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A review of graft versus host disease

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Abstract. Children undergoing hematopoietic stem cell transplant often require intensive care support due to their underlying disease, sepsis, infection, hemorrhage, respiratory failure and organ dysfunction. The majority of children requiring intensive care support have an allogeneic donor. These children carry a higher likelihood of graft versus host disease complicating their medical management. Understanding the process of graft versus host disease is important in the shared care of these children between pediatric intensive care physicians and the bone marrow transplant team.

Keywords: Allogeneic hematopoietic stem cell transplant, graft versus host disease, pediatrics

1. Introduction

Allogeneic hematopoietic stem cell transplant (AHSCT) offers the potential to cure many pediatric hematologic and metabolic diseases. The number of allogeneic transplants performed continues to grow annually. The indication for transplant has expanded in recent years through the development of novel strategies including umbilical cord blood transplantation and reduced intensity conditioning. Improvements in human leukocyte antigen (HLA) tissue typing, immunosuppressive medications, infectious prophylaxis, and supportive care have contributed to improved outcomes after AHSCT [1]. Despite these advances, graft versus host disease (GVHD) remains one of the most frequent and serious complications following AHSCT. While advances in the understanding of the pathogenesis of GVHD have led to new approaches in management, GVHD limits the application of AHSCT [2]. GVHD is the process in which donor-derived immune cells recognize host organs as foreign and mount an immune response against the patient's own tissue. This can have devastating effects mainly on the skin, gut and liver [3] as well as the lungs [4]. Children who receive unrelated allogeneic transplants have more than twice the odds of requiring intensive care support compared to children with a related donor. In fact, 22% of children post AHSCT presenting to the intensive care unit have GVHD [5].

2. Pathogenesis

In 1966, Billingham [6] described the three requirements for the development of GVHD. First, the graft must contain immunologically competent cells. Second, the recipient must express tissue antigens that are not present in the transplant donor, and third, the recipient must be incapable of mounting an effective response to eliminate the transplanted cells [6]. It is now known that the immunologically competent cells are T-cells, and GVHD can develop when tissues containing T-cells (bone marrow, blood products and solid organs) are transferred from one person to another who is not able to eliminate those cells [7, 8]. GVHD classically develops over five steps [9]. First, tissue damage from the conditioning

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regimen (chemotherapy, radiotherapy) releases pro-inflammatory cytokines that promote activation and maturation of antigen-presenting cells (APCs) [10]. This is furthered by damage to the gastrointestinal epithelium, allowing translocation of lipopolysaccharide, which can activate innate immunity through Toll-like receptors, furthering the cytokine cascade [11]. Second, donor T-cell activation is triggered by recipient antigens presented by host APCs and sustained by donor APCs mediated by HLA proteins encoded by the major histocompatibility complex. Major histocompatibility complex is the most powerful determinant of GVHD [12]. However, despite full 6/6, 8/8 or 10/10 matching, 40% of recipients develop GVHD due to minor histocompatibility antigens [13]. Third, T-cells proliferate and differentiate into central memory, effector memory, regulatory and other subsets. A delicate balance between these subsets and the productions of cytokines has been found to impact the manifestations of GVHD while central memory T-cells may be able to promote graft versus leukemia [2, 10]. Fourth, activated T-cells migrate from secondary lymphoid organs to target tissues (skin, gut, liver) [10]. Finally, once the T-cells reach target organs, they cause tissue destruction through direct cytotoxic activity as well as recruitment of other leukocytes [13].

The understanding of the pathophysiology of chronic GVHD (cGVHD) is not as advanced as acute GVHD. cGVHD is complex and similar to an autoimmune process. Alloreactive T-cells have been implicated in cGVHD; however, the precise role of specific T-cell subsets, autoantigens, alloantigens, and B-cells and the interaction of chemokines and cytokines has not been fully elucidated [2].

