Graft-vs-Host Disease Following Allogeneic Hematopoietic Cell Transplantation

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**Background:** Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy with proven efficacy in the management of hematologic malignancies. However, it is complicated by the syndromes of acute and chronic graft-vs-host disease (GVHD).

**Methods:** A narrative review is provided to summarize major biologic insights into the pathogenesis of these immune-mediated disorders, as well as advances in diagnosis, classification, prevention, management, and allied supportive care with the aim of providing essential understanding for clinicians with or without subspecialty experience in the field of blood and marrow transplantation.

**Results:** Major scientific advances have contributed to enhanced understanding of the pathogenesis of these disorders, and clinical investigation has provided more effective preventive and therapeutic strategies for GVHD. However, since acute GVHD and chronic GVHD remain leading sources of transplantation-related morbidity and mortality, ongoing investigation is needed to develop new approaches to addressing these syndromes.

**Conclusions:** The major challenge for future investigation will be to capitalize on biologic insights in order to develop novel strategies for the prevention and therapy of acute and chronic GVHD that will address the current shortcomings in existing therapeutic approaches.

**Introduction**

Allogeneic hematopoietic cell transplantation (HCT) is an intense and potentially curative therapy for patients with hematologic malignancies. Outside of primary disease relapse following HCT, arguably the most significant obstacle to success following this therapy is the onset of acute and later chronic graft-vs-host disease (GVHD). These syndromes pose a significant threat of morbidity, escalated and prolonged immunosuppressive therapy (with the attendant risk of infectious complications), organ dysfunction, impaired quality of life, and ultimately an increased risk for mortality. Major progress has been made through investigations conducted to date; however, deficiencies persist in the clinical and biologic prediction and classification of these syndromes as well as their associated prevention and therapy. Novel biologic insights and the conduct of allied clinical investigation hold promise for further advances to address these challenges.

This review critically examines the current understanding and ongoing challenges in the management of these syndromes. The greater proportion of patients surviving transplantation secondary to major advances in the field, the ultimate return of HCT recipients to their
primary hematologist/oncologist, and the recognized limited number of specialized transplantation centers and providers all speak to the relevance of these conditions to providers outside the immediate specialty of blood and marrow transplantation. The major objective of this review, therefore, is to provide clinicians with an essential understanding of the major scientific and clinical advances in the pathobiology, diagnosis, classification, prevention, and management of acute and chronic GVHD.

**Acute GVHD Biology**

Acute GVHD is a clinicopathologic syndrome that remains a clinical challenge and a major source of morbidity and mortality following allogeneic HCT. Early experiments provided key insights into the requirements for the development of the syndrome, as represented by Billingham’s postulates: The graft contains immunocompetent cells, the immunocompromised recipient is not capable of rejecting the transplanted cells, and finally the recipient expresses tissue antigens not present in the donor. Indeed, one of the major determinants for the development and severity of acute GVHD in human transplantation is disparity in major and minor histocompatibility antigens, with an increasing number of mismatched antigens predicting greater risk of acute GVHD and nonrelapse mortality. As well, more recent insights demonstrated that polymorphism in non-HLA genes, including cytokines such as tumor necrosis factor (TNF), interleukin 10 (IL-10), interferon gamma (IFN-γ), KIR polymorphism, and NOD2/CARD15 gene polymorphism, may also contribute to the development and severity of acute GVHD. Together, these factors provide a genetic basis for donor and recipient disparity that informs the risk for GVHD. Further advances have led to the development of an established conceptual model composed of phases that include tissue damage from conditioning therapy and activation of antigen-presenting cells, activation of donor T cells resulting in differentiation and migration, and finally an effector phase in which host tissue damage is mediated by inflammatory cytokines such as TNF-α and IL-1, and effector cells, most notably cytotoxic T cells. This model simplifies what is believed to be a complex and redundant network rather than a sequential series of distinct events. While insights into the biology of the syndrome have provided the rationale for therapeutic strategies for prevention and therapy, efforts targeting a single aspect of this cascade have not proven successful to date. Recent comprehensive reviews of acute GVHD biology are provided by Sun et al. and Paczesny et al.

