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Chronic Graft Versus Host Disease (GVHD) in Children

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Keywords

chronic graft versus host disease; hematopoeitic stem cell transplant

Introduction

Allogeneic transplantation in pediatrics

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative approach for many pediatric diseases. According to the most recent analysis from the Center of International Blood and Marrow Transplant Research (CIBMTR) data, approximately 4,500 allo-HSCTs are performed each year in children less than 20 years of age [1]. The majority of children are transplanted for malignancy, however increasing numbers receive an allo-HSCT for non-malignant diseases such as bone marrow failure, immunodeficiency and certain metabolic syndromes / disorders [2-7]. Concurrent with increasing indications for allo-HSCT, there has been a surge of interest in immune modulation to harness the graft versus tumor (GVT) effects when this procedure is used for hematologic malignancies. These factors along with improvements in the safety of allo-HSCT have led to an expanding population of long-term survivors, many of whom suffer from long-term toxicities, including chronic graft versus host disease (cGVHD).

Chronic Graft-Versus-Host Disease (cGVHD)

cGVHD is the most significant non-relapse cause of morbidity and mortality following allo-HSCT for malignant disease [8-12]. Although the rates of cGVHD tend to be lower in children (20-50%) than adults (60-70%) [13-16], the incidence of cGVHD in the pediatric population

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is substantial and has increased recently in association with the expanded use of peripheral blood stem cells and unrelated donors [17-22]. cGVHD has been historically characterized by autoimmune and alloimmune dysregulation occurring after the first 100 days of allo-HSCT [15,23]. A newer set of diagnostic criteria have been developed and refined the definition of cGVHD to include the development of diagnostic features of immune dysfunction that may be present before day 100 and almost always occur within 3 years post-transplant [24]. The median onset is of cGVHD is approximately 6 months following allo-HSCT [15]. As opposed to acute GVHD (aGVHD), which involves the skin, liver and gastrointestinal (GI) tract, cGVHD can involve almost any organ of the body. Importantly, cGVHD leads to significant morbidity, diminished quality of life and decreased overall survival.

Incidence of cGVHD in pediatrics

The rates of cGVHD in the pediatric population depend on several variables and can range from as low as 6% in matched sibling cord blood transplants [25] to as high as 65% in matched unrelated donor (MUD) peripheral blood stem cell (PBSC) transplants [26]. In 2000, Eurocord and the International Bone Marrow Transplant Registry (IBMTR) compared 113 sibling cord-blood HSCTs to 2,052 HLA-matched sibling bone marrow transplants (BMTs). All of these patients were 15 years of age or younger and received a myeloablative preparative regimen, and most received cyclosporine (CSA)-based GVHD prophylaxis. The cord blood population had a 6% 3-year cumulative incidence of cGVHD vs. 15% in the bone marrow recipients [27]. In 2002, Zecca *et al.* published a retrospective analysis of 696 consecutive pediatric patients that underwent transplant in Italy between 1991 and 1999. The indication for transplant was malignancy in two-thirds, almost all patients received bone marrow (BM) as the stem cell source and two-thirds had HLA-matched sibling donors. The overall incidence of cGVHD in this population was 25%, with a median time to diagnosis of 116 days after transplantation [19].

Pathophysiology

The scientific basis for the development of cGVHD is poorly understood and there are limited data specific to pediatrics. Historically, alloreactive donor T cells have been the primary factor implicated in the pathophysiology of cGVHD. However, a recent randomized trial failed to demonstrate that T cell depletion reduced cGVHD incidence [28]. Therefore, the role of direct T cell mediated allogeneic immune responses in cGVHD is not clear, and there is no strong correlation between the number of minor histocompatibility antigen specific T cells and cGVHD [29,30].

Evidence suggests that B cells also play a role in disease development [31]. B-lymphocytes have at least two important functions: production of antibodies and presentation of antigens to T cells, both of which may contribute to cGVHD [32-35]. A coordinated B-T response to minor histo-compatibility alloantigens (mHA) is well described [36,37], as is significant high titer antibody responses to mHA that correlate with cGVHD in patients [38]. Elevated levels of nonspecific auto-(vs. allo-) antibodies have repeatedly been described in association with cGVHD and include: anti-nuclear antibody (ANA) [32,33,39]; anti-dsDNA antibody [40]; anti-mitochondrial antibody[39]; anti-cardiolipin antibody[39]; anti-smooth muscle antibody (ASMA); platelet antibodies; and anti-neutrophil antibodies [23,33,40-42]. In addition, anti-platelet-derived growth factor receptor (PDGFR) antibodies have been associated with sclerotic cGVHD [43] and are implicated in the fibrosis in idiopathic scleroderma, which shares many clinical features with classic cGVHD [44]. Probably the best-documented, alloantibody association with cGVHD involves the H-Y antigen. Males who have received allo-HSCT from female donors are at higher risk for both aGVHD and cGVHD [37,45,46]. The Miklos group showed the H-Y antibodies develop 4-12 months after BMT in approximately 50% of males

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receiving allo-HSCT from female donors. The cumulative incidence of cGVHD in the presence of H-Y antibodies was found to be 89% at 5 yrs post BMT versus 31% in the absence of H-Y antibodies ($p<0.0001$). Moreover, responses to the anti-B cell therapy, Rituximab (anti-CD20 monoclonal antibody) in steroid-refractory cGVHD strongly suggest that B cells play a significant role in this disease [31,47].

