TRANSPLANT INFECTIONS

THIRD EDITION

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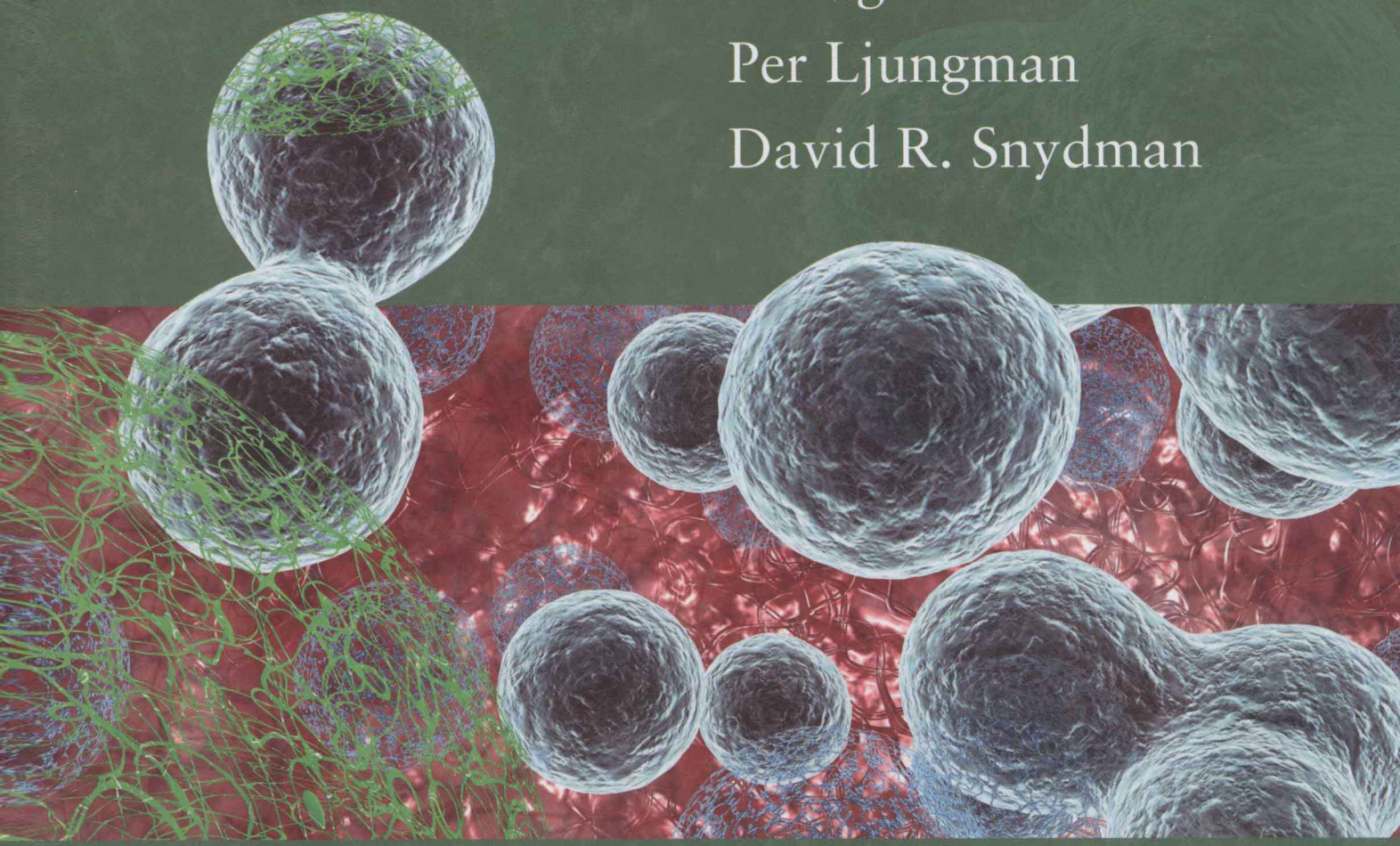

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Transplant Infections

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Foreword

Transplantation infectious disease has emerged as an important clinical subspecialty in response to a growing need for clinical expertise in the management of patients with various forms of immune compromise. The field is evolving rapidly. In the past, with fairly standardized immunosuppressive regimens, clinical expertise in the care of immunocompromised patients required an understanding of the common pathogens causing infection at various times after transplantation and an understanding of the common toxicities and interactions of immunosuppressive medications and antimicrobial agents. Some of these concepts have now reached the level of "transplant gospel." Thus, the equation of infectious risk after transplantation is determined by the relationship between two factors: the individual's epidemiologic exposures and a conceptual measure of all those factors contributing to an individual's infectious risk—"the net state of immunosuppression." In the absence of assays that measure an individual's absolute risk for infection, allograft rejection, or graft-vs.-host disease, any determination of the net state of immunosuppression is imprecise and is largely based on the clinician's bedside skills and experience. In practice, the lack of such assays predicts that most patients will suffer excessive or inadequate immunosuppression at some points during their posttransplant course provoking infection and/or rejection or GvHD.

