CHAPTER 76
Critical Care Aspects of Stem Cell Transplantation

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INTRODUCTION

Bone marrow and blood cell transplants are widely used to treat aplastic anemia, leukemias, lymphomas, myeloma, and immune deficiency disorders. Increasingly, transplants are used to treat other bone marrow disorders such as sickle cell disease and thalassemia. Morbidity and mortality associated with transplants usually result from regimen-related toxicity, such as adverse effects of drugs and radiation given pretransplant, complications of graft-versus-host disease (GvHD), as well as infections resulting from bone marrow failure. Morbidity and mortality of transplants has steadily decreased over the past four decades because of better supportive care. Recently, there is increased use of reduced-intensity conditioning allotransplants. Although this is associated with less immediate toxicity, treatment-related mortality by 1 year seems similar to conventional transplants. There are also increased transplants from partially HLA-matched related and unrelated donors. These transplants are associated with increased treatment-related morbidity and mortality for diverse reasons.

Pretransplant evaluation of recipients typically includes the following (1–9):

- Measurement of the left ventricular ejection fraction (LVEF), which should be at least 40% and a check for arrhythmias. This is arbitrarily chosen as an eligibility criteria as some studies have shown an association between poor cardiac function and the risk of developing posttransplant cardiotoxicity while others have not. Several recent studies also suggest that these are low-yield procedures (10).
- Pulmonary function tests, including carbon monoxide diffusing capacity (DL\(_{CO}\)), and forced vital capacity (FVC\(_1\)), which should be more than 50% of predicted.
- Liver function tests which should be in the acceptable range.
- Creatinine clearance, which should be more than 50 mL/min/1.73 m\(^2\) body surface area.
- A pretransplant performance score consistent with an independent life.

Because the risk of GvHD increases with age, allotransplants are typically done in subjects younger than 55 years (11). However, with the increased use of reduced-intensity conditioning regimens, allotransplants are increasingly being performed in older persons. Autotransplant recipients, on the other hand, are at risk for fewer treatment-related complications such as GvHD, so older transplant recipients are not excluded (12). The risk of infection is minimized by various preventative or isolation procedures (see below). Transplants are typically delayed in subjects with active infections until the infection resolves (13,14). The 100-day transplant-related mortality after autotransplants is 2% to 5%; after related allotransplants, it is 15% to 20%; and after alternative (unrelated) allotransplants, it is about 30% (13,14).

IMMEDIATE CONCERNS: THE FIRST 30 DAYS

Pretransplant Conditioning Regimens

In the setting of allotransplants, the pretransplant conditioning regimen needs to moderate or eliminate recipient immunity to prevent graft rejection (15,16). When the allotransplant recipient has cancer, the pretransplant conditioning regimen may also play an important anticancer role. Most allotransplant conditioning regimens contain cyclophosphamide and busulfan or total-body radiation (17,18). Antilymphocyte antibodies, such as antilymphocyte globulin (ALG), antithymocyte globulin (ATG), or alemtuzumab (anti-CD52), are often used in reduced-intensity conditioning regimens or in alternative donor transplants. In immune deficiency disorders such as severe combined immune deficiency (SCID), pretransplant conditioning is not necessary, as the host is already immune deficient.

For autotransplants, the choice of pretransplant conditioning regimen is based entirely on anticancer effect, a steep dose–response curve, lack of cross-resistance with other drugs, and low non–bone marrow dose-limiting toxicities. In general, these regimens contain alkylating drugs, such as melphalan or cyclophosphamide, combined with two or three other drugs. Immune suppression is unnecessary and an unwanted side effect of the conditioning regimen; radiation is not typically used in autotransplants.

Pretransplant conditioning regimens are typically empirically determined, as there are few large randomized trials. Consequently, it is difficult to determine which regimen, if any, is best (19). The choice of a pretransplant conditioning regimen depends not only on effectiveness of the regimen in a specific disease and the need for immune suppression but also on avoiding toxicity from prior therapy or current organ dysfunction. For example, prior mantle radiation or exposures to radiosensitizers, such as bleomycin or carmustine (BCNU), increase the pulmonary toxicity of total-body radiation, whereas prior therapy of testicular cancer patients with cisplatin increases the renal toxicity of platinum-based conditioning regimens. In some diseases and disease states, data from large observational databases, and occasionally from randomized trials suggest superiority of one regimen over another. Examples include total-body radiation regimens in persons with acute lymphoblastic leukemia (20) and cyclophosphamide and busulfan rather than total-body radiation in acute myeloid leukemia (21). Non–bone marrow dose-limiting toxicities of
Bone Marrow and Blood Cell Collection

Cells are collected in the operating room under general, epidural, spinal, or caudal anesthesia. The donor may be admitted on the day of the procedure and discharged the next day. Sometimes, an autologous unit of red blood cells is collected 3 to 4 weeks before the procedure for the next day. Sometimes, an autologous unit of red blood cells be admitted on the day of the procedure and discharged the next day. Sometimes, an autologous unit of red blood cells is collected 3 to 4 weeks before the procedure for the next day. Sometimes, an autologous unit of red blood cells is collected 3 to 4 weeks before the procedure for the next day. Sometimes, an autologous unit of red blood cells is collected 3 to 4 weeks before the procedure for the next day. Sometimes, an autologous unit of red blood cells is collected 3 to 4 weeks before the procedure for the next day.

The timing of apheresis correlates with the method used to increase numbers of cells collected: apheresis is usually done for 1 to 3 days, starting 4 days after beginning hematopoietic growth factor therapy. In contrast, when chemotherapy is used, apheresis is usually done for 1 to 3 days when neutrophils are present at a level of greater than or equal to 1 × 10^8 nucleated cells/kg recipient weight. This is more than 10-fold less than the 2 to 4 × 10^8 nucleated cells/kg recipient weight collected from the bone marrow.

Bone marrow and blood cells may be frozen in dimethyl sulfoxide (DMSO) for later use (29,30). The intracellular contents of cells destroyed in the freezing and thawing processes—and DMSO itself—may cause hypotension, anaphylaxis, or dysrhythmias, including transient heart block (31). To avoid complications, subjects are premedicated with diphenhydramine hydrochloride (Benadryl) and methylprednisolone sodium succinate (Solu-Medrol). Intubation equipment and epinephrine should be available at the bedside when cells are infused. If hypotension occurs, the infusion is slowed or temporarily interrupted until the blood pressure stabilizes. If the bone marrow or blood cells have not been frozen, the risk of anaphylaxis is similar to a standard blood transfusion, and premedication is unnecessary.

Bone Marrow and Blood Cell Infusion

Bone marrow and blood cells may be obtained from the umbilical cord and placental blood at the time of birth. The target is to collect 2 to 4 × 10^7 nucleated cells/kg recipient weight. This is more than 10-fold less than the 2 to 4 × 10^7 nucleated cells/kg recipient weight collected from the bone marrow.

Bone marrow and blood cells are routinely analyzed for quality control at various times during collection, processing, storage, and infusion. Approximately 1.2% of cultures obtained during these processes are found to contain bacteria (32). Most cultures show coagulase-negative Staphylococcus sp., which colonize the skin; pathogenic gram-negative bacteria are occasionally present. Bone marrow and blood cell collections inconvenience the donor and cost approximately $16,000. Thus, despite positive culture results, most
centers infuse the cells after appropriate antibiotic coverage; although controversial, this approach has generally been without adverse effects.

Fluids and Hypotension

High-dose chemotherapy and radiation damage vascular endothelial cells, resulting in extravascular leakage of fluids. Furthermore, GVHD and cytokines such as tumor necrosis factor (TNF), interleukin 2 (IL-2), and interferon-gamma (IFN-γ) contribute to a posttransplant capillary leak syndrome (33–36). In addition, subjects often receive large volumes of intravenous (IV) fluids from drug infusions, parenteral nutrition, and prophylaxis for hemorrhagic cystitis. Consequently, all transplant recipients gain weight, with the result that diuretics are frequently given to maintain baseline weight and mitigate fluid retention. If hypotension develops, emphasis should be placed on early invasive cardiovascular monitoring, inotropic support, and irradiated packed RBC transfusion to maintain intravascular oncotic pressure. Aggressive hydration may precipitate pulmonary and peripheral edema, even with normal pulmonary artery wedge pressure and right atrial pressure.