3. Acute GVHD

The incidence of acute GVHD is directly related to the degree of HLA mismatch. The incidence of GVHD in recipients who receive a full matched sibling donor graft ranges from 35–45% [14] and up to 60–80% in recipients of one-antigen HLA mismatched unrelated donor grafts [15]. Recipients of umbilical cord blood with the same degree of mismatch experience less GVHD with incidences ranging from 35–65% [16]. Historically, acute GVHD was defined as disease that occurred within the first 100 d post-transplant with cGVHD occurring after the 100-d mark [17]. Additionally, neutrophil engraftment was thought to necessary for GVHD to be diagnosed. However, as practice evolves, acute GVHD is better defined as a disease that can present early (prior to engraftment) as well as late, beyond 100 d post-transplant [18]. Consequently, the National Institutes of Health has developed a new classification that includes two new diagnoses: late onset acute GVHD and overlap syndrome. Late onset acute GVHD is defined as GVHD that occurs after the first 100 d post-transplant with no signs of cGVHD. Overlap syndrome is defined as GVHD that exhibits features of both acute and chronic disease [17]. The organs most commonly affected by acute GVHD are the skin (81%), gut (54%) and the liver (50%) [10, 13]. Over 50% of patients with acute GVHD will go on to develop chronic disease [19]. Staging and grading of GVHD is done by the number and extent of the organs involved (Table 1) [19].

The presence and severity of acute GVHD has a significant effect on survival with about 90% of patients with Grade I disease surviving to day 100

Table 1
Glucksberg scale of acute graft versus host disease*

Stage	Skin	Liver bilirubin (mg/dL)	Intestinal tract (mL diarrhea/d)
1	Maculopapular rash <25% of body surface	2–3 mg/dL	>500 mL
2	Maculopapular rash 25–50% of body	3–6 mg/dL	>1000 mL
3	Generalized erythroderma	6–15 mg/dL	>1500 mL
4	Generalized erythroderma with bullous formation and desquamation	>15 mg/dL	Severe abdominal pain with or without ileus
Clinical grading			
Grade	Skin	Liver	Intestine
I	Stage 1–2	None	None
II	Stage 1–3	Stage 1	Stage 1
III	Stage 2–3	Stage 2–3	Stage 2–3
IV	Stage 2–4	Stage 2–4	Stage 2–4

*Adopted from Ref. 58. Thomas ED, Storb R, Clift RA, Fefer A, Johnson L, Neiman PE, et al. Bone-marrow transplantation (second of two parts). N Engl J Med 1975;292(17):895-902.

post-transplant compared with about 60% of patients with grade II-III and only 20% of those with grade IV [20]. Hyperacute GVHD, or engraftment syndrome (ES), includes non-infectious fever, erythroderma, pulmonary edema, weight gain, liver dysfunction and/or encephalopathy occurring at the time of neutrophil recovery. ES is commonly described as a cytokine storm. This syndrome has the potential to progress to multiorgan dysfunction and death. In a recent study of 927 children and adults undergoing first transplant, 13% developed ES at a median of 10 d post transplant. These patients had a higher incidence of grade II–IV acute GVHD and higher non-relapse mortality at 2 yr. Early recognition and treatment with corticosteroids is effective at controlling the symptoms of ES, but does not alter the incidence of acute GVHD [21].

Skin is usually the first organ involved in acute GVHD and often coincides with engraftment of donor cells. The rash may appear before evidence of engraftment and disease manifesting in the first 14 d post-transplant is defined as hyperacute GVHD and is associated with poorer outcome [10, 13, 18]. The rash often presents as a maculopapular palmar/plantar pruritic rash that may spread to anywhere on the body, but generally spares the scalp [10, 17]. Generalized erythroderma can develop and progress to skin detachment [18–20]. These rashes can be difficult to differentiate from drug rashes or viral exanthemas [10]. Involvement of the face and palms or soles is more likely to represent GVHD than drug hypersensitivity reaction [22]. Biopsy findings are often inconclusive and include apoptosis, dyskeratosis and lymphocytic infiltration into the dermis [13]. However, these pathologic findings are often indistinguishable from other common causes of rash after transplant including irradiation dermatitis and drug reaction. Therefore, the role of skin biopsy remains controversial [20].

