CHAPTER 96  ■  CRITICAL CARE ASPECTS OF STEM CELL TRANPLANTATION

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Bone marrow and blood cell transplants are widely used to treat aplastic anemia, leukemias, lymphomas, myeloma, and immune deficiency disorders. Transplants are also increasingly 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 has also been an increased use of reduced intensity-conditioning regimens, with less attendant regimen-related toxicity, and an increase in transplants from unrelated donors with increased regimen-related toxicity because of more intensive pretransplant therapy.

Pretransplant evaluation of recipients typically includes the following (1-6):

1. Measurement of the left ventricular ejection fraction (LVEF), which should be at least 40%
2. Pulmonary function tests, including diffusing capacity (DLCO), and forced vital capacity (FVC), which should be more than 50% of predicted
3. Hepatic transaminases, which should be less than twice normal
4. Creatinine clearance, which should be more than 50 mL/minute
5. 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 of age (7). By way of contrast, autotransplant recipients may be as old as 70 years (8). 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 (9,10). The 100-day transplant-related mortality after autotransplants is 2% to 3%; after related allo-transplants, it is 15% to 20%; and after alternative (unrelated) allotransplants, it is about 30% (9,10).

IMMEDIATE CONCERNS—THE FIRST 30 DAYS

Pretransplant Conditioning Regimens

In the setting of allotransplants, the pretransplant conditioning regimen needs to moderate or eliminate recipient immnity to prevent graft rejection (11,12). When the allotransplant recipient has cancer, the pretransplant conditioning regimen must also eradicate it. Most allotransplant conditioning regimens contain cyclophosphamide and busulphan, or total-body radiation (13,14). 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—for example, 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 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 therapy. Radiation is not used in autotransplants, as the effective anticancer doses exceed nonbone marrow dose-limiting toxicity.

Pretransplant conditioning regimens are typically empirically determined, with few large randomized trials. Consequently, it is difficult to determine which regimen, if any, is best (15). 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 needed for engraftment, 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 irradiation (TBI), whereas prior therapy of subjects with testicular cancer with cisplatin increases kidney toxicity of platinum-based conditioning regimens. The nonbone marrow, dose-limiting toxicities of drugs in commonly used pretransplant conditioning regimens are listed in Table 96.1.

Bone Marrow and Blood Cell Collection

Cells used for transplants are most often collected from the blood but may also be collected from the bone marrow or umbilical cord blood (16-21). Collection of blood cells is an outpatient procedure accomplished with an apheresis device such as the Cobe Spectra. In the context of autotransplants, recipients often receive chemotherapy and/or hematopoietic growth factors to increase the number of blood cells collected. Normal autotransplant donors often receive only hematopoietic growth factors. The timing of apheresis correlates with the method used to increase the number of cells collected: apheresis is
TABLE 96.1
TOXICITY OF CONDITIONING REGIMEN DRUGS

<table>
<thead>
<tr>
<th>Drug/dose</th>
<th>Extramedullary dose-limiting toxicity</th>
<th>Other toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCNU</td>
<td>Interstitial pneumonitis</td>
<td>Renal insufficiency, encephalopathy, nausea, vomiting, veno-occlusive disease (VOD).</td>
</tr>
<tr>
<td>Busulphan</td>
<td>Mucositis, VOD</td>
<td>Seizures, rash, hyperpigmentation, nausea, vomiting, pneumonitis</td>
</tr>
<tr>
<td>CCNU (lomustine)</td>
<td>Interstitial pneumonitis</td>
<td>Renal insufficiency, encephalopathy, nausea, vomiting, VOD</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Heart failure</td>
<td>Hemorrhagic cystitis, syndrome of inappropriate antidiuretic hormone (SIADH), nausea, vomit, pulmonary edema, interstitial pneumonitis</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Mucositis, cerebellar ataxia</td>
<td>Pulmonary edema, conjunctivitis, rash, fever, hepatitis, toxic epidermal necrolysis</td>
</tr>
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<td>Pulmonary edema, conjunctivitis, rash, fever, hepatitis, toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Otoxicity, peripheral neuropathy</td>
<td>Renal insufficiency, hypomagnesemia, peripheral neuropathy</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Mucositis</td>
<td>Nausea, vomiting, hemorrhagic cystitis, pneumonia, hepatitis</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Encephalopathy, renal insufficiency</td>
<td>Hemorrhagic cystitis, renal tubular acidosis</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Mucositis</td>
<td>Nausea, vomiting, hepatitis, SIADH, pneumonitis, renal insufficiency</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Cardiotoxicity</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Mucositis</td>
<td>Peripheral neuropathy, bradycardia, anaphylaxis</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Mucositis</td>
<td>Interriginous rash, hyperpigmentation, nausea, vomiting</td>
</tr>
</tbody>
</table>