**Clinical Manifestations**

The clinical syndrome of acute GVHD manifests with erythematous skin eruption, cholestatic liver disease, and upper or lower gastrointestinal (GI) involvement either together or in isolation. The occurrence of acute GVHD has been historically limited to within 100 days following HCT. Diagnostic biopsy is relevant to exclude competing diagnoses such as cytomegalovirus enteritis or drug eruption from medications. Histologic changes in the skin most commonly include lymphocytic infiltration and dyskeratotic epidermal keratinocytes and cell apoptosis. Pathologic changes in the liver include bile duct damage with epithelial cell dropout and lymphocytic infiltration, while changes in the GI tract include crypt cell necrosis. The most consistent clinical predictors of the syndrome are donor relation (with a greater incidence of acute GVHD following unrelated donor HCT) and HLA disparity (with greater incidence and severity in mismatched HCT) between donor and recipient. Paczesny et al demonstrated that a proteomic biomarker panel including IL-2 receptor-alpha, tumor necrosis factor receptor-1, IL-8, and hepatocyte growth factor may be able to confirm acute GVHD and have prognostic ability independent of GVHD severity.

**Classification and Grading Criteria**

Clinical severity grading of the syndrome takes into account the clinical severity of individual organs, which inform a composite overall score. Compared to the original severity scoring per Glucksberg et al, this revised 1994 consensus scoring system by Przepiorka et al notably includes upper GI manifestations in the determination of GI severity as well as lower GI manifestations. Advancing acute GVHD severity is associated with increased mortality. An analysis of 4,174 recipients of matched sibling HCT for chronic myelogenous leukemia demonstrated that transplantation-related mortality significantly worsened for increasing severity of acute GVHD. With a reference of no acute GVHD, increasing grade of acute GVHD was associated with increased risk for mortality: grade I, hazard ratio (HR) = 1.52 (1.19–1.96); grade II, HR = 2.48 (1.95–3.14); grade III, HR = 5.76 (4.44–7.48); grade IV, HR = 14.7 (10.9–19.9). Advanced-grade acute GVHD, particularly disease refractory to first-line therapy, remains a major threat to survival following HCT. As well, response to initial therapy is predictive of long-term outcome. In an analysis of 740 recipients of bone marrow allografts with grade II-IV acute GVHD, those with complete response to primary therapy had nonrelapse mortality comparable to those without acute GVHD, whereas nonrelapse mortality significantly worsened for those with only partial response, no response, or progressive manifestations on therapy. Recently, Levine et al published an analysis from a randomized phase II trial of acute GVHD primary therapy. This trial studied the efficacy of 2 mg/kg methylprednisolone intravenously or prednisone 2.5 mg/kg per day orally in combination with each arm containing one of four additional immune suppressive agents —
mycophenolate mofetil, etanercept, denileukin difitox, or pentostatin. The authors examined response to primary acute GVHD therapy as a predictor of nonrelapse mortality and overall survival. Compared to complete response to primary therapy, nonresponse at 28 days was associated with a relative risk (RR) for nonrelapse mortality of 2.52 (1.44–3.73; P < .001), and RR for overall survival of 2.79 (1.71–4.55; P < .001) on multivariate analysis. These data highlight the importance of response to primary therapy for transplantation outcome.

**Acute GVHD Prevention**

Clinical investigation has led to successive improvements in the prevention of the syndrome. Early efforts established the superiority of combination (cyclosporine and methotrexate) therapy over single-agent methotrexate. The current standard of care in acute GVHD prevention is the combination of a calcineurin inhibitor (cyclosporine or tacrolimus) and methotrexate. Two large randomized phase III trials demonstrated that tacrolimus and methotrexate were superior to cyclosporine and methotrexate in the prevention of acute GVHD. Grade II-IV acute GVHD was significantly lower with tacrolimus/methotrexate compared to cyclosporine/methotrexate in both sibling donor (32% vs 44%; P = .01) and unrelated donor (56% vs 74%; P = .0002) transplant trials. Survival did not differ between these acute GVHD prophylaxis strategies. However, further progress is needed.

Protection from acute GVHD is incomplete since many will develop the syndrome despite these prophylactic agents. As well, toxicity associated with methotrexate in particular has led investigators to examine the activity of alternative agents such as tacrolimus combined with either mycophenolate mofetil or sirolimus. In particular, the combination of tacrolimus and sirolimus has demonstrated remarkable activity in the prevention of acute GVHD in phase II trials, and investigators are comparing this combination to tacrolimus and methotrexate in a current national phase III randomized trial including matched sibling transplants with myeloablative total body irradiation-based conditioning regimens through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Other approaches have utilized donor T-cell depletion to effectively prevent GVHD; however, this approach is associated with impaired immune reconstitution, infectious complications, and increased risk of primary disease relapse after HCT. Currently, this practice has marked interinstitutional variation outside of the clinical trials setting.

