How I treat chronic graft-versus-host disease

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Allogeneic stem cell transplantation (SCT) is now a commonplace procedure. Clinicians who care for patients with hematologic malignancies and aplastic anemia are almost certain to follow up patients after SCT. This review is intended to help clinicians observe patients for probably the most important late complication of SCT, chronic graft-versus-host disease (GVHD). It reviews the pathophysiology, risk factors, clinical manifestations, evaluation, treatment, and supportive care of chronic GVHD. (Blood. 2001;97:1196-1201) © 2001 by The American Society of Hematology

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Introduction

Chronic graft-versus-host disease (GVHD) remains the most common late complication of allogeneic stem cell transplantation (SCT). Although improvements have been made in the prevention of acute GVHD, these advances have not resulted in a concomitant decrease in the incidence of chronic GVHD. This sustained incidence of chronic GVHD is likely related to changes in clinical SCT practice. Allogeneic SCT is used in increasingly older patients, in whom the risk for chronic GVHD is greater. The use of unrelated donors and related but nonhuman leukocyte antigen (HLA)-identical donors is expanding. Acute and chronic GVHD are larger problems, both in incidence and in severity, in recipients of alternative-donor SCT. The use of donor lymphocyte infusion to treat relapsed disease or to achieve full donor chimerism after nonmyeloablative transplantation has resulted in the development of chronic GVHD in a substantial number of these patients. Finally, there is a suggestion that patients receiving allogeneic peripheral blood stem cell transplants have a lower incidence of acute GVHD but an equally high or a higher incidence of chronic GVHD than comparable patients receiving marrow grafts. For these reasons, chronic GVHD must be considered one of the major obstacles still facing the field of blood and marrow transplantation.

Pathogenesis

The pathophysiology of chronic GVHD is poorly understood, partially because of difficulties encountered as a result of the late onset of the disease. Clinical studies in patients with chronic GVHD are hampered by the fact that patients are frequently back in their local communities, and thus at a distance from the transplant center, by the time chronic GVHD develops. Early manifestations of GVHD may be undetected by physicians unfamiliar with the disease. Many of the published assumptions about chronic GVHD have been influenced by the frequency at which patients are re-examined at major transplant centers, which may or may not be valid. Animal models of chronic GVHD exist, but they are expensive and time labor intensive to establish. This has hampered the investigation of basic immunobiology and the evaluation of therapy in animal models.

Inoculation of T cells into allogeneic or congenic, immunoincompetent mice or rats leads to GVHD-related changes such as diarrhea, skin lesions, severe wasting, and death within 1 to 3 weeks.1,2 This model is consistent with acute GVHD. Surviving animals succumb to chronic GVHD usually 1 to 3 months after inoculation. Hepatosplenomegaly, immunodeficiency, and evidence of autoimmune phenomena develop before death. Symptoms of human chronic GVHD can be established in different ways, including performing SCT across an isolated class 1 barrier or transplanting parent to F1 (semiallogeneic SCT).1,2 The model of cyclosporine (CsA)-induced syngeneic GVHD reported by Hess et al3 also results in a condition that mimics chronic GVHD. Murine systems can be manipulated to alter the course and severity of GVHD. This does shed some light on potential factors that contribute to the development of chronic GVHD. Variables such as the number and proportion of CD4+ versus CD8+ lymphocytes injected, type and extent of recipient immunosuppression, age of donors and recipients, presence or absence of tissue injury caused by chemotherapy, radiation, or infection result in different manifestations of GVHD.4,6

The exact pathogenesis of chronic GVHD, however, remains ambiguous. In addition to donor-derived alloreactive T cells that are so important in acute GVHD, postthymic CD4+ T cells are thought to play an important role in chronic GVHD.4 The T-cell precursors may undergo aberrant “thymic education” after SCT that effectively makes them self-reactive or autoreactive. Additionally, the activation of different helper T-cell subsets (Th1 versus Th2) may be responsible for distinct manifestations of acute and chronic GVHD.5,6 The role of alloreactivity versus autoreactivity in the pathogenesis of chronic GVHD remains an area of intense debate. Alloreactivity to minor histocompatibility antigens is believed by some to explain chronic GVHD as a late phase of acute GVHD. The importance of autoreactivity, however, is suggested by clinical manifestations of chronic GVHD that frequently mimic those of autoimmune diseases, the finding of autoantibodies in some patients with chronic GVHD, and experimental data suggesting the importance of thymic education in the pathogenesis of chronic GVHD. As new information becomes available
about the pathogenesis of autoimmune disorders outside the setting of SCT, this might shed further light on the immunobiology of chronic GVHD.