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 $1 \times 10^9$ cells/L; this is usually 10 to 16 days after beginning chemotherapy. The advantages of collecting blood rather than bone marrow cells include no need for anesthesia; utility in subjects with hypocellular, fibrotic, or cancer-infiltrated bone marrow; and a more rapid bone marrow recovery post transplant. A disadvantage of using blood as opposed to bone marrow cells is an increased incidence and severity of chronic GVHD. This is probably because blood contains tenfold more T cells, the cells causing chronic GVHD (20). The cost of blood cell collection is similar to collecting bone marrow cells. The complications of blood cell collection are rare but include infection, anaphylaxis, and hypocalcemia. Cord blood cells are obtained from the umbilical cord and placental blood at the time of birth. The target is to collect 2 to $4 \times 10^7$ nucleated cells/kg donor weight. This is more than tenfold less than the 2 to $4 \times 10^8$ nucleated cells/kg recipient weight collected from the bone marrow. Cord blood cell transplants are often limited to children because of the small number of cells collected. The potential advantages of cord blood are a higher proportion of progenitor cells compared to bone marrow and possibly less GVHD from fewer T cells.

Bone Marrow and Blood Cell Infusion

Bone marrow and blood cells may be frozen in dimethyl sulfoxide (DMSO) for later use (22,23). 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 (24). To avoid complications, subjects are premedicated with diphenhydramine hydrochloride (Benadryl) and methylprednisolone sodium succinate (Solu-Medrol). Infusion 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 collections 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 (25). 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 reinforce the stem 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 post transplant capillary leak syndrome (26–29). In addition, subjects often receive large volumes of intravenous (IV) fluids from drug dilutions, parenteral nutrition, and prophylaxis for hemorrhagic cystitis. Consequently, all transplant recipients gain weight, and diuretics are frequently given to maintain baseline weight and prevent fluid retention. If hypotension develops, emphasis should be placed on early inotropic support, renal insufficiency, diuretics, and other medications. Ifosfamide, especially combined with carboplatin, causes a Fanconi syndrome-like renal tubular acidosis 3 to 7 days after the pretransplant conditioning regimen (30,31). 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 hypomagnesemia and hyperkalemia. Hypomagnesemia 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, urine acid, a major blood antioxidant, is markedly decreased soon after a transplant, independent of allopurinol which is often given (32).

**Electrolyte Balance**

Electrolyte abnormalities are common in transplant recipients, resulting from the underlying disease, prophyllactic hydration for hemorrhagic cystitis, diarrhea, parenteral nutrition, renal insufficiency, diuretics, and other medications. Ifosfamide, especially combined with carboplatin, causes a Fanconi syndrome-like renal tubular acidosis 3 to 7 days after the pretransplant conditioning regimen (30,31). 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 hypomagnesemia and hyperkalemia. Hypomagnesemia 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, urine acid, a major blood antioxidant, is markedly decreased soon after a transplant, independent of allopurinol which is often given (32).

**Blood Product Transfusions**

Subjects receiving transplants are immune compromised and at risk for transfusion-associated GVHD. All cellular blood products contain white blood cells (WBC), including immune-competent T cells, and should be irradiated (23 Gy) (33).

Cytomegalovirus (CMV) infection is another risk. All transplant recipients should receive CMV-negative blood product transfusions, especially when the recipient is CMV seronegative (34–37). If CMV seronegative blood is unavailable, removal of contaminating WBC with an in-line microfilter is an alternative (38,39). When an allotransplant recipient is CMV seronegative, no special CMV-related precautions are needed. Because autotransplant recipients do not develop GVHD or receive post transplant immune suppression, the risk of CMV-related infection is low (40), and no special CMV-related precautions are needed.

In the allotransplant setting, special consideration is needed regarding ABO compatibility between recipient and donor (41–43). As donor bone marrow engrafment occurs, there is a switch to the ABO type of the donor. However, there is a transition period when RBCs with both recipient and donor ABO types are present. 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 RBC, or that B cells in the graft may produce anti-A or -B antibodies against residual recipient RBC. This complexity of blood product transfusion support should be viewed in terms of whether there is a major or minor ABO incompatibility between the recipient and donor (Table 96.2). 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 RBC destruction, red blood cells should be removed from the graft. Post transplant, the recipient should receive recipient ABO-type RBC transfusions or O-type RBC transfusions from which plasma and platelets are removed. With a minor ABO incompatibility, the donor has anti-A and/or -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 B antibodies should be removed from the graft. Post transplant, the recipient should receive O-type RBC transfusions and recipient ABO-type plasma and platelets. When recipient and donor have anti-A and/or -B antibodies to each other's ABO type, for example, recipient A 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. Post transplant, 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 post transplant. Causes include fever, hepatic veno-occlusive disease (VOVD), drugs, infection, disseminated intravascular coagulation (DIC), and microangiopathic hemolytic anemia related to cyclosporine and/or GVHD (44).

