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SPECIAL CONSIDERATIONS IN THE DIAGNOSIS AND MANAGEMENT OF CHRONIC GRAFT-VERSUS-HOST DISEASE IN PEDIATRIC PATIENTS

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ABSTRACT

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapy for a variety of pediatric hematologic and non-malignant disorders, yet chronic graft-versus-host disease (cGVHD) remains the primary cause of long-term non-relapse morbidity and mortality. The incidence of cGVHD in children has been increasing, a trend associated with the expanded use of peripheral blood stem cells and unrelated donors. Despite generally lower rates than adults, cGVHD remains a significant and growing clinical problem with profound long-term implications for pediatric survivors, who have a much greater life expectancy.
Objective: This review aims to provide a focused and much-needed overview of cGVHD in children. Specifically, it delineates the unique epidemiological, pathobiological, and clinical characteristics that distinguish the disease in this population, including immunological distinctions, diagnostic challenges, and special considerations for long-term effects. This report highlights the pressing questions in treatment and research, addressing the historical lack of specialized data and emphasizing the principle that "children are not small adults" in the context of this complex condition.
Methods: This review was conducted by systematically analyzing and synthesizing peer-reviewed articles, clinical guidelines, and consensus statements related to pediatric cGVHD. A comprehensive literature search was performed across databases including PubMed, Scopus, and Embase using a combination of keywords such as "pediatric," "chronic GvHD," "children," "hematopoietic stem cell transplantation," "management," "diagnosis," and "long-term effects."
Summary: The lower incidence and severity of cGVHD in children are attributable to distinct biological factors, including superior thymic function and a greater use of bone marrow or cord blood grafts. However, diagnostic challenges persist due to non-specific symptoms and the limitations of adult-derived criteria. The profound and age-specific impacts of the disease and its treatments on growth, neurocognitive development, and infectious risk underscore the disproportionate long-term burden on pediatric survivors. The review discusses therapeutic strategies that prioritize steroid-sparing regimens and the integration of novel targeted inhibitors and cellular therapies.
Conclusion: A paradigm shift is necessary, advocating for dedicated pediatric research, age-adapted diagnostic tools, and a multidisciplinary, holistic approach to long-term survivorship care to optimize the functional status and quality of life for children with cGVHD.

KEYWORDS

Chronic Graft-Versus-Host Disease, Pediatric Transplantation, Hematopoietic Stem Cell Transplantation, Immunosuppression, Supportive Care

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has come a long way from being an unsafe, experimental therapy for end-stage patients to a curative approach to a variety of hematological malignancies and non-neoplastic diseases(Bosi et al., 2005). This complex process involves the intravenous infusion of histocompatible donor-donated hematopoietic stem and progenitor cells following pre-transplant conditioning of the recipient(Giralt & Bishop, 2009). Despite significant advances in high-resolution HLA typing, conditioning regimens, and support care, transplant-related death remains a significant barrier, and the predominant causes of morbidity and mortality are graft-versus-host disease (GvHD) and infection complications(van Lier et al., 2023). Among the late complications, chronic GvHD (cGvHD) is the most significant cause of long-term morbidity and non-relapse mortality in survivors beyond two years post-transplant(Presland, 2016). It presents as a diffuse, multi-organ, autoimmune-like inflammatory and sclerotic process with the ability to affect almost any organ system, such as skin, oral mucosa, liver, and eyes(Lee & Flowers, 2008).

The incidence of cGvHD in the pediatric population is high, with rates oftentimes reported in the range of 20% to 50%. This is typically lower than the rates in adult transplant recipients, up to 60% to 70 %(Baird et al., 2010). However, recent trends have shown an increase in the incidence of cGvHD in children, a phenomenon associated with the expanded use of peripheral blood stem cells and unrelated donors in pediatric transplantation(Meisel et al., 2007). This underscores that while cGvHD may be less frequent in children, it remains a significant and growing clinical problem. The pathophysiologic reasons behind this differential incidence are essential to understanding the peculiar nature of the disease in the pediatric group.

