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CURRENT PERSPECTIVES ON THE MANAGEMENT OF ACUTE GRAFT-VERSUS-HOST DISEASE IN PEDIATRIC TRANSPLANTATION

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ABSTRACT

Background: Hematopoietic stem cell transplantation (HSCT) has expanded its scope as a curative therapy for a wide range of severe pediatric diseases. However, its efficacy is frequently challenged by graft-versus-host disease (GVHD), a significant and potentially fatal complication. This is particularly relevant in the pediatric population, where unique immunological and physiological factors contribute to a distinct disease course.
Objective: This narrative review synthesizes the current evidence base on the treatment and management of GVHD in pediatric patients. It aims to provide a critical appraisal of the unique immunological determinants, current prophylactic and treatment interventions, and the long-term morbidities and clinical needs for this specific field.
Methods: A comprehensive systematic search of databases, including PubMed, Embase, and the Cochrane Library, was conducted to identify relevant literature. Articles were selected based on inclusion criteria focusing on GVHD management in patients aged 18 or younger, while excluding non-peer-reviewed articles and case reports. Data on study design, patient populations, treatment regimens, and key outcomes were extracted and synthesized.
Summary: The pathogenesis of acute GVHD (aGVHD) is described by the classic three-phase model, beginning with host tissue damage, followed by donor T-cell activation, and culminating in targeted organ destruction, particularly in the skin, liver, and gastrointestinal tract. Diagnostic methods have evolved from clinical and histological assessments to include advanced biomarker-driven approaches, such as the MAGIC algorithm, which provides more precise prognostic risk stratification. Current prophylaxis strategies primarily involve calcineurin inhibitors in combination with methotrexate or mycophenolate mofetil. Novel agents like ruxolitinib and vedolizumab are emerging as promising therapeutic tools for both prophylaxis and the treatment of steroid-refractory disease. Despite these advancements, significant clinical gaps persist, as many established guidelines for GVHD management are not tailored to the pediatric population. The evident age-related disparity in GVHD risk highlights the critical need for pediatric-specific research.
Conclusion: While substantial progress has been made in understanding and treating GVHD, there is a clear and urgent need for further research focused on pediatric-specific protocols. Continued efforts to validate existing therapies in pediatric cohorts, explore novel agents, and leverage biomarkers are essential to improve outcomes and the quality of life for young patients undergoing HSCT.

KEYWORDS

Acute Graft-Versus-Host Disease, Pediatric Transplantation, Hematopoietic Stem Cell Transplantation, Immunosuppression, Novel Therapies

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1. Introduction

Hematopoietic stem cell transplantation (HSCT) has evolved to become an anchor therapy for a heterogeneous and multifaceted group of severe pediatric diseases. Its application has been extended beyond the traditional hematologic malignancies, such as acute leukemia, to a broad list of non-malignant diseases, such as primary immunodeficiency diseases, hemoglobinopathies, inherited bone marrow failure syndromes, and other metabolic or genetic disorders(Guilcher, 2016; West et al., 2020). The achievement of this practice is that it holds the promise of providing a curative solution, as it develops a new, healthy hematopoietic system. The practice of HSCT has also increased with the increasing use of different sources of stem cells, including peripheral blood stem cells (PBSC) and cord blood, aside from the conventional bone marrow source(Foeken et al., 2010). The specific choice of stem cell source is a critical predictor of outcome after transplantation, since it may significantly affect risk and character of complications, including graft-versus-host disease (GVHD) (Yesilipek, 2014).

GVHD is a life-threatening and often fatal complication post-allogeneic HSCT. The immunopathological underpinning of the alloreactive reaction is based on host immunocompetent T-lymphocytes from the donor graft recognizing host tissue(Rai et al., 2016). This recognition is through histocompatibility disparities, primarily the human leukocyte antigen (HLA) and major histocompatibility complex (MHC). The ensuing immune reaction is polyvalent and leads to the proliferation and clonal expansion of donor T-lymphocytes which then initiate an intense attack on the recipient's healthy tissues(Triulzi & Nalesnik, 2001). This type of alloreactive response is a hallmark in the etiopathogenesis of GVHD(Tavaf et al., 2023). GVHD is traditionally categorized into acute GVHD (aGVHD) and chronic GVHD (cGVHD), traditionally distinguished by onset time and clinical presentation. Acute GVHD typically occurs within the first 100 days following transplantation but has a well-known late-onset variant beyond this period(Fiuza-Luces et al., 2016; Socie & Ritz, 2014). Contrarily, cGVHD usually arises after day 100, but can also arise de novo without the previous onset of the acute form(Zeiser et al., 2023).