Electrolyte Balance

Electrolyte abnormalities are common in transplant recipients, resulting from the underlying disease, prophylactic hydration for hemorrhagic cystitis, diarrhea, parenteral nutrition, renal insufficiency, diuretics, and other medications. Ifosfamide, especially when combined with carboplatin, causes a Fanconi syndrome–like renal tubular acidosis 3 to 7 days after the pretransplant conditioning regimen (37,38). The resulting normal anion gap acidosis may be treated with sodium bicarbonate. Other drugs associated with renal tubular wasting of electrolytes are amphotericin, foscarnet, and aminoglycosides. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may result from high-dose cyclophosphamide and/or ifosfamide. Cyclosporine may cause hypokalemia and hypokalemia or hyperkalemia; hypoglycemia increases the risk of cyclosporine-associated seizures. Tumor lysis syndrome is rare, as most transplant recipients have relatively few cancer cells and receive intensive hydration. Finally, uric acid, a major blood antioxidant, is markedly decreased soon after a transplant, independent of allopurinol, which is often given (39).

Blood Product Transfusions

Subjects receiving transplants are immune compromised and at risk for transfusion-associated GVHD. All cellular blood products contain white blood cells (WBCs), including immune-competent T cells, and should be irradiated to 25 Gy (40).

Cytomegalovirus (CMV) infection is another risk. Allo-transplant recipients should receive CMV-negative blood product transfusions, especially when the recipient is CMV seronegative (41–44). If CMV seronegative blood is unavailable, removal of contaminating WBC with an inline microfilter is an alternative (45,46). When an allotransplant recipient is CMV seropositive, no special CMV-related precautions are needed. Because autotransplant recipients do not develop GVHD or receive posttransplant immunosuppression, the risk of CMV-related infection is low (47), and no special CMV-related precautions are needed.

Special consideration is needed regarding ABO-compatibility between recipient and donor (48–50). As engraftment occurs, there is a gradual switch of RBCs to the donor ABO type with a transition period when RBCs with recipient and donor ABO types are present in the blood. When there is A and/or B incompatibility between recipient and donor, there is the possibility that residual anti-A or -B recipient antibodies may react against donor RBCs. Also, B cells in the graft may produce anti-A or -B recipient antibodies against residual recipient RBCs. This complexity of blood product transfusion support should be viewed in terms of whether there is major or minor ABO incompatibility between the recipient and the donor (Tables 76.2 and 76.3). A major ABO incompatibility occurs when the recipient has antibodies to the donor RBC phenotype, for example, recipient group O, donor group A. To prevent immediate RBC destruction by pre-existing recipient antibodies, RBCs should be removed from the graft. Posttransplant, the recipient should receive recipient ABO-type or O-type RBC transfusions from which plasma and platelets are removed. With a minor ABO incompatibility, the donor has anti-A and/or anti-B antibodies to the recipient’s RBC ABO type, for example, donor O type, and recipient A or B type. Donor anti-A and/or anti-B antibodies should be removed from the graft. Posttransplant, the recipient should receive O-type RBC transfusions and recipient ABO-type plasma and platelets. When recipient and donor have anti-A and/or anti-B antibodies to each other’s ABO type, for example, recipient A

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<th>TABLE 76.2 Donor-Recipient ABO Incompatibility</th>
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<td><strong>Major ABO Incompatibility</strong></td>
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**IMMEDIATE HEMOLYSIS**
- Prevent by RBC depletion of marrow
- Prevent by plasma depletion of marrow
- Prevent by RBC and plasma depletion of marrow

**DELAYED HEMOLYSIS**
- Occurs 2–4 weeks after SCT
- Occurs Day 9 to Day 16 after SCT

**DELAYED ERYTHROPOIESIS**
- Plasma exchange, erythropoietin, steroids

RBC, red blood cell; SCT, stem cell transplantation; +, positive.
When full ABO conversion has taken place, all patients receive products of their own type and donor B type, there is a combined major/minor ABO incompatibility. In this instance, RBC and plasma should be removed from the graft. Posttransplant, the recipient should receive O-type RBC transfusions and AB-type platelets and plasma.

Despite using ABO-compatible platelets, many subjects fail to respond to platelet transfusions early posttransplant. Causes include fever, hepatic sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD), drugs, infection, disseminated intravascular coagulation (DIC), and microangiopathic hemolytic anemia related to cyclosporine and/or GvHD (51).

### Infection Prevention

Tactics to prevent bacterial, viral, and fungal infections vary considerably between centers (52–54), reflecting the absence of definitive studies and frequent availability of new drugs. Types of infections in transplant recipients correlate with the interval posttransplant. Tactics to prevent bacterial infections early posttransplant are based on two considerations: most infections arise from endogenous microorganisms; and in studies of neutropenic animals, the oral inoculum of gram-negative bacteria required to cause death is increased by colonization of the gastrointestinal tract with anaerobic bacteria. This has led to selective aerobic gastrointestinal decontamination, first, with nonabsorbable antibiotics such as gentamicin, vancomycin, and nystatin, and later, with absorbable antimicrobials selective for aerobes such as oral quinolones (55–57).

Standards for prevention of infection vary from complete isolation in laminar airflow (LAF) rooms to none. In LAF rooms, the subject is in a sterile environment; persons entering must be gloved and gowned, and food is sterilized or has a low microbial content because it is autoclaved or microwaved (58–61). Prophylactic oral antibiotics are given to destroy enteric pathogens, which not only are reservoirs for infection, but also may function as super-antigens that increase the severity of GvHD (62). The minimal standards to prevent bacterial infections include the following:

- A transplant unit set aside from general hospital, patients, and visitor traffic.
- High-efficiency particulate air (HEPA) filtration to prevent iatrogenic Aspergillus sp. infection (63,64).
- Careful handwashing before entering a patient's room.
- A diet without fresh salads, vegetables, or fruits, as these may be contaminated with gram-negative bacteria, or without pepper, as this may be contaminated with an Aspergillus sp. (65).

Other measures, such as shoe covers, gloves, masks, and gowns and low microbial diets and anterooms are also commonly used but their effectiveness is debatable. Bacterial prophylactic measures are generally discontinued when granulocytes exceed $0.5 \times 10^9$ cells/L.

Tactics to prevent fungal infections include the use of oral triazoles, such as itraconazole, voriconazole, posaconazole, or fluconazole, given orally or intravenously for the first month posttransplant (66). The azole antifungals are effective against most Candida spp; in transplant recipients, fluconazole is ineffective and itraconazole, voriconazole, and posaconazole are more effective against Aspergillus spp. Most Aspergillus spp infections are iatrogenic and preventable by HEPA filtration of rooms. Subjects with prior aspergillosis infection are at high risk of recurrence (67), especially when there is:

- Prolonged posttransplant neutropenia
- Advanced cancer
- A brief interval from beginning systemic antifungal therapy to the transplant
- Severe acute GvHD

Persons with prior aspergillosis should receive amphotericin, voriconazole, posaconazole, or caspofungin early posttransplant (68).

Herpes simplex reactivation is usually prevented by using intravenous or oral aciclovir for the first month posttransplant (69,70). Treatment thereafter results in frequent aciclovir resistance and delays the development of natural immunity.

### Fever and Neutropenia

Transplant recipients are immune compromised because of neutropenia, breakdown in mucosal barriers (e.g., mucositis), invasive therapies (e.g., indwelling urinary bladder [IU/BC, Foley] catheter or central venous lines), immune suppressive drugs (e.g., cyclosporine, corticosteroids, and methotrexate), and GvHD. Lymphocyte function is also affected by thymic involution, weak proliferative responses to T- and B-cell mitogens, and inverted CD4+/CD8+ ratios for 6 months after autotransplants and more than 1 year after allotransplants (71, 72). When an allotransplant is complicated by chronic GvHD, normal lymphocyte function may never return (73). The risk of infection depends on the genetic link between the donor and the recipient, graft type, and posttransplant immune suppression.

