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# Graft-versus-Host Disease

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## Introduction

The number of allogeneic hematopoietic cell transplantations (HCT) continues to increase with more than 25,000 allogeneic transplantations performed annually. The graft-versus-leukemia / tumor (GVL) effect during allogeneic HCT effectively eradicates many hematological malignancies.1 The development of novel strategies that use donor leukocyte infusions, non-myeloablative conditioning and umbilical cord blood (UCB) transplantation have helped expand the indications for allogeneic HCT over the last several years, especially among older patients.2 Improvements in infectious prophylaxis, immunosuppressive medications, supportive care and DNA-based tissue typing have also contributed to improved outcomes after allogeneic HCT.1 Yet the major complication of allogeneic HCT, graft-versus-host disease (GVHD), remains lethal and limits the use of this important therapy.2 Given current trends, the number of transplants from unrelated donors is expected to double within the next five years, significantly increasing the population of patients with GVHD. In this seminar we review advances made in identifying the genetic risk factors and pathophysiology of this major HCT complication, as well as its prevention, diagnosis and treatment.

### Etiology and Clinical Features

Fifty years ago Billingham formulated three requirements for the development of GVHD: the graft must contain immunologically competent cells; the recipient must express tissue antigens that are not present in the transplant donor; and the recipient must be incapable of mounting an effective response to eliminate the transplanted cells.[3] We know now that the immunologically competent cells are T cells, and that GVHD can develop in various clinical settings when tissues containing T cells (blood products, bone marrow, and solid organs) are transferred from one person to another who is not able to eliminate those cells.[4, 5] Patients, whose immune systems are suppressed, and who receive white blood cells from another individual, are at particularly high risk for GVHD.

GVHD occurs when donor T cells respond to genetically defined proteins on host cells. The most important proteins are Human Leukocyte Antigens (HLA)[2, 6, 7], which are highly

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polymorphic and are encoded by the major histocompatibility complex (MHC). Class I HLA (A, B, and C) proteins are expressed on almost all nucleated cells of the body at varying densities. Class II proteins (DR, DQ, and DP) are primarily expressed on hematopoietic cells (B cells, dendritic cells, monocytes), but their expression can be induced on many other cell types following inflammation or injury. High-resolution DNA typing of HLA genes with polymerase chain reaction (PCR)-based techniques have now largely replaced earlier methods. The incidence of acute GVHD is directly related to the degree of mismatch between HLA proteins[8, 9] and thus ideally, donors and recipients are matched at HLA-A, -B, -C, and -DRB1, ("8/8 matches"), but mismatches may be tolerated for UCB grafts (see below).[10-12]

**Non-HLA Genetics—**Despite HLA identity between a patient and donor, approximately 40% of patients receiving HLA-identical grafts develop acute GVHD due to genetic differences that lie outside the HLA loci, or "minor" histocompatibility antigens (HA). Some minor HAs, such as HY and HA-3, are expressed on all tissues and are targets for both GVHD and GVL.[13] Other minor HAs, such as HA-1 and HA-2, are expressed most abundantly on hematopoietic cells (including leukemic cells) and may therefore induce a greater GVL effect with less GVHD.[13, 14]

Polymorphisms in both donors and recipients for cytokines that are involved in the classical `cytokine storm' of GVHD (discussed below) have been implicated as risk factors for GVHD.[15] Tumor Necrosis Factor (TNF)-α, Interleukin 10 (IL-10), Interferon-γ (IFNγ) variants have correlated with GVHD in some, but not all, studies.[16-18] Genetic polymorphisms of proteins involved in innate immunity, such as nucleotide oligomerization domain 2 and Keratin 18 receptors, have also been associated with GVHD.[19-22] Future strategies to identify the best possible transplant donor will probably incorporate both HLA and non-HLA genetic factors.

**Clinical Features of Acute GVHD:** Based on an early Seattle experience, acute GVHD was defined to occur prior to day 100, whereas chronic GVHD occurred after that time.[23-25] This definition is far from satisfactory, and a recent National Institutes of Health classification includes late-onset acute GVHD (after day 100) and an overlap syndrome with features of both acute and chronic GVHD.[26] Late-onset acute GVHD and the overlap syndrome occur with greater frequency after reduced-intensity conditioning (RIC), an increasingly widespread technique (see below). As shown in Table 1, the clinical manifestations of acute GVHD occur in the skin, gastrointestinal tract and liver.[27] In a comprehensive review, Martin et al found that at the onset of acute GVHD, 81% of patients had skin involvement, 54% had GI involvement, and 50% had liver involvement.[23] Recent data suggest that lungs might also be targets of experimental GVHD.[28]

Skin is most commonly affected and is usually the first organ involved, often coinciding with engraftment of donor cells. The characteristic maculopapular rash is pruritic and can spread throughout the body, sparing the scalp (Figure 1). In severe cases the skin may blister and ulcerate.[27] Apoptosis at the base of epidermal rete pegs is a characteristic pathologic finding. Other features include dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes, and a perivascular lymphocytic infiltration in the dermis.[29, 30]

Gastrointestinal tract involvement of acute GVHD usually presents as diarrhea but may also include vomiting, anorexia, and/or abdominal pain when severe.[29] The diarrhea of GVHD is secretory and often voluminous (greater than two liters per day). Bleeding, which carries a poor prognosis, occurs as a result of mucosal ulceration[31] but patchy involvement of the mucosa often leads to a normal appearance on endoscopy.[32]

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Radiologic findings of the gastrointestinal (GI) tract include luminal dilatation with thickening of the wall of the small bowel ("ribbon sign" on CT scan) and air/fluid levels suggestive of an ileus.[27] Histologic features include patchy ulcerations, apoptotic bodies in the base of crypts, crypt abscesses, and loss as well as flattening of the surface epithelium.33

Liver disease caused by GVHD may be difficult to distinguish from other causes of liver dysfunction following BMT such as veno-occlusive disease, drug toxicity, viral infection, sepsis, or iron overload. The histologic features of hepatic GVHD are endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis and bile duct destruction.[34,35] The liver is rarely biopsied because thrombocytopenia early after transplant greatly increases the risks of the procedure, usually making the diagnosis one of exclusion.