As with most good "rules" in medicine, exceptions to the rules have become common. Presentations of infection have been altered as transplantation has been applied to a broader range of clinical conditions, immunosuppressive regimens have become more diverse, and prophylactic antimicrobial regimens have been deployed. How do we proceed? Some components of the "risk equation" have changed little. While different factors control the risk for infection in the earliest (weeks) periods following either transplant surgery (technical issues) or hematopoietic transplantation (neutropenia), the full impact of immunosuppression on adaptive immunity has not yet been achieved. Thus, in both groups, colonization by nosocomial flora and mechanical or technical challenges dominate risk including postoperative fluid collections, vascular catheters and surgical drains, tissue ischemia, drug side effects, underlying immune deficits (e.g., diabetes), organ dysfunction, metabolic derangements, and antimicrobial exposures.

Following the earliest posttransplant time period, investigations into the pathogenesis of infection are beginning to unravel some of the underpinnings of host susceptibility via advances in microbiology, molecular biology, and immunology. While the equation of risk for infection balancing epidemiology and the "net state of immune suppression" remain valuable, at the basic science level, "susceptibility" to infection is now recognized to be a function of both the "virulence" of the organism and of host defenses, including both innate and adaptive immunity. The determinants of virulence of a particular organism are the genetic, biochemical, and structural characteristics that contribute to the production of disease. Susceptibility can be explained with reference to the presence or absence of specific receptors for pathogens, the cells and proteins determining protective immunity, and the coordination of the host's response to infection. The relationship between the host and the pathogen is dynamic. Thus, some of the alterations in susceptibility previously ascribed to "indirect effects" of the pathogen (e.g., for cytomegalovirus) can now be explained as virally mediated effects on processes including antigen presentation, cellular maturation and mobilization, and cytokine profiles. Much of the impact of these infections appears to be at the interface of the innate immune system (monocytes, macrophages, dendritic cells, and NK cells) and the adaptive immune system (lymphocytes and antibodies). Other effects are the result of alterations in cell-surface (e.g., toll-like) receptors and on the milieu of other inflammatory mediators—both locally and systemically. In an admittedly anthropomorphic description of these effects, the virus (and other pathogens) has altered the host to avoid detection and destruction and to promote successful parasitism and persistence. As host and pathogen "respond" during the course of infection (and are modified by antimicrobial therapy or immunosuppression), each modifies the activities and functions of the other and a dynamic relationship develops. The outcome of such a relationship depends on the virulence of the pathogen and the relative degree of resistance or susceptibility of the host, due largely to host defense mechanisms and to a more trivial degree, by antimicrobial therapies.

Investigations into immune mechanisms are beginning to provide assays that measure an individual's pathogen-specific immune function (T-cell subsets, HLA-restricted lymphocyte sorting using tetramers, antigen-specific interferon-γ release assays) as a suggestion of pathogen-specific infectious risk. This approach may be of particular relevance in the future in regard to development of vaccines for use in immunocompromised hosts and in the assessment of immune reconstitution following chemotherapy and hematopoietic stem cell transplantation.

The "equation of risk" has been further altered by a number of additional factors. Outbreaks of epidemic infections (West Nile virus, H1N1 "swine" influenza, SARS) have disproportionately affected transplant recipients. The epidemiology of infection has also been changed by the expanded population of patients undergoing immunosuppression for transplantation, notably in terms of parasitic, mycobacterial, and other endemic infections. Thus, Chagas disease and leishmaniasis are routinely considered in the differential diagnosis of infection in the appropriate setting. Donor-derived infections have been recognized in both hematopoietic and solid organ transplant recipients. Until recently, careful medical histories coupled with serologic and culture-based screening of organ donors and recipients, and routine antimicrobial prophylaxis for surgery have successfully prevented the transmission of most infections with grafts. With the emergence of antimicrobial-resistant organisms in hospitals and

