

Hematopoietic Cell Transplantation, Version 3.2025

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hematopoietic Cell Transplantation (HCT) provide expert, multi-disciplinary recommendations for autologous and allogeneic HCT based on current evidence. The NCCN Guidelines focus on pretransplant recipient evaluation, hematopoietic cell mobilization, conditioning, and the diagnosis and management of graft-versus-host disease (GVHD), a common complication of allogeneic HCT that is associated with significant morbidity. This selection from the NCCN Guidelines for HCT focuses on the diagnosis, workup, and management of acute and chronic GVHD, as well as important supportive care considerations.

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Overview

Allogeneic hematopoietic cell transplantation (HCT) involves the infusion of hematopoietic cells from a human leukocyte antigen (HLA)-compatible related or unrelated donor after preparation with cytotoxic conditioning regimens to eradicate malignant cells in the bone marrow and to immunosuppress the recipient so that engraftment of healthy donor cells can occur.¹ HCT is potentially curative for patients with certain types of hematologic malignancies. Acute myeloid leukemia, myelodysplastic syndromes, myeloproliferative neoplasms, and acute lymphoblastic leukemia are the most common malignancies treated with allogeneic HCT.² Outcomes of allogeneic HCT vary according to the type and stage of the disease being treated, the overall health and comorbidities of the patient, the degree of HLA-mismatch between donor and recipient, the source of the hematopoietic cells, and the immunosuppressive regimen given to prevent graft-versus-host disease (GVHD).^{1,3}

Advances in HCT treatment paradigms, including supportive care, have led to improved survival.⁴ However, disease relapse and posttransplant complications continue to pose a major threat to HCT recipients. GVHD is a common and significant risk in

allogeneic HCT recipients. In GVHD, donor lymphocytes recognize the recipient's tissues as foreign, resulting in immune-mediated cellular injury. Acute GVHD (aGVHD) typically manifests in the skin, gastrointestinal (GI) tract, and/or liver, while chronic GVHD (cGVHD) may affect any organ but most commonly affects the eyes, mucosal surfaces, skin/joints/fascia, muscles, liver, and lungs.

Management of GVHD

GVHD is a common complication of allogeneic HCT and may be associated with significant morbidities and nonrelapse mortality (NRM).⁵⁻⁷ Despite advances in many aspects of allogeneic HCT, such as improved donor selection, more effective GVHD prophylaxis, increasing use of reduced-intensity conditioning, and ursodiol prophylaxis, GVHD remains a significant clinical problem. Mild manifestations of GVHD limited to a single organ are often managed with close observation, topical treatment, or by slowing the tapering of immunosuppressive agents.⁸ More severe manifestations or multiorgan involvement typically require systemic corticosteroid treatment as the first line approach; addition of secondary agents may be

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To view disclosures of external relationships for the NCCN Guidelines panel, go to <https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels>

The full NCCN Guidelines for Hematopoietic Cell Transplantation are not printed in this issue of JNCCN. The complete and most recent version of these guidelines is available free of charge at [NCCN.org](https://www.nccn.org).

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus ($\geq 50\%$, but $< 85\%$ support of the Panel) that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available.

Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

required for patients who do not experience response to initial steroid therapy or who are unable to discontinue steroids.⁷ GVHD management can be optimized with coordinated care from a multidisciplinary team, preferably in medical centers with access to specialized transplant services.

Acute Graft-Versus-Host Disease

Up to 70% of allogeneic HCT recipients will develop aGVHD.^{4,9,10} Risk factors include degree of HLA-matching, donor type, and choice of GVHD prophylaxis, which are often interrelated, as well as use of total body irradiation in conditioning and graft source.⁷ The skin, GI tract (upper and lower), and liver are the 3 organs primarily affected by aGVHD, which is generally characterized by maculopapular rash, GI symptoms such as nausea, vomiting, and/or diarrhea, and hyperbilirubinemia, and elevated transaminases.^{9,11} Pathologic confirmation of aGVHD should be considered whenever possible, especially before starting or escalating systemic immunosuppression. Although biopsies are not absolutely sensitive or diagnostic, they may help exclude other diagnostic considerations.

Diagnosis and Grading

If aGVHD is suspected, organ-appropriate additional tests such as stool infectious disease testing, imaging studies, and/or viral testing should be performed to rule out non-GVHD causes of the symptoms (Figure 1). Organ-directed biopsies can then be performed as clinically indicated to support the presence of aGVHD or to exclude other diagnoses. GI biopsy (via esophagogastroduodenoscopy, colonoscopy, and/or flexible sigmoidoscopy) is recommended, whenever possible, for the diagnosis of GI aGVHD, particularly if stool infectious disease testing is unrevealing. Rectosigmoid biopsies were shown in one study to have higher sensitivity and negative predictive value than biopsies at other sites, whether the patient presented with diarrhea, nausea, or vomiting.¹² Liver function tests (LFTs) should be routinely monitored after allogeneic HCT for early detection of hepatic aGVHD, which is often asymptomatic and can manifest with elevated transaminases without elevated bilirubin. Liver biopsy may be considered in patients presenting with unexplained abnormal LFTs without evidence of aGVHD elsewhere if the information would inform treatment. Once the diagnosis of aGVHD is

made, the organ staging and overall grade of aGVHD should be determined to guide choice of therapy and disease monitoring.

After an aGVHD diagnosis, clinicians should remain attuned to the possibility of alternative diagnoses causing persistent or worsening symptoms. For example, persistent diarrhea in a patient with a history of GI aGVHD may be related to mucosal denudation with delayed healing due to compromised gut epithelial stem cell function, yet without active GVHD. On a case-by-case basis, repeat esophagogastroduodenoscopy/colonoscopy may therefore be indicated to differentiate which patients may benefit from additional immunosuppressive agents. Similarly, if one affected organ system has shown improvement with aGVHD management and another is worsening on therapy, an alternative explanation should be investigated, because it is unusual to have disparate responses in different organ systems.

The clinical grade of aGVHD is predictive of survival. Glucksberg aGVHD grading criteria were first proposed in 1974.¹³ Modified Glucksberg (consensus or Keystone) criteria were developed in 1994 (see page GVHD-A, available in these guidelines at NCCN.org, for modified Glucksberg grading criteria).⁵ The International Blood and Marrow Transplant Research (IBMTR) Severity Index was subsequently developed,¹⁴ and was shown to be more predictive of HCT outcome when compared with the original Glucksberg criteria.¹⁵ Minnesota criteria have also been devised to identify patients with "high-risk" aGVHD who could benefit from early escalated therapy.^{16,17} More recently, MAGIC (Mount Sinai Acute GVHD International Consortium) criteria were developed (see Acute GVHD: Staging and Grading in the algorithm for MAGIC grading criteria [available at NCCN.org]).¹⁸ A joint task force of the European Society for Blood and Marrow Transplantation (EBMT), NIH, and CIBMTR has published a position statement on standardized terminology for GVHD.¹⁹ Furthermore, blood biomarkers are being investigated for their utility as a predictive tool in aGVHD.²⁰⁻²³

First-Line Therapy of aGVHD**Grade 1**

Grade 1 aGVHD affects only the skin (stage I–II, $< 50\%$ body surface area [BSA] nonbullous rash), with no GI or liver involvement.⁵ First-line therapy options for these patients include continuing