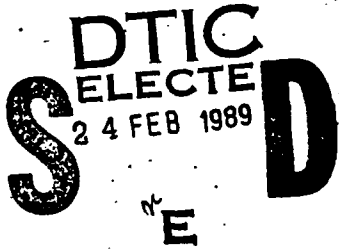


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Management of the Critically Ill Marrow Transplant Patient

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The management of the immunosuppressed patient is of increasing importance for intensivists. The average length of hospitalization for marrow transplantation is 4-6 weeks, and 25% of patients will spend one month in an intensive care unit. Optimal care of the patient during marrow transplantation requires the skills of oncologists, infectious disease specialists, and often, input from intensivists is required, most commonly to assist in the management of renal and pulmonary complications. Marrow transplantation represents a curative attempt at the treatment of malignant diseases of hematopoietic and nonhematopoietic origin, to correct marrow failure of diverse causes, and to treat a variety of genetic disorders (Table 45.1). In this chapter, we will focus on (a) the drugs that are commonly given

during the course of marrow transplantation, and that are otherwise not commonly used in the ICU, (b) management of the immunosuppressed patient, and (c) acute complications such as graft-versus-host disease (GVHD) and hepatic venoocclusive disease (VOD) that are relatively specific to marrow transplantation. Various aspects of marrow transplantation have been reviewed in recent years (1, 14, 19, 33, 45, 49, 55, 80, 81, 83).

Bone marrow transplantation can be divided into three phases consisting of (a) the preparative regimen, (b) marrow aspiration and infusion, and (c) engraftment and subsequent events. Preparative regimens are required both for their immunosuppressive and their antineoplastic potential (90). In order for cells from a genetically different donor to survive

Table 45.1
Applications of Marrow Transplantation

Malignant Disorders	Acquired Nonmalignant Disorders	Inherited Disorders
Acute lymphoblastic leukemia	Aplastic anemia	Ataxia telangiectasia
Acute nonlymphoblastic leukemia	Myelofibrosis	Blackfan-Diamond anemia
Chronic granulocytic leukemia	Paroxysmal nocturnal hemoglobinuria	Chediak-Higashi syndrome
Hairy cell leukemia	Pure red cell aplasia	Chronic granulomatous disease
Histiocytosis X		Chronic mucocutaneous candidiasis
Hodgkin's disease		Congenital agranulocytosis
Myelodysplastic syndrome		Congenital red cell aplasia
Myeloma		Fanconi's anemia
Neuroblastoma		Gaucher's disease
Non-Hodgkin's lymphoma		Infantile agranulocytosis
Selected "solid" tumors		Metachromatic leukodystrophy
		Mucopolysaccharidosis types I, II, VI
		Osteopetrosis
		Severe combined immunodeficiency
		Sickle cell anemia
		Thalassemia
		Wiskott-Aldrich syndrome

and replicate, the patient's immune system must be paralyzed or eradicated. To achieve this, immunosuppressive therapy ("conditioning") is given in preparation for the marrow infusion. For autologous (self) marrow transplantation, the regimen need only to be optimized for maximal tumor eradication since there is no immunological barrier to overcome. One advantage of chemotherapy in the setting of marrow transplantation is that "supralethal" doses can be given and the patient rescued by marrow infusion, thereby permitting dose escalation in settings in which marrow toxicity is normally the dose-limiting factor (21, 81). In addition, in allogeneic (non-self) transplantation, there is clinical and experimental evidence that the genetic nonidentity may also result in a graft-versus-tumor effect of immunocompetent donor cells (96). Such an effect could of course not be expected with syngeneic (identical twin) or autologous marrow.

The conditioning regimen must be chosen by an experienced clinician with attention to detail in order to avoid potentially lethal complications. For example, patients with Fanconi's anemia appear to be overly sensitive to the cytotoxic effects of cyclophosphamide and radiation, and therefore, require specially tailored conditioning protocols (30). In rare cases such as children with severe congenital immunodeficiency syndrome, a preparative regimen is not required and allogeneic engraftment can often be achieved simply by infusion of donor marrow since the patient's immune system is defective. Similarly, some patients with aplastic anemia who have identical twins may be cured simply by infusion of syngeneic marrow.

MODALITIES USED IN MARROW TRANSPLANTATION

Total-Body Irradiation

Conditioning regimens utilized for the treatment of malignant diseases classically have included total body irradiation (TBI) followed or preceded by chemotherapy. Radiation-induced marrow aplasia occurs after exposure to ~300–500 cGy (rad) TBI, and in a single exposure, ~1000 rad (10 Gy, 1 Gray unit = 100 rad) of TBI is the maximum tolerated dose that can be administered without causing lethal extramedullary damage. (Related information

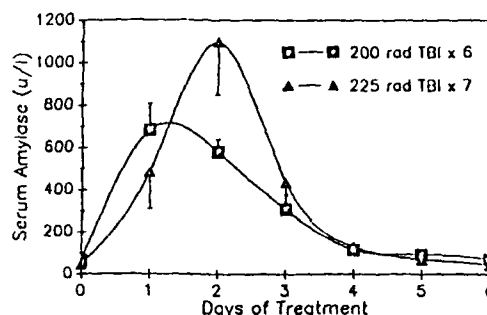


Figure 45.1. Effects of fractionated total-body irradiation (TBI) on serum amylase. Total serum amylase was measured on 30 patients treated with either 200 rad TBI daily for 6 days or 225 rad TBI daily for 7 days as preparation for marrow transplantation. Mean $\pm$ SEM is indicated.

may be found in Chapter 42). Because most tumor cells repair radiation-induced DNA damage poorly as compared with normal cells, fractionated doses of TBI permit the administration of higher cumulative doses (82). Severe mucositis, nausea, vomiting, diarrhea, and parotitis commonly develop during the several days following TBI (4, 12, 45, 69, 83). Some patients, particularly those who have been given chemotherapy that may sensitize ("radiation recall") to the effects of radiation, develop dermal erythema and desquamation after TBI. Pancreatitis develops occasionally after TBI. It is not commonly realized the TBI causes elevation of serum amylase levels in all patients following single-dose and fractionated TBI (Fig. 45.1), thus invalidating this commonly performed test in marrow graft recipients in the first week after TBI. The hyperamylasemia following TBI is self-limiting and involves parotid isoforms, so that patients with abdominal pain can still be evaluated for pancreatic disorders if isoenzyme fractionation is done.

Patients are treated with antiemetics to prevent emesis during TBI. Symptomatic relief from diarrhea has been reported with cholestyramine therapy (34). Allopurinol is given and the intravascular volume maintained during TBI in order to prevent tumor lysis syndrome. Approximately 80% of adults will develop reactivation of herpes simplex virus as a superinfection due to the immunosuppression that accompanies radiation-induced mucositis; these patients benefit from prophylactic administration of acyclovir (71). Late complications of TBI include growth retardation, cataracts, infertility, and malignancy (19, 77).