in the community, routine surgical prophylaxis for transplantation surgery may fail to prevent transmission of common organisms including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species, and azole-resistant yeasts. Highly sensitive molecular diagnostic assays have also allowed the identification of a series of uncommon viral infections (lymphocytic choriomeningitis virus [LCMV], West Nile virus, rabies virus, HIV) with allografts. These infections appear to be amplified in the setting of immunosuppression. Despite technological advances, deficiencies in the available screening assays are notable in that both false-positive assays (causing discarding of potentially usable organs) and false-negative assays (the inability to identify LCMV in a deceased donors transmitting LCMV to multiple recipients) have been recognized. Sensitive and specific diagnostic assays remain unavailable for some pathogens of interest and those that are available require careful validation and standardization. Improved molecular assays and antigen detection-based diagnostics may help to prevent graft-derived transmissions in the future.

Routine use of antimicrobial prophylaxis has also altered the presentation of infection following transplantation. In part, this manifests as a "shift-to-the-right" (late infections) due to common pathogens such as cytomegalovirus (CMV) in solid organ recipients. Increasingly, this is reflected in the emergence of antimicrobial-resistant pathogens. The impact of routine prophylaxis is difficult to measure—it is uncertain that there is a clear mortality benefit of these strategies. Sicker patients arrive at transplantation having survived multiple infections, organ failure, or malignancies that would have been fatal in the past. These individuals may become "Petri dishes" for organisms for which effective therapies are lacking. The need for new antimicrobial agents is increasing at a time when the pipeline for new agents appears to be contracting.

The net state of immunosuppression has also shifted. The duration of neutropenia following HSCT and with nonmyeloablative transplantation is shorter than that after traditional bone marrow transplantation. The duration of neutropenia has also been reduced with the introduction of chemotherapeutic agents targeting specific cellular sites (enzymes, proteasomes) rather than acting on rapidly dividing cancer cells. Among solid organ transplants, the recent introduction of experimental protocols that use combinations of HSCT with renal transplantation to induce immunologic tolerance carries the promise of immunosuppression-free lifetimes for patients.

A series of innovations will impact future clinical practice. The adoption of quantitative molecular and protein-based microbiologic assays in routine clinical practice has enhanced diagnosis and serves as a basis for the deployment of antiviral agents and modulation of exogenous immune suppression. In many ways, given currently available science, these assays may be the best measure of an individual's immune function relative to their own pathogens. Potent "biologic agents" in transplantation including antibody-based therapies to deplete lymphocytes (and other cells) have the capacity to reduce both graft rejection and graft-vs.-host disease in place of commonly used agents including corticosteroids and the calcineurin inhibitors. The short-term gain in terms of infectious risk and renal dysfunction from currently available agents must be balanced against longer term susceptibly to infections with organisms including mycobacteria, fungi, and viruses. Among the side effects of these therapies may be an increased risk for virally mediated malignancies (including PTLD) and BK (nephropathy) and JC polyomavirus-associated infections (i.e., progressive multifocal leukoencephalopathy, PML). The full impact of the biologic agents remains to be determined. High throughput sequencing and genome-wide association studies are beginning to determine the basis of both genetic susceptibility to infection and responses to antimicrobial therapies (e.g., hepatitis C virus and interferon). These observations will allow the application of specific drugs to the populations in which they are most useful and least toxic (pharmacogenomics). The introduction of clinical xenotransplantation (i.e., pig-to-human transplantation) may introduce a series of novel pathogens into the epidemiologic equation in the near future.

The evolution of the immunosuppression used in organ and hematopoietic stem cell transplantation has reduced the incidence of acute graft rejection and graft-vs.-host disease while increasing the longer term risks for infection and virally mediated malignancies. With introduction of each new immunosuppressive agent, a new series of effects on the presentation and epidemiology of infection have been recognized in the transplant recipient. In the absence of assays that measure "infectious risk," transplant infectious disease remains as much a clinical art form as a science. In the future, improved assays for microbiologic and immunologic monitoring will allow individualization of prophylactic strategies for transplant recipients and reduce the risk of infection in this highly susceptible population.