The prevalence of GvHD in children is high and clinically relevant. The incidence of cGVHD has been reported to range from as low as 6% for matched sibling cord blood transplants to as high as 65% for matched unrelated donor (MUD) PBSC transplants(Baird et al., 2010). Acute GVHD occurs in an estimated 50% of patients at any grade, with a Grade II-IV incidence of approximately 20%(Gottardi et al., 2023). The figures underscore the universal issue that GVHD poses to post-transplant survival and quality of life.

One of the core aspects of GVHD epidemiology in the pediatric group is the evident inverse correlation between recipient age and risk of disease. Numerous studies have proved that young children (2 to 12 years of age) have a significantly reduced risk of developing Grade II-IV aGVHD and cGVHD compared to adolescent and young adult (AYA) recipients (13 to 21 years of age) who are undergoing transplantation(Qayed et al., 2018). This phenomenon is particularly important as it reflects fundamental immunological differences between these age groups. Young children's immature immune system, particularly their increased thymic activity, may contribute to an increased T-cell repertoire and immune reconstitution and thereby alter the alloreactive response and decrease the overall risk of GVHD(Sobkowiak-Sobierajska et al., 2022). This age-related disparity raises fundamental clinical questions; furthermore, this is a critical point for future clinical research.

The objective of this systematic review is to synthesize the current evidence base on treating GVHD in the pediatric population. The report will provide a critical appraisal of the unique immunological and physiological determinants that drive the course of GVHD in children, discuss existing prophylaxis and treatment interventions, and describe the significant long-term morbidities and vital unmet clinical demands for this special field. By synthesizing these varied aspects of GVHD care, this review aims to be a starting point paper with the ability to inform clinical practice and guide future research endeavors.

2. Pathophysiology

The pathogenesis of aGVHD is a complex, multi-step process best described by the classic three-phase model. This cascade involves a coordinated sequence of host tissue damage, donor T-cell activation, and the subsequent destruction of target organs(Ferrara et al., 2003).

Phase 1: Initiation The initial trigger for aGVHD is the high-dose myeloablative conditioning regimen of chemotherapy and/or total body irradiation administered to the recipient prior to transplant. This regimen is designed to eradicate the patient's native immune system and malignant cells. In doing so, it causes widespread damage to host epithelial cells in the skin, GI tract, and liver. This tissue injury leads to the release of a self-limited burst of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1). These cytokines, in turn, serve to activate host antigen-presenting cells (APCs), such as dendritic cells, which prepare to present foreign antigens to the incoming donor T-cells(Hill et al., 2021; Zeiser & Blazar, 2017).

Phase 2: Donor T-Cell Activation and Proliferation. The second phase is a central immunological event. Upon infusion, donor T-cells recognize host alloantigens presented on the activated APCs as foreign. This recognition is a highly specific interaction between the donor T-cell receptor (TCR) and host major histocompatibility complex (MHC) or minor histocompatibility antigens (mHA). This antigen recognition, coupled with co-stimulatory signals, drives the vigorous proliferation and differentiation of donor T-cells into effector cells. This process is accompanied by the enhanced secretion of a new wave of proinflammatory, or Type 1, cytokines. These include interferon-gamma (IFN-γ) and interleukin-2 (IL-2), which amplify the immune response. The rapid and massive release of these cytokines is often referred to as a "cytokine storm," marking the onset of a full-blown systemic inflammatory state(Socie & Michonneau, 2022; Zeiser & Blazar, 2017).

Phase 3: The Effector Phase. The final phase is characterized by the migration of activated donor effector T-cells and the systemic circulation of cytokines to target organs. In these organs, the cellular and molecular effectors mediate direct tissue destruction. The mechanisms of injury include apoptosis, or programmed cell death, of target cells, which can be directly induced by cytokines such as TNF-α, often via the Fas antigen pathway. This tissue destruction is amplified by a synergistic effect between cellular effectors, such as cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells, and the inflammatory cytokines(Ferrara et al., 2003; Hill et al., 2021; Zeiser & Blazar, 2017).