The incidence of the severity of acute GVHD is determined by the extent of involvement of these three principal target organs (see Table 1). The overall grades are classified as I (mild), II (moderate), III (severe) and IV (very severe). Severe GVHD carries a poor prognosis, with 25% long term survival for grade III and 5% for grade IV.[36]

The incidence of acute GVHD is directly related to the degree of mismatch between HLA proteins and ranges from 35-45% in recipients of full matched sibling donor grafts[8,9] to 60-80% in recipients of one-antigen HLA mismatched unrelated donor grafts.[6, 37-39] The same degree of mismatch causes less GVHD using UCB grafts and incidence of acute GVHD is lower following the transplant of partially matched UCB units and ranges from 35-65%.[12]

**Clinical Features of Chronic GVHD:** Chronic GVHD is the major cause of late non-relapse death following HCT.[40] Its presentation may be progressive (active or acute GVHD merging into chronic), quiescent (acute GVHD that resolves completely but is later followed by chronic GVHD) or it may occur de novo. Older recipient age and a history of acute GVHD are the greatest risk factors for chronic GVHD,[41] and strategies to prevent acute GVHD may therefore help to prevent chronic GVHD. As shown in Table 2, the manifestations of chronic GVHD are somewhat protean, and are often of an autoimmune nature. Clinical signs often first appear in the buccal mucosa (see Figure 2). New consensus criteria for the diagnosis and staging of chronic GVHD have recently been developed.[26]

**Pathophysiology of Acute GVHD:** Two important principles are important to consider regarding the pathophysiology of acute GVHD. First, acute GVHD reflects exaggerated but normal inflammatory mechanisms mediated by donor lymphocytes infused into the recipient where they function appropriately, given the foreign environment they encounter. Second, the recipient tissues that stimulate donor lymphocytes have usually been damaged by underlying disease, prior infections, and the transplant conditioning regimen.[29] As a result, these tissues produce molecules (sometimes referred to as "danger" signals) that promote the activation and proliferation of donor immune cells.[42-45] Mouse models havebeen central to our identification and understanding of the pathophysiologic mechanisms of GVHD, and canine models have been critical to the development of clinically useful strategies for GVHD prophylaxis and treatment and to the development of donor leukocyte infusions.[36, 46, 47] Based largely on these experimental models, the development of acute GVHD can be conceptualized in three sequential steps or phases: (1) activation of the APCs; (2) donor T cell activation, proliferation, differentiation and migration; and (3) target tissue destruction (Figure 3).

**Phase I: Activation of Antigen Presenting Cells (APCs):** The first step involves the activation of APCs by the underlying disease and the HCT conditioning regimen. Damaged host tissues respond by producing "danger" signals, including proinflammatory cytokines

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(e.g., TNF-α), chemokines, and increased expression of adhesion molecules, MHC antigens and costimulatory molecules on host APCs.[42, 48-50] A recent report demonstrated that at one week after HCT, increased levels of TNF-α receptor I, a surrogate marker for TNF-α, strongly correlated with the later development of GVHD.[51] Damage to the GI tract from the conditioning is particularly important because it allows for systemic translocation of additional inflammatory stimuli such as microbial products including lipopolysaccaride (LPS) or other pathogen-associated molecular patterns that further enhance the activation of host APCs.[49] The secondary lymphoid tissue in the GI tract is likely the initial site of interaction between activated APCs and donor T cells.[52] These observations have led an important clinical strategy to reduce acute GVHD by reducing the intensity of the conditioning regimen. Experimental GVHD can also be reduced by manipulating distinct subsets of APCs.[53,54] In addition, non-hematopoietic stem cells, such as mesenchymal stem cells or stromal cells, can reduce allogeneic T cell responses, although the mechanism for such inhibition remains unclear.[2]

The concept that enhanced activation of host APCs increases the risk for acute GVHD unifies a number of seemingly disparate clinical associations with that risk, such as advanced stages of malignancy, more intense transplant conditioning regimens and histories of viral infections. APCs detect infections by recognizing conserved molecular patterns that are unique to microbes, called pathogen-associated molecular patterns (PAMPs). Among the classes of receptors that recognize such patterns, the Toll-like receptors (TLR) are the best characterized.[55] For example, TLR4 recognizes LPS[55] and mice with mutant TLR4 receptors that do not respond to LPS cause less GVHD when used as donors.[56] Other TLRs that recognize viral DNA or RNA also activate APCs and may enhance GVHD, providing a potential mechanistic basis for increased GVHD associated with viral infections such as cytomegalovirus (CMV).[57]

**Phase II: Donor T Cell Activation:** The core of the GVH reaction is Step 2, where donor T cells proliferate and differentiate in response to host APCs. The "danger" signals generated in Phase I augment this activation at least in part by increasing the expression of costimulatory molecules.[58] Blockade of co-stimulatory pathways to prevent GVHD is successful in animal models, but this approach has not yet been tested in large clinical trials.[2]

In mouse models, where genetic differences between donor and recipient strains can be tightly controlled, $CD4^+$ cells induce acute GVHD to MHC class II differences, and $CD8^+$ cells induce acute GVHD to MHC class I differences.[59-61] In the majority of HLA-identical HCTs, both $CD4^+$ and $CD8^+$ subsets respond to minor histocompatibility antigens and can cause GVHD in HLA-identical HCT.