In transplant recipients with fever—temperature greater than or equal to 38°C—and granulocytes less than $0.5 \times 10^9$ cells/L (74), one should try to identify a possible infection source using a chest radiograph, blood, and urine cultures and physical examination with emphasis on intravenous catheter sites, the perineal and, oropharyngeal regions and the sinuses. Often no source is identified and broad-spectrum antibiotics are begun. The choice of antibiotics may include an antipseudomonal penicillin.
amino glycoside and vancomycin, or a third-generation antipseudomonal cephalosporin or carbapenem. Transplant recipients commonly receive loop diuretics such as furosemide, which can additively increase ototoxicity. Allograft recipients receive cyclosporine, whose nephrotoxicity is increased by aminoglycosides. Recurrent or persistent fever for 3 to 5 days without source in a person with granulocytes less than 0.5 × 10^9/L is an indication for empiric antifungal therapy with amphotericin. The renal toxicity of amphotericin is enhanced by cyclosporine and aminoglycosides.

**Mucositis**

The severity of mucositis depends on the components of the pre conditioning regimen. The non–bone marrow dose-limiting toxicity of etoposide, busulfan, cytarabine, thiopeta, and taxel is mucositis; radiation also contributes to mucositis. Not surprisingly, conditioning regimens containing these drugs and/or radiation are associated with severe mucositis. Other risk factors include posttransplant methotrexate and pretransplant IFN-γ. Methotrexate should be withheld if severe mucositis develops, whereas IFN-γ should be discontinued at least 2 to 4 weeks before giving radiation.

Management of mucositis includes good oral hygiene, using, for example, saline, chlorhexidine, and nystatin rinses, and topical analgesics (75,76). Opioids are often needed, and should be given intravenously on a schedule—as opposed to PRN (as needed)—or using patient-controlled analgesia (PCA). Severe mucositis may require prophylactic intubation for airway protection. Ultimately, the resolution of mucositis generally correlates with recovery of blood granulocytes. New drugs, such as palifermin (recombinant human keratino- growth factor-1) reduce the incidence and severity of oral mucositis (77).

**Diarrhea**

Diarrhea in transplant recipients may be caused by high-dose drugs and radiation, antibiotics, bacterial and/or viral infections, GVHD, and other factors (78–80). The pretransplant conditioning regimen is the most common cause of diarrhea within 2 to 3 weeks posttransplant. Nevertheless, an infectious cause should always be considered, including Clostridium difficile and Escherichia coli (0157:H7), CMV, herpes simplex, adenoviruses, rotaviruses, echoviruses, astroviruses, Norwalk virus, Coxsackie virus, Strongyloides spp, Giardia spp, and Cryptosporidium spp. GVHD also causes diarrhea; the diagnosis can be confirmed by intestinal biopsy showing loss of crypts, vacuolization of crypt epithelium, karyorrhectic apototic debris, microabscesses, and, in severe cases, ulceration and denudation of the epithelium. Therapy is directed toward appropriate antibiotics for infections and immune suppression for GVHD. Conditioning regimen- and GVHD-associated diarrhea may respond to octreotide, a somatostatin analog whose mechanism of action is partly through the inhibition of secretory hormones (81). Some viral infections, such as CMV, respond to ganciclovir, foscarnet, or cidofovir (82).

**Hemorrhagic Cystitis**

Hemorrhagic cystitis, occurring 2 to 3 weeks posttransplant, usually results from drugs in the pretransplant conditioning regimen, such as cyclophosphamide, ifosfamide, or etoposide (83–85). Prophylaxis for hemorrhagic cystitis includes hydration and diuretics to maintain urine output at 2 mL/kg per hour (86,87). Sodium mercaptoethane sulfonate (Mesna) is often used, especially with high-dose cyclophosphamide or ifosfamide (88). Mesna is inert in plasma but is hydrolyzed in the urine to reactive monomers that conjugate alkylating drugs. It has a short half-life and is therefore given by continuous intravenous infusion. Complications of hemorrhagic cystitis are uncontrolled bleeding and clotting of the ureters or urethra, resulting in acute kidney failure. Obstruction of the ureters by clots may be asymptomatic or cause kidney colic from ureteral spasm. Severe pain may occur in the back or flank and radiate into the groin or genitals; occasionally it is necessary to insert ureteral stents or a ureterostomy.

Therapy of hemorrhagic cystitis consists of using a Foley catheter to irrigate the bladder with normal saline at 250 mL/hr to prevent intravesicular clotting. Platelets should be maintained at more than 50 × 10^9/L with platelet transfusions and RBC transfusion should be given to replace blood loss. Discomfort from local bladder spasm can be treated with antispasmodic agents such as oxybutynin chloride (Ditropan). In severe cases, arterial embolization or cystectomy may be necessary.

Hemorrhagic cystitis seen more than 2 weeks posttransplant can result from pretransplant conditioning or viral infection due to, for example, adenovirus, CMV, JC, or BK viruses of the bladder epithelium (89–91); except for CMV, there are no effective antiviral drugs.

**Sinusoidal Obstruction Syndrome/ Veno-Occlusive Disease of the Liver**

SOS/VOD of the liver is caused by drugs and/or radiation in the pretransplant conditioning regimen within 1 to 3 months posttransplant (92). Unlike the Budd-Chiari syndrome with thrombosis of the large hepatic veins, SOS/VOD arises from thrombosis of the central venule. High-dose therapy damages endothelial cells throughout the body. However, metabolism or activation of drugs by hepatocytes results in a high local concentration. Histologically, the central venule is occluded by concentric fibrosis best shown by a trichrome Masson stain. Lesions are composed initially of von Willebrand factor, soon replaced by collagen (93). Obliteration of the central venule results in intrahepatic hypertension, diminished or reversal of portal blood flow, and ascites.

SOS/VOD, with a reported incidence of 1% to 56%, is a clinical diagnosis suggested by elevated bilirubin, weight gain, ascites, and tender hepatomegaly (94–96) (Table 76.4). The incidence variability results partly from different pretransplant conditioning regimens and the clinical criteria used to diagnose SOS/VOD. For instance, although diagnostic criteria from Johns Hopkins and Seattle seem similar, a retrospective comparison showed SOS/VOD incidence rates of 32% versus 8% (97). Risk factors for SOS/VOD include increased pretransplant liver transaminases, conditioning regimen intensity, prolonged fever, and age (95). Prior hepatitis virus exposure does not increase the risk of SOS/VOD if pretransplant liver function tests are normal. Altered drug metabolism is probably responsible for the decreased incidence of SOS/VOD in children and increased risk for SOS/VOD in persons with abnormal pretransplant liver function. Cytokines that cause fever also damage endothelial cells and probably cause the
increased risk of SOS/VOD in persons with prolonged fever. In general, SOS/VOD incidence is not significantly different in recipients of allo- versus autotransplants.

Clinical symptoms of SOS/VOD are also associated with many common but unrelated transplant complications. For instance, jaundice may result from hemolysis—for example, ABO incompatibility, bacterial sepsis, hepatic candidiasis, parenteral nutrition, drugs such as cyclosporine and methotrexate, or GvHD. Initial evaluation for SOS/VOD should include ultrasound of the liver, with Doppler measurement of portal vein blood flow. Reversal or diminished portal flow is consistent with intrahepatic obstruction of blood flow secondary to SOS/VOD (98); ultrasonographic findings are generally present only in overt clinical disease (99). Although uncertain cases may require liver biopsy, a percutaneous biopsy is contraindicated because of ascites, coagulopathy, and low platelets. Transjugular biopsy may, in general, be performed safely and provides an opportunity to measure the hepatic venous pressure gradient, which, if greater than 10 mmHg, is consistent with SOS/VOD (100).

Therapy for SOS/VOD is predominantly supportive. Emphasis should be on avoiding hepatotoxic drugs that will further damage the liver. Persons with severe SOS/VOD may develop hepatorenal syndrome, marked by renal insufficiency and a low fractional sodium excretion. Therapy includes diuretics to maintain baseline weight and oral ursodeoxycholic acid to lower the bilirubin and prevent further liver injury from free radicals generated by bile acids (101). Some centers attempt to maintain intravascular volume and renal perfusion with RBC transfusions, aiming for a hemoglobin of 12 to 15 g/dL. Early studies of defibrotide, a single-stranded polyoxypolyribonucleotide with fibrinolytic, antithrombotic, and anti-ischemic properties, in severe SOS/VOD, suggested activity with complete response rates of 36% to 55% (102–104). No severe hemorrhage or other serious toxicity related to defibrotide was reported.