A critical element that extends the classic three-phase model is the self-amplifying feedback loop that involves the GI tract. The tissue damage that occurs in the effector phase compromises the integrity of the gut's mucosal barrier. This allows microbial products, such as endotoxin and lipopolysaccharide (LPS), to translocate from the gut lumen into the bloodstream. This endotoxin acts as a powerful secondary trigger, stimulating further cytokine production by gut-associated lymphocytes and macrophages, as well as keratinocytes and fibroblasts in the skin. This creates a vicious cycle where initial tissue damage leads to more inflammation, which causes more damage, propagating the systemic "cytokine storm". Therefore, the GI tract is an active amplifier of the disease process(Koyama & Hill, 2019; Mathewson et al., 2016; Schwab et al., 2014).

3. Clinical Manifestations

The clinical presentation of aGVHD is highly variable and depends on the specific organs involved. As the disease primarily affects rapidly proliferating epithelial tissues, the skin, GI tract, and liver are the most common sites of involvement(Ferrara et al., 2009).

Cutaneous aGVHD is often the earliest and most common manifestation of the disease, frequently appearing simultaneously with the engraftment of donor cells. It presents as a characteristic pruritic maculopapular rash that can resemble a heat rash or a sunburn. The rash typically begins on the palms of the hands and soles of the feet, or on the face, ears, neck, and shoulders, before spreading to cover the trunk and limbs. In severe cases, the rash can progress to a generalized erythroderma, which may be complicated by bullous formation and epidermal desquamation, akin to a severe thermal burn(Hong et al., 2023).

Gastrointestinal aGVHD can involve both the upper and lower segments of the GI tract. Upper GI involvement presents with symptoms such as persistent nausea, vomiting, and anorexia. Lower GI involvement is characterized by abdominal pain, cramping, and profuse diarrhea, which may be watery or bloody. In its most severe form, GI involvement can lead to significant fluid loss, severe abdominal pain, and ileus(Naymagon et al., 2017).

Liver involvement in aGVHD is defined clinically by jaundice, and by elevated liver enzyme levels, specifically bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Patients may also experience abdominal swelling and tenderness. A more detailed analysis of clinical presentation reveals that hepatic GVHD can manifest in distinct ways. The typical presentation is characterized by marked elevation of alkaline phosphatase and bilirubin with milder increases in AST and ALT, and it is usually preceded by skin rash and diarrhea. A separate and less common variant is characterized by sharp elevations in aminotransferases (greater than ten times the upper limit of normal) with only mild increases in alkaline phosphatase, and can present without the preceding skin or gut involvement. This variant is often associated with the tapering of immunosuppression(Matsukuma et al., 2016; Salomao et al., 2016).

4. Diagnosis

Acute GVHD is primarily a clinical diagnosis based on the presence of characteristic symptoms and their time of onset relative to the transplant. However, aGVHD is a diagnosis of exclusion. The clinical symptoms can mimic other common post-transplant complications, making differential diagnosis a critical first step. For example, diarrhea and abdominal pain can be caused by viral infections, such as cytomegalovirus (CMV) colitis, while a skin rash may be a manifestation of a drug reaction(Kuykendall & Smoller, 2003; Salomao et al., 2016).

To provide a definitive diagnosis and aid in the differential diagnosis, a tissue biopsy of the affected organ is recommended. The histopathological findings in aGVHD are distinct and organ-specific. In the skin, findings include dyskeratotic keratinocytes and necrosis of basal cells. In the GI tract, the hallmark feature is crypt-cell necrosis and dropout, which may be accompanied by mucosal sloughing. Liver biopsies typically reveal bile duct injury, apoptosis, and irregular biliary epithelial cells(Hong et al., 2023; Salomao et al., 2016).

Despite its utility, biopsy is not an absolute gold standard. Histological features of aGVHD are not always pathognomonic, and the disease can present in a patchy manner, particularly in the GI tract, which may necessitate multiple biopsy sites. Furthermore, a negative biopsy does not definitively exclude the diagnosis of aGVHD, especially if the biopsy is performed early in the disease course or after immunosuppressive therapy has been initiated, as these factors may reduce necroinflammatory activity. The diagnosis must, therefore, be made by integrating clinical history, physical findings, and laboratory results, with a biopsy serving as an important but not always conclusive tool(Salomao et al., 2016).