A much-needed focused review of cGvHD in children is critical since the patient population has historically been understudied compared to adults and thus has extremely limited specialized data on its pathophysiology, clinical presentation, diagnosis, and late effects(Sobkowiak-Sobierajska et al., 2022). The widely recognized principle that "children are not small adults" is particularly relevant in the context of cGvHD, as the developing immune system of a child presents unique challenges and results in distinct biological and clinical profiles(Sobkowiak-Sobierajska et al., 2022). As pediatric survivors of HSCT have a much larger life expectancy than their adult counterparts, the long-term implications of cGvHD and its impact on psychomotor development, functional status, and well-being are of extraordinary importance(Inagaki et al., 2015). It is hoped that this report will capture the current knowledge of pediatric cGvHD, highlighting its unique epidemiological, pathobiological, and clinical characteristics, and the pressing questions in the long-term treatment and research of cGvHD.

2. Pathophysiological and Immunological Distinctions

The clinical course of cGVHD in children often differs from that in adults, with a generally lower incidence and less severe disease presentation. This observed difference is not merely a statistical anomaly but is rooted in fundamental biological and clinical distinctions between the two populations. A key reason for this disparity is the innate adaptive biology and greater plasticity of the pediatric immune system, with a crucial factor being the stronger thymic function in children(Jandin et al., 2023; Qayed et al., 2018).

2.1. The Role of Thymic Function and Immune Plasticity

The thymus is an organ critical for the maturation and selection of T cells. In healthy individuals, the thymus ensures that self-reactive T cells are eliminated in a process known as negative selection(Sprent & Kishimoto, 2002). This mechanism, central to maintaining immune tolerance, is often compromised in HSCT recipients due to the damaging effects of conditioning regimens, prior chemotherapy, and age-related atrophy. However, children have a more functional thymus than adults, enabling a more efficient negative selection process. This improved thymic function allows for the de novo generation and differentiation of donor-derived lymphoid-myeloid progenitors into a diverse repertoire of T cells, which are less prone to attacking host tissues. This superior ability to generate new, tolerant T cells is thought to be a primary contributor to the lower rates and reduced severity of cGVHD in the pediatric population(Janeczko-Czarnecka et al., 2020; Lynch et al., 2009; Sakoda et al., 2007). This biological difference suggests that strategies aimed at protecting or rejuvenating the thymus could hold promise for preventing cGVHD, a research area that has seen some experimental success but has yet to translate into successful clinical trials(Qayed et al., 2018).

2.2. Influence of Graft Source and Underlying Disease

Beyond innate biology, clinical practice also contributes to the differing cGVHD landscape. Children are more likely to receive stem cells from bone marrow or umbilical cord blood, as opposed to the peripheral blood stem cells (PBSC) more commonly used in adult transplants(Keesler et al., 2018; Wall, 2004). The use of bone marrow and cord blood grafts is associated with a lower risk of cGVHD compared to PBSC transplants(Wynn et al., 2022) . Furthermore, the underlying diseases requiring HSCT in children often differ from those in adults. A higher proportion of pediatric transplants are performed for non-malignant conditions, such as inborn errors of immunity and benign hematologic disorders, whereas adult transplants are frequently for leukemias and myelodysplastic syndromes(Miskiewicz-Bujna et al., 2022). The combination of these factors - a more tolerant immune system, the use of different graft sources, and a distinct spectrum of underlying diseases - forms a multi-factorial causal chain that results in a more favorable cGVHD profile for many pediatric patients.

2.3. Immune Reconstitution and Therapeutic Response

Age-related differences in immune cell populations and cytokine profiles at the onset of cGvHD are notable. Comparative analyses have revealed that while both children and adults exhibit elevated levels of ST2 and naïve helper T (Th) cells and a depression of regulatory NK (NKreg) cells, significant differences exist in B cell and regulatory T cell (Treg) populations. In children with cGvHD, there is a broad suppression of newly formed B cells, whereas adults show an increase in specific transitional B cell subsets and a decrease in a population associated with regulatory B (Breg) cells. Furthermore, Treg abnormalities in children primarily involve the memory subset, while in adults, they are concentrated in the naïve Treg population. The onset of puberty appears to mark a transition, with the immune profiles of adolescents becoming more adult-like, suggesting that hormonal changes may influence immune dysregulation(Cuvelier et al., 2020).

The pattern of immune reconstitution post-transplant also reveals age-specific differences. While T-cell recovery is a slow, multi-year process in both populations, pediatric patients appear to have a more responsive regulatory T-cell compartment. This was demonstrated in a study of patients treated with low-dose interleukin-2 (IL-2) for cGVHD, where pediatric patients showed a greater increase in their number of regulatory T cells relative to natural killer (NK) cells compared to adults(Whangbo et al., 2019). This heightened regulatory T-cell response further reinforces the concept of a more tolerant pediatric immune system. This finding suggests, that children may respond better to immunomodulatory therapies designed to restore immune tolerance and could be particularly good candidates for future strategies that focus on expanding regulatory T-cell function.