### Risk factors for the development of chronic graft-versus-host disease

Understanding the predictors for development of chronic GVHD helps clinicians following up patients after SCT. HLA disparity is a potent factor in risk for chronic GVHD. Chronic GVHD occurs in approximately 40% of patients receiving HLA-identical sibling unmanipulated transplants, more than 50% of patients undergoing HLA-nonidentical–related SCT, and approximately 70% of those undergoing matched unrelated SCT. For those patients receiving transplants from mismatched unrelated donors, the incidence is even higher. Age of the recipient is very important. Among recipients of HLA-identical transplants from sibling donors, the risk for chronic GVHD rapidly rises, from 13% in those younger than 10 years of age to 46% in those older than 20. Prior acute GVHD is the most important predictor. The type of acute GVHD prophylaxis used influences the risk for chronic GVHD. Patients receiving marrow grafts vigorously depleted of lymphocytes have lower incidences of acute and chronic GVHD. Other risk factors reported include shorter duration of CsA prophylaxis, transfusion of nonirradiated donoruffy coat or marrow boosts, and latent herpes infections in either the donor or the recipient. Loughran et al examined the value of day 100 screening in predicting the development of chronic GVHD. Seventeen clinical and laboratory factors were evaluated in 169 patients. GVHD detected by skin biopsy or oral mucosal biopsy, despite the lack of clinically evident GVHD, or a history of acute GVHD independently predicted a 3-fold relative risk for chronic GVHD. Despite their predictive value, skin and oral mucosal biopsies are not routinely performed at most centers because of the lack of data showing a benefit to treatment initiated in the absence of clinically evident disease. It may blunt the graft-versus-leukemia effect. Patients identified by biopsy or by the other risk factors listed above certainly should be carefully monitored for the development of overt chronic GVHD.

### Timing of onset

The diagnosis of chronic GVHD is occasionally made earlier than 100 days after SCT and is rarely made later than 500 days after SCT. The median day of diagnosis is 201 after SCT from an HLA-identical sibling donor, 159 days after SCT from an HLA nonidentical–related donor, and 133 days after SCT from an unrelated donor.

### Diagnosis of chronic graft-versus-host disease

One of the most difficult aspects of the management of chronic GVHD is making a timely diagnosis. There is a tendency to assume that whenever a patient returns to the transplant center, the problem is chronic GVHD. In reviewing 123 patients referred to Johns Hopkins for the management of refractory chronic GVHD, we found that 9 patients had no evidence of ever having chronic GVHD and that 26 additional patients had no evidence of ongoing active disease. Clinical problems were resolved in many of these patients when an alternative diagnosis was made and they were spared toxicity from unnecessary immunosuppressive regimens. Conversely, patients with less common manifestations of chronic GVHD have been harmed by delays in the institution of appropriate therapy. For example, progressive limitation in range of motion may develop in a patient’s joints from fascitis without sclerodermatous skin disease. Thus, a critical step in the management of chronic GVHD is making a diagnosis.

The transplant center should help in the evaluation of posttransplantation problems. The center should have available clinicians who are experienced in the diagnosis and management of chronic GVHD and pathologists who have expertise in the histologic diagnosis. Often the centers will have ongoing clinical trials for which the patient may be eligible, helping the referring physician by providing a detailed care plan while trying to improve the treatment of this disease. Should the patient be unable to return to the transplant center, these physicians should be available to help in determining the cause of the patient’s difficulties and in reviewing biopsies.

### Evaluation

Once the diagnosis of chronic GVHD has been suspected clinically and confirmed histologically, the extent of involvement must be ascertained. The initial evaluation should be comprehensive. The physician should look at all organs or systems commonly involved in the disease, regardless of whether existing symptoms are referable to those organs. This initial evaluation can then be used as a baseline to assess progression of the disease or response to therapy. Elements of the initial and subsequent evaluations are shown in Table 1. As a baseline for all patients with chronic GVHD, we recommend a complete physical examination, good dental examination, pulmonary function tests, complete blood counts, liver function tests, ophthalmologic examination with Schirmer test, range-of-motion evaluation by a physical therapist, and consultation with a social worker. The latter is important because most patients have difficulty dealing with a chronic debilitating illness.