Soluble factors may also play a role in the pathogenesis of cGVHD. Upon activation during cGVHD, dendritic cells (DCs) and B-lymphocytes secrete inflammatory cytokines after recognition of their cognate antigen. DCs and macrophages produce monocyte chemoattractant protein-1 (MCP-1) [48,49], interleukin (IL)-6 [50,51], transforming growth factor-beta (TGF-ß) [52] and interferon-gamma (IFN-γ) which has been implicated in autoimmune disease and GVHD [53]. Soluble IL-2 receptor alpha (sIL-2Rα), as a marker of activated T cells, correlates with severity of aGVHD [54-56] and cGVHD [57] and with other autoimmune diseases [58, 59]. Specifically, cutaneous cGVHD has been associated with PDGF elevation [60,61], cGVHD-associated sclerosis with high levels of TGF-ß, fatigue and wasting with high levels of TNF-α, and immunodeficiency with high levels of IL-10 and TGF-ß [62]. Finally, cytokine polymorphisms of donor and recipient IL-1 and IL-6 genes, donor TNF receptor type II 169RR-homozygous genotype, recipient IL-10 GG-homozygosity, and recipient IL-1Rα polymorphisms may also play a role [31,63-66].

The Children's Oncology Group (COG) recently published an analysis of peripheral blood biomarkers found in 52 newly diagnosed children with extensive cGVHD. Peripheral blood samples were evaluated for 13 known or suspected biomarkers and were compared to 28 time-matched controls with no evidence of cGVHD. Four plasma biomarkers (soluble B cell activating factor (sBAFF,) sCD13, anti-dsDNA, and sIL2R α) and one cellular biomarker (Toll like receptor 9 (TLR9) high expressing cytosine-phosphate-guanosine (CpG) responsive B cells) correlated with the diagnosis of cGVHD [67] and in combination, had both high specificity (84%) and sensitivity (100%) for the diagnosis of cGVHD. Soluble BAFF, anti-dsDNA antibody, soluble IL-2 receptor α, and soluble CD13 were elevated in early onset cGVHD when compared to controls. Furthermore, sBAFF and anti-dsDNA were elevated in late onset cGVHD. Levels of sBAFF and sCD13 were higher in patients with hepatic cGVHD, whereas anti-dsDNA levels were higher in patients with joint, sclerodermatous, and ocular involvement. Elevated sBAFF was significantly associated with lichenoid skin rash and joint involvement, elevated IL-6, MCP-1 with joint, and elevated anti-cardiolipin antibody with ocular involvement. All of these associations were statistically significant. None of the markers evaluated were associated with gastrointestinal, pulmonary, or musculoskeletal cGVHD [68]. Biomarkers have the potential to help predict the risk of developing cGVHD, improving classification, and directing cGVHD research and treatment, but require further investigation and large study validation is required.

Risk Factors

Known risk factors that have been repeatedly associated with higher risks of cGVHD include: precedent aGVHD, unrelated donor, mismatched donor, PBSCs as donor source, older recipient or donor age, female donor into a male recipient, the use of Total Body Irradiation (TBI), and malignant disease (Table 1) [14,19,27,69,70]. By far, the strongest predictor for the development of cGVHD appears to be the severity of aGVHD [14,19]. Conversely, factors that have been found to be associated with lower rates of cGVHD include the use of cord-blood stem cells and the use of methotrexate (MTX) with CSA for GVHD prophylaxis [19,25,27, 69]. Lower donor or recipient age also reduces the incidence of cGVHD, which has been hypothesized to be due in part to a lower exposure of young donors and recipients to infections [71,72]. Importantly, the following factors have little or no impact on the risk of developing

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cGVHD: t-cell depletion of the stem cell graft [69,73-77], CD34+ cell dose in the graft [78], or the use of prolonged immunosuppression [79].

While *ex vivo* strategies to deplete donor T cells have not significantly influenced cGVHD rates [69,73-77], the addition of antithymocyte globulin (ATG) [80,81] or Campath-1H to the conditioning regimen [82] does appear to impact the development of cGVHD. ATG is widely used before allo-HSCT particularly with HLA-matched unrelated donors or mismatched relatives to prevent both graft rejection and GVHD. The addition of ATG has resulted in low rates of GVHD after pediatric mismatched cord blood transplant similar to those found in matched unrelated BM transplants [80]. Notably, many UCB transplant regimens incorporate ATG suggesting a possible contribution of this agent to the low rates of GVHD. Despite encouraging results, ATG may adversely impact post transplant immune reconstitution [83]. The reasons why *in vivo* T cell depletion is more effective in preventing GVHD compared to *ex vivo* depletion are incompletely understood. However, agents such as Campath and ATG have a long half-life in the recipient, affecting not only donor T cells, but also antigen presenting cells (APCs), Natural Killer (NK) cells, regulatory T cells, and B cells in both the graft and the recipient. The subsequent effects on post transplant proliferation, cell trafficking and signaling likely promoting a more tolerogenic environment [84,85].

Allo-HSCT using unrelated, volunteer donors remains a significant risk factor for the development of cGVHD. Fifty percent of allo-HSCT performed in patients less than 20 years of age are from unrelated donors [1]. Earlier studies of unrelated donor BMT in the pediatric population during the 1980s and early 1990s report high incidences of cGVHD (50-69%) [86,87] when compared to more recent studies showing rates below 50% (39-47%)[88-90]. Recent improvements and increasing utilization of high-resolution typing of both HLA class I and class II loci has further decreased the rates of cGVHD in the unrelated population to 30%, rates comparable to those seen in children transplanted from HLA-identical siblings [91].