3. Diagnosis in Children

3.1 Symptom Recognition

The diagnosis of cGvHD in children is often complicated by nonspecific symptoms and the inability of younger, non-verbal patients to articulate their experiences(Haroun et al., 2023). This is particularly challenging for assessing organ systems like the lungs, where symptoms of dyspnea can be difficult to evaluate, or for oral and ocular involvement, where sensations of dryness or pain must be inferred from observation(Haroun et al., 2023; Sobkowiak-Sobierajska et al., 2022). For example, the Lee cGvHD Symptom Scale, a validated tool in adults, shows only moderate concordance between symptoms experienced by children

and those reported by their caregivers (Haroun et al., 2023). Experienced pediatric transplant physicians have been shown to misclassify cGvHD in as many as 28% of cases, often mistaking it for late-acute GvHD (L - aGVHD) or other non-GvHD conditions like infections or drug reactions(Cuvelier et al., 2019).

3.2 Biomarkers

To improve diagnostic accuracy, significant research has focused on identifying biomarkers. However, their utility in pediatric cGvHD has limitations, as most studies have been conducted in mixed-age or adult-only cohorts, and immune reconstitution is an age-dependent process(Milosevic et al., 2022; Sobkowiak-Sobierajska et al., 2022).

Several promising biomarkers have been identified in pediatric cohorts. An early study found that soluble B-cell activating factor (sBAFF), anti-dsDNA antibody, soluble IL-2 receptor alpha (sIL-2Rα), and soluble CD13 (sCD13) were elevated in children with cGvHD(Fujii et al., 2008). While these markers demonstrated high specificity, their individual sensitivity was relatively low, ranging from 42% to 53%, though sensitivity improved when markers were analyzed in combination(Fujii et al., 2008).

More recent, large-scale prospective studies have confirmed and expanded upon these findings. The onset of pediatric cGvHD is characterized by decreased populations of NKreg cells, naive Th cells, and naive Tregs, alongside elevated plasma levels of CXCL9, CXCL10, CXCL11, ST2, ICAM-1, and sCD13(Cuvelier et al., 2023). Notably, sCD13 and ICAM-1 levels appear to be most significantly increased in prepubertal children(Cuvelier et al., 2020). Other studies have consistently identified low frequencies of CD19+CD27+ memory B-cells and increased frequencies of circulating CD19+CD21low B-cells, a hyperactivated subset, in children with active cGvHD (Lawitschka et al., 2019).

Given that single markers are unlikely to capture the heterogeneity of pediatric cGvHD, a machine learning-based diagnostic classifier combining multiple cellular, plasma, and clinical factors has been developed. This model achieved a high area under the curve (AUC) of 0.89, with a positive predictive value of 82% and a negative predictive value of 80%, suggesting it could be a powerful tool to aid clinicians in differentiating cGvHD from other conditions(Cuvelier et al., 2023). However, this classifier requires validation in future prospective studies before it can be implemented in clinical practice(Cuvelier et al., 2023).

3.3 Pediatric Consensus Criteria

The National Institutes of Health (NIH) Consensus Criteria are the standard for cGvHD diagnosis and staging but were developed primarily from adult data and have not been adequately validated in pediatric populations(Haroun et al., 2023; Sobkowiak-Sobierajska et al., 2022). A major challenge in applying these criteria to children is that some of the recommended evaluation methods are difficult to perform in younger patients. For instance, the diagnosis of pulmonary cGvHD relies heavily on pulmonary function tests (PFTs), which are unreliable or impossible to perform in children under the age of six(Haroun et al., 2023; Schoemans et al., 2018). This has led to the observation that the 2014 NIH criteria for bronchiolitis obliterans syndrome (BOS) perform poorly in children(Cuvelier et al., 2019).