### Staging

The current system of grading chronic GVHD as limited or extensive, based on the outcome of 20 patients, has been used for describing the clinical severity of the disease. Although it is highly reproducible among the transplant centers, the current grading system is of little practical use because it basically divides patients into those needing treatment (extensive chronic GVHD) and those who do not (limited chronic GVHD). However, it has been extremely difficult to devise a more helpful grading system. We have studied the disease-specific survival of 151 patients with chronic GVHD diagnosed and treated at Johns Hopkins between 1979 and 1998 to try to devise a new grading system. We examined 23 demographic and clinical features at diagnosis and at primary treatment failure. According to multivariate analysis, extensive skin involvement (more than 50% body surface area), thrombocytopenia (fewer than 100,000 platelets/μL), and progressive onset at the diagnosis of chronic GVHD significantly influenced survival after diagnosis. These 3 factors and Karnofsky performance status of less than 50% at primary treatment failure were significant predictors for survival after treatment failure. The effect of the presence of any combination of factors at diagnosis and at primary treatment failure on nonrelapse mortality rates was examined by the development of prognostic factor scores.
and PFS2, respectively). Patients with PFS1 of 0 (none of these factors), 0 to 2 (extensive skin involvement only or thrombocytopenia, progressive onset, or both), and 2 to 3.5 (extensive skin involvement plus either thrombocytopenia or progressive onset) had 10-year nonrelapse survival rates of 82%, 68%, and 34%, respectively. Patients with PFS1 of 3.5 or more (all 3 factors) had a 3% nonrelapse survival rate at 3 years. Patients with PFS2 of 0 to 2, 2 to 3.5, and 3.5 or more had 10-year nonrelapse survival rates of 91%, 74%, 14%, and 4%, respectively.

**Primary treatment**

The most successful treatment of patients with chronic GVHD results when a systematic approach to diagnosis, evaluation, and co-ordinated management is undertaken by a multidisciplinary team whose members share an interest in this complex disorder. In addition to bone marrow transplant physicians and nurses, team members should include dermatologists, ophthalmologists, dentists, dieticians, physical and occupational therapists, and social workers. Pathologists with expertise in the histologic features of GVHD are crucial. Because chronic GVHD can affect virtually any organ system, consultants in subspecialty areas such as rehabilitation medicine, gastroenterology, pulmonary medicine, neurology, and infectious diseases who are experienced in seeing patients with chronic GVHD can be invaluable resources to the team. Even if the patient is unable to return to the transplant center, this team should be able to help in management issues.

Whenever possible, patients found to have chronic GVHD should be entered on treatment protocols. If that is not feasible,
alternate-day CsA and prednisone is the regimen of choice. The Seattle group has studied CsA and prednisone in a randomized trial currently evaluating the combination (versus prednisone alone) as front-line therapy. In newly diagnosed patients with extensive disease in whom chronic GVHD develops after similar doses of immunosuppression, patients are treated with daily prednisone at 1 mg/kg per day and daily CsA at 10 mg/kg per day, divided into 2 doses and based on ideal or actual weight, whichever is lower. After 2 weeks, providing the disease has not progressed, the steroids are tapered (by 25% per week) to 1 mg/kg of prednisone on alternate days. Once the steroid taper has been completed without a flare in GVHD, CsA is reduced by 25% per week to alternate day dosing such that the patient takes CsA (10 mg/kg in 2 divided doses) 1 day and alternates with prednisone (1 mg/kg) the next day. Although the initial study gauged responses at 9 months of treatment, at Hopkins responses are evaluated 3 months after alternate day dosing is achieved. The 3-month time frame for evaluation of response to a given therapy is based on our own observation that 90% of patients who are ultimately going to respond to therapy will show signs of response at that point. If the disease has completely resolved, patients are gradually weaned from medication, with dose reductions made approximately every 2 weeks. Patients who continue to respond are kept on the same therapy and are re-evaluated in another 3 months. Once patients reach their maximal response, therapy is continued for another 3 months and then weaned. For those who have not responded by the 3-month time point or who progress, alternative salvage regimens should be instituted.