Recently, the impact of hematopoietic stem cell source on the incidence of cGVHD has been investigated. Mobilized PBSCs are now the primary stem cell source in the adult population. However, despite this dramatic increase in adults, BM remains the predominant stem cell source utilized in pediatric transplantation. CIBMTR data from 2003-06 show that the distribution of stem cell source for allo-HSCT in children is approximately 42% BM, 37% cord-blood, and 21% PBSC [1]. Though still modest, granulocyte colony stimulating factor (G-CSF) mobilized PBSC use is rising in pediatrics and is likely to continue escalate [17,92]. Adult studies have demonstrated higher incidences of cGVHD or refractory cGVHD when using PBSC versus BM [93,94]. Despite increased incidence of cGVHD in adults, the use of PBSC has been associated with decreased treatment-related-mortality (TRM) and decreased relapse rates in leukemia patients [95]. The data in children are less clear. One recent study showed no significant differences in TRM, aGVHD, cGVHD, OS, or relapse-free survival in pediatric PBSC recipients (n = 38) when compared to marrow (n=23) [26]. This is in contrast to previous studies that consistently show increased rates of cGVHD [17,96-98]. One study of 90 children undergoing PBSC transplants in Spain showed that patients with cGVHD had improved disease free survival with lower relapse rates and similar TRM [98]. However, a retrospective IBMTR analysis of pediatrics PBSC recipients reported poorer survival with PBSC transplants in comparison to BM despite similar rates of relapse. Patients in this study had similar rates of aGVHD, but rates of cGVHD were higher with a relative risk of 1.85 in the PBSC group [17]. Thus, despite the lack of randomized studies in children it appears that he risk of cGVHD with PBSC is higher than BM, though it is unclear of the overall effects on TRM and relapse free survival [96,97].

Because of the relatively limited stem cell doses in umbilical cord blood units, this source has been most frequently utilized in pediatric patients. The overwhelming majority of cord-blood

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units are from unrelated donors with only a small fraction coming from a suitably matched sibling. Initially UCB transplants were associated with poor engraftment and high TRM, however more recent results are promising with high engraftment rates (> 80%) and low incidence of acute and chronic GVHD (6-28%), allowing for a greater degree of HLA-mismatch [19,25,27,99-105]. In fact, degree of mismatch does not appear to effect the development of cGVHD in cord-blood transplants [101,105,106]. There is also a suggestion that cGVHD in unrelated UCBT is more responsive to therapy than recipients of unrelated BMT [107].

Staging and Grading

Signs and symptoms of cGVHD typically present 6 -18 months following allo-HSCT and the onset can be progressive (aGVHD progressed directly to cGVHD), quiescent (precedent aGVHD resolved), or *de novo* (no history of aGVHD). Grading of cGVHD severity was historically defined as limited or extensive [23]. Although there was prognostic significance to this categorization, investigators have tried to refine prognostic grading scales using survival as the primary endpoint. The two principal grading scales set forth by Akpek (2001) and Lee (2002) show that thrombocytopenia, progressive onset, extensive skin involvement, GI involvement, and low Karnofsky performance status at diagnosis of cGVHD are clearly associated with decreased survival [108,109]. A newly proposed cGVHD diagnosis and scoring system (*National Institutes of Health (NIH) consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report*) offers an updated definition of cGVHD where the diagnosis is based on the specificity of signs and histopathology rather than the traditional criterion of time of onset since transplantation (more or less than 100 days) [24]. The NIH consensus criteria further refines the grading system based on multiple clinical parameters into mild, moderate, and severe categories [24]. The prognostic and clinical significance of this grading system however, has yet to be validated.

Clinical manifestations

cGVHD most commonly involves the skin, eyes, oral cavity, GI tract, liver and lungs (Table 2). In addition, other organ systems such as the kidneys [110-112] or heart [113,114] can also be affected, though far less frequently. Manifestations of cGVHD can include more inflammatory and acute-type features such as erythematous rash, mucositis, diarrhea, transaminitis and pulmonary infiltrates, or can be more fibrotic and chronic in nature such as sclerotic or lichen planus-type skin changes, fasciitis, sicca syndrome, esophageal strictures, and bronchiolitis obliterans (BO). Age-based, multidisciplinary, ancillary supportive care is essential to the optimal management of cGVHD in the pediatric patient [115].

Cutaneous

The skin is the most commonly involved organ of cGVHD. Changes in the skin can be superficial, epidermal (hypo-, hyper-, or de-pigmentation) or deep into the subcutis and fascial layers. Features commonly seen that may overlap with aGVHD include erythema, maculopapular rash and pruritis. Diagnostic features of cGVHD include sclerotic, lichen planus-like, morphea-like or lichen sclerosus-like changes and poikiloderma (the combination of atrophy, telangiectasia, and pigmentary changes to the skin). The most severe and difficult-to-treat skin manifestation is sclerotic GVHD. Extensive, sclerotic skin changes with superficial or deep subcutaneous or fascial involvement develops in approximately 3-4% of patients with cGVHD and can be life-threatening [116]. The process is characterized by fibrosis of the skin or subcutaneous tissues and may result in joint contractures, severe wasting, and chest wall restriction. The mean onset of sclerotic skin changes following transplant is late (529 days in one study [117]). Other manifestations of disease include ichthyosis, keratosis

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pilaris and sweat gland impairment. Finally, the skin appendages may also be involved as manifested by nail loss or dystrophia, scalp changes and alopecia, or premature graying. Skin care should include topical moisturizers, antipruritic agents, and strict photoprotection as well as close surveillance for cutaneous malignancy.