As a reflection of the challenges posed by a rapidly changing field, the editors and contributors of this text have identified both the advances and the gaps in our knowledge in transplant infectious diseases. The unique risk factors and epidemiology for infection have been characterized for each of the major transplant populations. Important shifts in the epidemiology that have been identified include those due to donor-derived pathogens and the introduction of transplantation into geographically diverse populations. The clinical utility of the text is enhanced by discussions of common and important presentations of infection including infections of the lungs, skin, central nervous system, and gastrointestinal tract. Individual pathogens and therapies are addressed in detail. Vaccination for the immunocompromised host and innovative therapies entering clinical practice are clearly presented and assessed, including adoptive immunotherapy. In each case, clinically important management issues are identified including infection control, immunosuppressive adjustments, and prophylactic and therapeutic antimicrobials. The authors have, in addition, identified important controversies and trends for each topic so as to clue the reader into areas in which change is ongoing. In sum, this volume is an important addition to the currently available literature in transplantation for infectious disease and transplantation specialists, for both expert and novice alike. The availability of this information in a single volume will serve one group particularly well—our patients.

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Preface

The success of both the first edition of *Transplant Infections*, published in 1998, and the second edition, published in 2003, as a reference work to bring together information directed at the management of the infectious complications occurring specifically in immunocompromised individuals undergoing transplantation has led to the creation of this third edition. No other text focuses solely on exogenously immunosuppressed transplant patients, and no text combines solid organ and hematopoietic stem cell transplantation (historically referred to as bone marrow transplantation). Many texts focus on immunocompromised patients, but the field of transplant infectious diseases has evolved over the past 20 years as a field unto itself, with conferences devoted solely to this specialty, and guidelines, both national and international, being developed for the management of such patients. In addition, peer reviewed journals now exist which publish information on this specialized area, and training programs devoted to the subspecialty of transplant infectious diseases within the field of infectious disease are being developed.

The field of transplant infectious diseases has continued to grow and expand since the second edition was published in 2003. We have expanded the third edition to include a greater emphasis on surgical complications for each type of organ transplanted. In addition, there are new chapters on organ donor screening, drug interactions after transplantation, and new immunosuppressive agents. Chapters differentiating differences between solid organ and hematopoietic stem cell transplantation have been expanded, as have chapters discussing fungal infections, as more data accumulate for improved diagnosis and treatment and many new antifungal agents are developed. There is a new section in the cardiac transplant chapter on ventricular assist device infections, a problem the transplant infectious disease specialist must wrestle with often in patients awaiting cardiac transplantation. We have also expanded some chapters on viral infections, such as the polyomaviruses and adenovirus since recognition of the importance of these pathogens has grown. A chapter on rare viral infections has been updated as well. Transplant tourism as a topic has also been added to a section on transplant travel medicine and vaccines. A number of new authors have been added and chapters have been substantially revised or completely rewritten.

This edition remains a globally inclusive product of leading authors and investigators from around the world. Perspectives from Argentina, Brazil, Chile, New Zealand, Western Europe (Italy, Spain, Sweden, Germany, France, and Switzerland), Austria, the United States, Canada, and Israel have been synthesized in this edition.

We continue to believe that much can be learned regarding an appreciation of both the similarities and the differences in the pattern of infections and the resulting morbidity and mortality in various transplant settings. Our goal with this textbook is to provide background and knowledge for all practitioners who work with transplant patients, in order to improve both the care and outcomes of transplant recipients and to provide a framework for education of physicians, and transplant coordinators, and trainees in the field. As success in the field continues to grow we hope that this text would provide some small incremental knowledge base that would advance the field and make transplantation safer for all who need this lifesaving intervention. We thank all the contributors for their effort, and trust the reader will find this a valuable reference text as they care for transplant recipients.

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CHAPTER 1

Introduction to Hematopoietic Cell Transplantation

ANDREW R. REZVANI, H. JOACHIM DEEG

The lymphohematopoietic system is the only organ system in mammals that has the capacity for complete self-renewal. Therefore, donation of lymphohematopoietic stem cells does not result in a permanent loss for the donor. Reports on the therapeutic use of bone marrow to treat anemia associated with parasitic infections date back a century (1,2), but not until the observations on irradiation effects in Hiroshima and Nagasaki and the ensuing systematic research into hematopoietic cell transplantation (HCT) in animal models were the principles of HCT established (1,3,4).

In 1957, the first clinical transplant attempts of the modern era were undertaken (1,5,6). As predicted from animal studies, patients who underwent transplantation from allogeneic donors (i.e., individuals who were not genetically identical) developed graft-versus-host disease (GVHD) (4). Patients transplanted from syngeneic (monozygotic twin) donors generally did not develop GVHD, but many of them died from progressive leukemia, apparently because of a lack of the allogeneic graft-versus-leukemia (GVL) effect which had been described by Barnes and Loutit (7) in murine models. These studies immediately established that allogeneic HCT functioned as immunotherapy.