Regulatory T cells can suppress the proliferation of conventional T cells and prevent GVHD in animal models when added to donor grafts containing conventional T cells.[62] In mice, the Foxp3 protein functions as a master switch in the development of regulatory T cells, which normally constitute 5% of the CD4+ T cell population.[62] Regulatory T cells secrete anti-inflammatory cytokines IL-10 and Transforming Growth Factor(TGF)-β and can also act through contact-dependent inhibition of APCs.[62] It is likely that the use of regulatory T cells in clinical acute GVHD will require improved techniques to identify and expand them.

Natural Killer T cell (NKT) $1.1^+$ subsets of both the host and donors that have been shown to modulate acute GVHD.[63] Host NKT cells have been shown to suppress acute GVHD in an IL-4 dependent manner.[64] A recent clinical trial of total lymphoid irradiation used as conditioning significantly reduced GVHD and enhanced host NKT cell function.[65] By

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contrast, donor NKT cells can reduce GVHD and enhance perforin mediated GVL in an experimental model.[66]

Activation of immune cells results in rapid intracellular biochemical cascades that induce transcription of genes for many proteins including cytokines and their receptors. Th1 cytokines (IFN-γ, IL-2 and TNF-α) are produced in large amounts during acute GVHD. IL-2 production by donor T cells remains the principal target of many current clinical therapeutic and prophylactic approaches to GVHD, such as cyclosporine, tacrolimus and monoclonal antibodies (mAbs) directed against IL-2 and its receptor.[9] But emerging data indicate an important role for IL-2 in the generation and maintenance of $CD4^+$ $CD25^+$ T regs, suggesting that prolonged interference with IL-2 may have an unintended consequence of preventing the development of long term tolerance after allogeneic HCT.[67] IFN-γ has multiple functions and can either amplify or reduce GVHD.[68,69] IFN-γ may amplify GVHD by increasing the expression of molecules such as chemokines receptors, MHC proteins, and adhesion molecules; it also increases the sensitivity of monocytes and macrophages to stimuli such as LPS and accelerates intracellular cascades in response to these stimuli.[70] Early polarization of donor T cells so that they secrete less IFN-γ and more IL-4 can also attenuate experimental acute GVHD.[71] IFN-γ may amplify GVHD by directly damaging epithelium in the GI tract and skin and inducing immnosuppression through the induction of nitric oxide.[72] By contrast, IFN-γ may suppress GVHD by hastening the apoptosis of activated donor T cells.[69, 73]. This complexity means the manipulation of IFN-γ may have diverse effects *in vivo*, making it a challenging target with respect to therapeutic intervention. IL-10 plays a key role in suppression of immune responses, and clinical data suggest it may regulate acute GVHD.[17] TGF-β, another suppressive cytokine can suppress acute GVHD but exacerbate chronic GVHD.[74] Thus the timing and duration of the secretion of any given cytokine may determine the specific effects of that cytokine on GVHD severity.

**Phase III: Cellular and Inflammatory Effector Phase:** The effector phase of this process is a complex cascade of both cellular mediators such as cytotoxic T lymphocytes(CTLs) and NK cells and soluble inflammatory mediators such as TNF-α, IFN-γ, IL-1 and nitric oxide.[2, 29] These soluble and cellular mediators synergize to amplify local tissue injury and further promote inflammation and target tissue destruction.

**Cellular Effectors—**The cellular effectors of acute GVHD are primarily CTLs and NK cells.49 CTLs that preferentially use the Fas/FasL pathway of target lysis and appear to predominate in GVHD liver damage (hepatocytes express large amounts of Fas) whereas GVHD CTLs that use the perforin /granzyme pathways are more important in the GI tract and skin.2, 75 Chemokines direct the migration of donor T cells from lymphoid tissues to the target organs where they cause damage. Macrophage inflammatory protein-1alpha (MIP-1α) and other chemokines such as CCL2-5, CXCL2, CXCL9-11, CCL17 and CCL27 are over-expressed and enhance the homing of cellular effectors to target organs during experimental GVHD.76 Expression of integrins, such as α4β7 and its ligand MadCAM-1, are also important for homing of donor T cells to Peyer's patches during intestinal GVHD. 52, 77, 78

**Inflammatory Effectors—**Microbial products such as LPS that leak through a damaged intestinal mucosa or skin may stimulate secretion of inflammatory cytokines through Toll-like receptors (TLRs).[49, 79] The GI tract is particularly susceptible to damage from TNF-α, and plays a major role in the amplification and propagation of the “cytokine storm” characteristic of acute GVHD.49 TNF-α can be produced by both donor and host cells, and it acts in three different ways: first, it activates APCs and enhances alloantigen presentation;

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second, it recruits effector cells to target organs via the induction of inflammatory chemokines; and third, it directly causes tissue necrosis, as its name suggests.[80-82]

**Prevention of GVHD:** Based on the evidence from animal models regarding the central role of T cells in initiating GVHD, numerous clinical studies evaluating T cell depletion (TCD) as prophylaxis for GVHD were performed in the 1980's and 1990's. There were three principal TCD strategies: (1) negative selection of T cells *ex vivo*, (2) positive selection of $CD34^+$ stem cells *ex vivo*; and (3) anti-T cell antibodies *in vivo*.[83] Most strategies showed a significant limitation in both acute and chronic GVHD.[84-88] Unfortunately, the lower incidence of severe GVHD was offset by high rates of graft failure, relapse of malignancy, infections, and Epstein-Barr virus-associated lymphoproliferative disorders. Negative selection purging strategies using various anti-T cell antibodies achieved similar long-term results regardless of the breadth of antibody specificity.[89-93] One large registry study demonstrated that purging strategies using antibodies with broad specificities produced inferior leukemia-free survival than standard immunosuppression in patients receiving unrelated donor transplants.[94] Several studies have investigated partial T cell depletion, either by eliminating specific T cell subsets (e.g., $CD8^+$) or by titrating the dose of T cells present in the inoculum.[95-97] None of these approaches, however, has convincingly demonstrated an optimal strategy that improves long-term survival.