The prognosis of SOS/VOD is poor when bilirubin is more than 15 to 20 mg/dL. Thrombolytic therapy with tissue plasminogen activator and heparin has been used successfully but may be complicated by severe bleeding (105,106). Once the thrombus is replaced by fibrin and collagen, thrombolytic therapy is probably ineffective. However, in late SOS/VOD, another option is a transjugular, intrahepatic portosystemic shunt to decompress the portal vein (107–109). If there is engraftment without severe GvHD or recurrence of the underlying disorder prompting the transplant, consideration should also be given to a liver transplant (110–112).

**Respiratory Failure**

Transplant recipients who develop respiratory failure and require mechanical ventilation have a poor prognosis (113,114). Once endotracheally intubated, 80% of recipients are never able to be liberated from mechanical ventilation and, at 6 months, only 3% of subjects who required intubation survive. Except for procedures performed as a prelude to surgery, the reason for intubation is not correlated with a likelihood of survival, but age younger than 40 years and intubation being performed more than 100 days posttransplant correlated with better survival.

Respiratory failure within the first 30 days is usually caused by pretransplant conditioning, regimen-related epithelial cell damage, and/or infection (115–118). Early posttransplant radiotherapy and chemotherapy releases free radicals and cytokines, resulting in damage to pulmonary epithelial cells. This leads to blebs in the cell membranes, separation of junctions between cells, and necrosis, the end result being pulmonary edema, occasionally with focal or diffuse pulmonary alveolar hemorrhage (119). This may occur without an increase in pulmonary artery occlusion pressure (PAOP). Median time to the onset of alveolar hemorrhage posttransplant is about 4 months, but it may occur as late as 1 to 2 years. Symptoms are nonspecific and include dyspnea, hypoxia, and diffuse infiltrates; although hemoptysis is rare, bronchoalveolar lavage often shows intrapulmonary hemorrhage. Early in the course of respiratory distress, efforts should be directed to preventing intubation. Although not evaluated in prospective studies, and therefore of unproven benefit, management may include early invasive hemodynamic monitoring, RBC transfusions to maintain hemoglobin more than 12 g/dL, ultrafiltration to decrease intravascular volume, and anticytokine monoclonal antibodies or cytokine receptor antagonists. Use of high-dose corticosteroids is controversial but, in theory, inhibits generation of free radicals, decreases cytokine release, and decreases inflammation.

The repair process after high-dose chemotherapy and radiation may further interfere with gas exchange by causing interstitial fibrosis. Further, infection aggravates parenchymal inflammation and protracts the repair of the interstitium. Transplant recipients are especially susceptible to pulmonary infections because of bone marrow failure, immune suppressive drugs, mucositis, aspiration, and bronchial epithelial cell damage with impaired ciliary motility. Gram-negative and gram-positive pneumonias are common in the first 30 days posttransplant. Fungal infections of the lung also occur early posttransplant, and isolation of *Aspergillus* spp in a nasal or sputum culture should prompt initial therapy with amphotericin, voriconazole, or caspofungin. Risk factors for aspergillosis are long-term duration of impaired immunity pretransplant, for example, aplastic anemia or SCID; centers without HEPA filters to prevent inhalation of aerosolized spores; and prior invasive aspergillosis. Viral pneumonia is rare early posttransplant; the most common etiologic agent when this does occur is herpes simplex.

**Heart Failure**

Heart failure may result from volume overload or impairment of left ventricular function from sepsis or toxicity from pretransplant conditioning regimen drugs such as cyclophosphamide, ifosfamide, and/or anthracyclines (120–124). Pretransplant risk factors for cardiac failure are a prior history of heart failure or a low resting LVEF of less than 40% (4). Prior mediastinal radiation or a high cumulative anthracycline dose is not independent risk factors, provided the ejection fraction is normal. High-dose
cyclophosphamide causes hemorrhagic myocarditis; transient ST-segment depression and T-wave inversions are common during cyclophosphamide infusion but are not a reason to alter therapy. Cyclophosphamide damages cardiac capillary endothelial cells, leading to hemorrhage between, and separation of, myocytes. The end result is loss of voltage, heart failure, and/or pericardial effusion. Unlike anthracycline-related heart damage arising from myocyte damage, even severe cyclophosphamide-induced left ventricular dysfunction is reversible after an interval of weeks to months.

Renal Failure

Renal insufficiency is usually multifactorial. Cause includes the underlying disease—for example, cast nephropathy in myeloma, prerenal decrease in glomerular filtration, intrinsic renal dysfunction or postrenal obstruction. The most common reason for renal insufficiency early in the posttransplant period is drug related, especially with use of aminoglycosides, cyclosporine, and amphotericin (125,126). Mortality in persons requiring dialysis is about 85% (127). Prerenal causes of azotemia include hepatic SOS/VOD, diarrhea, diuretics, third-spacing from sepsis, hypoalbuminemia, and a capillary leak syndrome from high-dose drugs and radiation. Hepatic SOS/VOD, like other causes of pretransplant azotemia, is marked by decreased fractional excretion of sodium (FeNa+) in the urine. Azotemia from intrinsic renal failure may result from acute tubular necrosis (ATN), glomerulonephritis, interstitial nephritis, or renal vascular damage. Causes of ATN in transplant recipients include sepsis, hypovolemia, and drugs such as aminoglycosides, amphotericin, platinums, foscamet, and cyclosporine. In ATN, the FeNa+ is high, and the urine has muddy hyaline casts. Renal insufficiency from glomerulonephritis usually results from streptococcal or staphylococcal bacteriaemia. In glomerulonephritis, FeNa+ is low, and the urine sediment contains RBC casts and increased protein. Interstitial nephritis arising in the early stem cell transplantation (SCT) period is usually drug induced. Causes of allergic interstitial nephritis are penicillins, cephalosporins, sulfamethoxazole-trimethoprim, and fluoroquinolones. In allergic interstitial nephritis, the urine FeNa+ is high, and urine sediment contains WBCs, WBC casts, and eosinophils. Renal insufficiency from renovascular damage is usually caused by drugs such as cyclosporine or from hemolytic uremic syndrome (HUS), which is marked by schistocytes, thrombocytopenia, and azotemia. HUS arises from endothelial cell damage, which may be related to cyclosporine, GvHD, or high-dose drugs and radiation.

Postrenal kidney failure in transplant recipients may result from hemorrhagic cystitis with ureteral or urethral obstruction due to blood clots, retroperitoneal hemorrhage, urate nephropathy, or drugs that undergo intratubular crystallization and obstruction such as acyclovir ciprofloxacin, and triamterene. Regardless of the cause, posttransplant renal insufficiency may require a dose reduction of prophylactic immune suppressive drugs such as cyclosporine or methotrexate; this may increase GvHD.

Engraftment

Definition of graft failure is controversial. After a bone marrow graft, there is usually a rise in the WBC count by 3 weeks. After a blood cell transplant the WBC count usually rises by about 2 weeks. Platelet recovery, defined as more than 20 × 10⁹ cells/L without transfusions typically occurs 2 to 3 weeks later. Occasionally, recipients require platelet transfusions for months posttransplant. Generally, graft failure is defined as a neutrophil count less than or equal to 0.5 × 10⁹ cells/L by day 28. Causes of graft failure include too few normal hematopoietic cells, damage to the bone marrow microenvironment, immune-mediated graft rejection, or drug- or virus-related immune suppression (128,129).

The minimal number of bone marrow or blood cells needed for sustained engraftment is unknown. There are several reasons for this:

- It is not known which hematopoietic cell(s) are responsible for sustained engraftment.
- Different hematopoietic cells may operate under different circumstances and in different persons.
- After autotransplants there is no need for sustained engraftment because of autologous bone marrow recovery.
- There is no routinely used technique to identify the hematopoietic cell(s) responsible for sustained engraftment (130,131).