Beginning in the late 1950s and early 1960s, Dausset et al. characterized the first histocompatibility antigens in humans (8). Epstein et al. were the first to show the relevance of those histocompatibility antigens for the development of GVHD in an outbred species (9). Initially, the only source of hematopoietic stem cells (HSC) in clinical use was bone marrow. However, cells harvested from peripheral blood, either after recovery from chemotherapy or after the administration of hematopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF), were shown to result in accelerated hematopoietic recovery after autologous transplantation. These cells, as well as cord blood cells, are now being used with increasing frequency in allogeneic transplantation (10,11).

TABLE 1.1 Categories of Disease Treated with Hematopoietic Cell Transplantation

Malignant
Hematologic malignancies
Acute leukemias
Chronic leukemias
Myelodysplastic syndromes
Myeloproliferative syndromes
Non-Hodgkin lymphoma
Hodgkin lymphoma
Plasma cell dyscrasia (e.g., multiple myeloma)
Selected solid tumors
Renal cell carcinoma
Ewing sarcoma
Neuroblastoma
Breast, colon, ovarian, and pancreatic cancer (investigational)
Nonmalignant
Acquired
Aplastic anemia and red cell aplasias
Paroxysmal nocturnal hemoglobinuria
Autoimmune disorders (e.g., multiple sclerosis, lupus erythematosus, systemic sclerosis, rheumatoid arthritis)
Congenital
Immunodeficiency syndromes (e.g., SCID)
Hemoglobinopathies
Congenital anemias (e.g., Fanconi anemia)
Storage diseases (e.g., mucopolysaccharidoses)
Bone marrow failure syndromes (e.g., dyskeratosis congenita)
Osteopetrosis

RATIONALE AND INDICATIONS FOR HEMATOPOIETIC CELL TRANSPLANTATION

Current indications for HCT are summarized in Table 1.1. The majority of HCT is performed to treat malignant diseases. Myelosuppression is the most frequent dose-limiting toxicity of the chemoradiotherapy used to treat malignancies. Infusion of HSC—autologous or allogeneic—as a "rescue" procedure allows the dose escalation of cytotoxic therapy, such that toxicity in the next most sensitive organs (intestinal tract, liver, or lungs) becomes dose-limiting. This strategy, often referred to as high-dose therapy with stem cell rescue, has been used extensively in the past. However, progressive dose intensification, although possibly effective in disease eradication, has resulted in minimal, if any, improvement in survival because of an increase in therapy-related toxicity and mortality. These observations, combined with an increasing appreciation of the central role of immunologic graft-versus-tumor (GVT) reactions in the success of

allogeneic HCT, have led to new concepts of transplant conditioning (see "Modalities for Transplant Conditioning") (12).

"Replacement" therapy in patients with congenital or acquired disorders of marrow function, immunodeficiencies, or storage diseases represents a second indication for HCT. Patients with autoimmune diseases (e.g., rheumatoid arthritis or systemic sclerosis) can also be considered part of this category (13). In contrast to the benefit from GVT alloreactivity in the malignant setting, patients with these nonmalignant disorders are not thought to derive any benefit from alloreactivity beyond its "graft-facilitating" effect.

Finally, HSC (or their more mature progeny) may be effective vehicles for gene therapy (14) and for immunotherapy. Objectives of gene therapy include the replacement of defective or missing enzymes (e.g., adenosine deaminase, glucocerebrosidase) or of the defective gene (15,16). Experience with the use of allogeneic cells, often T lymphocytes, as immunologic bullets is more extensive. Donor lymphocyte infusion (DLI) for reinduction of remission in patients with chronic myelogenous leukemia (CML) who have relapsed after HCT has been remarkably successful, leading to broader application of this approach. A modification of this strategy is the use of genetically modified donor lymphocytes expressing a "suicide gene," which may be activated to abrogate the adverse effects of DLI, particularly GVHD (17).

The principle of immunotherapy is also exploited in reduced-intensity conditioning (RIC), also referred to as nonmyeloablative or "mini" transplants (both terms, however, are misleading, as the end result is intended to be "ablation" of the disease, and a mini-transplant is still a full transplant, albeit with a lower-intensity conditioning regimen). In this approach, the intensity of the conditioning regimen has been reduced with the objective of preventing early mortality, and donor antihost reactivity has been enhanced to eliminate host cells (Fig. 1.1) (18).