Alemtuzumab is a monoclonal antibody that binds CD52, a protein expressed on a broad spectrum of leukocytes including lymphocytes, monocytes, and dendritic cells. Its use in GVHD prophylaxis in a Phase II trial decreased the incidence of acute and chronic GVHD following reduced intensity transplant.[98] In two prospective studies, patients who received alemtuzumab rather than methotrexate showed significantly lower rates of acute and chronic GVHD,[99] but experienced more infectious complications and higher rates of relapse, so that there was no overall survival benefit. Alemtuzumab may also contribute to graft failure when used with minimal intensity conditioning regimens.[100]

An alternative strategy to TCD attempted to induce anergy in donor T cells by *ex vivo* antibody blockade of co-stimulatory pathways prior to transplantation. A small study using this approach in haploidentical HCT recipients was quite encouraging, but has not yet been replicated.[101] Thus the focus of most prevention strategies remains pharmacological manipulation of T cells after transplant.

Administration of anti-T cell antibodies *in vivo* as GVHD prophylaxis has also been extensively tested. The best studied drugs are anti-thymocyte globulin (ATG) or antilymphocyte globulin (ALG) preparations. These sera, which have high titers of polyclonal antibodies, are made by immunizing animals (horses or rabbits) to thymocytes or lymphocytes, respectively. A complicating factor in determining the role of these polyclonal sera in transplantation is the observation that even different brands of the same class of sera exert different biologic effects.[102] However, the side effects of ATG/ALG infusions are common across different preparations and include fever, chills, headache, thrombocytopenia (from cross-reactivity to platelets), and, infrequently, anaphylaxis. In retrospective studies, rabbit ATG reduced the incidence of GVHD in related donor HSCT recipients without appearing to improve survival.103, 104 In recipients of unrelated donor HSCT, addition of ALG to standard GVHD prophylaxis effectively prevented severe GVHD, but did not result in improved survival because of increased infections.105 In a long term follow-up study, however, pretransplant ATG provided significant protection against extensive chronic GVHD and chronic lung dysfunction.106

The primary pharmacologic strategy to prevent GVHD is the inhibition of the cytoplasmic enzyme, calcineurin, that is critical for in the activation of T cells. The calcineurin

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inhibitors, cyclosporine and tacrolimus, have similar mechanisms of action, clinical effectiveness and toxicity profiles, including hypomagnesemia, hyperkalemia, hypertension, and nephrotoxicity.[9, 107] Serious side effects include transplant-associated thrombotic microangiopathy (TAM) and neurotoxicity that can lead to premature discontinuation. Although clinically similar to thrombotic thrombocytopenic purpura, TAM does not reliably respond to therapeutic plasmapheresis, carries a high mortality rate, and removal of the offending agent does not always result in improvement.[108] Posterior reversible encephalopathy syndrome includes mental status changes, seizures, neurological deficits and characteristic magnetic resonance imaging findings; this syndrome has been seen in 1-2% of HCT recipients receiving and calcineurin inhibitors.109 Side effects of these drugs decrease as the dose is tapered, usually two to four months after HCT.

Calcineurin inhibitors are often administered in combination with other immunosuppressants, such as methotrexate, which is given at low doses in the early post-transplant period.[9, 107] The toxicities of methotrexate (neutropenia and mucositis) have led some investigators to replace it with mycophenolate mofetil (MMF). In one prospective randomized trial, patients who received MMF as part of GVHD prophylaxis experienced significantly less severe mucositis and more rapid neutrophil engraftment than those who received methotrexate.[110] The incidence and severity of acute GVHD was similar between the two groups, but the study closed early due to superiority of the MMF arm with respect to reduced mucositis and the speed of hematopoietic engraftment. A desire for faster neutrophil engraftment has led to the use of MMF in UCB blood transplants where graft failure is a major concern.111 MMF is also often used after RIC regimens for similar reasons.[112, 113]

Sirolimus is an immunosuppressant that is structurally similar to tacrolimus but does not inhibit calcineurin. In a small Phase II trial, it showed excellent efficacy in combination with tacrolimus;[114] the drug damages endothelial cells, however, and it may enhance TAM that is associated with calcineurin inhibitors.[115] The combination of tacrolimus and sirolimus is currently being compared in a large randomized multi-center trial.

RIC regimens attempt to suppress the host immune system sufficiently so that donor T cells can engraft and then ablate the lympho-hematopoietic compartment of the recipient. The term “non-myeloablative” is therefore somewhat misleading. RIC regimens produce less tissue damage and lower levels of the inflammatory cytokines that are important in the initiation of GVHD pathophysiology; this effect may explain the reduced incidence of severe GVHD following RIC compared to the full intensity conditioning used in historical controls.[98, 116] The onset of acute GVHD may be delayed after RIC until after day 100, however, and it may present simultaneously with elements of chronic GVHD (“overlap syndrome”).[116-120]

**Treatment of Acute GVHD:** GVHD generally first develops in the second month after HCT, during continued treatment with calcineurin-based prophylaxis.[23, 121] Steroids, with their potent antilymphocyte and anti-inflammatory activity, are the gold standard for treatment of GVHD. Many centers treat mild GVHD of the skin (Grade I) with topical steroids alone, but for more severe skin GVHD and any degree of visceral GVHD involvement, high-dose systemic steroids are usually initiated. Steroid therapy results in complete remission in less than half of the patients,[122] and more severe GVHD is less likely to respond to treatment.[123, 124] In a prospective randomized study, the addition of ATG to steroids as primary therapy did not increase the response rate.124 In a retrospective study, the use of ATG in patients who showed early signs of steroid-resistance was beneficial,[122] but not all studies show such benefit and ATG is not standardly used because of increased infection risks.[106, 125, 126].