Because of these limitations, surrogate markers are used to assess the hematopoietic-restoring functionality of grafts. For instance, CD34 is a surface membrane marker of immature hematopoietic cells. In animals and humans, retrovirus-transduced CD34+ cells sometimes contribute to long-term engraftment but are not a necessary condition (132). To ensure sustained engraftment in humans, most data suggest a threshold of 2 to 4 × 10⁸ mononuclear cells or 2 × 10⁹ CD34+ cells/kg of recipient body weight. Autotransplant recipients receiving extensive prior chemotherapy and/or radiation frequently have fewer CD34+ cells. It may be difficult to obtain large numbers of CD34+ cells from these persons, and recipients generally recover bone marrow function later than after grafts from normal or less extensively treated donors. This may reflect decreased numbers and/or function of CD34+ cells and/or damage to the bone marrow microenvironment.

Immune-mediated graft failure is theoretically impossible after an autotransplant but it is the most common cause of graft failure for allografts. Risk of immune-mediated graft failure correlates with the degree of HLA disparity between the donor and the recipient. Graft failure occurs in less than 1% after HLA-identical sibling allotransplants, 6% to 8% after unrelated HLA-matched allotransplants and in up to 20% after HLA-haplotype–matched allotransplants (133–135) (Tables 76.5 and 76.6). Immunity to non-HLA antigens, such as H-Y and KIR, also operates to increase risk of immune-mediated graft failure. Other variables influencing the risk of immune-mediated graft failure are transfusion-induced sensitization to HLA and non-HLA antigens, intensity of the pretransplant conditioning regimen and quantity of T cells in the graft. In persons with aplastic anemia, the volume of pretransplant RBC or platelet transfusions correlates with a higher rate of graft failure. This is presumed to result from sensitization of the recipient to disparate HLA and non-HLA antigens. These observations were made before microfilters were available to deplete WBC from transfused blood products. Whether this risk still operates is unknown. However, because of these considerations, potential allotransplant recipients should avoid unnecessary transfusions or receive microfiltered blood products. Removal of donor T cells from
the bone marrow graft to prevent GvHD also increases the risk of graft failure; compensation may be possible by more intensive pretransplant immune suppression (136,137). Graft-failure risk is also increased after male grafts to parous and/or transfused female recipients. Here, the recipient is presumed to be sensitized to donor H-Y antigens (138,139).

Several bone marrow suppressive drugs commonly used posttransplant may delay and/or reverse engraftment, for example, methotrexate and sulfamethoxazole-trimethoprim. Viruses, especially herpes simplex, parvovirus, HHV-6, parvovirus-B19, and CMV, cause bone marrow suppression, possibly because they infect bone marrow stroma cells. A decline in the WBC and/or platelets after recovery posttransplant should prompt a search for a drug- or virus-related cause. Declines are also temporarily associated with tapering immune suppression; whether these are related phenomena is unclear. The effect, if any, of acute GvHD on bone marrow function is poorly understood. However, there is a clear association of decreased bone marrow function and chronic GvHD (see below). The response of chronic GvHD to immune suppression is often correlated with improved bone marrow function.

Treatment for graft failure includes using molecularly cloned hematopoietic growth factors (G- or GM-CSF), a second graft, and/or increased immune suppression. Subjects with primary graft failure (i.e., no engraftment) have a poor prognosis, whereas those with secondary or late graft failure (unsustained engraftment) do better. When graft failure is associated with reemergence of host T cells, repeat pretransplant conditioning is usually given before the second graft based on the assumption that graft failure is immune mediated; this may be incorrect in some instances. Consequently, early or late bone marrow failure should be referred to as such and not as graft rejection.

**Acute Graft-Versus-Host Disease**

The principal manifestations of acute GvHD are rash, diarrhea, and jaundice, present individually or in combination (140,141). Histologically, there is involvement of the basal cell layer of the skin, biliary ductules of the liver, and crypts of the distal gastrointestinal tract. Symptoms occur close to the time of engraftment but may occur earlier or at any time within the first 100 days posttransplant. Acute GvHD is an allogeneic response mediated by donor T cells, which recognizes recipient tissues as foreign. The incidence and severity of acute GvHD increase with increasing recipient age and HLA and non-HLA disparity between the recipient and the donor (142,143) (see Tables 76.5 and 76.6).

The major HLA genes are inherited from both paternal and maternal chromosome 6. The classic HLA class-1 genes are A, B, and C, and more HLA molecules are being characterized. The classical HLA class-I molecules are present on the surface of all cells and function to present small intracellular peptides to T cells. HLA class-2 molecules are DR, DP, and DQ. These surface molecules present extracellular peptides that result from endocytosis of extracellular protein and degradation of these proteins into smaller peptides (144,145). Even after an HLA genotypically matched allotransplant, acute GvHD invariably develops when—usually inadvertently—no pretransplant immune suppression is given. This likely arises because of recognition of host-derived peptides presented by HLA molecules and recognized as foreign by donor T cells (146).

Skin involvement in acute GvHD results in a maculopapular, erythematous rash, often beginning on the palms and soles and which may become systemic. In severe cases, acute GvHD with skin involvement may be pruritic with bullae. The skin involvement in acute GvHD may be precipitated by exposure to sunlight and/or drugs. Histologically, one can see the dermal–epidermal border disrupted by vacuolar degeneration of epithelial cells, dyskaryotic bodies, acantholysis (i.e., separation of cell–cell contact), epidermolysis (separation of the epidermal and dermal layers), and lymphocytic infiltration. These clinical and histologic findings are not unique to acute GvHD and may occur from drug allergy or the effects of the high-dose chemotherapy and radiation used in the pretransplant conditioning regimen.

Gastrointestinal involvement with acute GvHD results in diarrhea, often accompanied by cramping abdominal pain. In severe cases, the diarrhea may be bloody or associated with a paralytic ileus. Histologically, lymphocytes and apoptotic cells are present and intestinal crypts are lost, which leads to epithelial denudation. Evaluation of gastrointestinal tract signs and symptoms should include stool cultures for bacteria, fungi, and viruses, especially CMV. Sigmoidoscopy with biopsy may be helpful if the diagnosis is in doubt and platelet levels are

<table>
<thead>
<tr>
<th>Degree of HLA Match</th>
<th>Acute GvHD Grade III or IV (%)</th>
<th>Chronic GvHD (%)</th>
<th>Graft Failure (%)</th>
<th>DFS-AML or ALL in Remission (%)</th>
<th>DFS-CML in Chronic Phase (%)</th>
<th>DFS-AML or ALL in Relapse (%)</th>
<th>DFS-CML in Transformation (%)</th>
<th>DFS-AA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related 4/6</td>
<td>45–50</td>
<td>50</td>
<td>21</td>
<td>10–40</td>
<td>—</td>
<td>10</td>
<td>10–30</td>
<td>—</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>50–100</td>
<td>&gt;50</td>
<td>20</td>
<td>40–45</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>30–40</td>
</tr>
<tr>
<td>Unrelated 6/6</td>
<td>45–50</td>
<td>50</td>
<td>6</td>
<td>45</td>
<td>45</td>
<td>20</td>
<td>20</td>
<td>30–40</td>
</tr>
</tbody>
</table>

GVHD, graft-versus-host disease; DFS, disease-free survival; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; AA, aplastic anemia.
sufficient. Acute GvHD with hepatic involvement presents as jaundice and an elevated alkaline phosphatase with or without elevated transaminases. The differential diagnosis includes SOS/VOD or infections with CMV or Candida spp and may require a transjugular liver biopsy for accurate diagnosis. In acute GvHD, the liver biopsy may show T-cell infiltration of the portal triad, with apoptosis of epithelial cells lining the biliary tree.

Acute GvHD and infections from immune suppression are major causes of early death after allotransplant. Consequently, acute GvHD prophylaxis is needed for all allotransplant recipients. One effective method to prevent acute GvHD is a 2- to 3-log depletion of T cells from the graft (147–149). However, benefits from preventing acute GvHD are offset by increased graft failure and leukemia relapse. Increased graft failure is presumed to result from immune-mediated graft rejection but may also reflect loss of the interaction of donor T cells and hematopoietic cells. Increased leukemia relapse is presumed to result from decreased T-cell-mediated antileukemia effects, sometimes referred to as graft-versus-leukemia or GvL. Experimental approaches to retain GvL while decreasing acute GvHD include selective T-cell depletion or adding back subsets of T cells or natural killer (NK) cells to the graft, use of cytokines, and modulation of costimulatory T-cell or chemokine pathways (150).