Prevention of acute GVHD in unrelated donor HCT, and particularly mismatched unrelated donor HCT, is a particularly daunting task. Based on the principle that alloreactive donor T cells are the primary mediator of the syndrome, investigators have studied antilymphocyte antibodies in the prevention of acute GVHD in unrelated donor HCT. These studies have largely consisted of matched unrelated donors, while earlier studies were completely composed of bone marrow rather than peripheral blood mobilized stem cells and principally utilized cyclosporine and methotrexate as pharmacologic acute GVHD prophylaxis. These conditions in part limit the relevance of the findings in light of current transplantation practices, particularly regarding the application to mismatched unrelated donor transplantation. As well, there is diversity in preparation of antilymphocyte antibodies, including the antithymocyte globulin (ATG) produced in rabbits, ATG Fresenius prepared in rabbits, and finally ATGAM derived from horses. Major therapeutic approaches in prevention have consisted of the following: ATG totaling 4.5 mg/kg over 3 days concluding on day 0, ATG totaling 7.5 mg/kg from day –4 to –3 or totaling 15 mg/kg from days –5 to –2, and ATG Fresenius total dose ranging from 30 mg/kg to 90 mg/kg, ending on day –1. Comparative data suggest that variation in the total dose and schedule of ATG and ATG Fresenius affect outcome.

Studies have demonstrated a consistent reduction in severe acute GVHD, and long-term follow-up has demonstrated significantly lower chronic GVHD, lung dysfunction, and late nonrelapse mortality in those treated with ATG. In a major randomized trial among recipients of unrelated donor HCT, ATG Fresenius significantly reduced the incidence of chronic GVHD but did not result in a difference in survival compared to control. However, there is an important association between ATG use and delayed immune reconstitution and infectious complications including cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Alongside the beneficial reduction in GVHD, the use of ATG confers an increased risk of EBV-associated posttransplant lymphoproliferative disease (PTLD). In a large analysis of risk factors for the development of PTLD following HCT, the following were determined to be important: patient age ≥ 50 years at transplantation, T-cell depletion of the graft, ATG use, and unrelated or HLA-mismatched grafts. Posttransplantation monitoring of EBV viral load and preemptive rituximab therapy is effective in controlling EBV and preventing PTLD. The role of prophylactic administration of rituximab for the prevention of EBV reactivation following ATG delivery in unrelated donor HCT has preliminary evidence that supports its feasibility. Other strategies for prevention of acute GVHD after HLA-mismatched unrelated donor HCT, including the use of novel agents such as bortezomib, may provide benefit as well. A greater degree of HLA disparity appears to be tolerated in the setting of umbilical cord blood transplantation, as supported by retrospective comparative analyses examining the risk of acute GVHD according to stem cell source. The predominant approach to pharmacologic acute GVHD prophylaxis in umbilical cord blood transplantation has been the combination of cyclosporine and mycophenolate mofetil.
**Therapeutic Strategies**

Upon failure of these preventive efforts, standard primary therapy employs 1 mg/kg to 2 mg/kg of prednisone or dose-equivalent corticosteroid. Systemic glucocorticoid therapy remains standard since combination therapy including glucocorticoids and additional immune suppressive agents (eg, the combination of corticosteroids and daclizumab) has not proven beneficial in prior investigation. As this accepted standard therapy provides complete remission of the syndrome in only 30% to 50% of cases, interest has persisted in developing more effective strategies. A recent phase II trial conducted by the BMT CTN has identified the combination of corticosteroids and mycophenolate mofetil as a promising strategy. This combination is now being compared in a phase III study against standard corticosteroid therapy alone in the primary therapy of acute GVHD. While the use of non-glucocorticoid systemic immune suppressive agents for the primary therapy of acute GVHD may be an alternative approach with comparable efficacy and less morbidity related to glucocorticoids, this requires further exploration in a prospective trial.

Acute GVHD that fails to respond to primary therapy is consistently associated with an adverse prognosis. Failure of primary corticosteroid therapy has been defined as acute GVHD progression within 3 days, failure to respond within 5 to 7 days, or incomplete response to 1 mg/kg to 2 mg/kg of prednisone therapy by 14 days. In this setting, multiple agents have been examined. However, most available therapeutic agents provide resolution in the minority of cases of refractory acute GVHD, and they impose additional toxicity. These agents broadly include antilymphocyte antibody approaches such as ATG and agents targeted to CD147, CD3, CD5, CD52 or CD25, immunotoxin-based agents including denileukin difitox (Ontak), agents targeting tumor necrosis factor alpha such as infliximab, pharmacologic agents including mycophenolate mofetil, pentostatin, and sirolimus, and extracorporeal photopheresis. Published data on the efficacy of these agents for the therapy of corticosteroid-refractory acute GVHD are more comprehensively reviewed elsewhere. In the near absence of comparative trials for this condition, there is no clear evidence-based rationale to select one over others. Additionally, the true benefit from any one agent in isolation is difficult to dissect; as in retrospective series as well as early-phase prospective trials, multiple agents are often used in succession to achieve control of this difficult syndrome. Ultimately, however, response remains incomplete to available therapeutic strategies, complications occur frequently, and survival is elusive for most.

