Journal of Medical and Health Studies
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
AL-KINDI CENTER FOR RESEARCH AND DEVELOPMENT

| RESEARCH ARTICLE

Acute Graft-Versus-Host Disease: A Comprehensive Review of Management and Recent Advances

Salman J. Khan[1] ✉ Seemab Sheikh[2] and Fnu Vishal[3]

[1]Division of Hematology and Medical Oncology, Mayo Clinic Florida, Jacksonville, FL, USA: Public Health, University of Massachusetts, Amherst, MA, USA

[2]Community Health Center, New Britain, Connecticut, USA

[3]Rochester Regional Health

Corresponding Author: Salman J. Khan, M.D, **E-mail**: salmanjkhan1@gmail.com

| ABSTRACT

Acute graft-versus-host disease (GVHD) is a severe complication that can arise after allogeneic hematopoietic cell transplantation (alloHCT), a life-saving procedure for various hematological malignancies and bone marrow disorders. GVHD occurs when donor immune cells recognize the recipient's tissues as foreign and start an immune response, leading to tissue damage and inflammation. Our objectives are to enhance understanding, prevention, and treatment strategies for acute GVHD. We employ an integrated approach involving epidemiology, risk factors, and clinical trial insights. Key findings highlight persistent challenges in GVHD incidence, particularly concerning HLA disparities and ethnicity's role. Acute GVHD remains associated with high mortality rates, emphasizing the need for improved strategies. We explore the disease's phases and discuss promising biomarkers for early diagnosis and prognosis. Our research underscores the importance of a multifaceted approach to GVHD management, ultimately contributing to enhanced patient care.

| KEYWORDS

Acute Graft-Versus-Host Disease, Allogeneic hematopoietic cell transplantation, Acute GVHD management

| ARTICLE INFORMATION

ACCEPTED: 02 September 2023 **PUBLISHED:** 29 September 2023 **DOI:** 10.32996/jmhs.2023.4.5.10

1. Introduction

Acute graft-versus-host disease (GVHD) is a critical complication following allogeneic hematopoietic cell transplantation (alloHCT), a life-saving procedure for various hematological disorders. Despite improved survival rates, acute GVHD remains a formidable threat with elevated mortality rates, underscoring the necessity for enhanced prevention and treatment strategies. Diverse risk factors contributing to acute GVHD development have been explored, including HLA mismatches, stem cell sources, conditioning regimen intensity, and prophylactic approaches. Emerging interventions like post-transplant cyclophosphamide offer hope for more effective prophylaxis. Management of acute GVHD entails a multifaceted approach involving first-line treatments, novel second and third-line therapies, clinical trials, and patient-centric care. Recent advancements, such as low-dose prednisone and innovative agents like ruxolitinib, are also beneficial to some patients. Second and third-line treatments, including MMF, infliximab, and JAK inhibitors, also have potential in refractory cases. Acute GVHD remains a complex issue in transplantation medicine. While progress has been made in treatments and patient support, research endeavors continue to address unmet needs. As alloHCT rates rise, innovative strategies for acute GVHD management become increasingly critical, offering a glimpse of improved prospects for patients undergoing this life-saving procedure. This article provides a comprehensive overview of acute GVHD, covering its epidemiology, risk factors, mechanisms, and management while highlighting its challenges and promising research directions.

The incidence of acute GVHD varies from 30- 50%, but in the absence of prophylaxis, the majority of patients undergoing alloHCT develop this condition [Aladağ, 2020]. The use of prophylaxis has reduced the incidence of acute GVHD; however, it still occurs, especially in patients with significant HLA disparities. Furthermore, studies suggest that ethnicity may impact the risk of developing acute GVHD, with conflicting results reported in different populations [Aladağ, 2020]. Despite improvements in overall survival rates for patients with acute GVHD over time, the condition remains associated with high mortality, emphasizing the need for better prevention and treatment strategies [Ramdial, 2005]. Patients who develop acute GVHD also experience longer hospital stays and increased overall mortality compared to those who do not [Ramdial, 2005].