Cyclophosphamide

The most common chemotherapeutic agent employed for conditioning is cyclophosphamide in large doses (81). High-dose cyclophosphamide causes nausea, vomiting, and alopecia in all patients. The dose-limiting toxicity, however, is cardiac. Cardiac failure affects equally patients with autologous and allogeneic grafts. Conditioning protocols for marrow transplantation commonly employ total doses of cyclophosphamide of 120–200 mg/kg given over 2–4 days, and at these doses, > 90% of patients develop decreased ECG voltage of the QRS complex, and the incidence of clinically significant cardiac toxicity may be as high as 15% (32). When heart failure develops, it usually occurs in the first week after therapy with cyclophosphamide and is encountered particularly with patients who had prior mediastinal radiation, concurrent TBI, or therapy with anthracyclines (13). It has recently been reported that the addition of cytosine arabinoside to the preparative regimen also potentiates the cardiac toxicity of cyclophosphamide (87). Clinically, patients develop tachycardia, rapid weight gain, cardiomegaly with or without a pericardial effusion, a loss of voltage on surface ECG, and a decrease in ejection fraction (13). The syndrome is acute and often refractory to therapy. Most patients die within a week of onset of symptoms. It is therefore important to carefully evaluate the past medical history in order to avoid cardiac toxicity from cyclophosphamide. There is evidence that the development of cardiac toxicity correlates better with dose per body surface area than with weight, and that in the absence of TBI, the maximum tolerated dose of cyclophosphamide is 1.55 g/m²/day for 4 days (32).

Other potential complications of high-dose cyclophosphamide therapy are also of importance. Plasma cholinesterase can be depleted and, as a consequence, the clearance of local anesthetics or neuromuscular blocking agents may be substantially prolonged (22, 103). Plasma cholinesterase levels should be measured, if possible, prior to any surgical procedure in a patient who has recently been prepared for marrow transplantation.

Hemorrhagic cystitis of varying severity occurs in ~30% of patients after high-dose cyclophosphamide. Therapy of cystitis is difficult as patients are thrombocytopenic, and in extreme cases, fulguration, bilateral nephrostomies, and even cystectomy may be required. Cystitis is mostly related to the cyclophosphamide metabolite acrolein. In order to minimize or prevent cystitis, a three-way Foley catheter should be inserted and the bladder continuously irrigated and drained. In addition, a brisk saline diuresis is initiated before administration of cyclophosphamide. Mesna (2-mercaptoethane sodium sulfonate), an investigational drug that acts as a sulfhydryl donor, has been shown to be effective in most instances in preventing cystitis (36). Mesna appears to have a role in patients who are particularly predisposed to hemorrhagic cystitis such as those with Fanconi's anemia (20, 30); however, it is not yet available commercially in this country.

In the differential diagnosis of hematuria, in addition to cyclophosphamide and the usual causes of hematuria, other disorders more specific to the marrow transplant patient should be considered. Reactivation of the BK type of human polyoma virus has recently been reported to be a common cause of hematuria in patients with allogeneic but not autologous marrow grafts (2). In addition, infection with other viruses such as adenovirus should be excluded. Hematuria that occurs in association with hypertension may be caused by radiation-induced nephritis (6). Finally, some patients develop the syndrome of inappropriate secretion of antidiuretic hormone or nephrogenic diabetes insipidus in association with high-dose cyclophosphamide treatment (26).

Treatment with cyclophosphamide alone (200 mg/kg) is sufficiently immunosuppressive to allow allogeneic engraftment, and is used without TBI as the conditioning regimen of choice for patients with aplastic anemia (61–83). Similarly, in combination with busulfan, cyclophosphamide has been used successfully as a conditioning protocol for patients with acute nonlymphocytic leukemia (68). In attempts to increase tumor kill, other agents such as cytosine arabinoside, etoposide (VP-16), daunomycin, and BCNU have been added to preparative regimens, or substituted for cyclophosphamide. The addition of these drugs, particularly in combination, often causes a substantial increase in acute toxicity that is frequently manifest as hepatic VOD (see "Veno-occlusive Disease").

Cyclosporine is the first agent that has reversible immunosuppressive effects that are relatively specific for T lymphocytes (3, 62). It

Cyclosporine

Cyclosporine is the first agent that has reversible immunosuppressive effects that are relatively specific for T lymphocytes (3, 62). It

is approved by the Food and Drug Administration (FDA) to be used for prevention of solid-organ rejection. In patients given marrow transplantation, it is commonly used, non-FDA approved, to prevent or treat GVHD and to reduce the risk of marrow graft rejection. Cyclosporine is most effective when given with other agents such as glucocorticoids or methotrexate (see "Methotrexate"). The drug is usually administered intravenously beginning several days before marrow transplantation. The drug is water insoluble; when administered orally, it must be given with lipids such as olive oil or milk in order to promote absorption. There can be severe impairments of cyclosporine absorption after marrow transplantation due to chemoradiotherapy-induced enteritis and to intestinal GVHD (99). Patients commonly have trough serum or whole blood cyclosporine levels measured by radioimmunoassay (RIA) two or three times weekly during the first month after transplantation. The dose is adjusted to maintain serum levels at ~100 ng/ml in order to minimize nephrotoxicity, although there is little information currently available to support the concept of "therapeutic" levels. The drug has a large volume of distribution and is predominantly metabolized in the liver. It is subject to enterohepatic recirculation and only a small fraction is excreted by the kidneys (99). Plasma clearance is age related; children require higher doses on a milligram-per-kilogram basis than do adults.

A number of drug-drug interactions have been reported (15, 62). Ketoconazole, cimetidine, diltiazem, and oral contraceptives have been reported to increase the plasma concentration of cyclosporine. Rifampin, trimethoprim, phenobarbital, and phenytoin may reduce the concentration of cyclosporine.

The hallmark of cyclosporine toxicity is renal impairment that is first recognized by an asymptomatic increase in the serum creatinine concentration. This is usually associated with increased serum levels of cyclosporine. Renal toxicity is potentiated by aminoglycosides and amphotericin B, and therefore, dose reduction is often necessary when given concurrently with drugs such as aminoglycosides, vancomycin, or amphotericin B (15, 40). Severe hypomagnesemia due to renal magnesium wasting is common in patients treated with cyclosporine after marrow transplantation but not after renal transplantation (39). Cyclosporine causes arterial hypertension, especially in patients treated concomitantly with glucocor-

ticoids (37, 44). In the treatment of cyclosporine-induced hypertension it is best to avoid diuretics and β -blockers that may precipitate or exacerbate renal impairment, to correct serum magnesium levels, and give calcium channel antagonists such as nifedipine. Hepatotoxicity has been ascribed to cyclosporine and is manifest by conjugated hyperbilirubinemia; in this setting, it must be distinguished from VOD and GVHD (62). Neurotoxicity consisting of tremor, seizures, and cerebellar symptoms has been reported and may in some cases be secondary to hypomagnesemia (84). Some patients experience paresthesia in palms and soles with intravenous infusion of cyclosporine that is likely due to cremophore, the vehicle used to dissolve cyclosporine.