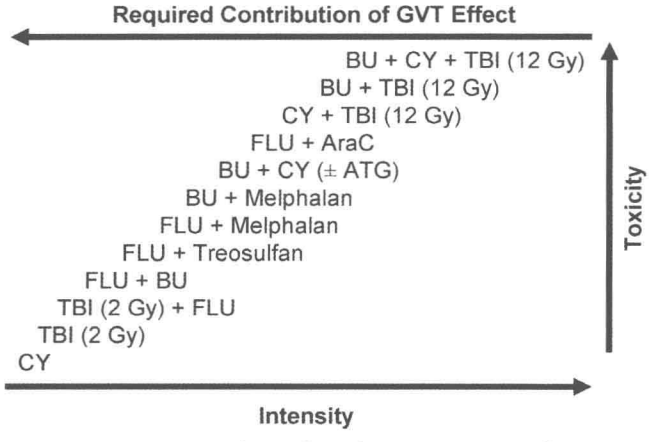

FIGURE 1.1. Commonly used conditioning regimens for hematopoietic cell transplantation, stratified by intensity, toxicity, and relative reliance on immunological graft-versus-tumor effects. Abbreviations: GVT, graft-versus-tumor; CY, cyclophosphamide; TBI, total body irradiation; Gy, gray; FLU, fludarabine; BU, busulfan; ATG, antithymocyte globulin; araC, cytarabine.

SOURCES OF HEMATOPOIETIC STEM CELLS AND DONOR SELECTION

HSC can be obtained from a variety of donors and cellular compartments, including the bone marrow, peripheral blood, cord blood, and the fetal liver. The choice of stem cell source is dependent upon several factors. Although autologous marrow or peripheral blood stem cells (PBSC) are theoretically available for every patient (feasibility has been reported even for patients with severe aplastic anemia), these would not be useful without genetic manipulation for genetically determined disorders, and would be suboptimal for malignant disorders, because of the concern of contamination with malignant cells and the lack of an allogeneic antitumor effect. An HLA-haploidentical donor (e.g., parent, sibling, child) is available for most patients, and, while clearly investigational at this time, early results show surprisingly low rates of GVHD and graft rejection (19).

Generally, each sibling has a 25% chance of sharing the HLA genotype of a patient. Phenotypically matched donors can be identified among family members in about 1% of patients, and somewhat less than 1% of patients will have a syngeneic (identical twin) donor. The lack of an HLA-identical related donor in more than 70% of patients has led to the development of (a) large data banks of volunteer unrelated donors; (b) research into alternative allograft sources such as HLA-haploidentical family members and umbilical cord blood, as indicated earlier; and (c) techniques to "purge" autologous cells of tumor contamination.

Supported by the efforts of the National Marrow Donor Program in the United States, the Anthony Nolan Appeal in the United Kingdom, and other groups internationally, more than 10 million volunteer donors have been typed for HLA-A and HLA-B, and a rapidly increasing number also for HLA-C, HLA-DR (DRB1), and HLA-DQ antigens (20). The probability of finding a suitably HLA-matched donor for a white patient in North America is about 70% to 80%. This probability is lower for other ethnic groups, in part because of lower representation in the data bank and in part because of greater polymorphism of the HLA genes (21).

Cord blood cells, generally not matched for all HLA antigens of the patient, are being used with increasing frequency (22), while fetal liver cells have been used only very rarely in recent years.

Autologous marrow or PBSC can be purged of contaminating malignant cells by chemical means or by antibodies that recognize tumor cells. However, slow engraftment and residual tumor cells that resist the purging regimen limit the usefulness of this approach. A complementary approach is aimed at purifying stem cells using specific antibodies to positively select cells bearing CD34, which is the closest that the research community has come to characterizing human HSC.

TRANSPLANT PROCEDURE

Transplant Conditioning

Rationale for Conditioning

1. To eradicate (ablate) the patient's disease, or at least to reduce the number of malignant or abnormal cells to below detectable levels (this applies to allogeneic, syngeneic, and autologous donors).
2. To suppress the patient's immunity and to prevent rejection of donor cells (this applies to allogeneic, but not to autologous, HCT). Immunosuppression is also needed in preparation for some syngeneic transplants, apparently to eliminate autoimmune reactivity which may interfere with sustained hematopoietic reconstitution.

The notion that conditioning is necessary to "generate space" in the transplant recipient has essentially been abandoned. Recent data show that donor cells, given in sufficient numbers, create their own space and proceed to repopulate the recipient's marrow (23).

Exceptions to the conditioning requirement exist in children with severe combined immunodeficiency (SCID), because of the nature of the underlying disease, which does not allow them to reject transplanted donor cells, and in patients in whom even partial donor engraftment can completely correct the genetic defect (24).