Several risk factors contribute to the development of acute GVHD. These include HLA disparities between donor and recipient, the source of stem cells (peripheral blood and bone marrow grafts are associated with higher risk), donor-recipient sex disparity, the intensity of conditioning regimens, and the type of GVHD prophylaxis [Gale, 1987]. Cytomegalovirus (CMV) status, donor age, and underlying malignancy status also influence the risk of acute GVHD. Recent studies have indicated that certain interventions, such as post-transplant cyclophosphamide (PTCy), can mitigate the negative impact of HLA disparities on acute GVHD risk, offering hope for more effective prophylaxis [Gale, 1987].

Acute GVHD occurs in three distinct phases: initiation, T cell activation, and the effector phase. Understanding these phases is crucial for developing targeted treatments [Malard, 2003]. The conditioning regimen used in alloHCT damages the recipient's tissues, releasing inflammatory cytokines that activate host antigen-presenting cells (APCs). The type and intensity of conditioning regimens impact the severity of GVHD. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) play pivotal roles in this phase. PAMPs are molecules derived from bacterial activation, while DAMPs result from the destruction of host cells. Also, the gut microbiota plays a significant role, as damage to the gut epithelium allows the translocation of bacteria, which can trigger GVHD initiation. In the T cell activation phase, alloreactive donor T cells recognize HLA differences between donor and recipient tissues, activating CD4+ and CD8+ T cells. The recognition of host antigens on host APCs is central to this process. In the effector phase, activated donor CD8+ T cells target host tissues, causing apoptosis. Pro-inflammatory cytokines such as IFNγ and TNF mediate tissue damage. Other cells, including endothelial cells, may also contribute to GVHD, particularly in less-recognized target tissues. Regulatory cells, including natural Treg cells, induced Treg cells, CD8+ Treg cells, regulatory B cells, mesenchymal stem cells, and myeloid-derived suppressor cells, play essential roles in suppressing acute GVHD and are promising areas for therapeutic intervention.

Early diagnosis, accurate screening, and effective prevention strategies help to reduce the burden of acute GVHD. Often, skin manifestations are the initial indicators, presenting as a maculopapular rash, typically in sun-exposed areas. These rashes may evolve into pruritic and painful lesions, progressing to bullous formations and ulcers in severe cases. Pathological findings include basal layer degeneration, dyskeratosis, lymphocytic infiltration, and dermo-epidermal disjunction [Murata, 2018]. Lower GI GVHD manifests as secretory diarrhea, abdominal pain, ileus, and hematochezia, whereas upper GI GVHD entails anorexia, nausea, and vomiting. Differential diagnosis is crucial, necessitating the exclusion of infections and drug toxicity. Endoscopy and histological examination often aid in diagnosis [Naymagon, 2017]. Although less common, liver involvement is frequently associated with skin and GI GVHD. Clinical features encompass hyperbilirubinemia and jaundice, with biopsy confirmation necessary to rule out alternative causes of liver dysfunction [6]. Acute GVHD can target diverse organs, including the lungs, kidneys, thymus, lymph nodes, bone marrow, and the central nervous system. These atypical manifestations may be subtle and challenging to differentiate from other post-transplant complications [Chesdachai, 2022]. Acute GVHD is systematically graded based on the extent of organ involvement and severity. This grading system is instrumental in determining the appropriate treatment approach [Gratwohl, 1985].

Promising research endeavors are underway to identify biomarkers facilitating the diagnosis and prognosis of acute GVHD [Kaviany, 2021]. A Composite Biomarker panel consists of four proteins, including IL-2Rα, TNF receptor 1, IL-8, and hepatocyte growth factor, which exhibit potential in distinguishing patients with and without acute GVHD, displaying robust discriminatory ability. Organ Damage Biomarkers such as elafin, REG3A, hepatocyte growth factor, and cytokeratin 18 (CK18) are linked to GVHD-related organ damage, offering potential utility in early diagnosis and monitoring. The Ann Arbor (AA) biomarker risk assessment tool employs serum concentrations of ST2 and REG3A to predict the risk of non-relapse mortality and resistance to GVHD treatment. It aids in devising risk-adapted treatment strategies.