**Infection Prevention**

Tactics to prevent bacterial, viral, and fungal infections vary considerably between centers (45–47). This reflects the fact that there are few definitive studies and frequent availability of new drugs. The types of infections occurring in transplant recipients correlate with the post transplant interval. Tactics to prevent bacterial infections early post transplant are based on two considerations: most infections arise from endogenous microorganisms; and in studies of neutropenic animals, the oral...
TABLE 96.2a

DONOR-RECIPIENT ABO INCOMPATIBILITY

<table>
<thead>
<tr>
<th>Major ABO incompatibility</th>
<th>Minor ABO incompatibility</th>
<th>Major and minor ABO incompatibility</th>
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<tbody>
<tr>
<td>Recipient has antibody to donor</td>
<td>Donor has antibody to recipient</td>
<td>Recipient has antibody to donor and donor has antibody to recipient</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 to 4 weeks after SCT
- Occurs Day 9 to Day 16 after SCT
- + Direct antiglobulin test
- + Direct antiglobulin test
- + Direct antiglobulin test

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

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Red cells</th>
<th>Platelets*</th>
<th>FFP</th>
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<tr>
<td><strong>MAJOR ABO INCOMPATIBILITY</strong></td>
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<td><strong>MAJOR AND MINOR ABO INCOMPATIBILITY</strong></td>
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*Occasionally, due to nonavailability of platelets of the requested group, group O platelets (labelled as “low titre,” i.e., low titre of anti-A and anti-B) may be used for patients of any group.

When full ABO conversion has taken place, all patients receive products of their new ABO group.

Inoculum of Gram-negative bacteria required to cause death is increased by colonization of the gastrointestinal tract with anaerobes. 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 like oral quinolones (48–50).

Standards for prevention of infection vary from strict isolation in laminar air flow (LAF) rooms to none. In LAF rooms, the subject is in a sterile environment; anyone who enters must be gloved and gowned, and the patient’s food is sterilized or has a low microbial content secondary to autoclave or microwave treatment (51–54). Prophylactic oral antibiotics are given to destroy enteric pathogens, which not only are reservoirs for infection, but also may function as superantigens that increase the severity of GVHD (55). The minimal standards to prevent bacterial infections include the following:

1. A transplant unit set aside from general hospital, patients, and visitor traffic
2. High-efficiency particulate air (HEPA) filtration to prevent iatrogenic Aspergillus species infection (56,57)
3. Careful hand-washing before entering a patient’s room
4. 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 species (58)

Other measures, such as donning shoe covers, gloves, masks, and gowns and low microbial diets and anterooms are also commonly used, but their cost-effectiveness is debatable. Bacterial prophylactic measures are generally discontinued when the neutrophil count is greater than 0.5 × 10⁹ cells/L. Tactics to prevent fungal infections include the use of oral triazoles such as itraconazole or fluconazole, given orally or intravenously for the first month post transplant (59). Theazole antifungals are effective against most Candida species, but in transplant recipients, fluconazole is ineffective and itraconazole is more effective against Aspergillus species. Most Aspergillus species infections are iatrogenic and preventable by HEPA.
filtration of rooms. Subjects with prior aspergillus infection are at high risk of recurrence (60), especially when there is
1. Prolonged neutropenia post transplant
2. A more advanced cancer state
3. Less than or equal to a 6-week interval from beginning sys-
temic antaspergillus therapy to the transplant
4. Severe acute GVHD

Persons with prior aspergillus should receive amphotericin, voriconazole, or caspofungin early post transplant (61). Herpes simplex reactivation is usually prevented by using in-
travenous or oral acyclovir for the first month post transplant (62,63). Treatment thereafter results in frequent acyclovir re-
sistance and delays the development of natural immunity.

**Fever and Neutropenia**

Transplant recipients are immune compromised from neu-
tropenia, breakdown in mucosal barriers (e.g., mucositis), inva-
sive therapies (e.g., 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-
or B-cell mitogens, and inverted CD4+/CD8+ ratios for 6
months after autotransplants and more than 1 year after allo-
transplants (64,65). When an allotransplant is complicated by
chronic GVHD, normal lymphocyte function may never return
(66). The risk of infection depends on the genetic link between
donor and recipient, graft type, and post transplant immune
suppression.

In transplant recipients with fever—temperature greater than or equal to 38°C—and a neutrophil count less than 0.5 × 10^9 cells/L (67), one should try to identify an infection source using a chest radiograph, blood and urine cultures, and physical
examination with emphasis on line sites and perineal, oralpha-
ryngeal, and sinus regions. Usually no focal source is found,
and broad-spectrum antibiotics are begun. The choice of antibi-
otics may include an antipseudomonal penicillin, aminoglyco-
side, and vancomycin or a third-generation antipseudomonal
cefalosporin. Transplant recipients commonly receive loop
diuretics such as furosemide. The ototoxicity of this drug is in-
creased by aminoglycosides and vancomycin. Allotransplant
recipients receive cyclosporine, whose nephrotoxicity is in-
creased by aminoglycosides. Recurrent or persistent fever for 3
to 5 days without source in a person with granulocytes less than
0.5 × 10^9 cells/L is an indication for empiric antifungal ther-
apy. The nonbone marrow dose-limiting toxicities of etoposide, busulfan, cytarabine, thiopeta, and pa-
clitaxel 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 post transplant methotrexate and pretrans-
plant interferon-gamma. Methotrexate should be withheld if
severe mucositis develops, whereas interferon-gamma should be
discontinued at least 2 to 4 weeks before giving radiation.