Modalities for Transplant Conditioning

Modalities used to prepare patients for HCT have been reviewed extensively elsewhere (25,26); commonly used regimens are listed in Figure 1.1. In principle, conditioning for HCT may include the following approaches:

1. Irradiation is in the form of total body irradiation (TBI), total lymphoid irradiation (27), or modifications thereof. Many conventional TBI regimens deliver 1200 to 1400 cGy over 3 to 6 days. In addition, bone-seeking isotopes (e.g., holmium) and isotopes (e.g., ^{131}I, ^{92}Y) conjugated to monoclonal antibodies (MAbs) directed at lymphoid or myeloid antigens (e.g., anti-CD20, CD45) are in use (28). TBI may also be a component of RIC regimens, usually at lower doses of 2 Gy (29).
2. Chemotherapy (e.g., cyclophosphamide, 120 to 200 mg/kg over 2 to 4 days) is included in many conventional regimens. Busulfan (available in oral and intravenous formulations) at 16 mg/kg (or lower doses), targeted to predetermined plasma levels, is often used in combination with cyclophosphamide. Other agents, including etoposide, melphalan, thiotepa, cytarabine, and more recently treosulfan (30), may be used either alone or in combination (with or without irradiation).
3. Biologic reagents (e.g., antithymocyte globulin (ATG)) or MAbs directed at T-cell antigens or adhesion molecules suppress recipient immunity. Others are directed at antigens expressed on the recipient's malignant cells; in addition, cytokines or cytokine antagonists are being investigated. Anti-T-cell therapy predisposes the individual to viral infections, in particular cytomegalovirus (CMV) and the development of Epstein–Barr virus (EBV)-related lymphoproliferative disorders (PTLD) after transplantation (31).
4. T-cell therapy is based on the observation that broad T lymphocyte depletion of donor marrow resulted in graft failure. This has led to protocols of selective T-cell add-back to ensure engraftment. The observation that DLI was effective in inducing remission in a proportion of patients who had experienced relapse after HCT renewed the interest in exploiting T-cell therapy for the treatment of leukemia. Other indications for T-cell therapy are viral infections such as CMV (32) or EBV, especially with the development of PTLD in the latter (33).

Other procedures involve plasmapheresis of the recipient's blood to remove isoagglutinins directed against the donor's ABO blood group or the removal of plasma from the donor marrow to remove the isoagglutinins directed at recipient cells. Alternatively, the donor red blood cells with which recipient antibodies may react can be removed, thus minimizing transfusion reactions. Due to the procedure by which they are obtained, these additional manipulations are generally not required with PBSC.

Marrow Harvest

The marrow donor receives general or regional (e.g., epidural, spinal) anesthesia, and, under sterile conditions, multiple aspirates of marrow are obtained from both posterior iliac crests (34). Additional potential aspiration sites are the anterior iliac crests and the sternum. Approximately 10 to 15 mL/kg of donor weight is collected. If no ABO incompatibility exists and if the marrow is not to be subjected to any in vitro purging procedure, the resulting cell suspension is infused intravenously without manipulation.

Alternative Stem Cell Sources

HSC circulate at low concentrations in blood (35). Their frequency increases dramatically during the recovery phase following cytotoxic therapy, and after the administration of recombinant hematopoietic growth factors such as G-CSF which dislodge cells from the marrow. Peak blood concentrations of $CD34^+$ cells are typically reached on day 4 to 5 after initiating G-CSF. A single leukapheresis may be sufficient to harvest the number of HSC required for a transplant. For autologous procedures, the goal is to collect at least 2 to 5×10^6 $CD34^+$ cells/kg recipient weight; for allogeneic transplants, the goal is 5 to 8×10^6 $CD34^+$ cells/kg, although the optimum dose has not been determined (36).

Umbilical cord blood represents a segment of the peripheral circulation of the fetus and is easily accessible (37). Also,

cord blood cells are less immunocompetent than adult cells, and might therefore carry a lower risk of inducing GVHD than adult cells. The concentration of HSC in umbilical cord blood is high, but the small volume that is usually available (80–150 mL) initially limited the use of these cells to children and smaller adults. In larger adults, approaches have included the use of two cord blood units to ensure adequate cell dose and engraftment (11), as well as ex vivo expansion of hematopoietic precursors in umbilical cord blood units for infusion together with an unmanipulated cord blood unit (38).