Efforts to prevent acute GVHD encompass pharmacological prophylaxis, T-cell depletion prophylaxis, and alternative approaches [Jamy, 2023]. Several pharmacological prophylaxes are being used in preventing GVHD. Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) in conjunction with methotrexate or mycophenolate mofetil (MMF) are conventional agents for GVHD prophylaxis. Exploration of alternatives like sirolimus, abatacept, and other agents is ongoing. However, calcineurin inhibitors are associated with toxicities, including nephrotoxicity and hypertension. For T Cell Depletion Prophylaxis, ex vivo T cell depletion methods, such as CD34-positive selection and αβ+ T cell receptor (TCR)/CD19 depletion, are effective but may heighten the risk of infections. In vivo, T-cell depletion using antibodies like anti-thymocyte globulin (ATG) or post-transplant cyclophosphamide (PTCy) has

displayed promise in reducing acute GVHD incidence. PTCy is particularly effective in haploidentical donor transplants. Other Approaches include monoclonal antibodies like alemtuzumab, vedolizumab, and others under investigation for GVHD prophylaxis. Tailoring prophylaxis based on donor type and conditioning regimen is imperative.

Managing acute GVHD involves a multifaceted approach, incorporating first-line treatments, second and third-line therapies, clinical trials, and comprehensive patient care [Patel, 2023]. Systemic steroids, primarily methylprednisolone, remain the standard first-line treatment for acute GVHD. However, their effectiveness varies depending on the disease grade. Recommendations dictate that topical steroids alone are sufficient in cases of grade I acute GVHD, while systemic steroids are reserved for grade II or higher disease. Recent studies have explored low-dose prednisone as an alternative to standard-dose treatment for grade II acute GVHD with specific clinical parameters [Etra, 2023]. Notably, low-dose prednisone appeared as effective as standard-dose treatment, with the added benefit of reduced risk in patients requiring secondary immunosuppressive therapy. However, caution is advised when considering low-dose prednisone for grade II acute GVHD with liver or extensive skin involvement, as it may increase the risk of needing secondary immunosuppression.

Clinical trials for acute GVHD with gastrointestinal involvement have compared the combination of prednisone plus beclomethasone to prednisone plus placebo [Hockenbery, 2007]. Beclomethasone, a non-absorbable oral steroid, demonstrated a reduced risk of GVHD treatment failure and improved survival. Therefore, non-absorbable oral steroids, including oral beclomethasone and budesonide when beclomethasone is unavailable, are recommended for patients with acute GVHD affecting the gastrointestinal tract. In cases of skin involvement alongside systemic steroid treatment, the addition of topical steroids is recommended until the skin rash resolves. This multifaceted approach to first-line therapy ensures that patients receive tailored treatments based on the severity and site of acute GVHD [Kim, 2019].

Despite first-line treatments, response rates with prednisone alone remain low, at approximately 50%. This underscores the need for additional therapies to improve response rates, especially in cases of steroid refractory GVHD. Several clinical trials have explored novel agents as potential second-line treatments for acute GVHD. One phase II study compared methylprednisolone plus various agents, including etanercept, MMF, denileukin diftitox, and pentostatin. MMF emerged as the most promising agent, leading to a subsequent phase III trial comparing methylprednisolone plus MMF to methylprednisolone plus placebo. This trial found similar complete response rates at day 28 between the two groups, suggesting that MMF could be an effective second-line therapy [Martin, 2012].

Other studies have investigated infliximab, a TNF-α inhibitor, in combination with methylprednisolone. These trials also demonstrated comparable response rates to methylprednisolone alone [Couriel, 2009]. Recently, a phase III study evaluated the JAK1 inhibitor itacitinib in combination with corticosteroids as an initial treatment for acute GVHD. While this study did not show a significant difference in overall response rates at day 28 between the two groups, ongoing research in this area continues to explore the potential benefits of JAK inhibitors in GVHD management [Zeiser, 2022].