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An increasingly common treatment for GVHD is extracorporeal photopheresis (ECP). During ECP, the patient's white blood cells are collected by apheresis, incubated with the DNA-intercalating agent, 8-methoxypsoralen, exposed to ultraviolet light (UVA), and returned to the patient. ECP is known to induce cellular apoptosis, which has strong anti-inflammatory effects in a number of systems, including prevention of rejection of solid organ grafts.[127] Animal studies show that ECP reverses acute GVHD by increasing the number of regulatory T cells.128 A Phase II clinical study of steroid-dependent or steroid refractory GVHD showed resolution of GVHD in a large majority of patients, with 50% long-term survival in this very high risk group.129 Randomized multi-center studies of this approach are needed to determine its place in the management of acute GVHD.

Another interesting strategy to treat GVHD is the blockade of the inflammatory cytokine TNF-α. TNF-α can activate APCs, recruit effector cells and cause direct tissue damage.[130] In animal models, TNF-α plays a central role in GVHD of the GI tract, which is central to the “cytokine storm” and plasma levels of TNFR I (a surrogate marker for TNF-α) rise in patients before the clinical manifestations of GVHD appear. [51] A recent Phase II trial of etanercept, a solubilized TNFR II, showed significant efficacy when added to systemic steroids as primary therapy for acute GVHD. Seventy percent of patients had complete resolution of all GVHD symptoms within one month, with 80% complete responses in the GI tract and the skin. The authors also showed that plasma levels of TNFR I were a significant biomarker for clinical GVHD.131

**Treatment of Chronic GVHD:** In contrast to acute GVHD, the pathophysiology of chronic GVHD remains poorly understood, and it is treated with a variety of immunosuppressive agents. The response of chronic GVHD to treatment is unpredictable, and mixed responses in different organs can occur in the same patient. Confounding variables such as infection and co-morbidities also make responses hard to measure. The use of corticosteroids (with or without a calcineurin inhibitor) is the standard of care, but a randomized trial of more than 300 patients with chronic GVHD found no difference between cyclosporine plus prednisone versus prednisone alone.[132] Chronic immunosuppressants, especially those containing steroids, are highly toxic and result in infectious deaths. Many second line therapies have been studied, but none has achieved widespread acceptance. As mentioned above, ECP shows some promise, with significant response rates in high-risk patients. The best responses were observed in skin, liver, oral mucosa, eye, and lung.133 This observation is particularly relevant because lung GVHD has the potential to be a particularly devastating complication necessitating lung transplant as the only therapeutic option.134, 135

**Essential Supportive Care in GVHD Patients:** Meticulous supportive care is critical for patients with both acute and chronic GVHD because of the extended duration of immunosuppressive treatments and because the multiple medications required may have synergistic toxicities. Such care includes extensive infectious prophylaxis, early interventions in cases of suspected infections, and prophylaxis against non-infectious side effects of medications (See Table 3). These complications often require rapid responses to prevent serious or irreversible damage, and are best handled in close collaboration between the primary physician and the transplant specialist.

All patients should receive at least fluconazole as prophylaxis against fungal infections. Invasive molds, especially aspergillus, are common in patients with prolonged steroid use. 136 Prophylaxis with voriconazole or posaconazole should be considered for these patients. Usual sites of infection are the lungs, sinuses, brain, skin,137 and serial galactomannan assays may aid in the early detection.[138] Candida can cause lesions in the lung and spleen, which may need screening with ultrasonography. Pneumocystis is another opportunistic infection that should receive cotrimoxazol (bactrim) prophylaxis.[139]

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Viral infections are frequent in these patients with GVHD. Cytomegalovirus causes interstitial pneumonia and gastritis. Patients who are at risk should have their blood monitored several times monthly. Techniques that directly detect virus should be performed, such as CMV PCR or pp65 antigen, and evidence of increased viral load should prompt preemptive treatment with ganciclovir or foscarnet prior to clinical manifestations of disease. Shingles is not uncommon and acyclovir prophylaxis may be beneficial.[140] Patients and caregivers should receive vaccinations against influenza, and treatment with neuraminidase inhibitors is recommended in the event of influenza infection.[141, 142]

Patients with GVHD often have $IgG_2$ and $IgG_4$ subclass deficiencies despite normal lgG levels, making them susceptible to infections with encapsulated organisms. Treatment of severe hypogammaglobulinemia with intravenous immunoglobulin is standard in many centers,[143] but the level that triggers replacement varies considerably among transplant specialists. There is little supporting evidence for the routine use of intravenous immunoglobulin as prophylaxis[144] but patients should receive routine prophylaxis (penicillin or its equivalent) due to the increased risk of streptococcal sepsis.[145] Pneumococcal conjugate and hemophilus influenza vaccine may provide additional protection and are also recommended for all patients, including those with chronic GVHD.[139, 146, 147] The sites of any indwelling catheters should be assessed regularly and early treatment of a suspected infection initiated. Early signs or symptoms of septic shock such as shaking chills or low blood pressure requires prompt evaluation with chest X-ray and/or CT scan, blood culture and broad spectrum antibiotics because shock may progress rapidly in these patients.

Chronic immunosuppressant therapy has multiple toxicities. Diabetes (which further increases the risks of infection), muscle weakness, osteoporosis, avascular necrosis (often requiring joint replacement) and other Cushingoid features are common with chronic steroid use. Frequent monitoring of blood glucose and screening bone density is recommended, and treatment includes insulin, calcium, Vitamin D and bisphosphonates.[148, 149] Calcineurin inhibitors frequently cause renal impairment, hypertension, and neurologic paraesthesias. Standard supportive care includes blood pressure monitoring, assessment of renal function, and monitoring of drug blood levels, which should be maintained within therapeutic parameters. To prevent renal dysfunction, most centers recommend vigorous oral outpatient hydration. Some patients will be unable to tolerate calcineurin inhibitors and will require different immunosuppressive medications altogether. Cytopenias sometimes require treatment with growth factors such as G-CSF or cessation of the offending agent. These maneuvers should always be performed in close consultation with a transplant specialist.