Management of mucositis includes good oral hygiene measures, for example, saline, chlorhexidine, and nystatin rinses, and top-
ical analogues (68,69). Opioids are often needed, and should be
given intravenously by schedule or using patient-controlled analgesia (PCA). Severe mucositis may require prophylactic in-
tubation for airway protection. Ultimately, the resolution of
mucositis generally correlates with recovery of the neutrophil
count bone marrow. New drugs, such as palfermin (recombi-
nant human keratinocyte growth factor-1) reduce the incidence
and severity of oral mucositis (70).

**Diarrhea**

Diarrhea in transplant recipients may be caused by high-dose
chemoradiotherapy, other drugs such as antibiotics, and bac-
terial or viral infections, as well as GVHD (71–73). The pre-
transplant conditioning regimen is the most common cause of
diarrhea within 2 to 3 weeks post transplant. Nevertheless,
an infection cause should always be considered, including
Clostridium difficile and Escherichia coli (0157:H7), CMV,
herpes simplex, adenoviruses, rotaviruses, echoviruses, astro-
viruses, Norwalk virus, Coxsackie virus, Strongyloides species,
Giardia species, and Cryptosporidium species. GVHD also
causes diarrhea; the diagnosis can be confirmed by intestinal
biopsy showing loss of crypts, vacuolization of crypt epithe-
lium, karyorrhectic apoptotic debris, microabscesses, and, in
severe cases, ulceration and denudation of the epithelium. Ther-
apy is directed toward appropriate antibiotics for infections
and immune suppression for GVHD. Conditioning regimen-
and GVHD-associated diarrhea may respond to omeprazole,
a somatostatin analog whose mechanism of action is partly
through the inhibition of secretory hormones (74). Some viral
infections—for example, CMV—respond to ganciclovir, fos-
carnet, or cidofovir (75).

**Hemorrhagic Cystitis**

Hemorrhagic cystitis, occurring 2 to 3 weeks post transplant,
usually results from drugs in the pretransplant conditioning
regimen, such as cyclophosphamide, ifosfamide, or etoposide
(76–78). Prophylaxis for hemorrhagic cystitis includes hydra-
ation and diuretics to maintain urine output at 0.2 mL/kg per
hour (79,80). Sodium mercaptopoethylene sulphate (Mesna) is of-
ten used, especially with high-dose cyclophosphamide or ifos-
famide (81). 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 in-
travenous 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.

Therapy of hemorrhagic cystitis consists of using a Fo-
ley catheter to irrigate the bladder with normal saline at 250
mL/hour to prevent intravesicular clotting. Platelets should be
maintained at more than 50 × 10^9 cells/L with platelet trans-
fusions, and RBC transfusion should be given to replace blood
Veno-occlusive Disease of the Liver

Veno-occlusive disease of the liver (VOD) is caused by drugs and/or radiation in the pretransplant conditioning regimen within 1 to 3 months post transplant (85). Unlike the Budd-Chiari syndrome with thrombosis of the large hepatic veins, 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 (86). Obliteration of the central venule results in intrahepatic hypertension, diminished or reversal of portal blood flow, and ascites.

VOD, with a reported incidence of 1% to 56%, is a clinical diagnosis suggested by elevated bilirubin, weight gain, ascites, and tender hepatomegaly (87–89) (Table 96.3). The incidence variability results partly from different pretransplant conditioning regimens and the clinical criteria used to diagnose VOD. For instance, although diagnostic criteria from Johns Hopkins and Seattle seem similar, a retrospective comparison showed VOD incidence rates of 32% versus 8% (90). Risk factors for VOD include increased pretransplant transaminases, conditioning regimen intensity, prolonged fever, and age (88). A positive hepatitis viral serology does not increase the risk of VOD if pretransplant transaminases are normal. Altered drug metabolism is probably responsible for the decreased incidence of VOD in children and increased risk for VOD in persons with abnormal pretransplant transaminases. Cytokines that cause fever also damage endothelial cells and probably cause the increased risk of VOD in persons with prolonged fever. In general, VOD incidence is not significantly different in recipients of allotransplants versus autotransplants.

Clinical symptoms of 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 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 VOD (91). Ultrasonographic findings are generally present only in overt clinical disease (92). Although uncertain cases may require liver biopsy, a percutaneous biopsy is contraindicated because of ascites, coagulopathy, and low platelets. Transjugular biopsy may be, in general, be performed safely and provides an opportunity to measure the hepatic venous pressure gradient, which, if greater than 10 mm Hg, is consistent with VOD (93).

Therapy for VOD is predominantly supportive. Emphasis should be on avoiding hepatotoxic drugs that will further damage the liver. Persons with severe VOD may develop the hepatorenal syndrome, marked by kidney 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 (94). Some centers attempt to maintain intravascular volume and kidney perfusion with RBC transfusions, aiming for a hemoglobin of 12 to 15 g/dL. Early studies of defibrotide, a single-stranded polydeoxyribonucleotide with fibrinolytic, antithrombotic, and antithrombocytopenic properties, in severe VOD suggested activity with complete response rates of 36% to 55% (95–97). No severe hemorrhage or other serious toxicity related to defibrotide was reported.