The limitations of symptom-based and histopathological assessments have driven a shift toward a more objective, biomarker-driven approach. It has been observed that the severity of symptoms at the time of aGVHD onset does not accurately define the ultimate risk of the patient. This has necessitated the search for biomarkers that can provide a more accurate, quantitative measure of tissue damage and prognosis. Two of the most widely studied plasma biomarkers are suppression of tumorigenicity 2 (ST2) and regenerating islet-derived 3-alpha (REG3α)(Huang et al., 2025; Solan et al., 2019). ST2 is a member of the interleukin-1 receptor family. Elevated levels of ST2 are associated with a higher risk of developing severe (Grade II-IV) aGVHD and a higher incidence of non-relapse mortality (NRM). It is also linked to a higher risk of treatment-resistant aGVHD, making it a valuable prognostic tool(Huang et al., 2025; Solan et al., 2019). REG3α: is produced in the pancreas and small intestine. Its levels are directly proportional to the degree of endothelial and mucosal damage caused by aGVHD. It is particularly useful for the diagnosis of gastrointestinal aGVHD, as it can differentiate aGVHD-related diarrhea from other causes, such as infection or drug toxicity, which is a major challenge in clinical practice(Solan et al., 2019).

5. Grading and Severity Assessment

The grading of aGVHD is crucial for guiding treatment decisions and for standardizing patient outcomes in clinical trials. This process has evolved significantly from early, symptom-based scales to modern, integrated algorithms(Sharma & Efebera, 2021).

The Glucksberg Classification

The Glucksberg scale, first proposed in 1974, is the historic standard for grading aGVHD. This system stages each of the three major target organs (skin, liver, and gut) on a scale from 0 to 4 based on objective clinical measures: the percentage of body surface area (BSA) affected by rash, serum bilirubin levels, and the volume of diarrhea. The organ stages are then combined to assign an overall aGVHD grade from I to IV(Glucksberg et al., 1974). While pioneering, this system and similar historical scales like the Minnesota and IBMTR classifications have been found to have varying abilities to predict outcomes and can assign different severity scores to a given patient, leading to challenges in data interpretation and consistency across institutions(Rowlings et al., 1997). The Table 1 shows the Glucksberg Classification.

Table 1. Glucksberg Organ Staging

Organ	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Maculopapular rash on <25% of body surface	Maculopapular rash on 25−50% of body surface	Generalized erythroderma	Generalized erythroderma with bullae and desquamation
Liver	Normal	Bilirubin 2−3 mg/dL	Bilirubin 3−6 mg/dL	Bilirubin 6−15 mg/dL	Bilirubin >15 mg/dL
Gastrointestinal Tract	No symptoms	Anorexia, nausea, or diarrhea (or both) of <500 mL/day	Diarrhea of 500−1000 mL/day	Diarrhea of 1000−1500 mL/day	Diarrhea of >1500 mL/day or severe abdominal pain with or without ileus

The NIH Consensus Criteria

The National Institutes of Health (NIH) Consensus Conference introduced new criteria that fundamentally changed the definition of aGVHD by moving away from a strict time-based categorization. The NIH criteria recognize "classic acute GVHD" occurring within 100 days of transplant and "late acute GVHD" which occurs after 100 days but with identical clinical features. The criteria also define an "overlap syndrome" for patients with features of both acute and chronic GVHD(Jagasia et al., 2015).

The MAGIC Model and Integrated Risk Stratification

The Mount Sinai Acute GVHD International Consortium (MAGIC) has developed a groundbreaking model that integrates clinical staging with biomarker data to provide a more accurate and dynamic assessment of patient risk. This model addresses the core limitation of previous systems: that clinical symptom severity at onset is an imprecise predictor of a patient's ultimate outcome. The MAGIC algorithm combines clinical staging, similar to the Glucksberg scale, with plasma levels of the key biomarkers ST2 and REG3α to generate a MAGIC algorithm probability (MAP) score. This MAP score stratifies patients into one of three Ann Arbor (AA) scores (AA1, AA2, or AA3). This system has been shown to successfully stratify patients for risk of non-relapse mortality and the likelihood of future disease flares. Notably, the predictive power of the AA scores holds true even in patients who are asymptomatic, suggesting that the MAGIC biomarkers detect subclinical damage to the GI crypts that may drive later, more severe clinical disease. This integrated approach allows for a more objective, personalized, and forward-looking assessment of patient risk, moving beyond static, symptom-based grading(Akahoshi et al., 2024).