**Future Directions:** As allogeneic transplantation becomes an increasingly attractive therapeutic option, the need for novel approaches to GVHD has accelerated. The number of patients receiving transplants from unrelated donors is expected to double in the next five years, significantly increasing the population of patients with GVHD. The advent of RIC regimens has reduced transplant-related mortality and lengthened the period during which acute GVHD may develop (many new cases present up to day 200) and the need for close monitoring of patients in this period has increased. Patients have often returned to the care of their primary hematologists by this time, increasing the need for these physicians to collaborate with transplant specialists in the management of GVHD and its complications. Identification of biomarkers for GVHD with diagnostic (and possibly prognostic) significance may eventually make the treatment of GVHD preemptive rather than prophylactic. The use of cellular component therapy, such as regulatory T cells that have been expanded *ex vivo*. will also enter clinical trials in the near future, but the extensive infrastructure required for such cellular approaches will likely limit their use initially to

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large academic centers, intensifying the need for close communication between transplant specialists and referring hematologists.

**Search Strategy and Selection Criteria:** Pubmed and Medline databases were searched using the search term GVHD that was thencross-referenced with each of the following words: clinical, cytokines, MHC and HLA antigens, biology and immunology. The criteria used to include mostly the peer-reviewed original and review journal articles published within the last decade except for those seminal articles that initially described the clinical features. All non-peer reviewed manuscripts, supplements and textbooks were excluded.

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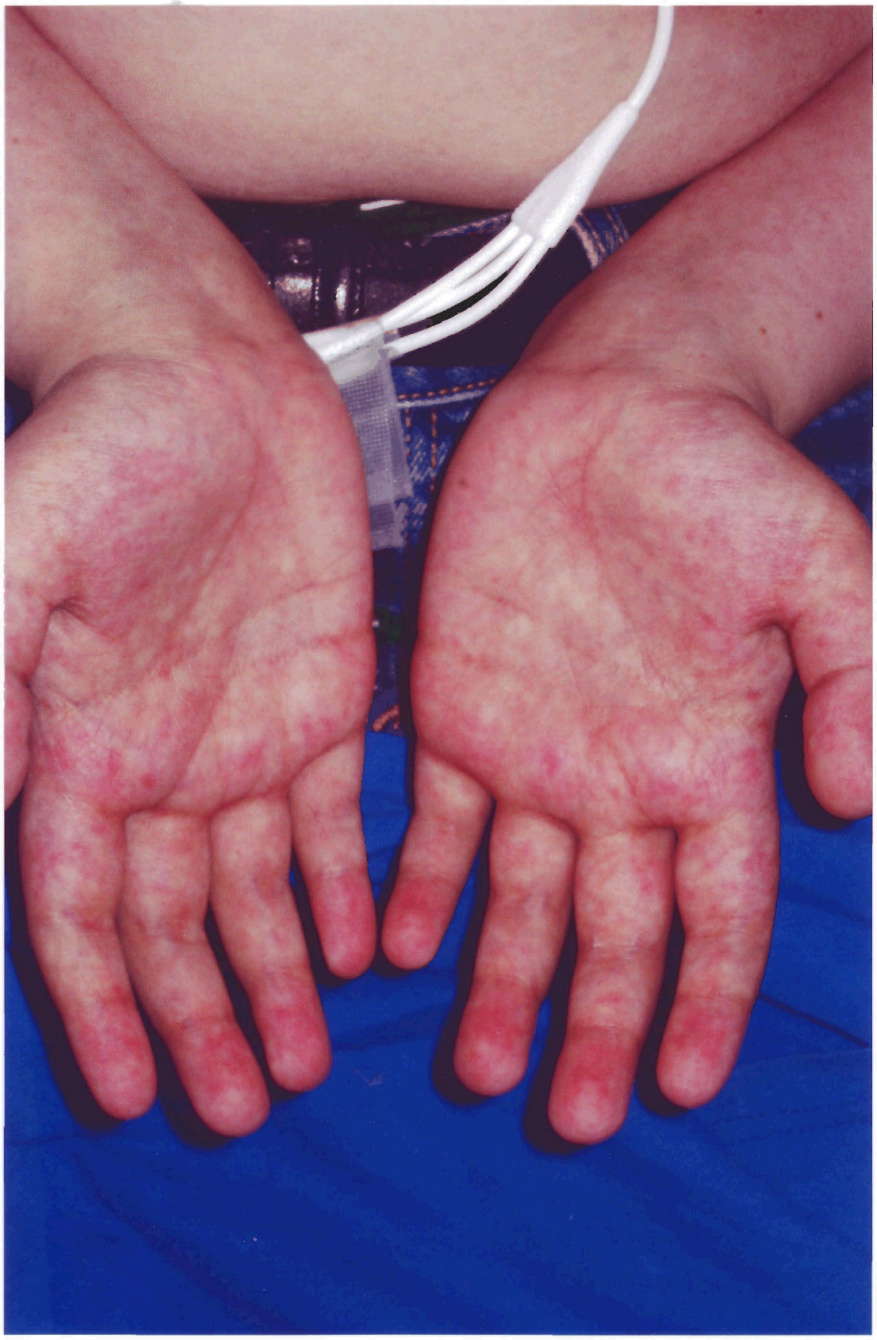