The prognosis of VOD is poor when bilirubin is more than 15 to 20 mg/dL. Thrombosis of portal or hepatic veins mandates urgent effort to reverse the cause. Portal or hepatic vein occlusion within 1 to 3 months post transplant, consideration should also be given to a liver transplant (103–105).

Respiratory Failure

Transplant recipients who develop respiratory failure and require mechanical ventilation have a poor prognosis (106,107). Once intubated, 80% of recipients are never extubated 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 more than 100 days post transplant 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 (108–111). Early post transplant 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 is pulmonary edema, occasionally with focal or diffuse pulmonary alveolar hemorrhage (112). This may occur without an increase in pulmonary artery occlusion pressure (PAOP). Median time to onset of
Chapter 96: Critical Care Aspects of Stem Cell Transplantation

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 (113–117). 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 -positive pneumonias are common in the first 30 days post transplant. Fungal infections of the lung also occur early post transplant, and isolation of Aspergillus species 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 severe combined immune deficiency (SCID); enteritis without HEPA filters to prevent inhalation of aerosolized spores; and prior invasive aspergillosis. Viral pneumonia is rare early post transplant; the most common etiologic agent when this does occur is herpes simplex.

Kidney Failure

Renal insufficiency is usually a multifactorial process whose cause includes the underlying disease—for example, cast nephropathy in myeloma, a prerenal decrease in glomerular filtration, intrinsic renal dysfunction, or postrenal obstruction. The most common reason for renal insufficiency early in the post transplant period is drug related, especially with use of aminoglycosides, cyclosporine, and amphotericin (118,119). Mortality in persons requiring dialysis is about 85% (120). Prerenal causes of azotemia include hepatic VOD, diuretics, diuretics, third-spacing from sepsis, hypalbuminemia, and a capillary leak syndrome from high-dose drugs and radiation. Hepatic VOD, like other causes of prerenal 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, foscarnet, and cyclosporine. In ATN, the FeNa+ is high, and the urine has muddy hyaline casts. Renal insufficiency secondary to glomerulonephritis usually results from streptococcal or staphylococcal bacteria. In glomerulonephritis, the FeNa+ is low, and the urine sediment contains RBC casts and increased protein. Intestinal nephritis arising in the early stem cell transplant period (SCT) period is usually drug induced. Causes of allergic interstitial nephritis are penicillins, cephalosporins, sulphamethoxazole-trimethoprim, and fluoroquinolones. In allergic interstitial nephritis, the urine FeNa+ is high, and urine sediment contains white blood cells (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 hemoyses, 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, extravascular hemorrhage, urate nephropathy, or drugs that undergo intratubular crystallization and obstruction such as acyclovir, ciprofloxacin, and trimethoprim. Regardless of the cause, post transplant 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 by 3 weeks. After a peripheral blood stem cell transplant, the WBC usually rises by about 2 weeks. Platelet recovery, defined as more than 20 × 10^9 platelets/L, without transfusion, typically occurs 2 to 3 weeks later. Occasionally, recipients require platelet transfusions for months post transplant. Generally, graft failure is defined as a neutrophil count less than or equal to 0.5 × 10^9 cells/L by day 28. Causes of graft failure include too few normal hematopoetic cells, damage to the bone marrow microenvironment, immune-mediated graft rejection, or drug-related immune suppression (121,122).

The minimal number of bone marrow or blood cells needed for sustained engraftment is unknown. There are several reasons for this:
1. It is not known what hematopoietic cell(s) are responsible for sustained engraftment.
2. Different hematopoietic cells may operate under different circumstances and in different persons.
3. After autotransplants, there is no need for sustained engraftment in the context of autologous bone marrow recovery.
4. There is no validated method to identify the hematopoietic cell(s) responsible for sustained engraftment (123,124).

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 contribute to long-term engraftment (but may not be necessary) (125). To ensure sustained engraftment in humans, most data suggest a threshold of 2 to 4 × 10⁶ mononuclear cells or 2 × 10⁷ CD34+ cells/kg of recipient body weight. Autotransplant recipients receiving extensive pretherapy before transplantation 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 autotransplants, but it is the most common cause of graft failure for allotransplants. Risk of immune-mediated graft failure correlates with the degree of HLA disparity between donor and recipient. Graft failure occurs in less than 1% after HLA-identical sibling allotransplants, 6% to 8% after unrelated HLA-haplotype matched allotransplants, and in up to 20% after HLA haplotype mismatched allotransplants (126–128) (Table 96.4). 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; complications may be possible by more intensive pretransplant immune suppression (129,130). 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 H-Y antigens (131,132).

Several bone marrow suppressive drugs commonly used post transplant may delay and/or reverse engraftment, for example, methotrexate and sulphamethoxazole-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 post transplant 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

<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>Haplo-identical</td>
<td>50–100</td>
<td>&gt;50</td>
<td>20</td>
<td>10–40</td>
<td>—</td>
<td>10</td>
<td>10–30</td>
<td>—</td>
</tr>
<tr>
<td>Related 6/6</td>
<td>45–50</td>
<td>55</td>
<td>6</td>
<td>45</td>
<td>40</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.