Methotrexate

Methotrexate is commonly given to marrow transplant patients for the prevention of GVHD and for the treatment of leukemia involving the central nervous system. Until recently a standard regimen involved the use of methotrexate; 15 mg/m² on day 1 and 10 mg/m² on days 3, 6, 11; and then biweekly for the first 3 months after transplant for the prevention of GVHD (76, 83). For the prevention of CNS leukemia intrathecal methotrexate is often given 12 mg/m² for two doses before transplantation and approximately five doses biweekly beginning 1 month after transplantation. The use of methotrexate in the general oncology patient in such modest doses would ordinarily be expected to result in little toxicity. The marrow transplant patient is, however, subject to rapid deterioration in renal function, generally from the concurrent administration of nephrotoxic agents, or from the sudden accumulation of ascites from VOD. It is important therefore for the intensivist to realize that decreased renal function and third-space fluids have profound impact on the pharmacokinetics of methotrexate that may severely aggravate mucositis and impair or prevent hematopoietic recovery. Folinic acid is an antidote of methotrexate and may be used to prevent toxicity in cases of delayed renal excretion. Serum methotrexate levels should be obtained 24 hours after each dose, and if the level is $> 5 \times 10^{-6}$ M, therapy is started with folinic acid. Methotrexate levels should again be obtained at 48 hours and if the level remains elevated, folinic acid "rescue" continued. (Further details on the phar-

macology of methotrexate can be found in Chapter 29.)

Antibody Therapy

Polyclonal immune serum globulin (ISG) or antilymphocyte immunoglobulin (ALG) antibodies or murine monoclonal antibodies are used with increasing frequency in marrow transplant patients (Table 45.2). ISG consists of purified human immunoglobulin preparations derived from multiple donors. ISG and CMV hyperimmune globulin, obtained from donors with high titers of antibodies to cytomegalovirus, are currently being tested in marrow transplant patients in order to prevent viral and bacterial infections. Both ISG and CMV hyperimmune globulin have been shown to prevent seroconversion and prevent interstitial pneumonitis in patients who are not infected with CMV before marrow transplantation (10, 98). However, the same effect can be achieved in CMV-seronegative transplant patients by giving CMV-negative blood products and by avoiding the use of CMV-positive marrow donors when possible (10). The role of ISG in the prevention of CMV pneumonia in seropositive patients is controversial. Complications from ISG are unusual, although patients can develop a positive Coombs test during therapy because ISG may contain red cell isoagglutinins (anti-A, anti-B and anti-A,B antibodies) (101).

ALG, usually prepared from horses or goats immunized with human lymphocytes or thymocytes, is used to treat acute GVHD. ALG is also used to treat patients with aplastic anemia who are not candidates for marrow transplantation. ALG, in contrast to ISG, is highly toxic. A test dose of 0.1 ml of ALG and normal horse serum (both diluted 1:1000 in normal saline) is given intradermally as two separate injections in order to test for an immediate hypersensitivity reaction; a positive reaction consists of any systemic symptoms or local erythema and/or wheal formation > 10 mm to both horse serum, and ALG is a contraindication for therapy due to the risk of anaphylaxis. Patients must be premedicated with antipyretics and corticosteroids as severe febrile reactions are common during antibody infusion. Other major complications of ALG include thrombocytopenia and the development of serum sickness. In addition, ALG often contains antibodies to human marrow progenitor

cells and can result in graft failure. Lymphocytes in the peripheral blood are rare or undetectable during therapy with ALG, and therefore patients are severely immunosuppressed and prone to infection.

ALG often is effective for treatment of GVHD that has been refractory to other therapy. By nature of the production process, however, ALG batches may differ significantly with regard to efficacy and toxicity.

Murine monoclonal antibodies are increasingly used because of specificity and lack of lot-to-lot variability. OKT3 is the first murine monoclonal antibody that has been approved by the FDA for prevention of solid-organ-graft rejection, and it is used without FDA approval to prevent or treat acute GVHD (25, 47). OKT3 is directed against the CD3 T cell antigen, and like ALG, is a potent immunosuppressant because it clears T cells from the circulation and blocks their biological effects. An acute symptom complex consisting of chills and high-grade fever occurs in nearly all patients with the first dose. This reaction is probably caused by lymphokines that are released upon destruction of lymphocytes. In severe cases, hypotension and pulmonary edema occur. As with ALG, patients should be premedicated with antipyretics and corticosteroids prior to therapy with OKT3. Delayed toxicity from OKT3 can also be formidable. Patients often develop antibodies to the murine antibody that prevent further therapy. In addition, potent immunosuppression may result in the development of lymphomas. The lymphomas are usually of B-cell origin and appear to be due to Epstein-Barr virus reactivation. They are unusual in renal transplant recipients and may be more common in marrow transplant patients, particularly those given prolonged courses of therapy (47, 67). Serum sickness also occurs 2-3 weeks after therapy in some patients, although this is unusual in marrow transplant patients, perhaps because they are unable to mount a sufficient immune response.

MARROW ABLATION

The major difference between bone marrow transplantation and cardiac and renal transplantation is that the conditioning protocol ablates rather than suppresses the host immune and hematopoietic systems. The intent of a successful marrow transplant is to reconstitute the hematopoietic system of the recipient with donor-derived hematopoietic and immu-

Table 45.2
Experimental Use of Immunoglobulins in Marrow Transplantation*

Antibody Preparation	Dose (mg/kg)	Indication	Comments	Reference
Polyclonal antibodies				
Hyperimmune CMV	0.1–0.15 g/kg i.v. every 1–3 weeks	Prevention of CMV infection	Appears more effective when combined with ganciclovir (DHPG)	10
Immune globulin	0.5–1.5 g/kg i.v. every 2–3 weeks	Chronic GVHD, prevention of CMV infection	May cause false-positive Coombs test	99
Antilymphocyte globulin	15 mg/kg i.v. q.o.d. for 7 doses	Acute GVHD, aplastic anemia	Premedicate with methylprednisolone 1 mg/kg i.v. and give diphenhydramine and acetaminophen p.r.n. Chills, fever and thrombocytopenia are common, serum sickness, pulmonary edema and hypotension occur occasionally	60
Monoclonal antibodies				
CD3 (OKT3)	5 mg/day i.v. for 2 weeks	Acute GVHD	Premedicate for first dose with methylprednisolone and acetaminophen; side effects similar to ATG	25
CD18 (anti-LFA-1)	0.1 mg/kg i.v. daily for 5 doses	Prevention of graft failure		28

*These agents are being tested experimentally and should only be used on an investigational basis. GVHD, graft-versus-host disease; CMV, cytomegalovirus; ATG, antithymocyte globulin.

nological precursors. The most serious complications that result from marrow ablation are bleeding and infection (Table 45.3) (23, 49, 86).