**Figure 1. Acute GVHD of the skin (Grade I). Photograph courtesy of J. Levine, M.D.**

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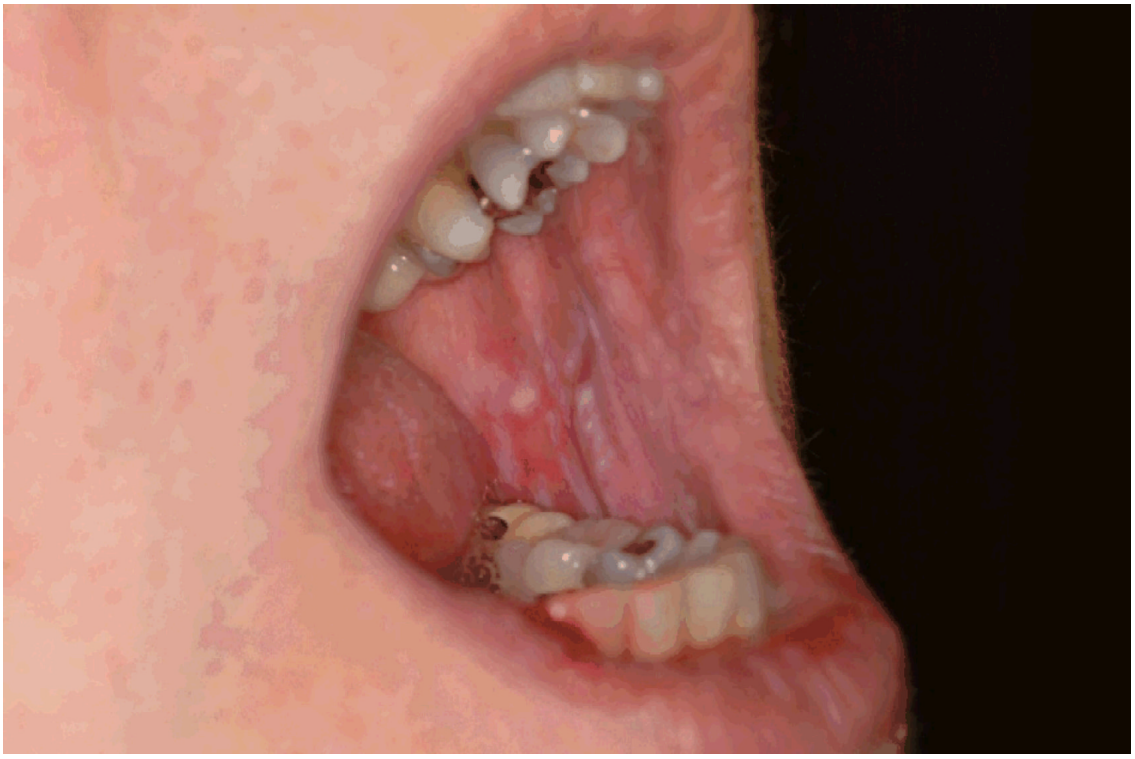

**Figure 2. Chronic GVHD: Lichenoid changes of the buccal mucosa. Photograph courtesy of J. P. Guadagrini, D.D.S.**

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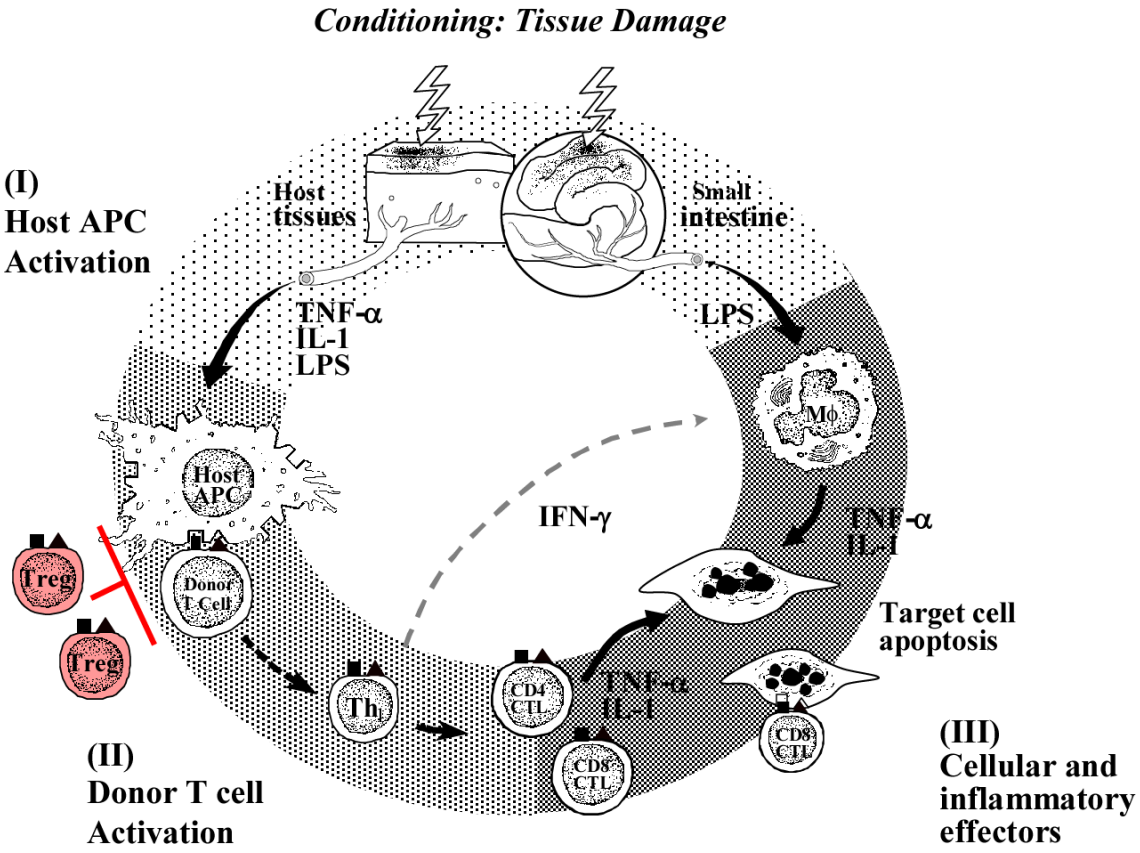