The JAK2 inhibitor ruxolitinib has garnered attention for its efficacy in steroid-refractory or steroid-dependent acute GVHD [Jagasia, 2015]. A phase III trial demonstrated higher overall response rates at day 28 in the ruxolitinib group compared to the control group, leading to FDA and EMA approvals for ruxolitinib as a second-line treatment. However, challenges remain, as a significant proportion of patients do not achieve a complete or partial response, necessitating further research into third-line therapies. Previously, second-line treatments for GVHD included a range of therapies, from anti-thymocyte globulin to mesenchymal stem cells and extracorporeal photopheresis. However, these options are now primarily considered third-line therapies due to the emergence of promising agents like ruxolitinib.

The management of patients with steroid-resistant and ruxolitinib-resistant acute GVHD remains a significant challenge. Recommendations suggest enrolling such patients in clinical trials to explore potential breakthrough therapies. In cases where clinical trial participation is not feasible, third-line treatments are chosen based on center-specific practices, emphasizing the need for further research [Fan, 2022]. Given the high failure rate of acute GVHD treatment, inclusion in clinical trials of new therapies is strongly recommended. Efforts have been made to develop risk-adapted approaches using biomarker risk scores that predict response to steroid treatment, survival, and transplant-related mortality more accurately than traditional grading criteria. The overall clinical response rate at day 28 remains a validated surrogate for survival and serves as a primary endpoint in clinical trials.

Managing acute GVHD also involves addressing treatment-related complications, including infectious diseases and corticoid-induced toxicity. Prophylactic measures against invasive fungal infections and monitoring for CMV infection are crucial components of supportive care [Fan, 2022]. When necessary, close monitoring for corticoid-induced toxicity is recommended to initiate early preventive or curative treatments, such as insulin, calcium, vitamin D, or bisphosphonates. Patients with acute GVHD should also

receive routine antibiotic prophylaxis to guard against bacterial infections. Assessing patients' quality of life is integral to their care. Several questionnaires, such as FACT-BMT and SF-12, have been employed to evaluate patients' physical and mental well-being with acute GVHD in case they progress to chronic GVHD [Fiuza-Luces, 2016]. These tools have highlighted the impact of acute GVHD on patients' lives, emphasizing the need for comprehensive support and care.

2. Conclusion

In conclusion, this study seeks to deepen the understanding of acute graft-versus-host disease (GVHD) within the context of hematopoietic cell transplantation. Our objectives included elucidating GVHD's complexities, refining prevention and treatment strategies, and uncovering biomarkers for early diagnosis. Throughout our research, we identified critical factors influencing GVHD incidence, emphasized the persistent challenge of high mortality rates, and elucidated the multi-phased pathogenesis of the disease. By highlighting the importance of a multifaceted therapeutic approach, we shed light on the significance of ongoing efforts to enhance GVHD outcomes. However, it's vital to acknowledge the study's limitations, including the dynamic nature of medical research and the focus on acute GVHD only. There is a need for retrospective studies and clinical trials for the exploration of factors associated with treatment failures, and finding out new management strategies. Ultimately, our study contributes to the existing literature by consolidating current knowledge and emphasizing the need for continuous research and innovation to address this critical complication in hematopoietic cell transplantation fully.

Funding: This research received no external funding.
Conflicts of Interest: The authors declare no conflict of interest.
Ethical approval: There is no need for ethical approval for this study as it is a review of the literature.
Informed consent: There is no need for informed consent for this study as it is a review of literature.
Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers.