Musculoskeletal

Musculoskeletal involvement of cGVHD in children can result in myositis, fasciitis, muscle weakness, cramping, edema and pain. Functional limitations from joint contractures, arthralgias and fatigue can be severe, and therefore, close monitoring for decreased range of motion and early intervention with physical therapy, occupational therapy, and splinting is essential. Rarely, surgical joint capsular release may be indicated to help preserve range of motion in involved joints although such intervention has been associated with mixed and transient responses [118]. Other commonly seen musculoskeletal complications include osteoporosis and avascular necrosis [119,120], complications that are the direct result of steroid therapy for cGVHD. Careful follow-up with bone density studies and use of vitamin D and calcium supplementation in conjunction with biphosphonates in select patients are therefore warranted.

Ocular

GVHD of the eyes is relatively common and affects up to 80% of patients with cGVHD [121]. Patients typically present with as “dry” or “gritty” eyes (sicca syndrome), photophobia, erythema or edema. Patients can suffer from lacrimal gland dysfunction and conjunctival inflammation leading to cicatrical conjunctivitis, keratoconjunctivitis, punctate keratopathy and blepharitis. Topical therapies, such as corticosteroid or cyclosporine drops, can be quite effective and optimization of these therapies is warranted. Patients may also benefit from local measures such as punctual plugs or scleral lenses, which provide significant symptomatic relief. It is important to follow these patients closely with serial Schirmer tests to assess the degree of wetting and to intervene early at the onset of ocular involvement even prior to the evolution of symptoms. Schirmer test without anesthesia may be difficult to perform and is not recommended in younger children; an ophthalmologist’s input may be needed for objective scoring in these children [122]. Ocular care consists of photoprotection along with regular evaluation for infection, cataract formation, and increased intraocular pressure. For children who are old enough to tolerate the procedure, routine Schirmer evaluation should be done to monitor tear production. Regional care may include artificial tears, ocular ointments, punctal occlusion, humidified environment, occlusive eye wear, moisture chamber eyeglasses, or gas-permeable scleral contact lens.

Oral

Oral cGVHD can involve the mucosa or the salivary glands. Symptoms include oral pain, dry mouth, taste changes, and food sensitivity. Examination may reveal mucosal erythema, lichen-type changes, xerostomia, mucosal atrophy, mucoceles, and ulcers. The largest single-center series of oral cGVHD in pediatric patients, described the findings of 49 patients seen at a multidisciplinary pediatric HSCT clinic at the Dana-Farber Cancer Institute [123]. Oral mucosal involvement was identified in nearly half (45%) of patients, however only 8% of patients reported mouth pain and all patients reported being able to eat well. The most common manifestation was erythema (42%), followed by reticular (36%) and ulcerative (21%) forms. Forty-five percent of patients required specific therapy for their oral mucosal cGVHD despite being currently treated with at least one systemic immunomodulatory agent. Salivary gland and sclerotic disease were rarely observed [123]. Often, children with isolated oral cGVHD can be treated with topical steroid rinses, though responses to topical therapy are varied and many patients require systemic treatment. Other treatment options include topical tacrolimus

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and agents that stimulate salivary gland function, but no strategy has been shown to have significant benefit over another and some may lead to increased rates of oral squamous cell carcinoma [124]. Secondary infections with viruses (especially herpes simplex) and yeasts are common; therefore using a local antifungal preparation in combination with the steroid rinse is recommended. Patients should adhere to strict oral hygiene and have close regular follow up with an experienced oral health care specialist.

Gastrointestinal (GI) tract

Children with cGVHD may have varied GI complaints consisting of nausea, anorexia, abdominal pain, weight loss, cramping or diarrhea. While these symptoms may be related to cGVHD, the only finding that is strictly diagnostic of cGVHD of the GI tracts is esophageal sclerosis in the form of an esophageal web or stricture [24]. Many GI symptoms are attributable to other causes including late aGVHD, infection, dysmotility, lactose intolerance, pancreatic insufficiency, or drug-related side effects [108]. As many of these problems can be remedied by other means, full evaluation of symptoms, including upper and lower endoscopy, is important before increasing or continuing immunosuppressive medication, as these may not treat the cause and may actually worsen the child's symptoms [125].

Weight loss and reduced body mass index (BMI) remain poorly understood, but critical issues in children with multi-organ cGVHD. Maintaining adequate nutrition is essential and careful evaluation of growth and head circumference in infants is required. In adults with cGVHD, low BMI is a predictor for mortality. A retrospective study of 18 children with extensive cGVHD found that patients with multi-organ involvement had a mean maximal decrease in BMI of 20.9% in contrast to patients with one organ system involved that had a mean maximal decrease in BMI of 5%. Weight loss often preceded overt signs and symptoms of cGVHD, suggesting an altered metabolic state and/or subclinical malabsorption in these patients. Thus, weight loss and malnutrition (as reflected by a decrease in BMI) are clinically significant issues in children with multisystem cGVHD and are likely systemic manifestations of the disease, which may contribute, to increased mortality in this group [126]. Treatment of GI manifestations may include dietary modification, enzyme supplementation for malabsorption, gastroesophageal reflux management, and esophageal dilatation.