### Table 96.4b

<table>
<thead>
<tr>
<th>INCIDENCE OF GRADES III–IV ACUTE GRAFT VERSUS HOST DISEASE IN CML ACCORDING TO THE NUMBER OF MISMATCHED CLASS I AND CLASS II ALLELES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (%)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>0 Class II</td>
</tr>
<tr>
<td>1 Class II</td>
</tr>
<tr>
<td>≥ 2 Class II</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

There were 467 chronic myeloid leukemia unrelated donor-recipient pairs.
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 (that is, no engraftment) have a poor prognosis, whereas those with secondary graft failure (unassisted engraftment) do better. When graft failure is associated with re-emergence of host T cells, repeat preemptant conditioning is usually given before the second graft based on the assumption that graft failure is immune mediated; this may not be correct in all instances.

**Acute Graft versus Host Disease (GVHD)**

The principle manifestations of acute GVHD are rash, diarrhea, and jaundice, present individually or in combination (133,134). 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 post transplant. Acute GVHD is an alloimmune 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 donor (135,136) (Table 96.4).

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-1 molecules are present on the surface of lymphocytes 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 (137,138). Even after an HLA genotypically matched allotransplant, acute GVHD invariably develops when—usually inadvertently—no post transplant 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 (139).

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 of the skin, biliary ductules of the liver, and crypts of the distal gastrointestinal tract. Acute GVHD may present as diarrhea or hepatic involvement, with or without elevated transaminases. In severe cases, acute GVHD may present as a maculopapular rash with or without elevated transaminases. The differential diagnosis includes VOD or infections with CMV or *Candida* species and may reflect loss of the interaction of donor T cells and hematopoietic cells. Acute GVHD unresponsive to this approach is termed acute GVHD resistant (aGVHD(pts)). Cyclosporine and methotrexate (MTX) are the most common preventative regimen (144). Other regimens include cyclosporine and prednisolone or cyclosporine, methotrexate, and methylprednisolone (145).

Cyclosporine is given in doses of 3–5 mg/kg per day for 2 months. The response of acute GVHD to immune suppression is often correlated with improved bone marrow function. 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 sufficient. Acute GVHD with hepatic involvement presents as jaundice and an elevated alkaline phosphatase with or without elevated transaminases. The differential diagnosis includes VOD or infections with CMV or *Candida* species 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 to use T-cell depletion. Cyclosporine and methotrexate given on days 1, 3, 6, and 11 post transplant are the most common preventative regimen (144). Other regimens include cyclosporine and prednisolone or cyclosporine, methotrexate, and methylprednisolone (145). In HLA-identical sibling transplants, weekly intravenous immunoglobulin (IVIG) until day 28 results in a lower incidence of acute GVHD (146). 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 least, whereas less intensive regimens are used when the leukemia relapse risk is highest 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 score (Table 96.5). 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 per 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 antithymocyte globulin (ATG) or alemtuzumab (anti-CD52), or cytokines such as dacluzimab or infliximab. Dacluzimab 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 (147). Several reports suggest that giving IVIG—a cytokine typically used for...
GRADING OF ACUTE GRAFT VERSUS HOST DISEASE

<table>
<thead>
<tr>
<th>Organ</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>+1</td>
<td>A maculopapular eruption involving less than 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 (greater than 15 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>

CMV infection prevention (see below)—is associated with less acute GVHD, but these data are inconsistent.

INTERMEDIATE CONCERNS (DAYS 30 TO 100)

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 disease (148). Surveillance CMV-PCR is started 2 weeks before transplantation and continued until day 100 post procedure. A positive CMV-PCR usually prompts giving full-dose ganciclovir for 2 weeks or until the CMV-PCR becomes negative, and then for another 2 weeks at one-half dose (149–152). Valaciclovir is then given as prophylaxis until day 100. G-CSF may be given if there is bone marrow suppression, or therapy may be changed to foscarnet, which is associated with less bone marrow suppression.

Pneumonitis

Between 30% and 50% of early post transplant deaths are associated with respiratory failure (153,154). 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 allotransplantation (40%) as compared to autotransplantation (10%). Risk factors include a radiation-based pretransplant conditioning regimen, severe GVHD, older age, and post transplant use of methotrexate. The median time to onset of interstitial pneumonia is about 50 days post transplant, with only rare cases developing after 6 months. Affected persons are hypoxic and/or hypocapnic; physical examination often shows basilar crackles; and the chest roentgenogram shows an interstitial
Following resolution of acute GVHD. Most often, acute GVHD clinically diagnosed acute GVHD, after a quiescent interval following resolution of acute GVHD. Most often, acute GVHD evolves into the chronic process (165,166). 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 allosimmunity and autoimmunity.