Pharmacologic approaches to prevent acute GvHD are simpler and more widely used than T-cell depletion. Cyclosporine and methotrexate given on days 1, 3, 6, and 11 posttransplant are the most common preventative regimens (151). Other regimens include cyclosporine and prednisolone or cyclosporine, methotrexate, and methylprednisolone (152). In HLA-identical sibling transplants, weekly intravenous immunoglobulin (IVIG) until day 100 results in a lower incidence of acute GvHD but the effect size is small and this approach is not often used, especially because of substantial cost (153). GvHD is associated with a lower leukemia relapse rate, and, therefore, the aim should not be to completely eliminate acute GvHD, but rather to balance the risk of acute GvHD against the risk of a leukemia relapse. Thus, more intensive immune suppressive regimens are used when GvHD risk is high, for instance, in HLA-mismatched transplants, and when the leukemia relapse risk is low, whereas less intensive regimens are used when the leukemia relapse risk is high such as in advanced leukemia and when acute GvHD risk is least. Convincing data supporting these approaches are lacking.

Clinical staging of acute GvHD considers individual tissue/organ involvement scores, which are combined for an overall grade (Tables 76.7 and 76.8). Grade 1 acute GvHD is not clinically important and requires no specific therapy. Grades 2 through 4 acute GvHD are typically treated with corticosteroids such as methylprednisolone, 1 to 2 mg/kg/day, with or without cyclosporine. Acute GvHD unresponsive to this approach has a poor prognosis. Further therapies include monoclonal or polyclonal antibodies to T cells, such as ATG or alemtuzumab (anti-CD52), or cytokines such as daclizumab or infliximab. Daclizumab binds to the high-affinity IL-2 receptor found on activated T cells, whereas infliximab binds to TNF-α, a cytokine involved in acute GvHD (154). Several reports suggest that giving IVIG, typically used for CMV-infection prevention (see below), is associated with less acute GvHD, but these data are inconsistent.

### CMV Prophylaxis

Prophylaxis for CMV infection after autotransplants is unnecessary. In allotransplants, ganciclovir is often given when a surveillance blood culture or bronchoalveolar lavage (BAL) is CMV-positive by quantitative polymerase chain reaction (PCR). Subjects with CMV viremia and CD4+ T cells less than 0.1 x 10^9 cells/L are at greatest risk of developing CMV infection prevention (see below), is associated with less acute GvHD, but these data are inconsistent.

### TABLE 76.7 Grading of Acute Graft-Versus-Host Disease

<table>
<thead>
<tr>
<th>Organ</th>
<th>Grade</th>
<th>Severity of Individual Organ Involvement Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>+1</td>
<td>A maculopapular eruption involving &lt;25% of the body surface</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>A maculopapular eruption involving 25–50% of the body surface</td>
</tr>
<tr>
<td></td>
<td>+3</td>
<td>Generalized erythroderma</td>
</tr>
<tr>
<td></td>
<td>+4</td>
<td>Generalized erythroderma with bullous formation and often with desquamation</td>
</tr>
<tr>
<td>Liver</td>
<td>+1</td>
<td>Moderate increase of AST (150–750 IU) and bilirubin (2.0–3.0 mg/dl)</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>Bilirubin rise (3.1–6.0 mg/dl) with or without an increase in AST</td>
</tr>
<tr>
<td></td>
<td>+3</td>
<td>Bilirubin rise (6.1–15 mg/dl) with or without an increase in AST</td>
</tr>
<tr>
<td></td>
<td>+4</td>
<td>Bilirubin rise (&gt;5 mg/dl) with or without an increase in AST</td>
</tr>
<tr>
<td>Gut</td>
<td>+1</td>
<td>Diarrhea, nausea, and vomiting graded +1 to +4 in severity. The severity of gut involvement is assigned to the most severe involvement noted.</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>Diarrhea more than 500 mL/day</td>
</tr>
<tr>
<td></td>
<td>+3</td>
<td>Diarrhea more than 1,000 mL/day</td>
</tr>
<tr>
<td></td>
<td>+4</td>
<td>Diarrhea more than 2,000 mL/day; or severe abdominal pain with or without ileus</td>
</tr>
</tbody>
</table>

*AST, aspartate transaminase.

### TABLE 76.8 Overall Grade of Graft-Versus-Host Disease*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>Gut</th>
<th>Liver</th>
<th>ECOG Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+1 to +2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>+1 to +3</td>
<td>+1 to +2</td>
<td>And/or +1 to +2</td>
<td>0 to 1</td>
</tr>
<tr>
<td>III</td>
<td>+2 to +4</td>
<td>+2 to +4</td>
<td>And/or +2 to +4</td>
<td>2 to 3</td>
</tr>
<tr>
<td>IV</td>
<td>+2 to +4</td>
<td>+2 to +4</td>
<td>And/or +2 to +4</td>
<td>3 to 4</td>
</tr>
</tbody>
</table>

*ECOG, Eastern Cooperative Oncology Group. AST, aspartate transaminase.

*If no skin disease, the overall grade is the higher single organ grade.

suppression, or therapy may be changed to foscarnet, which is associated with less bone marrow suppression.

**Pneumonitis**

Between 30% and 50% of early posttransplant deaths are associated with respiratory failure (160,161). Although bacterial and fungal pulmonary infections can occur, the two most common causes are idiopathic and CMV-related interstitial pneumonia.

Interstitial pneumonia is more common after an allotransplant (40%) compared with an autotransplant (10%). Risk factors include a radiation-based pretransplant conditioning regimen, severe GvHD, older age, and posttransplant use of methotrexate. The median time to onset of interstitial pneumonia is about 50 days posttransplant, with only rare cases developing after 6 months. Affected persons are hypoxic and/or hypoxic; physical examination often shows basilar crackles; and the chest roentgenogram shows an interstitial reticular-nodular infiltrate; between 40% and 65% of cases of interstitial pneumonia are CMV related. Diagnosis is usually by bronchoscopy with BAL. Early intervention with combined IVIG and ganciclovir has reduced mortality of CMV pneumonia to about 50% (162,163). It is very rare for a subject to develop CMV pneumonia when routine screening for CMV activation by PCR is carried out and appropriate interventions taken. Adoptive immunotherapy, giving CMV-specific cytotoxic T cells has also been used to treat CMV pneumonia (164). Other opportunistic infections causing interstitial pneumonia, such as *Chlamydia trachomatis* and *Legionella pneumophila*, are less common. Prophylaxis for *Pneumocystis carinii* pneumonia with sulfamethoxazole-trimethoprim (Bactrim) is usually begun after engraftment and continued for 1 year.

The cause(s) of 30% to 50% of posttransplant interstitial pneumonias are unknown (165–167). Etiologies are complex and poorly understood; likely contributors include the toxicity of the pretransplant conditioning regimen, chronic GvHD, and unidentified infectious organisms such as human herpes virus-6 (HHV-6) and respiratory syncytial virus (RSV) (168). Carmustine (BCNU)-related interstitial pneumonia may respond to corticosteroids, but most cases of idiopathic pneumonia syndrome do not.

**Epstein–Barr Virus Posttransplant Lymphoproliferative Disease**

Infection of B cells by Epstein–Barr virus (EBV) results in B-cell proliferation. In a normal person, infection-induced, EBV-specific cytotoxic T cells prevent uncontrolled B-cell proliferation. In immune-deficient allotransplant recipients, failure of immune surveillance by EBV-specific cytotoxic T cells results in a polyclonal or, less often, monoclonal proliferation of donor or recipient B cells (169). EBV-lymphoproliferative syndrome (EBV-LPS) occurs in about 0.5% of allotransplant recipients. Risk factors include T-cell–depleted grafts and the use of ATG or anti-CD3 antibodies posttransplant to prevent acute GvHD. EBV-LPS typically develops 45 days to 1.5 years posttransplant; the median time to onset is 70 to 80 days. Presenting features of early-onset EBV-LPS include fever and extranodal involvement; the course is typically unfavorable. Later-onset EBV-LPS generally has a more indolent course, manifested by fever and lymph node enlargement. Antiviral therapy of EBV-LPS is generally ineffective. Rituximab (anti-CD20 monoclonal antibody) has been used and is very effective (170). Giving donor EBV-specific cytotoxic T cells sometimes results in prompt remission of polyclonal and monoclonal EBV-LPS (171).