Purging

Several rationales exist for purging collected donor cells or fractionating them into subpopulations. In the autologous setting, the goal is to eliminate contaminating tumor cells, either by negative selection (removal of tumor cells with antibodies or physicochemical means) or by positive selection (purification of $CD34^+$ cells from the graft). Conversely, one may want to retain certain populations (e.g., $CD4^+$ cells) with potential for later uses such as posttransplant DLI.

Hematopoietic Stem Cell Infusion: The Actual Transplant

Donor cells are infused intravenously via an indwelling central line, often a Hickman catheter. Directed by surface molecules which interact with receptors on endothelial cells, HSC home to the marrow cavity. The actual infusion of stem cells is generally uneventful, though it can occasionally cause transient mild hypotension or hypersensitivity reactions.

CARE AFTER TRANSPLANTATION

Complications of HCT, including infections, are related to several factors: the underlying disease, the preparative regimen, and the interactions of donor cells with recipient tissue (GVHD with immunosuppression and end-organ damage). All patients experience at least transient pancytopenia, although this may be mild with RIC regimens. Patients undergoing high-dose conditioning generally develop severe pancytopenia, including neutropenia, within days after completion of conditioning. This period may last 2 to 4 weeks with marrow allografts, 10 to 12 days with mobilized PBSC grafts, or 4 to 6 weeks with umbilical cord blood grafts. The period of neutropenia ends with engraftment of the donor cells, clinically defined by stable increases in the white blood cell count. Cytopenias are less pronounced after RIC, and the pattern of engraftment may be less apparent in the peripheral white blood cell count. Engraftment in these patients is generally documented by demonstrating donor chimerism by cytogenetic or molecular means in peripheral blood leukocytes and bone marrow.

Most patients prepared with high-dose regimens require transfusion support with platelets, red blood cells, or both.

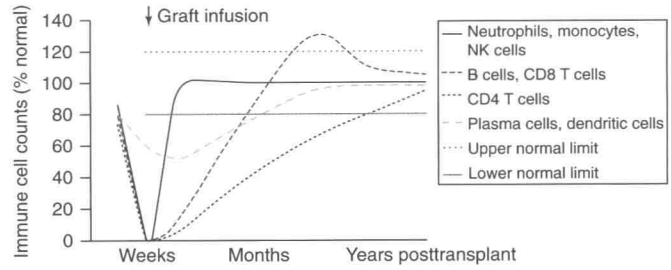

FIGURE 1.2. Approximate trends in immune cell counts after myeloablative hematopoietic cell transplantation. With the use of reduced-intensity conditioning, nadirs are higher and occur later. These recovery rates may be influenced by clinical variables such as graft-versus-host disease, stem cell source, and patient age. (Adapted from Storek J. Immunological reconstitution after hematopoietic cell transplantation—its relation to the contents of the graft (Review). *Expert Opin Biol Ther.* 2008;8:583–597.)

Transfusion requirements are substantially reduced in patients prepared with RIC regimens, because the nadir of cells often is in a range in which no transfusions are required (39). Erythropoietin administration after HCT accelerates reticulocyte recovery and moderately reduces red blood cell transfusion requirements in patients undergoing allogeneic (though not autologous) HCT (34).

Quantitative and functional deficiencies of granulocytes and T-lymphocytes for various periods after HCT are responsible for most of the infectious complications seen after HCT (Fig. 1.2). Although all patients receive prophylactic antimicrobials, granulocyte transfusions are not routinely given. Laminar air flow (LAF) rooms and gastrointestinal decontamination may reduce the frequency of infections and the duration of febrile episodes, but neither is used routinely because of the high cost of LAF and the availability of effective broad-spectrum antibiotics (40).

The most widely used modality of GVHD prophylaxis is the in vivo administration of immunosuppressive agents, such as methotrexate, cyclosporine (CSP), glucocorticoids, tacrolimus (FK506), mycophenolate mofetil (MMF), sirolimus and others, either alone or in combination (41). At many institutions, the current standard is a combination of a calcineurin inhibitor with methotrexate or MMF, but several other combinations are used. Due to the nonselectivity of these agents, recipients are broadly immunosuppressed and thus susceptible to infections. In vitro T-lymphocyte depletion of donor marrow may obviate the need for immunosuppressive treatment after HCT; however, the elimination of mature T-cells is associated with a risk of rejection, delayed immunologic reconstitution, an increased risk of PTLD, and, for some disorders, disease recurrence. Both immunodeficiency and therapeutic immunosuppression predispose the patient to infections. Whether the selective removal of naive T-cells will lead to successful transplants without GVHD remains under investigation.