A large prospective study assessing the application of the NIH criteria in 27 pediatric centers found the criteria to be feasible and reliable overall. However, it revealed that 28.2% of cGvHD cases initially reported by transplant centers were reclassified upon central review, most commonly as L-aGVHD(Cuvelier et al., 2019). This high rate of reclassification underscores the diagnostic ambiguity and the need for careful, standardized assessment. Furthermore, one study in a pediatric cohort found that the initial global severity score proposed by the NIH criteria had limited correlation with GvHD-specific outcomes like the duration of immunosuppressive treatment, possibly due to the generally favorable response to therapy in children(Lee et al., 2011). While there is an unmet need for pediatric-adapted GvHD assessment tools, current recommendations suggest using weight-adapted measures for diarrhea and appropriate reference values for lung function, while relying on clinical evaluation and imaging for lung GvHD in young children who cannot perform PFTs(Schoemans et al., 2018).

4. Special Considerations in Pediatric GvHD

Chronic graft-versus-host disease (cGVHD) presents distinct and considerable challenges in the pediatric population. The protracted timeline of growth and development in these patients, coupled with their greater life expectancy relative to adults, renders the long-term consequences of the disease and its treatment particularly critical. The developing organ systems of a child are uniquely vulnerable to the systemic inflammation and therapeutic toxicities inherent to cGVHD, leading to a spectrum of late effects that can alter their entire life course. This subsection will delineate the specific impacts of cGVHD on pediatric growth, neurocognitive function, and infectious risk, in addition to the overarching issues that affect long-term survivorship and quality of life.

4.1 Growth and Developmental Impacts

The clinical management of cGVHD in pediatric patients is complicated by the profound effects the disease exerts on physical growth and development. Both the pathophysiology of the disease and its primary therapeutic interventions, particularly prolonged corticosteroid therapy, contribute to significant long-term endocrinologic and musculoskeletal sequelae (Khandelwal et al., 2025).

Compromised nutritional status is a frequent and early complication. Children with multi-organ cGVHD exhibit a heightened risk for weight loss, failure to thrive, and a significant reduction in body mass index (BMI). This wasting syndrome may precede overt signs of organ involvement, potentially indicating an underlying altered metabolic state or subclinical malabsorption that disrupts the efficient utilization of nutrients(Baird et al., 2010; Haroun et al., 2023). This suboptimal nutritional state can subsequently impede normal growth trajectories. Indeed, cGVHD and its requisite treatments are known contributors to attenuated linear growth velocity, which may culminate in a reduced final adult height. Although a subset of younger patients may exhibit compensatory "catch-up" growth following the resolution of cGVHD and cessation of steroids, sufficient data to reliably predict this outcome are currently lacking, making proactive nutritional support and the pursuit of steroid-sparing regimens critical(Khandelwal et al., 2025).

Furthermore, pubertal development is susceptible to disruption. Retrospective data indicate that extensive cGVHD is an independent risk factor for delayed puberty in both female and male patients(Haroun et al., 2023; Khandelwal et al., 2025). This delay can have significant psychological repercussions, affecting self-esteem and peer relationships during a critical period of social development. The putative underlying mechanism involves an alloimmune-mediated assault on ovarian or testicular tissues, a hypothesis substantiated by murine models that demonstrate donor T-cell infiltration and resultant damage to ovarian follicles and Leydig cells(Khandelwal et al., 2025).

Skeletal health represents another area of significant concern. The chronic administration of corticosteroids for cGVHD management, a cornerstone of therapy, confers a substantial risk for the development of osteopenia, osteoporosis, and avascular necrosis in pediatric survivors (Baird et al., 2010; Haroun et al., 2023). These pathologies, characterized by reduced bone mineral density and bone tissue death due to insufficient blood supply, can result in debilitating pain, fractures from minimal trauma, and chronic mobility impairments, thereby exacerbating the physical burden of the disease(Sobkowiak-Sobierajska et al., 2022).

4.2 Neurocognitive and Psychological Effects

The ramifications of cGVHD extend beyond somatic health, significantly affecting the neurocognitive and psychological well-being of pediatric survivors. A confluence of factors, including the primary underlying pathology, intensive therapeutic regimens, protracted hospitalizations, and social isolation, collectively constitutes a significant risk for the emergence of long-term deficits in domains such as attention, memory, and executive function (Schofield et al., 2022).