**LATE CONCERNS (BEYOND DAY 100)**

**Chronic GvHD**

Chronic GvHD usually occurs after day 100 posttransplant. Chronic disease may seemingly develop de novo without prior clinically diagnosed acute GvHD, or after a quiescent interval following resolution of acute GvHD. Most often, acute GvHD evolves into the chronic process (172,173). The most important risk factors for developing chronic GvHD are older recipient age and severity of acute GvHD. Whereas acute GvHD is predominately an alloimmune disorder, chronic GvHD has features of alloimmunity and autoimmunity.

Skin involvement in chronic GvHD involves scleroderma-like changes with hypopigmentation and hyperpigmentation, loss of hair follicles, thickened skin, and joint contractures. Mucosal involvement manifests by dryness, pain, ulceration, and lacy white buccal mucosal membranes. Ocular features include sicca conjunctivitis, ectropion, and, in severe cases, corneal ulceration. In contrast to acute GvHD of the gastrointestinal tract, which is marked by watery or bloody diarrhea, chronic gastrointestinal GvHD manifests as nausea, anorexia, malabsorption, dysphagia, and weight loss. Ulcerations, strictures, and narrowing may occur at any site along the gastrointestinal tract. Hepatic involvement in chronic GvHD presents similarly to acute GvHD with predominance of cholestasis—that is, increased bilirubin and alkaline phosphatase.

Chronic GvHD may have various autoimmune features, including antibodies to DNA, mitochondria, smooth muscle, or connective tissue. Autoimmune syndromes associated with chronic GvHD include polymyositis, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, and thyroiditis. Chronic GvHD of the lung presents with cough and dyspnea caused by progressive obstructive small airway disease with hyperinflated lungs and reduced midexpiratory flows; histologically, the process resembles bronchiolitis obliterans. Chronic GvHD results from underlying immune dysregulation, which also causes immune deficiency that predisposes to infection independent of the immune suppressive drugs used to treat GvHD.

Chronic GvHD may be limited or extensive (Table 76.9). Limited-stage chronic GvHD has a favorable prognosis and

<table>
<thead>
<tr>
<th>TABLE 76.9 Chronic Graft-Versus-Host Disease Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited</strong></td>
</tr>
<tr>
<td><strong>Extensive</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
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</table>
requires no therapy. Extensive-stage chronic GvHD has a poor prognosis; therapy is needed (174). Adverse prognostic variables in persons with extensive-stage GvHD include thrombocytopenia (<100 × 10^9 cells/L) and poor performance status. Standard therapy of extensive-stage chronic GvHD is alternate day corticosteroids. Other options include thalidomide, extracorporeal photopheresis, psoralen, and ultraviolet irradiation (PUVA) for chronic cutaneous GvHD, and ursooxycholic acid for chronic hepatic GvHD (175). Clinical trials with thalidomide analogs, such as pomalidomide, are beginning. The natural history of chronic GvHD is to “burn out” or for subjects to die from an opportunistic infection. The therapy paradox here is that one is forced to use immune suppression to treat a disease that kills subjects because of intrinsic immune suppression.

**Herpes Zoster**

Varicella zoster occurs in 20% of autotransplant (176) and 20% to 50% of allotransplant recipients, usually 100 days to 1 year posttransplant (177,178). Infection may present with cutaneous or visceral involvement. Persons with visceral involvement may present with severe acute abdominal pain from virus reactivation in the celiac plexus, which spreads to the pancreas and small bowel. If cutaneous or visceral herpes varicella zoster is suspected, the subject should be hospitalized, placed in isolation, and given IV aciclovir.

**New Cancers**

Transplant recipients are at increased risk to develop cancer (179–181). Autotransplants are associated with increased clonal cytogenetic changes in bone marrow cells posttransplant. Some of these abnormalities are typical of therapy-related myelodysplastic syndrome (MDS), including monosomy 5 or 7 (del[5] and del[7]), and translocations involving 11q23. These abnormalities are reported in up to 9% of recipients at 3 years posttransplant and are likely related to the effects of exposing the bone marrow to drugs and radiation as part of disease therapy and as part of pretransplant conditioning. Allotransplant recipients have a four- to sixfold age-adjusted risk of developing cancer. Risk factors include pretransplant conditioning with radiation and acute GvHD equal to or greater than grade 2. The 10-year cumulative incidence of solid cancers after allotransplants is about 3%, whereas the 13-year probability is about 6% for persons not receiving radiation versus 20% for persons receiving radiation.

**Relapse**

Relapse of disease after autotransplants or allotransplants may be treated with a second auto- or allotransplant (182–185). If the first pretransplant conditioning regimen included radiation, it should not be used prior to the second transplant; if, however, the first pretransplant conditioning regimen lacked radiation, it should be considered for the second transplant if this is disease appropriate. If the first transplant was an autotransplant, it is unlikely that a second autotransplant will succeed, and thus, an allotransplant is preferred.

Subjects relapsing less than 1 year after autotransplant or allotransplant are often not reasonable candidates for a second transplant because of substantial transplant-related morbidity and mortality and a low likelihood of leukemia control. Subjects retransplanted less than 6 months after a first transplant have done particularly poorly. Sometimes leukemia relapse can be reversed by discontinuing posttransplant immune suppression or by giving donor lymphocytes, or both (186–188). Donor lymphocyte infusions are effective in many subjects with recurrent chronic phase chronic myelogenous leukemia provided they are done in early relapse (189). In acute myeloid leukemia, about 30% of subjects with relapse respond; the interval to remission after donor lymphocyte infusion is 1 to 3 months. Complications include bone marrow failure and worsening of acute GvHD. Mixed chimeras have a lower risk of bone marrow failure than persons with only recipient hematopoiesis. The risk of acute GvHD after donor lymphocyte infusion is about 80% with a tendency to cause hepatic acute GvHD. Attempts to modulate precipitating acute GvHD by genetically engineering donor lymphocytes to express herpes simplex virus thymidine kinase (HSVTK) and treating with ganciclovir if acute GvHD develops are reported (190).

**Hypothyroidism**

For the first 3 to 6 months, posttransplant recipients may have a “euthyroid sick syndrome” with decreased triiodothyronine (T3), decreased thyroxine (T4), and low thyroid-stimulating hormone (TSH) (191,192). As in other nonthyroid diseases associated with a euthyroid sick syndrome, these abnormalities are reversible and probably are normal physiologic responses to decreased protein catabolism. Replacement therapy with thyroxine is unnecessary.

Primary hypothyroidism postransplant is caused by high-dose radiation in the pretransplant conditioning regimen (193–195). Primary hypothyroidism—elevated TSH and low T4—occurs in less than 2% of recipients not receiving radiation (196), but in about 10% of radiation recipients. A greater proportion of subjects have compensated primary hypothyroidism with increased TSH but normal T4. The time interval to onset of primary hypothyroidism is 6 to 41 months posttransplant, with a median of 13 months. The risk of primary hypothyroidism is greater after single-dose than fractionated radiation. Whereas overt hypothyroidism is treated with hormone replacement, compensated disease may be treated with close follow-up or hormone replacement.

**Growth and Development**

Child and adolescent transplant recipients have delayed or interrupted growth and development; the composition of the pretransplant conditioning regimen is a major determinant (194,197). Other risk factors for growth retardation are central nervous system (CNS) radiation, single-dose radiation pretransplant, chronic GvHD, corticosteroid use, and age. Children receiving only high-dose cyclophosphamide do not, in general, have growth retardation. Radiation regimens, on the other hand, adversely affect the rate of height and growth. Radiation may also inhibit normal dental and facial skeletal development, especially in children younger than 6 years. Although chemotherapy regimens were originally not thought to alter growth, combined busulfan and cyclophosphamide pretransplant conditioning causes growth retardation comparable to that of cyclophosphamide combined with fractionated radiation (198). How pretransplant conditioning regimens cause
growth retardation is incompletely understood but includes direct injury to the growth plates, decreased pituitary and hypothalamic growth hormone production, and primary gonadal failure with decreased estrogens and testosterone, as well as elevated luteinizing hormone and follicle-stimulating hormone. In premenopausal transplant recipients, secondary sexual characteristics and menarche are usually delayed. Growth hormone therapy may improve final height in children younger than 10 years at transplant but has no impact on older children (199).