Bleeding Complications

Bleeding complications result primarily from the combination of thrombocytopenia and mucosal damage. Thrombocytopenia occurs as a necessary side effect of all conditioning regimens and develops within a week following initiation of therapy. Platelet transfusions are then necessary to support the patient's platelet count and prevent bleeding complications until the third or fourth week post-transplant platelet, when production usually becomes self-sustaining. Bleeding that occurs in the first several weeks post-transplant is usually from mucosal surfaces that have been damaged as a result of the conditioning regimen. Mucosal damage can be worsened in the early transplant period by multiple factors such as herpes simplex stomatitis, methotrexate therapy for the prevention of GVHD, and the onset of acute GVHD itself. Serious internal bleeding as a result of clotting factor deficiencies is not common in the setting of marrow transplantation, presumably because of the plasma present in the other blood products the patients receive,

the relatively long half-life of the clotting proteins, and extramedullary sources of factor production.

Several syndromes are now recognized that may cause a delayed risk of bleeding as a result of recurrent thrombocytopenia. As many as 37% of patients after transplantation will develop an isolated acquired thrombocytopenia that occurs more than a month after marrow infusion and subsequent to the initial recovery of the megakaryocytic lineage (27). In some patients this has been attributed to the suppressive effects of concomitant cytotoxic drug therapy. Trimethoprim/sulfamethoxazole has been implicated in several cases of transient drug-induced thrombocytopenia. Transient thrombocytopenia has also been associated with acute GVHD due to both marrow suppression and to decreased platelet survival. A more chronic and persistent form of thrombocytopenia can present in as many as a quarter of bone marrow transplant survivors that develop chronic GVHD, and is associated with a poor prognosis.

Topical agents such as thrombin, sucralfate, and silver nitrate are often used as therapy of mucosal bleeding. The mainstay of therapy for the treatment of bleeding complications of marrow transplantation, however, is the transfusion of platelets and red cells. In addition to the usual serology for hepatitis B and HIV,

Table 45.3
Major Post-transplant Periods and Their Associated Complications*

	Early (0-30 days)	Middle (30-100 days)	Late (>100 days)
Patient Condition	Patient usually hospitalized the entire period; central venous access required for support	Patient usually can be followed in a closely monitored outpatient setting	Patient usually independent of i.v. support and able to return to care by referring physician. If all goes well, a patient should be able to resume full activities, including work and school, by 1 yr.
Requirements	Complete transfusion support; hyperalimentation; vigorous hygiene and/or isolation; pain control; surveillance cultures and/or prophylactic antibiotics	Available transfusion and alimentary support (central venous access maintained); limited external contact; physiological support; frequent observation and monitoring; antibiotic prophylaxis for <i>P. carinii</i> and encapsulated organisms	Continued bacterial prophylaxis for 1 yr; regular visits with referring physician; periodic visits with marrow transplant unit
Major Complications	Bacterial infection; fungal infections; herpes simplex; stomatitis/cystitis; veno-occlusive disease of the liver	Acute GVHD; interstitial pneumonia; CMV infection	Chronic GVHD; relapse; bacterial infections with encapsulated organisms; varicella zoster; cataracts

*From Thompson CB, Thomas ED: Bone marrow transplantation. *Surg Clin North Am* 66:589-601, 1986.

etc., it is important that the products be evaluated for cytomegalovirus (see "Infections Complications"). Finally, a unique risk of transfusion therapy in marrow graft recipients is the possibility that red cells and platelets will contain sufficient "passenger" lymphocytes to cause GVHD (95). To avoid this complication, all blood products which transplant patients receive for at least the first year after marrow transplantation should be irradiated (2000 rad) to prevent proliferation of the transfused immune cells.

There is frequently ABO incompatibility of donor and recipient in allogeneic marrow grafts because of the independent inheritance of the ABO and HLA regions. This is managed by either removing the red blood cells from the bone marrow to be infused or using procedures to deplete the recipient of isoagglutinins (5, 8). Both procedures are effective in preventing transfusion reactions at the time of bone marrow infusion. If required, isoagglutinins in the donor's marrow can be removed by separating cells from the plasma. Conversion to the donor's ABO blood group can usually be expected to occur within 2-3 months following marrow engraftment. In cases of ABO incompatibility with the marrow donor, the patient is usually supported with recipient type or group O blood products, and units are screened and selected to prevent transfusion of units containing high titer anti-AB antibodies. Blood products can also be concentrated to minimize plasma content. Once a significant proportion of circulating red blood cells is of donor type, a switch in red cell transfusion can be made to the donor's blood group. In addition, the presence of circulating blood cells of donor type can be used as evidence of successful allogeneic marrow engraftment.

Infectious Complications

In the early post-transplant period, the principal infectious complications are associated with granulocytopenia (23, 49). Following ablation and reinfusion of marrow, granulocyte counts are less than $0.1 \times 10^9/\text{liter}$ for ~2 weeks. The granulocyte count does not usually exceed $1 \times 10^9/\text{liter}$ until the third or fourth week after transplant. A rise in the serum transcobalamin II level precedes the rise in the peripheral granulocyte count and therefore may serve as an early marker of marrow regeneration (53). The use of cyclosporine rather than methotrexate for GVHD prophylaxis has short-

ened this period of severe neutropenia. The disruption of mucosal immunity as a result of the toxic effects of the conditioning regimen on the gastrointestinal mucosa contributes to the risk of infection. Long-term indwelling central venous catheters, used in virtually all patients, also provide a portal for infection (59). This early period of neutropenia is usually characterized by bacterial infections predominantly of a bacteremic nature and occasional fungal infections. The hallmark of bacteremia in this early neutropenic period is fever, and with the initial manifestation of a fever patients are treated with broad spectrum antibiotics that confer coverage consistent with the epidemiological experience of the transplant center. Therapy is maintained until appropriate culture information has been obtained and a suitable antibiotic choice can be made, or until neutropenia resolves. Fever unresponsive to therapy with broad-spectrum antibiotics after 72 hours and the absence of microbiological diagnosis often warrants the addition of systemic antifungal therapy. The most common viral infection in the early post-transplant period is herpes simplex (HSV). Oropharyngeal herpes simplex infection often causes severe local disease that predisposes to secondary bacterial infections and may spread to involve both the esophagus and the lungs. The use of acyclovir for both treatment and prophylaxis of HSV infections has substantially reduced this complication of the early post-transplant period (71).