Hepatic

cGVHD of the liver can be one of the most difficult manifestations to diagnose, as many possible causes for liver inflammation and damage exist in this population: infection, drug toxicity, iron overload, focal nodular hyperplasia, etc. To confirm the diagnosis evaluation must include viral studies for hepatitis A, B, C, and EBV, CMV, VZV, and adenovirus to exclude infection as a cofactor or cause of hepatic dysfunction. Liver biopsy is often required to confirm the diagnosis, particularly important for those patients with no other signs or symptoms of cGVHD. The typical appearance of hepatic cGVHD is that of fibrosis resulting in obstructive jaundice, with elevations of alkaline phosphatase, gamma-glutamyl transferase (GGT), and serum bilirubin. Liver biopsies can show portal fibrosis and bile duct dropout and can ultimately progress to cirrhosis and bridging necrosis [127]. Ursodeoxycholic acid can be used for patients with hyperbilirubenemia. While cholestasic hepatic cGVHD is the classic manifestation of liver involvement, hepatitic cGVHD is being identified more often, with some patients presenting with isolated elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [128,129]. First described in adult patients, more recently this hepatitic pattern has also been recognized in pediatric patients. The histologic pattern reveals bile duct epithelial damage, significant portal/periportal inflammation, and lobular necro-inflammation. The clinical and histologic patterns of hepatitic cGVHD described in this pediatric study are similar to that described in adults [130].

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Pulmonary

Two forms of chronic pulmonary dysfunction are common in patients surviving greater than 100 days following allo-HSCT: obstructive lung disease (OLD) and restrictive lung disease (RLD) [131]. The incidence of lung toxicity ranges from 30% to 60% [132]. Collagen deposition and the development of fibrosis either in the interstitial (RLD) or peri-bronchiolar (OLD) space are believed to contribute to lung dysfunction. While both RLD and OLD exist as late-onset, non-infectious lung complications following allo-HSCT, they can be distinguished by a number of clinical parameters as described below (Table 3).

The most common and recognizable form of OLD is bronchiolitis obliterans (BO). BO is a serious life-threatening manifestation of cGVHD that is characterized by an inflammatory process resulting in bronchiolar obliteration, fibrosis and progressive obstructive lung disease. The presence of BO post transplant is diagnostic for cGVHD [24]. There are no effective therapies for BO, and patients frequently develop progressive and debilitating respiratory failure despite the initiation of enhanced immunosuppression. Mortality approaches 100% in some studies, with a mean fatality rate of 61% [130,[133]. Patients with BO may be asymptomatic early in the time course of disease, but typically present with a cough, wheezing or dyspnea on exertion [24,134]. As suggested, pulmonary function tests (PFTs) show obstructive lung mechanics with general preservation of forced vital capacity (FVC), reductions in forced expiratory volume in one second (FEV1) and associated decreases in the FEV1/FVC ratio with or without significant declines in the DLCO.

The most recognizable form of RLD after allo-HSCT is bronchiolitis obliterans organizing pneumonia (BOOP). Clinical features include dry cough, shortness of breath and fever and radiographic findings show diffuse, peripheral, fluffy infiltrates consistent with airspace consolidation. Although reported in less than 10% of allo-HSCT recipients, the development of BOOP is strongly associated with prior acute and chronic GVHD [135]. Importantly the term BOOP should not be used interchangeably with bronchiolitis obliterans (BO) to describe a patient with chronic lung dysfunction after allo-HSCT, although such usage is unfortunately widespread [136]. The two disorders differ with respect to histopathology, pulmonary function characteristics, and most importantly, response to therapy; BOOP after HSCT is quite responsive to corticosteroids whereas BO is not (Table 3).

In addition, other clinical diagnoses (e.g. pneumonias, chest wall fibrosis) can be associated with signs and symptoms of lung dysfunction, therefore an extensive work-up of the affected individual is recommended. Testing should include high-resolution, computer-assisted tomography (CT) scan of the chest, which may reveal an infectious process or air trapping and when clinically possible, serial complete PFTs that include an assessment of lung volumes, spirometry and diffusion capacity (DLCO). When evaluating lung function in this context, it is important to keep some key elements in mind. Specifically, pediatric allo-HSCT patients may not continue on the normal growth curves for height and weight. Also recipients of total body or chest wall irradiation may not have proportional chest wall growth. Care must therefore be taken to not only follow percent-predicted values, but also to evaluate actual lung volumes over time; since PFTs are scored as a percentage of the predicted norms, from healthy age-matched controls, a drop in the percent-predicted value may actually reflect poor lung growth rather than a physiologic drop in lung function. A broncho-alveolar lavage may be necessary to evaluate for possible concurrent infection and aggressive therapy of proven infection is essential. A biopsy may be needed for definitive diagnosis, however this is commonly avoided due to the risks of the procedure. When a definitive tissue diagnosis cannot be made, the term bronchiolitis obliterans syndrome is applied. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are rare and often represent advanced disease. Ancillary support requires infection surveillance, Pneumocystis prophylaxis and treatment of gastroesophageal reflux. Initial therapy for pulmonary cGVHD should include a trial of enhanced systemic

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immunosuppression. Benefit may also been observed with inhaled corticosteroids, bronchodilators, supplementary oxygen, and pulmonary rehabilitation. As noted below, novel targeted therapies may also hold promise. Consideration of lung transplantation is given to the rare appropriate candidate with severe bronchiolitis obliterans.