GVHD of the gastrointestinal tract often presents with diarrhea, but may also include nausea, anorexia, vomiting and pain; hematochezia may be present and is associated with poorer outcomes [10, 13, 23]. Diarrhea is often secretory and may exceed a volume of 2 L/d. Severity of disease is determined by the volume of diarrhea/d [10]. Additionally, isolated upper gastrointestinal tract disease may occur and is manifested by anorexia, dyspepsia, food intolerance, nausea, and vomiting. Patients who fail initial treatment for upper gastrointestinal tract disease generally progress to lower tract involvement [23]. Diagnosis of gastrointestinal GVHD is difficult due to the non-specific nature of the symptoms and the numerous differential diagnoses [17].

Esophagogastroduodenoscopy and flexible sigmoidoscopy are often used as diagnostic tools; histiologic features include apoptosis, crypt abscesses and loss and flattening of the surface of the endothelium. Biopsy samples are also sent for infectious disease studies and can help distinguish infections from GVHD [23]. Duodenal biopsies are controversial in children post transplant, as the duodenum appears to be vulnerable to biopsy induced hematomas especially in children with thrombocytopenia or other coagulation abnormalities. Gastric antrum biopsies are usually sufficient to diagnose upper gastrointestinal GVHD [24, 25]. Computerized tomography and magnetic resonance imaging have limited use in the diagnosis of GVHD, due to non-specific findings of bowel wall thickening. However, the development of contrast-enhanced ultrasound (CEUS) is promising; in one small study, CEUS identified gut GVHD with 75–100% specificity. Unfortunately, CEUS requires equipment and personnel that are not widely available [17].

GVHD of the liver is a result of damage to the bile canaliculi, which can lead to cholestasis with hyperbilirubinemia and increased alkaline phosphatase levels. Severity of disease is based on the serum bilirubin [10]. Hepatic dysfunction following AHSCT may be secondary to a variety of causes including infections, drugs, hepatic veno-occlusive disease (VOD), GVHD, viral hepatitis, and disease relapse [26]. Definitive diagnosis can be established by biopsy; however, this often is not performed due to the risk of bleeding associated with thrombocytopenia. Therefore, the diagnosis is generally one of exclusion [17] whereas VOD is diagnosed by clinical criteria within the first 21 d of transplant. Baltimore and modified Seattle criteria for VOD include the following: bilirubin >2 mg/dL, hepatomegaly, and weight gain >2–5% pre-transplant weight ± ascites and right upper quadrant pain [25]. Acute GVHD can also affect the bone marrow and result in refractory cytopenias [10].

4. cGVHD

cGVHD is the most common complication in long-term survivors and a major cause of late non-relapse mortality following AHSCT [27–30]. The increased risk of treatment-related mortality among patients with

cGVHD include the involvement of multiple organs or sites, decreased clinical performance score, thrombocytopenia, hyperbilirubinemia and progressive onset of cGVHD from prior acute GVHD [31]. Mortality is usually the result of chronic immune suppression and resultant infections. The incidence of cGVHD ranges from 6–80%. The wide range is due to variable conditioning regimens, donor sources, lack of standardized diagnostic guidelines, observer experience and limited transplant follow up [31]. cGVHD is associated with decreased quality of life, impaired physical and functional status, e.g., joint contractures, end stage lung disease or poor vision. Factors increasing the incidence of cGVHD are prior acute GVHD and donor characteristics (female donors for male recipients, multiparous female, peripheral blood stem cells) [32]. Organ fibrosis with collagen deposition and atrophy are the hallmarks of cGVHD. Clinical manifestations involving multiple organs similar to other autoimmune disorders are common in cGVHD. Symptoms usually present within the first 3 yr post AHSCT [31].