Skin involvement in chronic GVHD involves sclerodermalike changes with hypopigmentation and hyperpigmentation, loss of hair follicles, thickened skin, and joint contractures. Mucoal 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. Ulceration, 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, mitochrondria, smooth muscle, or connective tissue. Autoimmune syndromes associated with chronic GVHD include polynsouts, 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 96.6). Limited-stage chronic GVHD has a favorable prognosis and requires no therapy. Extensive-stage chronic GVHD has a poor prognosis; therapy is needed (167). Adverse prognostic variables in persons with extensive-stage GVHD include thrombocytopenia (less than 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 photophoresis, psoralen and ultraviolet light irradiation (PUVA) for chronic cutaneous GVHD, and ursoxychoholic acid for chronic hepatic GVHD (168). Clinical trials with thalidomide analogs, such as lenalidomide and

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**Epstein-Barr Virus 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 allograft recipients, failure of immune surveillance by EBV-specific cytotoxic T cells results in a polyclonal or, less often, monoclonal B-cell proliferation of donor or recipient origin (162). EBV-lymphoproliferative syndrome (EBV-LPS) occurs in about 0.5% of allograft recipients. Risk factors include T-cell-depleted grafts and the use of ATG or anti-CD3 antibodies post transplant to prevent acute GVHD. EBV-LPS typically develops 45 days to 1.5 years post transplant; 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 sometimes effective (163). Giving donor EBV-specific cytotoxic T cells sometimes results in prompt remission of polyclonal and monoclonal EBV-LPS (164).

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**LATE CONCERNS (BEYOND DAY 100)**

**Chronic GVHD**

Chronic GVHD usually occurs after day 100 post transplant. Chronic disease may seemingly develop de novo without prior clinically diagnosed acute GVHD, after a quiescent interval following resolution of acute GVHD. Most often, acute GVHD evolves into the chronic process (165,166). 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 allosimmunity and autoimmunity.

**TABLE 96.6**

<table>
<thead>
<tr>
<th>CHRONIC GRAFT VERSUS HOST DISEASE GRADES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited</strong></td>
</tr>
<tr>
<td>1. Generalized skin involvement</td>
</tr>
<tr>
<td>a. Liver histologic features showing chronic progressive hepatitis, bridging necrosis, or cirrhosis</td>
</tr>
<tr>
<td>c. Involvement of minor salivary glands or oral mucosa</td>
</tr>
</tbody>
</table>

**Extensive**

1. Generalized skin involvement
2. Limited skin involvement or hepatic involvement and
   a. Liver histologic features showing chronic progressive hepatitis, bridging necrosis, or cirrhosis
   b. Eye involvement (Schirmer’s test with less than 5 mm wetting)
   c. Involvement of minor salivary glands or oral mucosa
   d. Involvement of any other organ
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 (169) and 20% to 50% of allotransplant recipients, usually 100 days to 3 years post transplant (170,171). 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 acyclovir.

**Second Cancers**

Transplant recipients are at increased risk to develop a second cancer (172–174). Autotransplants are associated with increased clonal cytogenetic changes in bone marrow cells post transplant. Some of these abnormalities are typical of therapy-related myelodysplastic syndrome (MDS), including monosomy 5 or 7 (del5/7) and del(7q), and translocations involving 11q23. These abnormalities are reported in up to 9% of recipients at 3 years post transplant and are likely related to the effects of exposure to drugs and radiation as part of disease therapy and as part of pretransplant conditioning. Allotransplant recipients have a fourfold to sixfold age-adjusted risk of developing a 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 autotransplants is about 3%, while the 15-year probability of a second cancer 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 autotransplant or allotransplant (175–178). 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 transplanted less than 6 months after a first transplant have done particularly poorly. Sometimes leukemia relapse can be reversed by discontinuing post transplant immune suppression or by giving donor lymphocytes, or both (179–181). Donor lymphocyte infusions (DLI) are effective in many subjects with recurrent chronic phase chronic myelogenous leukemia (CML) provided DLI is done in early relapse (182). In acute myelogenous leukemia (AML), about 30% of subjects with relapse respond; the interval to remission after DLI is 1 to 3 months. Complications of DLI 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 DLI 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 (183).

**Hypothyroidism**

For the first 3 to 6 months, post transplant recipients may have a “euthyroid sick syndrome” with decreased tri-iodothyronine (T3), decreased thyroxine (T4), and low thyroid-stimulating hormone (TSH) (184,185). 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. Hormone replacement therapy is unnecessary.

Primary hypothyroidism post transplant is caused by high-dose radiation in the pretransplant conditioning regimen (186–188). Primary hypothyroidism—elevated TSH and low T4—occurs in less than 2% of recipients not receiving radiation (189) but in about 10% of radiation recipients. A greater proportion of subjects have low T4 with TSH in the normal range and radiation recipients (190). 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 (187,190). 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 of age. 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 (191). 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 increased clonal cytogenetic changes in bone marrow cells post transplant. Some of these abnormalities are typical of therapy-related myelodysplastic syndrome (MDS), including monosomy 5 or 7 (del5/7) and del(7q), and translocations involving 11q23. These abnormalities are reported in up to 9% of recipients at 3 years post transplant and are likely related to the effects of exposure to drugs and radiation as part of disease therapy and as part of pretransplant conditioning. Allotransplant recipients have a fourfold to sixfold age-adjusted risk of developing a 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 autotransplants is about 3%, while the 15-year probability of a second cancer is about 6% for persons not receiving radiation versus 20% for persons receiving radiation.