Accordingly, these outcomes underscore the need for novel acute GVHD prophylaxis and primary therapy strategies that may more effectively prevent the occurrence of refractory acute GVHD altogether. High-quality clinical trials that test novel prevention and therapy approaches based on rational understanding of acute GVHD pathogenesis will further advance the field. The results of major national trials are awaited, including BMT CTN 0402, a randomized trial of tacrolimus/methotrexate vs tacrolimus/sirolimus for the prevention of acute GVHD, as well as BMT CTN 0802 in acute GVHD primary therapy, which is comparing standard dose glucocorticoids vs glucocorticoids with mycophenolate mofetil.

The reader is directed to Przepiórka et al for a comprehensive description of consensus acute GVHD grading.

**Chronic GVHD Biology**

Chronic GVHD has benefited from a resurgence of interest and investigation that has offered new insights into the biology of the syndrome, clinical classification, and novel therapeutic strategies. Insights into the pathobiology of the syndrome are ongoing. Allied clinical observations suggest the role of alloreactive donor T cells. Peripheral blood mobilized stem cell products, which contain a greater dose of donor T cells compared to bone marrow-harvested stem cells, impose a greater risk for the occurrence and severity of chronic GVHD and an associated prolonged duration of immune suppression. Ex vivo T-cell depletion strategies, as well as in vivo strategies such as ATG or alemtuzumab, are associated with a decreased risk of chronic GVHD. However, new insights implicate other mechanisms. As recently reviewed by Martin, preclinical murine models and correlative human studies have advanced several hypotheses as mechanisms of chronic GVHD pathogenesis. First, thymic damage, in part mediated by prior acute GVHD, may impair the process of negative selection by thymic medullary epithelial cells that eliminate pathogenic T cells responsible for autoimmunity. Second, the potential role of transforming growth factor-beta (TGF-β) has been supported by amelioration of chronic GVHD manifestations after neutralization of this cytokine in murine models, and the clinical observation of an inverse relationship between TGF-β signaling in CD4 and CD8 cells and the risk of chronic GVHD. Third, B cells may play a role in chronic GVHD pathogenesis, as supported by the following: (1) Preclinical evidence suggests a role for pathogenic B cells in the development of a chronic GVHD-like syndrome consisting of cutaneous sclerosis and glomerulonephritis. (2) Anti-CD20 antibody therapy has demonstrated activity in the treatment of corticosteroid-refractory chronic GVHD. (3) Chronic GVHD-affected HCT recipients have elevated levels of B cell activating factor, which is important for survival and differentiation of activated B cell. (4) Agonistic antibodies directed against platelet-derived growth factor receptor (PDGFR) have been detected in serum of chronic GVHD-affected HCT recipients. (5) Ongoing investigation aims to discern the relationship between regulatory T cells (Treg) and chronic GVHD. Early clinical
Clinical Manifestations

Chronic GVHD occurs in up to 60% to 80% of those who survive beyond 100 days post-HCT. The impact of chronic GVHD on the overall health, functional ability, and quality of life of HCT survivors is of utmost importance. The syndrome is a leading source of late HCT-related morbidity and death as well as a predictor of prolonged immune suppressive therapy and impaired quality of life. The syndrome is characterized by diverse clinical manifestations, but the most commonly affected organs are the skin, eyes, mouth, and liver. Common skin manifestations include lichen planus-like changes and poikiloderma, as well as more advanced cutaneous and subcutaneous sclerosis. Oral findings include lichen planus-like changes, hyperkeratotic plaques, and decreased oral range of motion. Both the eyes and mouth can suffer from sicca symptoms, including dry mouth and dry or gritty eyes. Hepatic manifestation of chronic GVHD includes a cholestatic pattern of elevated alkaline phosphatase and bilirubin. In the GI tract, diagnostic chronic GVHD features include esophageal web, stricture, or concentric rings on endoscopic or radiographic study. Other manifestations such as anorexia, nausea/vomiting, and diarrhea are shared between acute and chronic GVHD. Bronchiolitis obliterans is a less common manifestation of chronic GVHD. Biopsy-proven bronchiolitis obliterans represents a diagnostic manifestation of chronic GVHD and is characterized by clinical symptoms (eg, cough, dyspnea) and respiratory physiologic abnormalities (FEV1/FVC ratio < 0.7, FEV1 < 75% predicted value, evidence of air trapping or bronchiectasis on CT scan, residual volume of > 120%, presence of another chronic GVHD manifestation, and absence of infectious etiology). However, most organs can be involved, with parallels to other systemic immune-mediated disorders such as systemic lupus erythematosus, Sjögren disease, and systemic sclerosis.

