

**TABLE 139e-1 CLINICAL STAGING AND GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE**

Clinical Stage	Skin	Liver—Bilirubin, μmol/L (mg/dL)	Gut
1	Rash <25% body surface	34–51 (2–3)	Diarrhea 500–1000 mL/d
2	Rash 25–50% body surface	51–103 (3–6)	Diarrhea 1000–1500 mL/d
3	Generalized erythroderma	103–257 (6–15)	Diarrhea >1500 mL/d
4	Desquamation and bullae	>257 (>15)	Ileus
Overall Clinical Grade	Skin Stage	Liver Stage	Gut Stage
I	1–2	0	0
II	1–3	1	1
III	1–3	2–3	2–3
IV	2–4	2–4	2–4

The incidence of acute GVHD is higher in recipients of stem cells from mismatched or unrelated donors, in older patients, and in patients unable to receive full doses of drugs used to prevent the disease.

One general approach to the prevention of GVHD is the administration of immunosuppressive drugs early after transplant. Combinations of methotrexate and either cyclosporine or tacrolimus are among the most effective and widely used regimens. Prednisone, anti-T cell antibodies, mycophenolate mofetil, sirolimus, and other immunosuppressive agents have also been or are being studied in various combinations. A second general approach to GVHD prevention is removal of T cells from the stem cell inoculum. While effective in preventing GVHD, T cell depletion has been associated with an increased incidence of graft failure, infectious complications, and tumor recurrence after transplant; as yet, it is unsettled whether T cell depletion improves cure rates in any specific setting.

Despite prophylaxis, significant acute GVHD will develop in ~30% of recipients of stem cells from matched siblings and in as many as 60% of those receiving stem cells from unrelated donors. The disease is usually treated with glucocorticoids, additional immunosuppressants, or monoclonal antibodies targeted against T cells or T cell subsets.

Chronic GVHD occurs most commonly between 3 months and 2 years after allogeneic transplant, developing in 20–50% of recipients. The disease is more common in older patients, in recipients of mismatched or unrelated stem cells, and in those with a preceding episode of acute GVHD. The disease resembles an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, and bile duct degeneration and cholestasis. Single-agent prednisone or cyclosporine is standard treatment at present, although trials of other agents are under way. Mortality rates from chronic GVHD average around 15%, but range from 5–50% depending on severity. In most patients, chronic GVHD resolves, but it may require 1–3 years of immunosuppressive treatment before these agents can be withdrawn without the disease recurring. Because patients with chronic GVHD are susceptible to significant infection, they should receive prophylactic trimethoprim-sulfamethoxazole, and all suspected infections should be investigated and treated aggressively.

Although onset before or after 3 months after transplant is often used to discriminate between acute and chronic GVHD, occasional patients will develop signs and symptoms of acute GVHD after 3 months (late-onset acute GVHD), whereas others will exhibit signs and symptoms of both acute and chronic GVHD (overlap syndrome). There are as yet no data to suggest that these patients should be treated differently than those with classic acute or chronic GVHD.

From 3–5% of patients will develop an autoimmune disorder following allogeneic HCT, most commonly autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. Unrelated donor source and chronic GVHD are risk factors, but autoimmune disorders have been reported in patients with no obvious GVHD. Treatment is with prednisone, cyclosporine, or rituximab.

**Infection** Posttransplant patients, particularly recipients of allogeneic transplantation, require unique approaches to the problem of

infection. Early after transplantation, patients are profoundly neutropenic, and because the risk of bacterial infection is so great, most centers initiate antibiotic treatment once the granulocyte count falls to <500/μL. Fluconazole prophylaxis at a dose of 200–400 mg/d reduces the risk of candidal infections. Patients seropositive for herpes simplex should receive acyclovir prophylaxis. One approach to infection prophylaxis is shown in **Table 139e-2**. Despite these prophylactic measures, most patients will develop fever and signs of infection after transplant. The management of patients who become febrile despite bacterial and fungal prophylaxis is a difficult challenge and is guided by individual aspects of the patient and by the institution's experience.

**The general problem of infection in the immunocompromised host is discussed in Chap. 169.**

Once patients engraft, the incidence of bacterial infection diminishes; however, patients, particularly allogeneic transplant recipients, remain at significant risk of infection. During the period from engraftment until about 3 months after transplant, the most common causes of infection are gram-positive bacteria, fungi (particularly *Aspergillus*), and viruses including CMV. CMV infection, which in the past was frequently seen and often fatal, can be prevented in seronegative patients transplanted from seronegative donors by the use of either seronegative blood products or products from which the white blood cells have been removed. In seropositive patients or patients transplanted from seropositive donors, the use of ganciclovir, either as prophylaxis beginning at the time of engraftment or initiated when CMV first reactivates as evidenced by development of antigenemia or viremia, can significantly reduce the risk of CMV disease. Foscarnet is effective for some patients who develop CMV antigenemia or infection despite the use of ganciclovir or who cannot tolerate the drug.

*Pneumocystis jiroveci* pneumonia, once seen in 5–10% of patients, can be prevented by treating patients with oral trimethoprim-sulfamethoxazole for 1 week before transplant and resuming the treatment once patients have engrafted.

The risk of infection diminishes considerably beyond 3 months after transplant unless chronic GVHD develops, requiring continuous immunosuppression. Most transplant centers recommend continuing trimethoprim-sulfamethoxazole prophylaxis while patients are receiving any immunosuppressive drugs and also recommend careful monitoring for late CMV reactivation. In addition, many centers recommend prophylaxis against varicella-zoster, using acyclovir for 1 year after transplant. Patients should be revaccinated against tetanus, diphtheria, *Haemophilus influenzae*, polio, and pneumococcal pneumonia starting at 12 months after transplant and against measles, mumps, and rubella (MMR), varicella-zoster virus, and possibly pertussis at 24 months.

**TABLE 139e-2 APPROACH TO INFECTION PROPHYLAXIS IN ALLOGENEIC TRANSPLANT RECIPIENTS**

Organism	Agent	Approach
Bacterial	Levofloxacin	750 mg PO or IV daily
Fungal	Fluconazole	400 mg PO qd to day 75 posttransplant
<i>Pneumocystis carinii</i>	Trimethoprim-sulfamethoxazole	1 double-strength tablet PO bid 2 days/week until day 180 or off immunosuppression
Viral		
Herpes simplex	Acyclovir	800 mg PO bid to day 30
Varicella-zoster	Acyclovir	800 mg PO bid to day 365
Cytomegalovirus	Ganciclovir	5 mg/kg IV bid for 7 days, then 5 (mg/kg)/d 5 days/week to day 100