Following the recovery of neutropenia as a result of successful marrow engraftment, the spectrum of organisms that induces infectious complications in marrow transplant recipients shifts. Bacterial infections with enteric pathogens remain common in the intermediate time period, however, infections resulting from encapsulated bacterial organisms and *Pneumocystis carinii*, which were previously seen in high frequency during this time period, are now seen rarely because of the instigation of trimethoprim/sulfamethoxazole prophylaxis. A variety of fungal infections can occur in this time period. While infection with *Candida* and *Aspergillus* species are most common, a number of rare fungal infections caused by organisms usually considered "nonpathogenic" have been reported.

The most serious of the infections during this intermediate time period are the viral infections. Reactivation or primary infection with cytomegalovirus (CMV) is the most severe of the infections, with CMV pneumonia occur-

ring in approximately 15% of all patients undergoing allogeneic marrow transplantation and having an approximate 85% fatality rate. Other viruses that occur frequently in this time period are adenovirus and Epstein-Barr virus (EBV). Fatal lymphoproliferative diseases associated with EBV infection have occurred, predominantly in patients treated with either antithymocyte globulin or anti-T-cell monoclonal antibodies for the treatment of acute GVHD (47, 70). Some of the lymphomas appear to respond to therapy with acyclovir and discontinuation of immunosuppressive therapy.

The final period of infectious complications from marrow transplantation begins 3–4 months after transplantation at a time when the marrow graft is fully established and mucosal injury has been repaired. Bacterial infections at this time are usually associated with the development of chronic GVHD and include frequent sinopulmonary infections thought to be related to IgA deficiency and sicca syndromes. In addition, the presence of functional hyposplenism or asplenia that occurs in most patients in combination with a naive immune system predisposes to spontaneous bacteremias associated with encapsulated organisms. Most patients receive trimethoprim/sulfamethoxazole, daily oral penicillin, or infusions of immune serum globulins as prophylaxis. The major viral syndrome associated with this time period is the recurrence of varicella-zoster, which occurs in approximately one-third of all patients and in half of patients with chronic GVHD. Virtually all of these infections are due to reactivation of latent virus, although the clinical syndrome may resemble that of primary varicella infection. It is important for the physician caring for these patients to remember that it takes at least a year for the immune system to fully develop after successful transplantation, and that live-viral vaccines are contraindicated. The tempo of immune recovery is delayed, however, in patients who develop chronic GVHD. Vaccinations involving killed organisms are unlikely to be effective.

ACUTE GRAFT-VERSUS-HOST DISEASE

Background and Epidemiology

For graft-versus-host diseases (GVHD) to occur, three conditions must be met (7): (a) Immunocompetent cells, capable of replication

must be transferred from one individual to another. (b) There must be a histoincompatibility between the two individuals. (c) The recipient must be unable to reject and destroy the transferred cells. All those requirements are met with allogeneic marrow transplantation, as well as in some instances of blood (leukocyte) transfusions to patients who receive chemotherapy or fetuses who receive accidental intrauterine maternofetal transfusions or therapeutic exchange transfusions (95). Unexpectedly a GVHD-like syndrome has also been observed occasionally with syngeneic transplants or autologous marrow reinfusion (35).

GVHD is more frequent and often more severe in patients who are given an HLA-non-identical ("mismatched") transplant. For unclear reasons the incidence of GVHD increases with age. It is conjectural whether the probability of GVHD is influenced by the patient's original diagnosis or whether GVHD is more frequent in male patients given a graft from a female donor (18).

GVHD can occur in an acute form, usually within 2–8 weeks (31) or in a chronic form which generally develops within 3 months to 1 year of transplantation (79). Often acute GVHD will progress into the chronic form. The present discussion will be limited to acute GVHD.

Pathophysiology

Donor T lymphocytes react to recipient histocompatibility antigens, proliferate, and attack recipient tissues, leading to tissue damage and the clinical syndrome of GVHD. The immunological attack, usually associated with organ dysfunction, subsides as donor T cells begin to accept the new environment as "self". The onset of GVHD is associated with the presence of nonspecific suppressor cells that are replaced by specific (host-directed) suppressor cells as tolerance develops and GVHD resolves. GVHD and nonspecific suppression are associated with profound immunoincompetence, while patients regain immunocompetence with the emergence of specific suppressor T cells (88, 89). Damage suffered by target organs may require prolonged periods of time for complete healing.

It is thought that acute GVHD can be aggravated and propagated by cross-reactivity of donor T cells with microorganisms contaminating skin and gastrointestinal tract (91). There

is experimental and clinical evidence that the treatment of patients in laminar airflow isolation rooms and attempts at decontamination of skin and intestinal tract decreases the incidence and severity of acute GVHD (75). Exposure to ultraviolet light with sunburn may initiate or cause chronic GVHD to flare.

Clinical Spectrum of the Disease

The three major target organs are the skin, liver, and intestinal tract. Clinical onset is often marked by pruritus and a maculopapular rash that characteristically involves palms and soles but may spread over the entire body. The median time to onset of the rash is ~19 days after marrow infusion. The rash can progress to bullae and burn-like blister formation. Breakdown of the skin may result in considerable fluid, electrolyte, and protein loss and further increase the risk of infections. In some patients, in particular after HLA incompatible transplants or if no GVHD prophylaxis is given, GVHD can present within a few days of transplantation in a hyperacute form (78). These patients have high fever, hyperemia of skin and internal organs, diffuse edema, and may appear quite toxic. Presumably, there is endothelial damage and capillary leak associated with this syndrome (58). With hepatic GVHD the only symptom may be right-upper-quadrant pain. Often there is a striking rise of serum bilirubin (indirect and direct) associated with elevated serum alkaline phosphatase, aspartate

aminotransferase, and γ -glutamyltranspeptidase. Liver dysfunction can progress relentlessly and lead to hepatic encephalopathy and, in rare instances, death due to hepatic failure.

The first intestinal manifestation is usually diarrhea; however, patients may present with nausea and vomiting, often associated with abdominal pain and distension. In severe cases paralytic ileus may develop. Lesions in the gastrointestinal tract range from single-cell necrosis of mucosal epithelial cells and crypt abscesses to diffuse mucosal denudation (66). The mucosal damage may be so profound that drugs normally considered nonabsorbable, such as vancomycin and oral aminoglycosides, may achieve potentially nephrotoxic serum concentrations (63). The stool often is of greenish color. The fluid and electrolyte loss may be severe with stool volumes up to several liters per day (45).