Historically, cGVHD was diagnosed by the time of onset post transplant (>100 d) regardless of the clinical manifestation. However, the diagnosis of cGVHD currently requires the 1) exclusion of acute GVHD, 2) the presence of one diagnostic clinical sign or the presence of at least one distinctive manifestation (oral or vaginal lichenoid finding, ocular sicca, skin dyspigmentation, scleroderma or bronchiolitis obliterans [BO]) confirmed by pertinent biopsy or other relevant tests, and 3) by the exclusion of other possible diagnoses such as drug effect, infection, malignancy, scarring and residual post-inflammatory damage (Table 2). Diagnostic clinical signs refer to the manifestations that establish the presence of cGVHD without further testing, while distinctive signs and symptoms refer to manifestations that are not ordinarily found in acute GVHD, but are not considered sufficient to establish an unequivocal diagnosis [31]. The diagnosis of cGVHD is based on clinical signs, laboratory data, radiologic findings, pulmonary function testing, degree of organ involvement and pathologic confirmation. Some features of cGHVD that may affect the pediatric intensivist include skin changes, chronic diarrhea, musculoskeletal and pulmonary involvement. Skin cGVHD ranges from poikiloderma and lichen planus-like eruption to deep sclerotic features. Children with cGVHD of the skin experience poor wound healing, ulcers from minor trauma, sweat impairment, intolerance to temperature change [31] and fibrotic changes hindering intubation, ventilation and line placement. Gastrointestinal cGVHD is often associated with diarrhea, poor absorption, pancreatic exocrine insufficiency making nutrition challenging [31]. Diarrhea as a result of cGVHD versus "cord colitis" remains controversial and treated with corticosteroids or antibiotics dependent on the transplant center [33]. Myositis is a rare complication of cGVHD but may cause proximal myopathy [31].

5. Pulmonary

Pulmonary complications significantly contribute to late mortality after AHSCT. Late onset non-infectious pulmonary complications are strongly associated with cGHVD and not fully understood [34]. The only recognized pulmonary diagnostic manifestation of cGVHD is bronchiolitis obliterans (BO) or BO syndrome (BOS) [31] although there are other cGVHD signs and symptoms that can affect ventilation. Sclerodermatous changes of the skin over the thorax can restrict chest expansion. BO results from obstruction and/or obliteration of the small airways. It is characterized by luminal occlusion of the terminal and respiratory bronchioles by inflammatory and fibrous tissue. BO/BOS is believed to be immune mediated and associated with cGVHD [35]. Symptoms may include dyspnea on exertion, cough or wheezing. Objective findings include forced expiratory volume-1 (FEV) <75% predicted, evidence of air trapping or small airway thickening or bronchiectasis on chest computerized tomography. The presence of an infection must be excluded [31, 34]. The decision to biopsy must be made carefully, weighing the risks of potential complications and the expected clinical consequences following biopsy results. Open lung biopsy may be considered in patients with peripheral lesions whereas transbronchial biopsy may be useful in diffuse lung pathology or larger lesions (>1 cm) located in close proximity to major bronchi [34]. The incidence of BO/BOS in adult HSCT patients ranges from 1–10% [36]. Few published studies exist regarding BO/BOS in children. Mortality ranges from 11–67% [37]. Risk factors for developing BO/BOS following AHSCT include acute and cGVHD, mismatched HLA donor, older donor, abnormal pre-HSCT pulmonary function, GVHD prophylaxis with methotrexate, myeloablative conditioning, busulfan, prior history of interstitial