Relapse of disease after autotransplants or allotransplants may be treated with a second autotransplant or allotransplant (175–178). 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 transplanted less than 6 months after a first transplant have done particularly poorly. Sometimes leukemia relapse can be reversed by discontinuing post transplant immune suppression or by giving donor lymphocytes, or both (179–181). Donor lymphocyte infusions (DLI) are effective in many subjects with recurrent chronic phase chronic myelogenous leukemia (CML) provided DLI is done in early relapse (182). In acute myelogenous leukemia (AML), about 30% of subjects with relapse respond; the interval to remission after DLI is 1 to 3 months. Complications of DLI 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 DLI 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 (183).

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related renal failure. and HUS that can be confused with or complicate transplant-may cause a similar picture of hypertension, renal insufficiency, occasionally hemolytic uremic syndrome (HUS). Cyclosporine plant and is characterized by hypertension, edema, uremia, and dif-
tioning regimens. Onset is typically 3 to 7 months post trans-
dysfunction consistent with radiation nephropathy occurring
are rare, there are occasional reports of late-onset renal dysfunc-
tion consistent with radiation nephropathy occurring after multidrug and radiation-containing pretransplant condi-
tioning regimens. Onset is typically 3 to 7 months post trans-
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 Pulmonary Effects
Late-onset noninfectious pulmonary complications (LONIPC) occur in 10% to 25% of subjects (204–206). These are further classified as bronchiolitis obliterans, bronchiolitis obliterans with organizing pneumonia, interstitial pneumonia, and dif-
usual cause of LONIPC. The return of men-
within 10 years after radiation occurs in more than
of patients who were younger than 18 years of age at the time of transplant and in 10% to 15% of recipients older
than 18 years of age at the time of transplant. Post transplant
nal failure is often associated with symptoms of estro-
gen deficiency, including hot flashes, dyspareunia, dysuria, and vaginal dryness, which may be helped by hormone replace-
therapy (195). Cases have been reported of cryopreser-
ation and orthotopic transplantation of ovarian tissue that
has resulted in recovery of ovarian function and subsequent pregnancy (196,197).

Antiproliferative Drugs
Myophenolate mofetil (MPA), used to modify GVHD in allotransplants, is metabolized to mycophenolic acid, a po-
tent, reversible noncompetitive inhibitor of inosine monophos-
phate dehydrogenase (IMPDH). IMPDH is the first of two en-
yzymes 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 path-
way of purine biosynthesis. MPA treatment decreases GTP and
dGTP in lymphocytes that inhibit DNA synthesis and GTP-
dependent metabolic events resulting in immune suppression (207).
Cyclophosphamide is a common component of pretrans-
plant conditioning. It is a cyclic phosphamide ester of mechloretamine inactive in its native form. Cyclophos-
phamide is converted in the liver to active alkylating metabo-
lites, acrolein, and phosphoramide mustard, which prevent cell
division by cross-linking DNA strands. High-dose cyclophos-
phamide, 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 Suppressant Drugs
Prednisone is widely used in oncology for antitumor and im-
mune suppression effect. The agent is highly active in acute lymphoblastic leukemia (ALL) 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 it 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, and 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 tacrolimus is not chemically related to cyclosporine, it 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.

Interleukin-2 (IL-2) and its receptor (IL-2R) are important in T-cell-mediated immunity. Monoclonal antibodies to these moieties, basiliximab and dacluzimab, are used to treat corticosteroid-resistant, acute GVHD (211). Rare side effects include hypersensitivity reactions. Infliximab is also used in the treatment of corticosteroid-refractory GVHD (147,209).

Thalidomide, a member of immunomodulating compounds, termed ImiDs, has been used to prevent and/or treat chronic GVHD (210). 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 analogue, is also used to treat bone marrow disorders, including myelodysplastic syndrome (MDS) and multiple myeloma. Clinical trials of lenalidomide and pomalidomide, a third ImiD, in chronic GVHD are beginning.

Altemuzumab (Campath-H) directed at the CD52 molecule on the surface of all lymphocytes is sometimes used to remove T cells from allografts. Altemuzumab is also sometimes used to treat corticosteroid-resistant, acute GVHD (211). Infusion-related adverse effects may occur, including fever, chills, nausea and vomiting, and allergic reactions. There is also increased susceptibility to infections, particularly with fungi, viruses, and protozoa.


38. Blajchman MA. The clinical benefits of the leukoreduction of blood prod-


35. Takami A, Mochizuki K, Asakura H, et al. High incidence of cy-

34. Russell JA, Poon MC, Jones AR, et al. Allogeneic bone-marrow transplan-


32. Druker BJ, Talal N, recognised its potential importance and.


29. Spach DH, Bauwens JE, Myerson D, et al. Cytomegalovirus-induced hem-


24. McQuilling JA, Martin NA, and in a study of 355 patients.


22. Overall, 83 of 99 patients (85%).


Section IX:


Section IX: Organ Transplantation