A grading scheme for severity of GVHD is given in Table 45.4 (18, 31, 83). The grading system is based upon the degree of individual organ dysfunction of the skin, liver, and intestinal tract, and on overall performance status so that a clinical grade II would be assigned to a patient with 1+ to 3+ skin rash, 1+ gut or 1+ liver involvement (or both), and a mild decrease in performance status. In cases where the severity of one organ-related symptom differs widely from that in another, the overall clinical grade assigned is that of the most severely affected organ. For example, a patient with a serum bilirubin concentration of 20 mg/dl, severe intestinal cramping and 1+ skin

Table 45.4
Clinical Grading of Acute GVHD

Organ	Grading by Organ System			Overall Clinical Grade			
	Extent of Involvement		Severity	I	II	III	IV
Skin	Rash (% of body surface)	<25	1+	x	x		
		25-50	2+	x	x	x	x
		>50	3+		x	x	x
	Desquamation		4+				x
Liver	Bilirubin (mg%)	2-3	1+		x		
		3-6	2+			x	x
		6-15	3+			x	x
		>15	4+				x
Intestine	Diarrhea (ml/day)	>500	1+		x		
		>1000	2+			x	x
		>1500	3+			x	x
	Pain/ileus		4+			x	x
	Impairment of Performance		1+		x		
			2+			x	
			3+				x

involvement (rash limited to the palms and soles) would be assigned an overall clinical grade IV. The incidence of moderate to severe (grades II to IV) GVHD in patients given HLA-matched marrow varies from ~30–50%. Grade I acute GVHD is often self-limited and may not require any specific therapy. In contrast, mortality with grade IV acute GVHD is ~30%.

Differential Diagnosis

The fully developed picture of acute GVHD with typical involvement of skin, intestinal tract, and liver is clinically quite specific. However, all these organs can be affected by other diseases, and when only a single organ is involved the diagnosis is more difficult. A tissue biopsy with characteristic histology often (but not always) will be helpful. Histologically, the skin alterations due to radiochemotherapy cannot be differentiated reliably from GVHD until about 2½ weeks post-transplant. Viral exanthems and drug reactions can resemble GVHD. The typical involvement of palms and soles is often helpful. Hepatic dysfunction after transplantation can have numerous causes. It may be related to chemoradiotherapy given in preparation for transplantation and must be differentiated from VOD, which usually develops within 1–3 weeks of transplant or from cyclosporine-induced hyperbilirubinemia (45). In patients conditioned with high-dose cyclophosphamide there may be a transient rise of serum bilirubin and lactate dehydrogenase (but not other enzymes) due to hemolysis. It may be difficult or impossible to differentiate non-A, non-B hepatitis from hepatic GVHD. Hepatic biopsy—if not contraindicated by thrombocytopenia or ascites—may be helpful.

The intestinal tract can be severely affected by chemoradiotherapy, resulting in nausea, vomiting, and profuse diarrhea, often lasting through the first week post-transplant. If diarrhea persists longer than 1 week an infectious cause or GVHD must be considered. Pathogens such as adenovirus, coxsackievirus, and rotavirus that often cause mild diarrhea can cause severe infection in marrow graft recipients (100). GVHD may be a diagnosis of exclusion unless a rectal or endoscopic gastric/duodenal biopsy reveals characteristic changes of GVHD (65). Biopsy is not useful in the diagnosis of GVHD in the first 3 weeks after transplantation as histologic abnormalities due to the conditioning therapy may be confused with GVHD; in the absence of GVHD, intestinal histology be-

comes normal by day 21 after transplantation (45).

Prevention

The classic approach to GVHD prevention has been the administration of immunosuppressive drugs to the patient following infusion of bone marrow. Several agents used in a standard fashion or on an experimental basis are listed in Table 45.5.

The use of methotrexate was described previously. Alternatively, cyclophosphamide has been given at 7.5 mg/m² on days 1, 3, 5, 9 and then weekly (67). With this approach the incidence of acute GVHD has ranged from 40 to 70%. Although the usefulness of both methotrexate and cyclophosphamide for GVHD prevention has at times been questioned (43), it is now generally accepted that omission of GVHD prophylaxis results in a very high incidence of GVHD and transplant related mortality (78). Both drugs are myelosuppressive, which may delay hemopoietic recovery, and both can prolong or aggravate mucositis.

More recently, cyclosporine, a new drug apparently lacking marrow toxicity, has been used widely for GVHD prophylaxis (3, 62). Initially only a poorly tolerated intramuscular preparation and an oral preparation with a bioavailability of approximately 27% were used. Subsequently an intravenous preparation became available. Several randomized studies compared cyclosporine (3–5 mg/kg/day intravenously or 10–12.5 mg/kg/day orally) with either methotrexate or cyclophosphamide and failed to show significant differences in the incidence of GVHD (reviewed in 17, 62).

Table 45.5
Drugs for Prevention and Treatment of
Graft-versus-Host Disease

Methotrexate
Azathioprine
6-Mercaptopurine
2-Deoxycoformycin
Cyclophosphamide
Procarbazine
Cytosine arabinoside
Chlorambucil
L-Asparaginase
Glucocorticoids
Cyclosporine
Antithymocyte globulin (ATG)
Monoclonal antibodies
4-Hydroperoxycyclophosphamide
Thalidomide

Next, several agents were combined in an attempt to improve results. A combination of methotrexate, prednisone, and antithymocyte globulin significantly reduced the incidence of GVHD to 21% as compared with 48% in a control group given methotrexate only (60). With a regimen of methotrexate on days 1, 3, 6, and 11 combined with daily cyclosporine starting the day before marrow infusion the incidence of acute GVHD in two trials was 33% and 18% respectively compared with 54% and 53% in the control arms given single-agent cyclosporine or methotrexate respectively (73, 74). Similar results are achieved with combinations of cyclosporine and methylprednisolone (29).

Other agents listed in Table 45.5 have so far only been used experimentally. For example, thalidomide, initially used as a sedative, was found to be effective in the treatment of hypersensitivity reactions that occur during the treatment of leprosy. The immunosuppressive effects of thalidomide were tested in rats given marrow transplants and found to be effective in the therapy of GVHD (92). A more recent approach to GVHD has been the elimination of T lymphocytes in vitro from the donor marrow (9). A major benefit of this technique is that the profound immunosuppression associated with drug administration that renders patients highly susceptible to infections, by viral, bacterial, fungal, and protozoan organisms could be avoided. Of concern, however, is the observation that this approach may result in an increased graft failure rate (in some reports 30–40%) not only with HLA-incompatible but even with HLA-identical transplants (9, 57). A second concern is that an increased recurrence rate of leukemia was reported for both chronic myelocytic leukemia and acute leukemias, which were presumably due to the loss of graft-versus-leukemic effect.