Hematopoietic system

Cytopenias are common following allo-HSCT. The mechanisms contributing to marrow dysfunction are not clearly defined and are likely to be multifactorial. Cytopenias may result from stromal damage, but antibody mediated autoimmune neutropenia [137], anemia [138], and thrombocytopenia [139] are also common. It is also important to eliminate drug toxicity, infection, graft failure, or disease relapse as the underlying cause. Thrombocytopenia is the most common hematopoeitic manifestation of cGVHD and occurs in approximately 35% of affected patients [22]. Thrombocytopenia alone does not meet the diagnostic criteria for cGVHD, however a number of studies have shown that thrombocytopenia at the time of cGVHD diagnosis confers a poor prognosis [108,140], although, thrombocytopenia may be a poor prognostic factor independent of GVHD [141]. Eosinophilia is also frequently seen in children and can precede the development of overt cGVHD [142].

Immune system

Patients with cGVHD have associated immune dysregulation and delayed immune reconstitution as a direct consequence of GVHD and immunosuppressive therapy. Additionally, patients with mucosal involvement (skin, oral, or GI) lack intact barriers thus increasing the risk for infections [143-145]. Thus, opportunistic infections are common and remain the leading cause of death in patients with active cGVHD [23,146,147]. Functional asplenia, evidenced by persistence of Howell-Jolly bodies and a higher incidence of pneumococcal sepsis [148,149], is also commonly seen and can remain for life despite resolution of cGVHD. Therefore lifelong prophylaxis against encapsulated organisms is recommended. Patients should also receive prophylaxis against *Pneumocystis jiroveci* until complete resolution of cGVHD and for at least six months after discontinuation of immunosuppressive therapy. Supplemental intravenous immunoglobulin (IVIG) replacement is typically utilized when patients have the combination of severe hypogammaglobunemia, (IgG < 400 mg/dl) and recurrent infections. Patients at risk for CMV should be monitored closely with CMV PCR or antigenemia. Patients receiving steroid rinses for oral GVHD are at high risk for local Candidal infections and topical antifungal prophylaxis (e.g. nystatin swishes or clotrimazole troches) should be used. For patients on steroids doses equal to or greater than the equivalent of prednisone 0.8 mg/kg/day, patients should also be given antifungal and antiviral prophylaxis. The decision to discontinue anti-fungal and anti-viral therapy is dependent on each patient and the intensity of the therapy they are receiving. Up-to-date recommendations from the Centers for Disease Control (CDC) and Prevention for infection prophylaxis are available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm. Vaccinations are critical to enhance immunity against specific organisms but are typically delayed until 6 – 12 months after HSCT as per institutional guidelines [41] or according to CDC recommendations (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm). Live vaccines should be avoided in this patient population.

Treatment

The treatment of cGVHD in pediatrics is highly variable and mostly extrapolated from the experience in adults. While there is no proven “standard therapy,” prednisone and CSA are commonly employed as frontline therapy. This combination therapy is based on an alternate day regimen that improved survival in high-risk patients with thrombocytopenia and extensive

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skin involvement [140]. The general approach to treatment is immediate initiation of therapy, typically high dose steroids (1-2 mg/kg/day) with calcineurin inhibitor, with steady weaning of steroid until the lowest allowable dose without cGVHD flare is achieved. The mean duration of therapy for patients with cGVHD is 3 years, with approximately half of patients able to discontinue therapy by 5 years post HSCT [150,151]. Patients should be evaluated for response to treatment and monitored for side effects of therapy at a minimum of every 3 months. Therapy is typically continued for at least 3 months after maximal response and weaned off with careful monitoring for a recurrent flare of cGVHD. Investigators at Johns Hopkins observed that 90% of patients who ultimately respond to a therapy show signs of response by 3 months [152].

Salvage Regimens

Sirolimus

Sirolimus (Rapamycin), is a macrocyclic triene antibiotic with immunosuppressive, antifungal and anti-tumor properties which inhibits signal transduction and cell cycle progression after binding to FKBP12 and inhibiting mammalian target of rapamycin (mTOR) [153]. Sirolimus has been shown to have activity in the prevention and treatment of aGVHD [154-157] and has more recently been evaluated in the chronic setting. Several recent studies show good overall response rates (63%-93%) in cGVHD [156-158]. However, no studies have been performed on a pediatric population so dosing and pharmacokinetics remain incompletely defined and are usually based on data from solid organ transplant populations. Toxicities include hyperlipidemia, cytopenias, and hemolytic uremic syndrome, which may be potentiated by the combination of sirolimus with a calcinuerin inhibitor [156].

Mycophenolate Mofetil (MMF)

MMF is an antimetabolite used as an alternative immunosuppressant that inhibits the proliferation of T and B lymphocytes and is currently in use for aGVHD prophylaxis. MMF is generally well tolerated and when in combination with calcineurin inhibitor, has shown a steroid-sparing effect with response rates ranging from 50 – 79% [159-163]. MMF has been evaluated in several pediatric trials, which show similar response rates and tolerability as seen in the adult trials [160]. Investigators in Seattle reported a very promising CR rate of 65% in 26 pediatric patients who had previously progressed on therapy with prednisone and CSA. Responses were slow and CR was not achieved until up to 3 years following initiation of therapy in several cases. Despite that, the drug was remarkably well-tolerated and only 1 patient experienced transient leukopenia [161]. Unfortunately, a large multi-center, randomized trial using MMF for the initial treatment of cGVHD was recently closed prematurely secondary to lack of efficacy in the treatment arm [151].