Classification and Grading Criteria

Major changes in the classification and severity grading of the syndrome have been suggested by the 2004 NIH Chronic GVHD Consensus Conference. Among the proposed changes is the elimination of the previously accepted division between acute and chronic GVHD according to the landmark of 100 days post-HCT. Rather, the guidelines propose a definition of chronic GVHD according to diagnostic manifestations of the syndrome rather than the time of onset post-HCT. Accordingly, manifestations of acute GVHD occurring before day 100 are defined as acute GVHD, while those acute GVHD manifestations occurring after day 100 are considered persistent, recurrent, or late acute GVHD based on the prior occurrence of acute GVHD in the patient. Classic chronic GVHD is defined based on the definitive manifestations of the syndrome in the absence of concurrent acute GVHD manifestations. Diagnosis of chronic GVHD requires the presence of at least one diagnostic clinical sign of chronic GVHD or the presence of at least one distinctive manifestation confirmed by biopsy or allied diagnostic test. The concurrent presentation of both confirmed chronic GVHD and acute GVHD manifestations operationally defines the overlap syndrome. A comprehensive report of the proposed chronic GVHD diagnosis and staging criteria is provided in Filipovich et al. In addition, consensus guidelines for chronic GVHD severity grading were proposed to replace the previously accepted scheme based on limited vs extensive involvement. In the prior scheme, limited involvement was defined according to localized skin involvement or hepatic dysfunction, and extensive chronic GVHD was defined by the presence of generalized skin involvement or the presence of aggressive chronic hepatitis, bridging necrosis or cirrhosis in liver biopsy, or involvement of other target organs such as the eye, mouth, or lung. Rather, chronic GVHD severity according to the NIH Chronic GVHD Consensus is scored according to objective criteria for each organ involved, which is summarized for an overall global severity score of mild, moderate, or severe. These criteria are described in Filipovich et al. As well, standardization of response criteria was proposed, which should facilitate communication of response in clinical practice and, importantly, quantification of response in therapeutic trials. Here, complete response is defined as complete resolution of all manifestations, while partial response indicates 50% or greater response in measurable disease activity, with no concurrent worsening in any other involved areas. Proposed response criteria for clinical trials in chronic GVHD therapy are explained in Pavletic et al.

Several additional publications from the consensus meeting seek to make progress in allied areas of chronic GVHD diagnosis and management, including pathology, biomarkers, conduct of clinical trials, and supportive care. A multicenter consortium of allied chronic GVHD investigators is currently conducting observational and interventional research in chronic GVHD. As part of this mission, data from a prospectively accrued chronic GVHD cohort will evaluate the association of the proposed NIH chronic GVHD severity grading with measures of disease activity, short-term therapeutic endpoints, and long-term outcomes including survival and nonrelapse mortality.

Predictive Variables

Clinical predictors for the development of chronic GVHD reported in published literature — importantly prior to these proposed changes in chronic GVHD diagnosis and severity grading — most consistently include increasing age of the donor or recipient, donor/recipi-
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HCT. Other important components of supportive care for chronic GVHD-affected HCT recipients include vaccination appropriate in the post-HCT course, maintenance of skin integrity and skin care, attention to oral cavity health and symptom control, management of ocular sicca symptoms, supportive care for vulvovaginal manifestations of GVHD, physical therapy for musculoskeletal impairment, prevention and management of osteopenia and osteoporosis that complicate prolonged corticosteroid therapy, management of fatigue, and psychosocial support. A comprehensive review of appropriate, evidence-based ancillary care is provided in Couriel et al.81

A major resurgence of investigation into chronic GVHD pathogenesis, diagnosis, classification, and therapy offers promise for improved patient outcomes. Validation of the proposed NIH Consensus diagnostic and severity classification criteria will be achieved through the collection of prospective observational data through the Chronic GVHD Consortium. Novel preventive and therapeutic strategies based on detailed understanding of chronic GVHD pathogenesis will advance the field. Standardization of best response criteria will help to advance the state of chronic GVHD clinical trials. Finally, attention to patient-reported outcomes, including symptom burden, functional limitations, and quality of life, is needed in both clinical practice and novel clinical investigation to fully capture the experience of patients with chronic GVHD.

The reader is directed to Filippovich et al81 for a comprehensive description of chronic GVHD diagnosis, classification, and severity grading.

References