Multiple studies have documented a decline in cognitive function among pediatric patients subsequent to hematopoietic stem cell transplantation (HSCT), with cGVHD identified as a material contributing factor(Schofield et al., 2022). An investigation involving children with Severe Combined Immunodeficiency (SCID) identified a statistically significant decline in the Mental Developmental Index (MDI) at one-year post-HSCT. Although these scores tended to stabilize over subsequent years, the initial decrement suggests that patients acquire developmental skills at a decelerated rate compared to their healthy peers. This developmental lag is presumably exacerbated by the protective isolation and prolonged hospitalization that curtail exposure to essential social, environmental, and educational stimuli necessary for normal cognitive maturation(Lin et al., 2009). Congruently, a study of pediatric

HSCT survivors in China reported that a notable percentage of children aged 3 to 6 years presented with deficits across cognitive, motor, language, and social domains(Luo et al., 2019).

The psychological burden imposed upon this pediatric population is considerable. Survivors exhibit an elevated risk for the development of anxiety, depression, and post-traumatic stress disorder, conditions that may persist for several years post-transplantation and interfere with academic and social progression(Haroun et al., 2023). School-aged children and adolescents may manifest symptoms of social phobia, school phobia, interpersonal sensitivity, and hostility, reflecting the profound disruption to their lives(Luo et al., 2019). These psychological sequelae can manifest as difficulties in peer relationships, social withdrawal, and diminished self-esteem, thereby complicating the process of social reintegration(Haroun et al., 2023). Ultimately, the presence of cGVHD is recognized as one of the most potent factors correlated with diminished quality of life, which negatively affects both physical and mental health and results in lasting functional impairments(Baird et al., 2010).

4.3 Management of Infections and Vaccination Schedules

Pediatric patients with active cGVHD exhibit a state of profound immunocompromise, which predisposes them to a heightened risk of life-threatening infections. This susceptibility arises from a confluence of factors, including immune dysregulation intrinsic to cGVHD, delayed T- and B-cell immune reconstitution, functional asplenia, and the consequences of long-term immunosuppressive therapies(Baird et al., 2010; Haroun et al., 2023). The compromised mucosal barriers often seen in cGVHD further lower the threshold for pathogen invasion. In this patient cohort, opportunistic infections represent a principal cause of non-relapse mortality (Baird et al., 2010).

In light of this elevated risk, the implementation of comprehensive infectious prophylaxis is imperative. Prophylactic treatment against encapsulated bacteria, such as *Streptococcus pneumoniae*—a particular threat in the context of functional asplenia—is recommended for patients undergoing active treatment for cGVHD(Ifversen et al., 2021; Sobkowiak-Sobierajska et al., 2022). Likewise, prophylaxis for *Pneumocystis jirovecii* pneumonia is of critical importance and ought to be maintained for a minimum of six months following the cessation of all immunosuppressive therapy(Baird et al., 2010). For patients receiving high-dose corticosteroids or other intensive immunosuppressive regimens, prophylaxis against mold infections is also advised(Sobkowiak-Sobierajska et al., 2022). In cases of severe hypogammaglobulinemia (IgG < 400 mg/dL) accompanied by recurrent infections, intravenous immunoglobulin (IVIG) replacement is frequently employed to provide passive immunity (Baird et al., 2010).

Revaccination constitutes a critical component of long-term management, as patients experience a loss of pre-existing immunity to vaccine-preventable diseases after HSCT. Consensus guidelines advocate for the initiation of revaccination with inactivated vaccines at six months post-HSCT, irrespective of cGVHD status(Ifversen et al., 2021); Reynolds et al., 2023). This regimen typically encompasses a primary series of the DTaP/IPV/HBV/Hib combination vaccine and the 13-valent pneumococcal conjugate vaccine (PCV13)(Ifversen et al., 2021). Although immunogenicity may be attenuated in patients receiving immunosuppressive therapy, the administration of inactivated vaccines is generally regarded as safe. In contrast, the use of live attenuated vaccines (e.g., MMR, varicella) is strictly contraindicated in patients with active cGVHD due to the risk of inducing vaccine-strain disease. Their administration should be deferred until at least 24 months post-HSCT and is permissible only after the patient has been withdrawn from all immunosuppressive therapy for a minimum of three months and is deemed immunocompetent(Haroun et al., 2023; Ifversen et al., 2021; Reynolds et al., 2023).

4.4 Long-Term Survivorship and Quality of Life Issues

Chronic GvHD has enduring and significant repercussions for pediatric transplant survivors, adversely affecting their long-term health, functional status, and overall quality of life(Haroun et al., 2023; Sobkowiak-Sobierajska et al., 2022). Beyond the immediate challenges of the disease, moderate-to-severe cGVHD persists as a primary contributor to late treatment-related mortality, shaping the survivorship experience in fundamental ways(Sobkowiak-Sobierajska et al., 2022).