Pentostatin

Pentostatin is a nucleoside analog that irreversibly inhibits adenosine deaminase resulting in severe immunosuppression. Pentostatin causes decreased T-cell responses to IL-2, reduced T-cell number and function, reduced natural killer cell numbers and lymphocyte counts, thus affecting both antibody and non-antibody cytotoxicity [164,165]. In an open-label phase II study of pentostatin for patients with steroid refractory cGVHD, patients were dosed at 4 mg/m^2 intravenously every 2 weeks for 12 doses. Of the 58 patients enrolled, 55% had an objective response, however when stratified for age, younger patients (<33 years) had a better response rate (77%). Twenty percent of patients experienced grade 3 to 4 infection and survival at 2 years was 70%, with cGVHD with or without infection accounting for the majority of deaths [166].

Other agents including Hydroxychloroquine, a lysosomotropic 4-aminoquinoline antimalarial drug that has been used to effectively treat autoimmune disorders [167,168], and thalidomide

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have been studied in small numbers of pediatric and adult patients. Both agents are reasonably well tolerated and have shown varying degrees of promise (including steroid sparing effects) in individuals with steroid refractory cGVHD [10] [169-171].

Extracorporeal Photochemotherapy (ECP)

ECP is a therapeutic procedure originally brought into clinical medicine for the treatment of cutaneous T-cell lymphoma (CTCL) [172]. During ECP, the patient's peripheral blood mononuclear cells are collected by apheresis, incubated with the photoactivatable drug 8-methoxypsoralen (8-MOP) and UV-A irradiation and re-infused into the circulation. Phase I and II data suggest that ECP is an effective treatment for both acute and chronic GVHD, with response rates ranging from 40% to 81% [173-177]. Studies evaluating ECP for GVHD are primarily in adults, but there have been several trials, which have either included or exclusively enrolled children. Salvaneschi *et al.* treated 18 children with extensive cGVHD with a 78% response rate and 67% were able to taper steroids. ECP was safe and well tolerated without increase in infections in this study [178]. Messina et al. evaluated the use of ECP in 44 pediatric patients with acute and cGVHD. They reported an overall response rate of 59%, 44% of patients were able to discontinue all other immunosuppression and 29% were able to reduce immunosuppression [179]. Currently, a combined phase II/III, randomized, open label, multicenter, prospective study comparing the addition of ECP vs. calcineurin-inhibitor combined with prednisone and sirolimus for the upfront treatment for cGVHD is available through the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN).

Targeted Therapies

Various monoclonal antibodies and anti-cytokine therapies such as infliximab and etanercept (anti-TNF-α) and daclizumab (anti-IL2R-α) that have been evaluated in the treatment of aGVHD are being further explored in the treatment of cGVHD [180]. In general these targeted therapies exhibit more favorable side effect profiles to this patient population. Etanercept (Enbrel) is a recombinant, human, soluble tumor necrosis factor (TNF-α) receptor fusion protein that inhibits TNF-α, a major mediator in the pathogenesis of GVHD. Preliminary data suggest that Enbrel may be a safe and effective in treating pediatric and adult allo-HSCT recipients with manifestation of cGVHD of the lung [181]. More recently, the safety and efficacy of etanercept was evaluated in 21 patients with steroid-refractory aGVHD (n = 13) and cGVHD (n = 8). Overall, 52% responded to treatment with etanercept, including 5 patients (62%) with cGVHD, with 1 CR and 4 PRs. [182].

Given the aforementioned possible contribution of B cells to the pathogenesis of cGVHD, rituximab an anti-CD20 monoclonal antibody, has been investigated as a novel therapeutic option. Cutler et al. evaluated 21 patients who were treated with 38 cycles of rituximab in a phase I/II study. Rituximab was well tolerated and toxicity was limited to infectious events. A clinical response rate of 70% was reported, although limited to patients with cutaneous and musculoskeletal manifestations [47].

Finally, a new agent on the horizon that has peaked the interest of cGVHD community is Imatinib Mesylate. After the discovery of stimulatory antibodies to the PDGF receptor and success in the treatment of idiopathic scleroderma patients, investigators looked to identify similar antibodies in patients with cGVHD. Similar antibodies were indeed identified in the majority of patients with cGVHD, higher in patients with skin disease and extensive disease [42]. Several preliminary studies have shown promise in both sclerotic skin and non-skin manifestations of cGVHD [183,184].

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Supportive care

Ancillary and supportive care measures have been reviewed above with each organ specific manifestation. In general, topical or local care applied to the skin, eyes or mouth is strongly encouraged to help minimize the toxicities of systemic therapy. In addition, patients should be monitored closely for neurological and psychological dysfunction. Individuals may benefit from treatment for depression, pain or neuropathic syndromes with tricyclic antidepressants, selective serotonin reuptake inhibitors, or anticonvulsants.