Treatment

The development of acute GVHD, unless it is mild and self-limited, always presents a dilemma. GVHD by itself is immunosuppressive, the patient is usually receiving immunosuppressive drugs for GVHD prophylaxis, and finally, virtually all known therapeutic options for GVHD again involve immunosuppressive drugs (17). All this sets the stage for overwhelming infectious complications and interstitial pneumonitis (51). Although there is no clear indication that the response to treatment is more likely with early institution

of therapy, it is likely that progression of GVHD will cause more tissue damage and increase the probability of infection. It is generally agreed that acute GVHD of grades II–IV requires treatment. Glucocorticoids, ATG, cyclosporine, and monoclonal antibodies are being used widely. With individual drugs, generally either glucocorticoids or ATG, responses are achieved in 30% of patients. With combinations of drugs such as cyclosporine plus ATG as many as 60% of patients have responded. The usual dose of methylprednisolone is 2 mg/kg/day in divided doses given for 1–2 weeks and then gradually tapered. ATG is given at doses of 10–15 mg of IgG/kg for six to eight doses over 2 weeks.

ORGAN FAILURE SYNDROMES

Pulmonary Complications

Approximately half of patients develop respiratory complications after marrow transplantation and pneumonia is the major cause of mortality in the first 100 days following transplantation (33, 42, 49). The differential diagnosis of new-onset pulmonary symptoms varies with respect to time from transplantation. In the first 2 weeks after transplantation there are two conditions to consider in addition to the myriad of disorders that result in pulmonary infiltrates in the immunocompromised host (97). Patients may develop a generalized "capillary leak" syndrome due to what has been termed "hyperacute GVHD" (58, 78). This generally occurs in the setting of HLA-nonidentical transplantation. One must exclude acute congestive heart failure due to cardiac necrosis consequent to the conditioning regimen (13). Fat embolism may rarely occur in the first several days after transplantation if the marrow infusion was inadequately filtered (56, 72). Unlike the case of the multiple-trauma victim, this syndrome may be difficult to recognize because of the nonspecificity of petechiae in a thrombocytopenic patient.

In the intermediate period (30–100 days) after transplantation, nonbacterial interstitial pneumonia is the major complication (Table 45.3) (42, 49, 50). Viral pneumonia due to cytomegalovirus occurs in ~25% of patients and has a mortality rate approaching 100% in those patients who require tracheal intubation and mechanical ventilation. Severe pneumonia due to CMV rarely occurs in non-marrow-transplant patients, and in fact, occurs almost

exclusively in patients after allogeneic grafts and rarely after syngeneic (identical twin) or autologous grafts. Acute GVHD is a major risk factor for the development of CMV pneumonia (51, 52), presumably due to the immunosuppression caused by GVHD, or from the immunosuppressive treatment given for GVHD. The clinical presentation varies from a prolonged fever followed by the development of a nonproductive cough to a fulminant case of acute respiratory distress syndrome that is fatal within 24 hours of clinical onset. Effective therapy for established CMV pneumonia has not been available until recently. New drugs that are relatively specific for CMV such as ganciclovir (dihydroxypropoxymethyl guanine, DHPG) may prove useful (24), particularly when combined with ISC; a preliminary report indicates that mortality of CMV pneumonia may be decreased to < 50% (11). Fortunately, there is an established role for the prophylaxis of CMV infection after marrow grafting. CMV pneumonia may result from a primary infection acquired during the peritransplant period or from reactivation of latent infection. Approximately 30% of patients are seronegative prior to transplantation, and they may be prevented from acquiring the infection by the use of blood products derived exclusively from CMV seronegative donors (10). Finally, if available, a seronegative marrow donor should be used for seronegative recipients.

The other major cause of nonbacterial pneumonia during the intermediate period after transplantation is termed "idiopathic" pneumonia and is presumably caused by damage from radiation and chemotherapy (39, 41, 42, 50, 102). The presentation may be identical to CMV pneumonia, and in order to obtain a diagnosis, an open lung biopsy is often required in order to exclude infectious etiologies, recurrent neoplasm, etc. The prognosis of "idiopathic" pneumonia is better than for CMV pneumonia as up to 50% of patients will recover. There is no established therapy other than supportive measures and the withdrawal of potentially harmful antimicrobial agents such as amphotericin B. Corticosteroids are often given although they have never been shown to be helpful.

P. carinii pneumonia was formerly a frequent pathogen in marrow graft recipients although presently, it rarely occurs due to the routine prophylactic administration of trimethoprim/sulfamethoxazole. All patients should be evaluated for latent mycobacterial infections prior to transplantation; antituber-

culous prophylaxis is indicated in patients with evidence of past infection (54). Pulmonary thromboembolism is rarely documented in patients following marrow transplant, suggesting that they do not become "hypercoagulable" in the presence of prolonged hospitalization.

Gastrointestinal and Hepatic Complications

The most pervasive gastrointestinal problems associated with marrow transplantation are the result of the intensive chemotherapy and radiation required for marrow conditioning (45). The combined modality therapy required for successful bone marrow ablation frequently leads to extensive necrosis of the intestinal crypts. This damage results in diffuse mucositis, anorexia, crampy abdominal pain, and watery diarrhea (12, 45, 69). As a rule, the intestinal damage consequent to the conditioning protocol is entirely reversible, unlike the liver injury that may occur (see below). Most patients receiving allogeneic marrow transplantation require complete parenteral alimentation during the 3-4 weeks required for resolution of this intestinal damage. Because of the protein loss it is difficult to prevent the patients from developing a negative nitrogen balance, even with aggressive nutritional support. Complications of prolonged hyperalimentation include abnormal liver function tests, gallbladder atony, and sludge formation in the biliary tract (48, 94). Severe gastrointestinal bleeding is rarely seen during this time period, although gastrointestinal fluid losses need to be monitored and replaced appropriately.