**Figure 3. GVHD Pathophysiology**

In Phase I, the recipient conditioning regimen damages host tissues and causes release of inflammatory cytokines such as TNFα, IL-1 and IL-6. Increased levels of these cytokines leads to activation of host antigen presenting cells (APCs). In Phase II, host APCs activate mature donor cells. The subsequent proliferation and differentiation of these activated T cells produces additional effectors that mediate the tissue damage, including Cytotoxic T Lymphocytes, Natural Killer (NK) cells, TNFα and IL-1. Lipopolysaccharide (LPS) that has leaked through the damaged intestinal mucosa triggers additional TNFα production. TNFα can damage tissue directly by inducing necrosis and apoptosis in the skin and GI tract through either TNF receptors or the Fas pathway. TNFα plays a direct role in intestinal GVHD damage which further amplifies damage in the skin, liver and lung in a “cytokine storm.”

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**Table 1**

Acute GVHD Symptoms

| | |
|---|---|
| Skin | maculopapular skin rash |
| upper GI tract | nausea and/or anorexia PLUS positive histology |
| lower GI tract | watery diarrhea ≥ 500ml +/- severe abdominal pain +/- bloody diarrhea or ileus (after exclusion of infectious etiology) |
| Liver | cholestatic hyperbilirubinemia |

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**Table 2**

Chronic GVHD Symptoms

| | |
|---|---|
| Skin | Dyspigmentation, new onset alopecia, poikiloderma, lichen planus-like eruptions or sclerotic features |
| Nails | Nail dystrophy or loss |
| Mouth | Xerostomia, ulcers, lichen-type features, restrictions of mouth opening from sclerosis |
| Eyes | Dry eyes, sicca syndrome, cicatricial conjunctivitis |
| Muscles, fascia, joints | Fasciitis, myositis, or joint stiffness from contractures |
| Female Genitalia | Vaginal sclerosis, ulcerations |
| GI tract | Anorexia, weight loss, esophageal web or strictures |
| Liver | Jaundice, transaminitis |
| Lungs | Restrictive or obstructive defects on pulmonary function tests, bronchiolitis obliterans, pleural effusions |
| Kidneys | Nephrotic syndrome (rare) |
| Heart | Pericarditis |
| Marrow | Thrombocytopenia, anemia, neutropenia |

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**Table 3**

Recommendations for Supportive Care

| Complication | Clinical symptoms | Routine Monitoring | Prophylaxis | Recommended Intervention |
|---|---|---|---|---|
| **Bacterial infections:** | | | | |
| Catheter-related | Fever, chills Pain and/or erythema | Assessment of catheter sites | Sterile dressing, Regular line maintenance | Obtain cultures Immediate IV antibiotic treatment, remove line |
| Other | Fever, chills Sepsis symptoms | Clinical signs, Chest X ray or CT scan for possible pneumonia | Antibiotic prophylaxis in high risk patients (high dose corticosteroids or asplenism) IVIG if IgG level < 400 mg/dl | Obtain cultures Immediate IV broad spectrum antibiotics as risk of over-whelming sepsis within hours |
| **Viral infections:** | | | | |
| CMV | Gastroenteritis Interstitial pneumonia | Blood CMV PCR **OR** pp65 antigen levels | Preemptive treatment in patients with reactivation | Antiviral therapy: Ganciclovir, Valganciclovir, or Foscarnet |
| Respiratory Viruses | Symptoms of upper/lower respiratory tract infections | Clinical monitoring | Annual influenza vaccination against influenza (starting at 6 months post HCT) Vaccination of caregivers | Early treatment with neuraminidase inhibitors (Influenza), other antivirals |
| Varicella-zoster virus | Vesicular skin lesions | Clinical monitoring | Acyclovir prophylaxis | Treatment doses of antivirals |
| **Fungal and other infections:** | | | | |
| Aspergillosis; other emerging fungal infections | Pulmonary lesions Sinusitis Skin nodules | Galactomannan assays in high risk patients CT scan if signs of infection | Voriconazole **OR** Posaconazole prophylaxis in high risk patients (eg, high dose steroids) | Antifungal therapy |
| Candida | Thrush Pulmonary lesions | Clinical exam CT scan if signs of infection | Fluconazole (Aspergillus prophylaxis protects against Candida as well) | Antifungal therapy |
| Pneumocystis | Fever Hypoxia Respiratory distress | Clinical assessment | Cotrimoxazole **OR** Pentamadine until one month off IS | Treatment doses of anti-PCP medications |
| **Other Toxicities of immunosuppressive agents:** | | | | |
| Calcineurin inhibitors (CNI) | Tremor | Clinical assessment Drug levels | Adjust dose to desired trough levels | |
| | Neurotoxicity | Assess mental status | | Stop CNI |
| | Renal impairment | Creatinine levels & GFR | Adequate fluid uptake (~3L/day) | IV fluids |
| | Hypertension | Blood pressure monitoring | | Antihypertensive treatment (ACE inhibitors, ß blocking agents) |
| | Transplant associated microangiopathy | Assess blood smear for hemolysis, schistocytes | | Stop CNI Plasmapheresis |
| Corticosteroids | Cushing's symptoms | Clinical assessment | Taper as recommended | |

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| Complication | Clinical symptoms | Routine Monitoring | Prophylaxis | Recommended Intervention |
|---|---|---|---|---|
| | Diabetes | Blood glucose levels | Nutritional guidance | Insulin treatment |
| | Osteoporosis | Assessment of bone density | Calcium /Vit D supplementation | Bisphosphonate treatment if osteoporosis |
| | Myopathy | | Physiotherapy | |
| **Late graft failure** | Bleeding symptoms Anemia | Blood counts | Stop or switch responsible drugs | Growth factors: G-CSF Erythropoetin Transfusions |