Survivors with a history of cGVHD experience an elevated burden of chronic health conditions. These individuals are at a heightened risk for the development of metabolic syndrome, hypertension, dyslipidemia, and premature arteriosclerotic cardiovascular(Khandelwal et al., 2025). The persistent inflammatory milieu characteristic of cGVHD, which shares pathogenic pathways with atherosclerosis, in conjunction with the adverse effects of therapies such as corticosteroids, contributes to this augmented cardiometabolic

risk(Khandelwal et al., 2025). Moreover, cGVHD and the associated immunosuppressive treatments are established risk factors for the development of subsequent malignant neoplasms, with a particular predisposition for squamous cell carcinomas of the skin and oropharynx, likely due to impaired immune surveillance and chronic tissue inflammation(Haroun et al., 2023).

The functional capacity of survivors may be substantially curtailed, impacting their ability to participate in age-appropriate activities, including education and social events. A retrospective analysis revealed that among pediatric patients with cGVHD who survived beyond five years, 34% exhibited persistent functional impairment, with 22% having a Karnofsky performance score below 70, indicating a need for considerable assistance with daily activities(Haroun et al., 2023). Even upon reaching adulthood, long-term survivors frequently report persistent challenges, including debilitating fatigue and insomnia, which further detract from their well-being(Beer et al., 2025). This complex interplay of physical, psychological, and cognitive challenges underscores the necessity for a multidisciplinary and lifelong model of follow-up care for pediatric patients affected by cGVHD, with the objectives of mitigating long-term toxicities and optimizing their quality of life.

5. Therapeutic Strategies for Pediatric cGVHD: Key Differences from Adults

First-line treatment for cGVHD in children, as in adults, relies on systemic glucocorticoids, often administered at a dose of 1 mg/kg/day, in combination with a calcineurin inhibitor such as cyclosporine or tacrolimus(Penack et al., 2024). While this regimen can achieve disease control, prolonged exposure to corticosteroids in the pediatric setting carries a disproportionate risk of adverse outcomes, including impaired linear growth, osteonecrosis, osteoporosis, and psychosocial sequelae(Kim et al., 2024). Consequently, a more aggressive pursuit of steroid-sparing strategies has become a defining feature of pediatric cGVHD management, in contrast to the adult population where tolerance to steroid toxicity is generally higher(Sobkowiak-Sobierajska et al., 2022).

Several agents have been investigated as alternatives or adjuncts to corticosteroids in children. Mycophenolate mofetil has demonstrated overall response rates of 50 to 79 percent in pediatric cohorts, with some patients achieving long-term remission. Sirolimus, a mammalian target of rapamycin inhibitor widely used in adult practice, has shown promising response rates in pediatric studies, although robust pharmacokinetic data in children remain limited(Baird et al., 2010). Pentostatin has been associated with high response rates in younger patients, yet its use is tempered by an increased incidence of infectious complications(Jacobsohn et al., 2009). Extracorporeal photopheresis has emerged as a particularly attractive modality in pediatrics, with response rates approaching 60 to 78 percent and an ability to reduce or discontinue corticosteroids in nearly half of patients, while offering a favorable safety profile(Baird et al., 2010).

Targeted therapies have further expanded the therapeutic landscape in pediatric cGVHD. Rituximab, an anti-CD20 monoclonal antibody, has demonstrated efficacy in skin and musculoskeletal involvement, though its use is largely extrapolated from adult and mixed-population studies(Kim et al., 2010). More recently, small molecule inhibitors have been incorporated into pediatric care. Ruxolitinib, a Janus kinase 1/2 inhibitor, has shown overall response rates of approximately 70 percent in children with steroid-refractory disease, though the risks of cytopenia and opportunistic infection necessitate careful monitoring(Wang et al., 2022). Belumosudil, a selective ROCK2 inhibitor, received regulatory approval for children aged 12 years and older after two or more prior lines of therapy, with encouraging response rates of 75 percent(Cutler et al., 2021). Similarly, ibrutinib, a Bruton's tyrosine kinase inhibitor, is now available for children as young as one year with refractory cGVHD(Carpenter et al., 2022). Most recently, axatilimab, an anti-CSF1R antibody targeting macrophage-driven fibrosis, was approved in 2024 for patients over 40 kilograms who have failed at least two systemic regimens, representing a new macrophage-directed approach(Keam, 2024).