Patients with chronic GVHD usually have hepatic and esophageal involvement (45). Intestinal fibrosis resembling that caused by scleroderma may result in dysphagia, retrosternal pain, and aspiration associated with esophageal dysfunction. Webs and strictures of the distal esophagus are also frequently seen and may require bougienage. Chronic liver disease occurs in almost 90% of patients with chronic GVHD. Because of the high incidence of infectious complications in patients with chronic GVHD, vigilance must be maintained to exclude infectious etiologies for deteriorating liver function. Among the agents to be excluded are chronic viral infections with non-A, non-B hepatitis, cytomegalovirus, and hepatitis B virus or infiltrative bacterial liver dis-

ease with agents such as tuberculosis. In addition, hepatotoxic reactions can occur, most frequently from trimethoprim/sulfamethoxazole, and cholestasis has been associated with the use of cyclosporine and azathioprine for the treatment of chronic GVHD. The possibility of extrahepatic biliary obstruction due to cholelithiasis must always be considered as a potential underlying etiology of worsening liver disease. Although some patients with chronic GVHD may have hyperbilirubinemia for years, hepatic failure, portal hypertension and cirrhosis are unusual complications of this disease.

Veno-occlusive Disease

Veno-occlusive disease of the liver (VOD) occurs in up to 20% of patients after transplantation and is becoming more common due to the use of more aggressive conditioning protocols, and to the fact that patients have been more intensively pretreated prior to transplantation (45, 46, 64). The signs of VOD usually develop during the first 2 weeks after marrow transplantation. Most patients first develop a gradual weight gain with jaundice appearing at 1 week. These signs are followed by the development of abdominal pain, hepatomegaly, ascites, and even encephalopathy within 6–10 days. Weight gain is due to pre-renal oliguria, suggesting that postsinusoidal obstruction activates renal salt retention prior to the onset of ascites. Jaundice is a virtual sine qua non of the syndrome, with the serum bilirubin reaching a maximum usually between 2 and 3 weeks after transplant. Abdominal pain can be a prominent symptom, and encephalopathy will develop in as many as half of the patients. VOD is characterized histologically by a centrilobular hemorrhage. The terminal hepatic venules and sublobular veins may be damaged and activation of clotting factors within the venules may be responsible for the early manifestations of VOD.

The clinical course of patients with VOD ranges from cases of fulminant hepatic failure leading to death within 1–2 weeks after transplant to a mild transient illness with complete recovery by week 3. To date, no intervention appears likely to alter the course of this disease, and therapy is directed at maintaining intravascular volume and renal perfusion while simultaneously attempting to minimize extravascular fluid accumulation (45, 46). Sodium intake should be restricted and the judicious use of spironolactone or furosemide can help

achieve a negative sodium balance. Encephalopathy should be treated with protein restriction and lactulose. Drugs that are metabolized in the liver should be monitored carefully during periods in which ongoing liver disease is present. Drugs associated with renal toxicity should also be reduced and monitored closely because of renal hypoperfusion. Drugs that distribute into third-space fluids usually have to be reduced or withheld if ascites develops. While other forms of VOD are thought to be responsive to anticoagulant therapy, this approach is relatively contraindicated in marrow graft recipients during this time period of marrow transplantation.

The diagnosis of VOD must be made on a clinical basis as liver biopsy is usually contraindicated due to thrombocytopenia and ascites. Patients that exhibit any two of the three major criteria of VOD (jaundice, hepatomegaly or hepatic pain, ascites or unexplained weight gain) within 30 days of transplantation have an ~85% probability of having VOD (46). The major differential diagnoses that require consideration are acute GVHD of the liver, post-transfusion hepatitis, and the Budd-Chiari syndrome (64). Liver involvement in acute GVHD usually manifests as cholestatic jaundice without evidence of significant hepatocellular damage or portal hypertension and occurs 3 weeks or later after transplantation, whereas VOD occurs in the first 3 weeks of transplantation. The patient with acute GVHD develops mild hepatomegaly with an increased serum alkaline phosphatase concentration and hyperbilirubinemia, and elevations of transaminase levels are not usually pronounced. Imaging techniques such as computed tomography and magnetic resonance imaging (MRI) usually reveal sparing of the caudate lobe of the liver in patients with the Budd-Chiari syndrome, while patients with VOD have total hepatic involvement. Pericentral hepatocyte necrosis is a pathologically distinct lesion from VOD that produces a clinical syndrome that is similar to VOD (45).

Neurological Complications

The most common CNS side effect reported in association with bone marrow transplantation is metabolic encephalopathy as a result of failure of other organ systems. Metabolic encephalopathy is treated primarily by therapy for the underlying condition such as hemodialysis for acute renal failure. The second most common CNS complications are adverse ef-

fects from various drugs. As with other patients in the ICU, corticosteroids have been associated with psychosis reactions. Parenteral acyclovir therapy has been reported to induce tremors and transient hemiparesis (93). Cyclosporine has been associated with seizure disorders, cerebellar ataxia, tremors, and depression, all which appear to be corrected by magnesium therapy (84). Infectious CNS complications are also reported in marrow transplant patients and fatal CNS infections have been reported involving *Aspergillus*, herpes simplex virus types I and II, *Listeria monocytogenes*, and toxoplasmosis. Despite the frequency of bacteremia in the post-transplant period, however, surprisingly few episodes of bacterial meningitis/encephalitis are seen. This suggests that, contrary to some reports, the blood-brain barrier is remarkably resistant to the conditioning protocols used for allogeneic marrow transplantation.

The most devastating neurological complication of marrow transplantation is the development of idiopathic leukoencephalopathy. Patients develop a progressive syndrome consisting of lethargy, slurred speech, ataxia, seizures, confusion, spasticity, and decerebrate posturing. Pathological findings are those of degeneration of the white matter with a multifocal pattern of noninflammatory necrosis. Onset is usually insidious, beginning 3–6 months following marrow transplantation and is nearly always fatal. Leukoencephalopathy has not been reported in patients transplanted for nonmalignant disorders, suggesting that the prior cytotoxic therapy may predispose to the development of leukoencephalopathy. In addition, almost all of these patients have been treated with post-transplant intrathecal methotrexate to prevent CNS recurrences of hematological malignancy. A recent report suggests that the incidence of leukoencephalopathy is associated not only with the preparative regimen but also with a history of pretransplant CNS therapy and the extent of post-transplant CNS therapy (85). In patients with a history of previous CNS therapy who received post-transplant intrathecal methotrexate as prophylaxis to prevent recurrent CNS disease, the incidence of leukoencephalopathy may be as high as 15%. At the onset of symptoms consistent with leukoencephalopathy other reversible etiologies should be excluded. For example, hypomagnesemia is common in patients that are treated with cyclosporine and may result in seizures, Parkinsonian symptoms, and cerebellar signs similar to leukoen-

cephalopathy (84). Similarly, the syndrome of D-lactic acidosis found in patients with severe intestinal malabsorption that may occur with chronic GVHD can cause slurred speech and cerebellar symptoms that resolve after treatment with antimicrobials and correction of metabolic acidosis (16). Finally, progressive multifocal leukoencephalopathy, caused by infection with JC virus, must be distinguished by brain biopsy, from idiopathic leukoencephalopathy.

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