# Management of Graft-Versus-Host Disease

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**KEYWORDS**

• Allogeneic stem cell transplant • Graft-versus-host disease • Acute • Chronic • Management • Complications

**KEY POINTS**

- Graft-versus-host disease (GVHD) is a major cause of late nonrelapse mortality in allogeneic hematopoietic stem cell transplant recipients.
- GVHD is a complex, polymorphic disease that affects numerous organ systems and warrants prompt evaluation, management, and referral.
- GVHD treatment requires close monitoring for disease response, drug trough levels, and side effects.
- There are numerous complications that can occur from GVHD and its management, such as drug toxicity/side effects, renal insufficiency, endocrinopathies, and secondary malignancies.
- Primary care providers should be familiar with screening allogeneic stem cell transplant recipients for GVHD, monitoring drug levels and side effects, and screening for complications.

## INTRODUCTION

Hematopoietic stem cell transplant (HSCT) possesses the potential to cure many malignant and nonmalignant hematologic diseases. Autologous HSCT uses cells collected from the patient to treat many lymphomas, multiple myeloma, and germ cell tumors. Allogeneic HSCT (allo-HSCT) includes all transplants in which the patient receives donor stem cells after a chemotherapeutic conditioning regimen. Donor stem cells are collected from family members (eg, siblings, parents, children), voluntary unrelated donors, and umbilical cord blood units. Between 2006 and 2014, there were 400,301 allo-HSCTs performed worldwide.[1] The curative potential of allo-HSCT was first reported in the 1950s when leukemic mice were irradiated before receiving allogeneic bone marrow transplants and were noted to have successful disease eradication; however, leukemic mice receiving stem cells from identical twins had persistent

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disease, suggesting a graft-versus-tumor effect caused by the genetic differences of donor cells.[2] Subsequently, the development of novel strategies that use nonmyeloablative conditioning regimens, donor leukocyte infusions, umbilical cord blood transplantations, and haplo-identical transplantation has helped expand the immunotherapeutic benefits of allo-HSCT.[3] Despite these advances, allo-HSCT is often associated with a major intrinsic complication: graft-versus-host disease (GVHD).

GVHD occurs when the graft (donor cells) recognizes the host (recipient) as foreign and launches an immune attack against the host cells causing organ dysfunction and/or failure. There are three defining factors that must be present for GVHD to develop: (1) the donor graft must contain immune competent cells; (2) the host must express tissue antigens not present in the donor (also described as histocompatibility differences); and (3) the host must be unable to reject or eliminate transplanted donor cells.[4] Although the pathophysiology of GVHD remains to be fully elucidated, GVHD occurs in three phases.[5] First, the conditioning regimen for the allo-HSCT damages host tissues, which causes the release of proinflammatory cytokines. Then upon engraftment of donor cells and immune reconstitution, donor T lymphocytes are stimulated by circulating cytokines and interact with various antigens on host cells, which leads to T-cell activation and initiation of immune response.[6] One of the most important proteins recognized by donor T cells are human leukocyte antigens (HLAs) encoded by the major histocompatibility complex. Class I HLA (A, B, C) proteins are expressed on all nucleated cells of the body in various densities. Class II proteins (DR, DQ, and DP) are mainly expressed on hematopoietic cells, but their expression is induced on many other cell types after inflammation or injury. After activation, donor-derived T cells proliferate and differentiate into effector cells, and activated T cells migrate to target tissues (ie, skin, liver, and gut) where they cause destruction through direct cytotoxic activity and recruitment of other leukocytes.

Risk factors for development of GVHD have been extensively studied. The degree of HLA mismatching is the most important risk factor because the donor immune system is more likely to recognize recipient cells with more antigen mismatch.[7] Furthermore, the source of donor stem cells is a critical factor.[7–9] Peripheral blood stem cells contain donor T lymphocytes, which directly mediate the development of GVHD. However, stem cells derived from umbilical cord blood units contain naive immune cells, which minimizes the risk of developing GVHD. Gender disparity also increases the risk of GVHD if a female donor is used for a male recipient.[7] This may be explained by minor histocompatibility antigens that are encoded by the Y chromosome in males, which would presumably increase reactivity of donor cells. These factors, among others, are carefully taken into account when selecting an optimal donor to mitigate the risk of GVHD.

GVHD can be divided into two general categories: acute (aGVHD) and chronic (cGVHD). Historically, GVHD occurring within the first 100 days after allo-HSCT was defined as aGVHD, and occurrence after Day 100 was classified as cGVHD.[10–12] However, the terminology was redefined by the National Institutes of Health Consensus group, which recognized that signs of aGVHD and cGVHD can occur irrespective of the arbitrary 100-day mark. According to the established criteria, aGVHD and cGVHD are distinguished by clinical manifestations and not by time after allo-HSCT.[13] These criteria were later updated in 2014 by the National Institutes of Health Consensus group.[14]

## CLINICAL FEATURES OF ACUTE GRAFT-VERSUS-HOST DISEASE

aGVHD is a potentially life-threatening complication of allo-HSCT that requires prompt diagnosis and therapeutic intervention. Clinical manifestations, staging, and grading