6. Management

The European Society for Blood and Marrow Transplantation (EBMT) recently revised its guidelines for GVHD prophylaxis and treatment to directly address the approval of new therapeutic agents by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). However, these guidelines do not include recommendations for the pediatric population. The authors attribute this omission to differing perspectives regarding GVHD prophylaxis strategies in pediatric transplant recipients. Additionally, the guidelines are explicitly based on European clinical experience and do not reflect global practices(Penack et al., 2024).

6.1 Prophylaxis

Effective prophylaxis of GVHD in pediatric populations necessitates rigorous donor selection criteria to optimize transplant outcomes. Lower rates of both acute and chronic GVHD have been demonstrated in matched sibling donors (MSD), compared to matched unrelated donors (MUD) and related mismatched donors (MMD). Significantly, MUD transplants carried a lower risk of acute grade 2-4 GVHD than related MMD, but not chronic GVHD or acute grade 3-4 GVHD(Shaw et al., 2010).

Prophylactic regimens for both acute and chronic GVHD traditionally include calcineurin inhibitors (CNI) in combination with either methotrexate (MTX) or mycophenolate mofetil (MMF) in HLA-matched HSCT(Olivieri & Mancini, 2024). This is supported by both the 2020 and 2024 EBMT guidelines(Penack et al., 2024; Penack et al., 2020). However, a 2020 Lawitschka et al. survey on GVHD prophylaxis and treatment in pediatric patients revealed deviations from recommendations. The survey classified patients into subgroups based on both the conditioning and donor type(Lawitschka et al., 2020).

In patients undergoing HCT following myeloablative conditioning, MSD, MMD, and MUD groups were analyzed. According to current guidelines, MTX is a preferred antimetabolite (over MMF) for patients undergoing myeloablative conditioning. However, in patients with contraindications to MTX and those in need of rapid engraftment, MMF can be administered instead(Penack et al., 2024). The MSD group received Cyclosporine A (CsA) alone or with a short course of MTX, and 21% centers reported additional ATG therapy. The MUD group received CsA combined with MTX, with 81% of centers reporting adding anti-thymocyte globulin (ATG) to the regimen. The MMD group received CsA and MTX, and 96% of centers used ATG. Additionally, in the MMD group, 67% of responding centers reported employing ex vivo T-cell depletion (TCD) (Lawitschka et al., 2020). ATG (Thymoglobulin or Grafalon) is recommended for patients undergoing MUD HSCT. It can also be recommended for patients undergoing matched related donor (MRD) peripheral blood stem-cell transplantation(Penack et al., 2024). In Lawitschka's survey, ATG was administered on three consecutive days, with a median dose of Thymoglobulin of 2.5 mg/kg and Grafalon of 10mg/kg. Some centers combined both agents(Lawitschka et al., 2020).

Ex vivo CD34+ cell enrichment has been shown to effectively reduce the occurrence of GVHD in both related and unrelated donor transplantations(Watkins & Qayed, 2023). Furthermore, a pediatric study by Locatelli et al. reported a lower incidence of GVHD in patients who received a,b T- and B-cell-depleted haploidentical HSCT(Locatelli et al., 2017). Similarly, another study found that depletion of naïve T cells (CD45RA+) was associated with a reduced incidence of both acute and chronic GVHD(Bleakley et al., 2022). In Lawitschka's survey, ex vivo TCD included positive selection with anti-CD34 antibodies and negative selection. CD3/19 depletion was used in 93% of centers; the remaining 7% added Alemtuzumab to the stem cell infusate(Lawitschka et al., 2020).

In patients undergoing HCT following reduced-intensity conditioning, CsA + MTX was the most commonly administered therapy(Lawitschka et al., 2020). However, the 2024 guidelines suggest MMF as a preferred antimetabolite for patients receiving non-MAC or reduced-intensity conditioning(Penack et al., 2024).

An emerging prophylactic tool against GVHD is post-transplant cyclophosphamide (PTCy). Its significance is reflected in the new EBMT guidelines, which go beyond PTCy's classical use in haploidentical allogenic HSCT. The combination of PTCy, MMF, and tacrolimus broadly expanded access to haploidentical donor grafts(Watkins & Qayed, 2023). PTCy is recommended in patients receiving HSCT from unrelated MMD; however, PTCy is not preferred over ATG, despite some evidence. Similarly, in MRD cases, PTCy should not be preferred over ATG in GVHD prevention. In addition, recipients of HSCT from MUD should receive PTCy or ATG(Penack et al., 2024).