Evaluation of response is a difficult issue. For patients with lichenoid lesions or hepatic disease, monitoring response to treatment is relatively straightforward. For patients with sclerodermatous disease or fasciitis, response is harder to gauge. The underlying sclerosis is going to resolve slowly, if ever. Patients with active sclerotic disease have progressive sclerosis, frequently with erythema at the leading edge of the sclerosis. Responding patients will have no erythema and no new areas of sclerosis. Range-of-motion studies should show stability or improvement. When tapering these patients off immunosuppression, frequent range-of-motion studies and documentation of the areas of sclerosis are helpful to detect flares.

Salvage regimens

There is no standard approach for patients who are refractory to initial therapy. Again, the best choice is a clinical trial. There have been several phase II/I trials in patients with relapsed/refractory chronic GVHD. These patients were included in both the Seattle study, evaluating the combination of alternate-day CsA and prednisone, and the Baltimore study of thalidomide. For patients receiving steroids alone or an investigational therapy, combination CsA and steroids, as outlined above, is the first choice. For patients who have not responded or who have had recurrences after CsA plus prednisone, there are several potential therapies. We are currently studying, in a phase II trial, the combination of mycophenolate mofetil and tacrolimus. A retrospective review of 26 patients with refractory chronic GVHD treated with this steroid-sparing combination showed that it was well tolerated, and nearly half the patients showed an objective response. Other potential approaches include thalidomide, azathioprine, tacrolimus, PUVA, and photopheresis. Thalidomide is now available commercially. It should not be considered for patients with pre-existing neuropathies, and the sedation and constipation seen with thalidomide may be intolerable to some patients. Azathioprine is sometimes used in patients refractory to steroids, but it is probably better avoided because of its myelosuppressive effect. The use of tacrolimus (FKS06) in steroid-resistant patients has been reported by Tzakis et al. Among 17 patients with extensive chronic GVHD after failure of at least 2 months of first-line therapy, persistent disease, or adverse reactions to first-line medication, 6 were judged to have had an unequivocal beneficial response. The pharmacology of this drug, with highest concentrations achieved in the liver, make it particularly appealing for patients with hepatic disease, though this initial report did not demonstrate such an effect in the liver. Another modality being explored is the use of extracorporeal photopheresis, extracorporeal exposure of peripheral blood mononuclear cells to a photosensitizing compound and UV-A light to selectively eliminate lymphocytes. In one report of 15 patients, skin, liver, and oral manifestations of steroid-refractory chronic GVHD improved.

Special treatment considerations

Particularly challenging are those patients with refractory sclerodermatous chronic GVHD. We have recently reviewed the Baltimore experience with etretinate, a synthetic retinoid, in 32 such patients. This group was heterogeneous, but all had sclerodermatous GVHD that failed to improve or progressed on standard immunosuppressive therapy. The addition of etretinate to the treatment regime led to clinical responses in 20 of 32 patients. Etretinate is no longer available, and a more rapidly cleared close derivative, acitretin, is being used. In patients responding to treatment, we add acitretin to try to increase the cutaneous response. In addition, in patients without evidence of sclerodermatous disease worsening after immunosuppression, acitretin can be used to try to decrease sclerosis. Borrowing from the experience in the treatment of non-GVHD dermatologic conditions, Lee et al reported encouraging results using clofazimine. This antimycobacterial drug has anti-inflammatory activity and has been used successfully in treating leprosy and chronic autoimmune skin disorders. Based on its effectiveness in dermatologic diseases and backed by in vitro studies, Plaquenil (Sanofi Winthrop, New York, NY) is another agent of interest in chronic GVHD therapy. In patients who do not tolerate acitretin because of skin drying, flaking, or ulceration, Plaquenil (Sanofi Winthrop) is an interesting compound to add. A large phase III trial of initial therapy of chronic GVHD (cyclosporine plus prednisone with or without Plaquenil [Sanofi Winthrop]) is under way through the Children’s Oncology Group.