Toxicity and late effects

The treatment of cGVHD in pediatrics must include consideration of the possible impact therapy will have on growth, nutrition, organ function, psychosocial functioning, and immune reconstitution. Post-transplant patients are at high risk for many late effects such as osteonecrosis, chronic renal insufficiency, hypothyroidism, growth hormone deficiency, hypogonadism, osteopenia, cataracts, and pulmonary dysfunction [185]. The addition of cGVHD and chronic immunosuppressive agents significantly compounds the risks of these complications. As steroids remain the foundation of cGVHD therapy, the consequences of long-term steroid use in children are well described and long-term deleterious effects on growth and bone density persist even after discontinuation of therapy [186,187].

Additional concerns for the cGVHD population include impaired functional status and diminished quality of life (QOL). The strongest association between reduced QOL following HCT is the presence of cGVHD [188]. cGHVD negatively impacts an individual's physical and mental health, and can lead to the development of functional impairments and activity limitations over their lifetime [109,188,189].

Conclusions and Future Directions

Five-year childhood cancer survival rates now exceed 80% [190] and with the significant progress made by the transplant community in developing less toxic conditioning regimens and in the treatment of post-transplant complications, allo-HSCT contributes significantly to that population of long-term survivors. In this context, the acute and long-term toxicities of cGVHD have assumed an ever-increasing impact on organ function, quality of life, and survival; patients and families that initially felt great relief to be cured from their primary disease, now face the challenge of a chronic, debilitating illness for which preventative and treatment strategies are sub-optimal. Hence, the development of novel strategies that reduce and or control cGVHD, preserve GVT effects, facilitate engraftment and immune reconstitution and enhance survival after allo-HSCT represents one of the most significant challenges facing physician scientists and our patients. Data and research focused on cGVHD in pediatrics are limited; most studies are small and children are often grouped into larger adult series. However, given the impact of cGVHD on non-relapse mortality, it is critical that clinical trials be designed to include pediatric patients with accrual goals of sufficient numbers to produce statistically significant conclusions. In addition, such trials should integrate biologic studies whenever possible in order to maximize discovery in pediatric cGVHD.

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Table 1

cGVHD Risk Factors

	Patient	Donor/Graft	Transplant
Increased cGVHD risk	Older age Malignancy	Female donor to male patient Mismatched Unrelated Peripheral Blood Stem Cells Donor Lymphocyte Infusions Older age	Acute GVHD Total Body Irradiation in preparative regimen
Possible increased cGVHD risk	*CMV positive* *CMV reactivation*	*CD 34+ cell dose*	
Decreased cGVHD risk	Younger age	Cord blood	Anti-thyroglobulin in preparative regimen Campath-1H in preparative regimen
Possible decreased cGVHD risk			*Methotrexate and cyclosporine prophylaxis*

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Table 2

Manifestations of cGVHD

Organ	Signs	Symptoms
Skin, Nails, Hair	Sclerosis, lichen sclerosus-like, lichen planus-like features Sweat impairment Ichthyosis Keratosis pilaris Hypo-, hyper -, de-pigmentation Erythema, poikiloderma Maculopapular rash Nail dystrophy Pterygium unguis Alopecia Scaling, papulosquamous lesions of scalp Hair depigementation	Pruritus Dryness Longitudinal ridging, splitting of nail Nail loss Thinning of hair Premature graying
Vulvovaginal	Lichen planus-like features Vaginal scarring or stenosis Erosions, fissures, ulcers	Dyspareunia Vaginal dryness
Muscles, Fascia, Joints	Fasciitis Sclerosis Myositis or polymyositis Edema	Joint stiffness or contractures Muscle cramps or pain Arthralgia or arthritis Weakness
Eyes	Cicatricial conjunctivitis Keratoconjunctivitis sicca Punctate keratopathy Blepharitis	Dry, gritty, or painful eyes Photophobia
Mouth	Erythema Lichen-type features Hyperkeratotic plaques Xerostomia Mucocele Mucosal Atrophy Pseudomembrane formation Ulcers Gingivitis, mucositis	Dry mouth Pain Difficulty swallowing Oral sensitivity Change in taste Increased dental caries
GI Tract	Esophageal web or strictures Exocrine pancreatic insufficiency Vomiting Diarrhea	Anorexia Nausea Weight loss, failure to thrive Abdominal cramping
Liver	Hyperbilirubinemia Tranaminitis	Jaundice
Lung	Bronchiolitis obliterans BOOP	Dyspnea on exertion
Hematopoeitic/Immune	Anemia, Thrombocytopenia, Eosinophilia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA, ITP)	
Other	Effusions Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality Cardiomyopathy Coronary artery fibrotic changes	Varied

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Table 3

Clinical factors present in OLD vs. RLD.

Clinical Factor	Obstructive lung disease	Restrictive lung disease
Diagnostic entity	Bronchiolitis obliterans (BO)	Bronchiolitis obliterans organizing pneumonia (BOOP)
Onset	Late (3 to 12 months)	Early (within 3 months)
Symptoms	Dyspnea, non-productive cough	Dyspnea, non-productive cough
Physical exam	Wheezing	Rales
PFTs	Obstructive physiology	Restrictive physiology
FEV1/FVC	Decreased	Normal
TLC	Normal	Decreased
DLco	Decreased	Decreased
CT scan findings	Air trapping (expiration) Bronchial wall thickening “Ground glass” opacities Centrilobular nodules	“fluffy” consolidations “Ground glass” opacities
Laboratory data	non-specific	Increased CRP Peripheral neutrophila
Chronic GVHD	Strong association	variable, positive with BOOP