Cellular therapies and graft engineering strategies have become increasingly relevant in the pediatric context. Remestemcel-L, a mesenchymal stromal cell therapy, received FDA approval in late 2024 for children as young as two months with steroid-refractory acute GVHD, and ongoing studies suggest potential applicability in the chronic setting as well. Manipulation of the graft itself, particularly through selective depletion of naïve T cells, has shown promise in dramatically reducing the incidence of cGVHD in pediatric recipients, with early studies reporting reductions from 30–60 percent to single digits(Mahat et al., 2025). Such approaches underscore the unique opportunities available in pediatric transplantation, where long-term horizon and lower baseline cGVHD incidence support the integration of preventive strategies.

Supportive care remains integral to pediatric cGVHD management and highlights further differences from adult practice. Local therapies, such as topical corticosteroids, ocular lubricants, and oral rinses, are prioritized to minimize systemic immunosuppression. Infection prophylaxis through immunoglobulin

replacement and antimicrobial regimens is often emphasized more strongly in children, given their immunologic immaturity and greater vulnerability to infectious morbidity. Moreover, multidisciplinary care is indispensable, encompassing endocrinologic surveillance for growth and bone health, physical rehabilitation to mitigate contractures, and psychosocial support to ensure developmental well-being(Kim et al., 2024).

Taken together, the management of cGVHD in children diverges from that of adults not only in the choice and sequence of pharmacologic agents but also in the overarching philosophy of care. Pediatric strategies prioritize minimization of corticosteroid exposure, careful adjustment of drug dosing in the absence of robust pediatric pharmacokinetic data, and greater reliance on cellular and graft-based innovations. In addition, the integration of supportive, developmental, and psychosocial interventions distinguishes pediatric care, reflecting the long-term horizon these patients face. As novel targeted agents and cellular therapies continue to evolve, pediatric-specific clinical trials will be essential to refine therapeutic algorithms and ensure that the unique needs of children with cGVHD are addressed(Sobkowiak-Sobierajska et al., 2022).

6. Conclusions

Chronic graft-versus-host disease represents the most critical barrier to long-term survival and quality of life following allogeneic hematopoietic stem cell transplantation in the pediatric population. Although children exhibit biological advantages—namely superior thymic function and immune plasticity—that result in a generally lower incidence and less severe disease phenotype than adults, the complexity and long-term sequelae of cGVHD remain substantial and distinct. The present analysis underscores the need for pediatric-specific protocols across the disease spectrum. Pathophysiologically, the differential influence of graft source and an inherently more responsive T-regulatory compartment distinguish the pediatric response. Diagnostically, the limitations of applying adult-derived tools, such as the NIH consensus criteria, coupled with the difficulties in assessing subjective symptoms in young patients, necessitate the validation and integration of multidimensional biomarkers and machine learning-based classifiers for enhanced diagnostic accuracy. The consequences of cGVHD in children are amplified by their extended life expectancy and ongoing development. Systemic inflammation and prolonged corticosteroid exposure confer disproportionate risk for attenuated growth, delayed puberty, skeletal morbidity (osteoporosis, avascular necrosis), and significant neurocognitive and psychological impairment. This susceptibility mandates a shift in therapeutic focus. Management strategies must pivot toward minimizing systemic toxicity. The aggressive pursuit of steroid-sparing regimens through second-line agents like extracorporeal photopheresis (ECP) and targeted small-molecule inhibitors (ruxolitinib, belumosudil, ibrutinib, axatilimab) is paramount. Furthermore, integrating graft-engineering techniques and cellular therapies (Remestemcel-L) holds immense promise for both prevention and treatment by mitigating the alloreactivity while preserving or enhancing tolerance. In conclusion, the effective long-term management of pediatric cGVHD transcends pharmacologic intervention. It demands a multidisciplinary, lifelong commitment to survivorship, encompassing comprehensive infectious prophylaxis, endocrinologic surveillance, functional rehabilitation, and integrated psychosocial support. Future research must prioritize dedicated pediatric clinical trials to solidify pharmacokinetic data, validate dose-optimized regimens, and establish outcomes measures that accurately capture the unique developmental and quality-of-life needs of this vulnerable population. Only through such focused investigation can we ensure that HSCT fully realizes its potential as a curative modality for children.

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