Another novel method of prophylaxis against GVHD is Abatacept, approved by the FDA in 2021. While the ABA2 trial demonstrated promising results in Abatacept's ability to prevent acute GVHD in MMD patients, the EBMT panel chose not to include Abatacept in their recommendations, as the results supporting its use were deemed insufficient(Penack et al., 2024). Furthermore, the ABA2 trial found no statistically significant difference in acute GVHD incidence in MUD recipients, as well as chronic GVHD among all the examined groups receiving Abatacept(Watkins et al., 2021). Currently, the ABA3 trial examining Abatacept dosing is ongoing(NCT04380740); the results may be of interest to both clinicians and researchers.

Alemtuzumab, a monoclonal antibody, has demonstrated a reduced incidence of GVHD in both related and unrelated donor transplantations when incorporated into a fludarabine-based conditioning protocol(Olivieri & Mancini, 2024). Alemtuzumab has also been recommended by the EBMT/ESID inborn errors working party for HSCT for inborn errors of immunity to prevent graft rejection as well as GVHD(Lankester et al., 2021; Penack et al., 2024).

A 2024 phase 3 trial by Chen et al. evaluated lower gastrointestinal (GI) acute GVHD-free survival at day 180 following allo-HSCT in patients treated with Vedolizumab compared to placebo. The incidence of lower GI acute GVHD events or death was reduced by 55% in the Vedolizumab group (Chen et al., 2024). Additionally, Chopra et al. reported a decreased rate of GI GVHD in patients with inflammatory bowel disease who received Vedolizumab prior to allo-HSCT for inborn errors of immunity(Chopra et al., 2024).

Current evidence indicates that Maraviroc does not provide additional benefit compared to standard prophylactic regimens for GI acute GVHD(Bolanos-Meade et al., 2019). Furthermore, the phase II pediatric study of Maraviroc faced difficulties ensuring consistent administration due to elevated bilirubin levels and transaminases, although these laboratory abnormalities were not caused by Maraviroc. Together, these findings suggest limitations in both efficacy and feasibility for Maraviroc use in a pediatric setting(Khandelwal et al., 2019).

Sirolimus represents a viable alternative to Tacrolimus for the prevention of GVHD in patients undergoing haploidentical HSCT. In a 2023 clinical trial, adult recipients of haploidentical HSCT received either Sirolimus or Tacrolimus in combination with PTCy. The incidence of grade II-IV acute GVHD at day 100 and chronic GVHD at two years was comparable between the two treatment groups(Elmariah et al., 2024). In contrast, a 2017 pediatric study evaluated the addition of Sirolimus to Tacrolimus/MTX for GVHD prophylaxis in children. Although the frequency of grade II-IV acute GVHD was significantly lower in the Sirolimus group, the rates of grade III-IV acute GVHD and chronic GVHD were not significantly different. Additionally, overall survival did not improve with Sirolimus(Pulsipher et al., 2014).

Microbiota transplantation has been investigated as a prophylactic technique for GVHD prevention based on evidence linking microbiota diversity to overall survival. Increased intestinal diversity correlates with reduced mortality in patients undergoing allogenic HCT (Peled et al., 2020). Although this approach has been studied in adults(Reddi et al., 2025), there is currently no published evidence of similar trials conducted in pediatric populations.

Other promising GVHD prophylactic agents include: Sitagliptin(Farag et al., 2021; Qiao et al., 2023) and Ruxolitinib(DeFilipp et al., 2022; DeFilipp et al., 2025).

6.2 First-line Treatment:

Standard systemic treatment for aGVHD is recommended for grades II to IV. According to EBMT guidelines, treatment should begin based on clinical signs. Although biopsies are advised prior to treatment, therapy should not be postponed pending biopsy results (Penack et al., 2024).

Methylprednisolone at an initial dose of 2 mg/kg/day serves as the first-line treatment for aGVHD. Pediatric centers routinely implement this regimen. For grade I or II skin involvement, a reduced dose of 1–2 mg/kg/day is administered(Lawitschka et al., 2020). Furthermore, a dose of 1mg/kg/day is recommended for grade II upper GI manifestations. Dose reduction is not recommended during the first 7 days of treatment; however, parenteral steroids may be substituted with oral formulations during this period(Penack et al., 2024). Notably, 25% of pediatric centers reported initiating dose reduction after only 5 days(Lawitschka et al., 2020). Dose tapering should proceed gradually and be guided by patient response. Upon achieving a complete response, the steroid dose should be reduced to 10% of the initial dose over approximately 4 weeks. EBMT guidelines recommend topical steroids for grade I skin aGVHD. In more advanced stages, topical steroids are used in addition to systemic therapy to improve treatment outcomes. GI aGVHD cases can also be treated with non-absorbable oral steroids like budesonide or beclomethasone, in addition to standard systemic therapy(Penack et al., 2024).