Patients with refractory lichenoid GVHD may also benefit from the addition of nonpharmacologic approaches, such as PUVA (8-methoxypsoralen plus ultraviolet A irradiation). This approach was originally reported in 1985 by the Baltimore group and in 1986 by Atkinson et al. A review of 40 patients treated with PUVA at Johns Hopkins with either refractory disease (n = 35) or high-risk disease (n = 5) was recently undertaken. Eleven patients had disease limited to the skin, and 5 obtained a complete response. Among 22 patients with systemic lichenoid disease, 11 had complete skin responses and 6 had partial skin responses. Unfortunately, no systemic effects were seen in the patients with multi-organ disease. PUVA may be an effective therapy for cutaneous lichenoid chronic GVHD. For patients with lichenoid disease who have chronic GVHD that affects the skin only after donor lymphocyte infusion and in whom immunosuppression therapy should be avoided or minimized, PUVA is an attractive choice for initial therapy. Others have reported the use of low-dose total lymphoid irradiation. In a report of 9 patients receiving 100 eGy
Thoraco-abdominal irradiation for chronic GVHD, significant improvement was reported in 6 of them.22,23

Although virtually all patients with extensive disease require systemic therapy, patients with symptomatic disease limited to the oral cavity may benefit from topical steroids, thus, sparing them the effects of systemic immunosuppression. Decadron elixir (0.5 mg/5 mL) can be effective local therapy when the patient rinses the mouth with 10 mL for 2 to 3 minutes at least 4 times a day. Topical steroids such as Lidex (Syntex, Palo Alto, CA) have been tried. When local steroids alone fail to control oral disease, CsA swishes can be tried. If the oral disease fails to resolve with topical therapy, a trial of intraoral PUVA or systemic immunosuppressive therapy may be warranted, depending on the patient’s symptoms.

Supportive care

Chronic GVHD is a cause of significant morbidity. Supportive care measures aim to improve length and quality of life for patients with chronic GVHD.

Infection prophylaxis

Infection is the primary cause of death in patients with chronic GVHD. Having a high index of suspicion for and aggressively investigating potential infections is important to minimize morbidity and mortality. All patients should receive antimicrobial prophylaxis. This is perhaps the most important factor in caring for these patients. It should include Pneumocystis carinii prophylaxis (such as TMP-SMX) and prophylaxis against encapsulated organisms including pneumococcus (such as penicillin). Although the risk from P. carinii pneumonia probably decreases once immunosuppressive anti-GVHD therapy is completed, poor splenic function persists. For this reason, P. carinii pneumonia prophylaxis is discontinued 6 months after GVHD therapy is completed, but patients are maintained on penicillin prophylaxis for life. Additionally, patients should receive antibiotic prophylaxis for dental and other invasive procedures, according to the endocarditis prophylaxis recommendations of the American Heart Association.

Topical antifungal prophylaxis with clotrimazole troches or nystatin swishes should be used in all patients receiving local steroid therapy for oral GVHD. If thrush occurs despite this, systemic antifungal therapy is indicated. Acute episodes of herpes infections should be treated with antiviral therapy. Patients who were serologically positive to cytomegalovirus (CMV) at the start of the transplantation procedure should undergo frequent surveillance cultures or testing for CMV antigenemia. Patients with documented CMV disease must be treated with ganciclovir, and immunoglobulin infusions should be added for those with evidence, detected by imaging, of pulmonary disease.

Additional protection is afforded patients by supplemental intravenous IgG therapy if they have very low serum IgG levels and recurrent infections. The goal of such therapy is to keep the IgG level above 500 mg/dL. While they are still receiving immunosuppressive therapy, most patients with chronic GVHD will not respond to vaccination. Vaccinations used in transplant recipients should be delayed until 1 year after GVHD therapy has been completed and then only given when there is no evidence of active disease. Antibody titers can be used to check responses to vaccines that are typically given to patients after SCT, such as inactivated polio, diphtheria, and tetanus toxoid. Patients can also be immunized against polyvalent influenza, pneumococcus, and Hemophilus influenzae B at that time. Recent Centers for Disease Control and Prevention recommendations on vaccination are available on their Web site (www.cdc.gov/mmwr/mmwr_r.html); detailed citations for the recommendations are included.

Symptom management

Symptom management is very important for patients with chronic GVHD. Dry skin should be aggressively lubricated. Agents that are free of perfume and preservatives are best. Petroleum jelly offers excellent lubrication, but patients often complain about its messiness. We advise patients to apply petroleum jelly liberally before bedtime and to wear old nightclothes. Trauma should be avoided because many of these patients have frail skin that can easily be abraded. Patients should avoid sunburn and should wear sunscreen with a skin protection factor of at least 15. For those whose sweat glands are affected, precautions must be taken to avoid overheating. Unfortunately, heat prostration and heat stroke may occur in occasional patients who do not take precautions during extreme weather.