References

[1] Aladağ E, Kelkitli E, Göker H (2020). Acute Graft-Versus-Host Disease: A Brief Review. *Turk J Haematol*. 37(1):1-4. doi:10.4274/tjh.galenos.2019.2019.0157
[2] Chesdachai S, Udompap P, Yetmar ZA (2022). Infectious complications in acute graft-versus-host disease after liver transplantation. *Transpl Infect Dis*. 24(4):e13843. doi:10.1111/tid.13843
[3] Couriel DR, Saliba R, de Lima M. (2009). A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. *Biol Blood Marrow Transplant*.15(12):1555-1562. doi:10.1016/j.bbmt.2009.08.003
[4] Etra A, Capellini A, Alousi A. (2023). Effective treatment of low-risk acute GVHD with itacitinib monotherapy. *Blood*. 141(5):481-489. doi:10.1182/blood.2022017442
[5] Fan ZY, Han TT, Zuo W (2022). CMV infection combined with acute GVHD associated with poor CD8+ T-cell immune reconstitution and poor prognosis post-HLA-matched allo-HSCT. *Clin Exp Immunol*. 2022;208(3):332-339. doi:10.1093/cei/uxac047
[6] Fiuza-Luces C, Simpson RJ, Ramírez M, Lucia A, Berger NA. (2016). Physical function and quality of life in patients with chronic GvHD: a summary of preclinical and clinical studies and a call for exercise intervention trials in patients. *Bone Marrow Transplant*. 51(1):13-26. doi:10.1038/bmt.2015.195
[7] Gale RP, Bortin MM, van Bekkum DW, (1987). Risk factors for acute graft-versus-host disease. *Br J Haematol*. 1987;67(4):397-406. doi:10.1111/j.1365-2141.1987.tb06160.x
[8] Gratwohl A, Hermans J, Apperley J (1995). Acute graft-versus-host disease: grade and outcome in patients with chronic myelogenous leukemia. Working Party Chronic Leukemia of the European Group for Blood and Marrow Transplantation. *Blood*. 86(2):813-818.
[9] Hockenbery DM, Cruickshank S, Rodell TC (2007). A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. *Blood*. 109(10):4557-4563. doi:10.1182/blood-2006-05-021139
[10] Jamy O, Zeiser R, Chen YB. (2023). Novel developments in the prophylaxis and treatment of acute GVHD [published online ahead of print, 2023 Jul 20]. *Blood*. 2023; blood.2023020073. doi:10.1182/blood.2023020073
[11] Jagasia M, Perales MA, Schroeder MA (2015). Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. *Blood*.135(20):1739-1749. doi:10.1182/blood.2020004823
[12] Kim YJ, Lee GH, Kwong BY, Martires KJ (2019). Evidence-based, Skin-directed Treatments for Cutaneous Chronic Graft-versus-host Disease. *Cureus*. 11(12):e6462. Published 2019 Dec 25. doi:10.7759/cureus.6462
[13] Kaviany S, Kitko CL (2021). The role of biomarkers in risk stratification, treatment and outcome in acute GVHD. *Curr Opin Hematol*. 28(6):401-407. doi:10.1097/MOH.0000000000000681
[14] Malard F, Holler E, Sandmaier BM, Huang H, Mohty M (2003). Acute graft-versus-host disease. *Nat Rev Dis Primers* 9(1):27. Published 2023 Jun 8. doi:10.1038/s41572-023-00438-1
[15] Murata M (2018). *Rinsho Ketsueki*. 2018;59(5):540-548. doi:10.11406/rinketsu.59.540
[16] Martin PJ, Rizzo JD, Wingard JR (2012). First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2012;18(8):1150-1163. doi:10.1016/j.bbmt.2012.04.005
[17] Naymagon S, Naymagon L, Wong SY (2017). Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. *Nat Rev Gastroenterol Hepatol*. 2017;14(12):711-726. doi:10.1038/nrgastro.2017.126

[18] Patel DA, Crain M, Pusic I, Schroeder MA. (2023). Acute Graft-versus-Host Disease: An Update on New Treatment Options. *Drugs*. 83(10):893-907. doi:10.1007/s40265-023-01889-2

[19] Ramdial JL, Mehta RS, Saliba RM (2005). Acute graft-versus-host disease is the foremost cause of late nonrelapse mortality. *Bone Marrow Transplant*. 2021;56(8):2005-2012. doi:10.1038/s41409-021-01274-1

[20] Zeiser R, Socié G, Schroeder MA (2022). Efficacy and safety of itacitinib versus placebo in combination with corticosteroids for initial treatment of acute graft-versus-host disease (GRAVITAS-301): a randomised, multicentre, double-blind, phase 3 trial. *Lancet Haematol*. 9(1):e14-e25. doi:10.1016/S2352-3026(21)00367-7