6.3 Steroid-refractory aGVHD:

In cases of steroid resistance or dependence, second-line treatment is recommended(Penack et al., 2024). Approximately 50% of grade III and IV patients are SR(Jamy et al., 2023).

Acute GVHD steroid refractoriness is defined as either:

1. progression in any organ within 3-5 days of steroid therapy with at least 2 mg/kg/day of prednisone equivalent,
2. failure to improve within 5-7 days of steroid therapy,
3. lack of complete response after 28 days of steroid therapy(Schoemans et al., 2018).

Acute GVHD steroid dependence (SD) is defined as either:

1. inability to taper prednisone below 2 mg/kg/day after an initially successful treatment lasting over 7 days.
2. recurrence of aGVHD activity during steroid taper(Schoemans et al., 2018).

In 67% pediatric centers, SR was diagnosed within the first 5 days of treatment, and 87% of centers reported diagnosing aGVHD SR by failure to improve in the individual organ rather than in the overall severity grading. SR was diagnosed early in the occurrence of progression; however, 56% of centers allowed a 2-week period for diagnosis of SR when failure to improve in the overall severity grading was considered. Second-line treatment for SR aGVHD varies significantly between different pediatric centers. Most commonly administered treatments include MMF and extracorporeal photopheresis (ECP)(Lawitschka et al., 2020). The UK Expert Photopheresis Group suggests considering the ECP as a second-line treatment combined with other agents for patients with grade II-IV aGVHD in cases of SR, steroid dependence, and steroid intolerance(Das-Gupta et al., 2014). Ruxolitinib, which has been recently approved by both the FDA and EMA, is recommended in adults with SR aGVHD by EBMT. And while no such recommendation for pediatric patients has been made, studies on pediatric use of Rexolitinib have shown promising results(Cheng et al., 2025; Locatelli et al., 2024). Other agents employed in the management of SR aGVHD in pediatric cases are Infliximab(Sleight et al., 2007), Alemtuzumab(Khandelwal et al., 2016), Vedolizumab(Cisek et al., 2024), and Tocilizumab(Kolb et al., 2015).

Fecal microbiota transplantation (FMT) has also shown promising results in the treatment of SR GI aGVHD in both adult(Malard et al., 2023) and pediatric patients(Fałkowska et al., 2023).Recently, an allogeneic bone marrow-derived mesenchymal stromal cell (MSC) therapy, Remestemcel-L, has been approved by the FDA in pediatric SR aGVHD patients over 2 months. The approval was based on a phase 3 trial, which showed a significant improvement in overall response and survival rate in patients treated with Remestemcel-L. Those results may lead to further investigation of MSC usefulness in the treatment of aGVHD(Kurtzberg et al., 2020).

7. Conclusions

In conclusion, hematopoietic stem cell transplantation has become a life-saving, curative therapy for a diverse range of severe pediatric diseases. However, its success is inextricably linked to the management of graft-versus-host disease, a persistent and life-threatening complication. This review has highlighted the multifaceted nature of GVHD, from its complex immunopathological origins to its varied clinical presentations. Critical to advancing our understanding and management has been the evolution from symptom-based grading systems to more precise, biomarker-driven risk stratification tools, such as the MAGIC algorithm. These innovations are paving the way for more personalized and effective therapeutic interventions.

Despite significant progress in both prophylaxis and treatment, including the emergence of novel agents like ruxolitinib and vedolizumab, many clinical guidelines still lack specific recommendations for the pediatric population. This gap underscores the fundamental need for further research that is specifically focused on the unique immunological landscape of children, particularly the age-related disparity in GVHD risk. Future studies should aim to validate existing adult-based regimens in pediatric cohorts, explore the potential of emerging therapies such as fecal microbiota transplantation, and continue to leverage biomarkers to guide treatment decisions. By addressing these vital unmet clinical demands, we can continue to improve outcomes and the quality of life for young patients undergoing HSCT.

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