For patients with sicca syndrome, the use of preservative-free artificial tears at least every 4 hours during the day and preservative-free ointment at night is important. Careful ophthalmologic follow-up is needed to prevent long-term damage to the eyes. Artificial saliva may be used for dry mouth. Topical analgesic products may be used, with caution, in patients with painful oral GVHD. Patients with dry mouth are at increased risk for dental caries, so close dental follow-up is essential.

Muscular aches and cramps are common symptoms, but the cause of these cramps is unclear. Electrolyte imbalances should be corrected. If the cramps persist, quinine may be added. If the cramps are disabling, dantrolene may be tried, but it must be used cautiously and monitored carefully because of the side effects—muscle weakness, drowsiness, diarrhea, abnormal liver function findings, and sun sensitivity. It should not be used in patients treated with PUVA.

Wasting is common in these patients, and malnutrition may result. The cause of the wasting is probably multifactorial and includes increased caloric requirement, oral disease, dry mouth, altered taste, and side effects of drugs. Additionally, infections in the mouth or the esophagus may contribute to poor oral intake. Nutritional assessment and monitoring is important to maintain the patient’s well being. Patients who are unable to maintain adequate caloric intake by mouth may need parenteral nutrition or enteral feeds through surgically placed tubes. Chronic GVHD may have a significant impact on the growth and development of children.34

Physical and occupational therapy

A thorough physical therapy evaluation and an individually designed program of activities can be invaluable for maintaining and increasing strength, range of motion, and mobility. For patients with sclerodematous chronic GVHD, range-of-motion exercises may preserve joint mobility and decrease the pain associated with joint contractures. Although detailed literature on its efficacy is lacking, it is our practice to have all patients evaluated by a physical therapist familiar with the disease. Patients receive a personal prescription for activities and exercises with the initial evaluation, and their progress is monitored approximately every 3 months. Occupational therapy may be instrumental for maximizing functional capabilities in activities of daily living, employment opportunities, and sexual satisfaction. Support groups or individual therapy may benefit patients as they learn to cope with this chronic illness.
Prognosis

Wingard et al\textsuperscript{22} evaluate the factors that predict poor outcome from chronic GVHD. In 85 patients with chronic GVHD, baseline characteristics before therapy were examined to determine whether there were risk factors for death. In a multivariate proportional hazards analysis, 3 baseline factors emerged as independent predictors of death: progressive presentation of chronic GVHD, lichenoid changes on skin histology, and elevated serum bilirubin level. In an expanded analysis of 151 patients diagnosed with chronic GVHD at Johns Hopkins, 21 demographic and clinical variables were examined at diagnosis and progression for factors influencing survival. Multivariate analysis shows that diffuse (less than 50\%) skin involvement, platelet count less than 100 000/\mu L, and progressive onset were predictors of poor survival at diagnosis. At progression, diffuse skin involvement, progressive onset, poor performance status, and hyperbilirubinemia level predicted poor outcome.\textsuperscript{22}

In a similar analysis of 143 patients treated with alternate-day CsA and prednisone, Sullivan et al\textsuperscript{20} identified progressive onset, advanced stage of malignancy, and thrombocytopenia as independent risk factors for death. Patients with extensive rather than limited disease have higher rates of death.

Mortality in chronic GVHD is largely attributable to infection. Death may also result from pulmonary failure caused by bronchiolitis obliterans but is rarely caused by other organ dysfunction. Death from the autoimmune manifestations of the disease is uncommon.

Future directions

With the increasing number of allogeneic SCTs being performed, particularly those involving donors other than HLA-identical sibling donors, chronic GVHD will continue to be a large challenge. Additional research is needed to better understand the pathogenesis of this entity so that new therapeutic approaches may be developed. Several new therapies are under evaluation, including pentostatin, daclizumab, and infliximab. New strategies, potentially using sequential therapies to turn off immunologic and cytokine damage, must be developed. Transplant centers and referring physicians must partner to provide the complex care these patients require.

References

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