Lean meats such as skinless chicken breast, turkey, baked fish
- Cooked vegetables
- Other beverages ensure and Boost
- Continue to avoid red meat, fried meat, and raw vegetables

With GVHD of the gut, patients will need to avoid certain types of foods to prevent further cramping, pain, and diarrhea. It is best to follow this diet for two weeks, then slowly start adding foods back into the diet as tolerated. Encourage patients to try a small amount of one new food per day to see how it is tolerated. If severe symptoms return, hold off on that particular food for another week or two.

Low Lactose Lactose is the sugar found in milk and is digested by the lactase enzyme which lives in the gut. With GVHD, the amount of lactase is significantly decreased, impairing normal digestion.

Include	Avoid
Soy/rice milk, mocha mix, and lactaid	Milk, milkshakes, yogurt, and ice cream
Oral supplements (Ensure and Sustecal)	Cheeses

Low Fiber Insoluble fiber can irritate the intestinal tract, especially the colon.

Include	Avoid
White breads and flour tortillas	Whole wheat breads and grains
White rice and pasta	Dried beans
Oatmeal and cream of wheat	
Cheerios, rice krispies, and corn flakes	Raisin bran, grape nuts, and shredded wheat
Peeled apples and potatoes, bananas	Raw crunchy fruit
Soft cooked vegetables	Raw crunchy vegetables

Low Fat High fat or greasy foods will not be fully digested and will increase diarrhea.

Include	Avoid
Lower fat snack foods	All fried foods—potatoes, chips, and donuts
Baked or broiled meats, chicken, fish	Red meat
Baked or steamed vegetables	

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