**Fertility**

Primary gonadal failure, for example, hypergonadotropic hypogonadism, is common posttransplant (194,197,200,201). Recovery of gonadal function depends on recipient age and pretransplant conditioning regimen. In postmenopausal women receiving cyclophosphamide only, gonadal dysfunction is usually transitory. Gonadal failure occurs in about one-half of recipients of busulfan and cyclophosphamide (201), whereas almost all recipients of radiation-containing pretransplant conditioning regimens develop gonadal failure. The return of menstruation within 10 years after radiation occurs in more than 90% of recipients who were younger than 18 years at the time of transplant and in 10% to 15% of recipients older than 18 years at the time of transplant. Posttransplant gonadal failure is often associated with symptoms of estrogen deficiency, including hot flashes, dyspareunia, dysuria, and vaginal dryness, which may be helped by hormone replacement therapy (202). Cases have been reported of cryopreservation and orthotopic transplantation of ovarian tissue that has resulted in recovery of ovarian function and subsequent pregnancy (203,204).

**Cataracts**

Corticosteroids and radiation cause cataracts within a median of 2.5 to 5 years posttransplant (205–208). The incidence of cataracts, both subclinical and clinical, is 85% to 100% for unfractioicated radiation recipients, 30% to 50% for fractionated radiation recipients, and 5% to 20% for persons not receiving radiation. Eye shielding decreases the cataract risk but is not generally done because of the concern of increasing leukemia relapse, as blood cells in the eye would escape irradiation.

**Late Renal Effects**

Reversible renal dysfunction is common early posttransplant, with causes that are multifactorial including, but not limited to, drugs and infections (209,210). Although long-term complications are rare, there are occasional reports of late-onset renal dysfunction consistent with radiation nephropathy occurring after multidrug and radiation-containing pretransplant conditioning regimens. Onset is typically 3 to 7 months posttransplant and is characterized by hypertension, edema, uremia, and occasionally hemolytic uremic syndrome (HUS). Cyclosporine may cause a similar picture of hypertension, renal insufficiency, and HUS that can be confused with or complicate transplant-related renal failure.

**Late Lung Effects**

Late-onset noninfectious pulmonary complications (LONIPC) occur in 10% to 25% of subjects (211–213). These are further classified as bronchiolitis obliterans, bronchiolitis obliterans with organizing pneumonia, interstitial pneumonia, and diffuse alveolar disease. These abnormalities are thought to result from the pretransplant conditioning regimen, especially radiation. Chronic GvHD and pretransplant pulmonary function are the main determinants predicting worsening pulmonary function in long-term survivors posttransplant (213). Bronchiolitis obliterans presents as cough and wheezing. Studies typically show severe obstructive lung disease with a hyperinflated thorax resulting from obliteration of small bronchioles. This typically occurs 3 months to 2 years posttransplant. Although usually associated with allotransplants complicated by chronic GvHD, bronchiolitis obliterans occurs rarely after autotransplants. Corticosteroids are usually used to treat bronchiolitis obliterans, but the results, at best, are poor. Lymphocytic interstitial pneumonia is characterized by a lymphocytic interstitial infiltrate that may progress to fibrosis. The cause is not clear but is thought to be immune mediated, and is also treated with corticosteroids. Survival of persons with LONIPC is poor; death usually results from respiratory failure and/or infections.

### IMMUNE SUPPRESSIVE DRUGS

#### Antiproliferative Drugs

Mycophenolate mofetil (MPA), used to modify GvHD in allograft transplants, is metabolized to mycophenolic acid, a potent, reversible noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is the first of two enzymes that convert inosine monophosphate (IMP) to guanosine monophosphate (GMP). GMP is normally converted to GDP, GTP, and dGTP. IMPDH is not involved in the salvage pathway of purine biosynthesis. MPA treatment decreases GTP and dGTP in lymphocytes that inhibit DNA synthesis and GTP-dependent metabolic events resulting in immune suppression (214).

Cyclophosphamide is a common component of pretransplant conditioning. It is a cyclic phosphamide ester of mechloethamine, inactive in its native form. Cyclophosphamide is converted in the liver to active alkylating metabolites, acrolein, and phosphoramide mustard, which prevent cell division by cross-linking DNA strands. High-dose cyclophosphamide, if given without mesna, results in hemorrhagic cystitis via acrolein formation. Prior pelvic radiation also increases the risk of cyclophosphamide-related hemorrhagic cystitis.

#### Corticosteroids and Other Immune Suppressive Drugs

Prednisone is widely used in oncology for anticancer and immune suppression effect. The agent is highly active in acute lymphoblastic leukemia and lymphomas. Prednisone is also used to palliate symptomatic advanced cancers where it enhances appetite and produces a sense of well-being. Corticosteroids are also powerful immune suppressive drugs used to prevent and/or treat GvHD. The relatively high mineralocorticoid activity of cortisone and hydrocortisone with resultant fluid retention makes them unsuitable for long-term immune suppression. Prednisone has predominantly glucocorticoid activity, and is the corticosteroid most commonly
used for long-term immune suppression in chronic GvHD. The maintenance dose of prednisone in this setting should be kept as low as possible to minimize adverse effects, including peptic ulcers, proximal myopathy, osteoporosis, kidney suppression, hirsutism, weight gain, susceptibility to infections, euphoria, depression, cataracts, impaired healing, among others.

Cyclosporine, a calcineurin inhibitor, is a potent immune suppressive drug that adversely affects the kidney but not the bone marrow. Cyclosporine is widely used to prevent and/or treat GvHD.

Tacrolimus is also a calcineurin inhibitor. Although not chemically related to cyclosporine, tacrolimus has a similar mode of action and side-effect profile. The incidences of neural and renal toxicity are greater with tacrolimus than cyclosporine. Additionally, cardiomyopathy and glucose intolerance are reported; hypertrichosis is less a problem with tacrolimus than cyclosporine. Tacrolimus is not commonly used in bone marrow and blood cell allotransplants.

IL-2 and its receptor (IL-2R) are important in T-cell-mediated immunity. Monoclonal antibodies to these moieties, basiliximab and daclizumab, are used to treat corticosteroid-resistant GvHD (215). Rare side effects include hypersensitivity reactions. Infliximab is also used in the treatment of corticosteroid-refractory GvHD (154, 216).

Thalidomide, a member of a class of immune modulating compounds, termed ImiDs, has been used to prevent and/or treat chronic GvHD (217). It is also used, combined with other drugs, to treat multiple myeloma. Thalidomide causes drowsiness, constipation, thrombosis, and neuropathy. Because of its teratogenic effects, it should not be given to sexually active persons without proper precautions. Lenalidomide, a thalidomide analog, is also used to treat bone marrow disorders, including MDS and multiple myeloma. Clinical trials of lenalidomide and pomalidomide, a third ImiD, in chronic GvHD are beginning.

Alemtuzumab (Campath-1H) directed at the CD52 molecule on the surface of all lymphocytes is sometimes used to remove T cells from allografts. Alemtuzumab is also some-

Key Points

- Pretransplant assessment of a person’s fitness for a transplant is essential.
- Different pretransplant conditioning regimens have different risks and benefits.
- Posttransplant complications may arise from effects of the conditioning regimen, graft failure, GvHD, or posttransplant suppression.
- Bacterial, fungal, and viral infections are common.
- Chronic GvHD is common and has considerable morbidity. Incidence and severity may be reduced with ATG.
- Complications are common in many long-term survivors. Regular medical surveillance is needed.

References


92. Bearman SI. Veno-occlusive disease of the liver.


CHAPTER 76

Critical Care Aspects of Stem Cell Transplantation

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