Table 2
Signs and symptoms of chronic graft versus host disease*

Organ or site	Diagnostic (sufficient to diagnose chronic graft versus host disease)	Distinctive (seen in chronic graft versus host disease, but unable to establish diagnosis alone)	Other features	Common (both acute and chronic graft versus host disease)
Skin	Poikiloderma, lichen planus-like features, sclerotic features, morphea-like features lichen sclerosis-like features	Depigmentation	Sweat impairment, ichthyosis, keratosis pilaris, hypopigmentation, hyperpigmentation	Erythema, maculopapular rash, pruritus
Nails		Dystrophy, longitudinal ridging, splitting, or brittle features, onycholysis, pterygium unguis, nail loss**		
Scalp and body hair		New onset scarring or non-scarring alopecia (after recovery from chemoradiotherapy,scaling, papulosquamous lesions)	Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes), premature gray hair	
Mouth	Lichen-type features, hyperkeratotic plaques, restriction of mouth opening from sclerosis	Xerostomia, mucocele, mucosal atrophy, psuedomembranes, ulcers**		Gingivitis, erythema, pain
Eyes		New onset dry, gritty, or painful eyes***, cicatricial conjunctivitis, ketatoconjunctivitis sicca***, confluent areas of punctate kertatopathy	Photophobia, periorbital hyperpigmentation, blepharitis	
Genitalia	Lichen planus-type features, vaginal scarring or stenosis	Erosions**, fissures**, ulcers**		
GI tract	Esophageal web, strictures or stenosis in the upper to mid third of the esophagus**		Exocrine pancreatic insufficiency	Anorexia, nausea, vomiting, diarrhea, weight loss, failure to thrive
Liver				Total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase >2 × upper limit of normal**
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with pulmonary function tests and radiology***		Bronchiolitis obliterans organizing pneumonia
Muscles, fascia, joints	Fasciitis, joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis**	Edema, muscle cramps, arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia, eosinophilia, lymphopenia, hypo or hypergammaglobulinemia, autoantibodies	
Other			Pericardial or pleural effusions, ascities, peripheral neuropathy, nephrotic syndrome, myasthenia gravis, cardiac conduction abnormality or cardiomyopathy	

*Adopted from Ref. 31. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11(12):945-56. **In all cases, infection, drug effect, malignancy or other causes must be excluded. ***Diagnosis of chronic graft versus host disease requires biopsy or radiology confirmation (or Schirmer test for eyes).

pneumonitis, female donor to male recipient, peripheral blood stem cell donor, respiratory viral infection within the first 100 d following transplant and low immunoglobulin levels following AHSCT [34, 38]. A single institution retrospective study of pediatric HSCT patients found the incidence of BO to be 8.3%. All patients diagnosed with BO/BOS had cGVHD and were receiving immune suppression at the time of diagnosis. Forty-four percent had at least one additional risk factor. Twenty-eight percent of children who developed BO had either an anaphylactic reaction to a drug, toxic epidermal necrolysis or Stevens-Johnson syndrome in the first 100 d following transplant compared to 2% of the non-BO group. A 38.9% mortality rate was reported in this study. None of the patients had complete resolution of disease [38]. A standard effective treatment for BO has not been established as it has often reached an irreversible stage by the time that it is diagnosed [34, 38, 39].

Early diagnosis and treatment of BO/BOS may be more beneficial before fibrotic changes have occurred. Treating with inhaled steroids ± bronchodilator when patients FEV1 drops more that 5% over 1 yr or is <80% predicted may result in an improvement in pulmonary function tests and clinical symptoms. If no improvement occurs or progressive disease is noted, initiation of systemic immunosuppressive treatment is suggested. First line treatment is prednisolone at 1 mg/kg/d plus the continuation of other immunosuppressive therapy (calcineurin inhibitors [CI]) [34]. As resolution or stabilization of BO is not often durable, second line therapy is often warranted. Sirolimus or mycophenolate mofetil (MMF) are frequently added to the cGVHD regimen empirically although no clinical trials exist. Extracorporeal photopheresis (ECP) has been reported with some success in several studies [34, 40–42]. Azithromycin has demonstrated efficacy with low toxicity in the treatment of BO following lung transplant and in a few case reports following AHSCT [38, 39, 43]. Although the mechanism of action is not fully understood, azithromycin appears to result in a reduction of neutrophilic inflammation [34]. A regimen of azithromycin, in adults, of 500 mg daily for 3 d followed by 250 mg three times a week for 12 wk was used with improvement in FEV1 and forced vital capacity in seven of eight patients [43]. Tumor necrosis factor alpha blockade with infliximab or etanercept has not been established in the treatment of BO or pulmonary cGVHD and has an associated infectious risks [34].

6. GVHD prevention

Partially suppressing the new graft while balancing the risk of rejection, relapse, and/or delayed immune reconstitution, is the key to preventing GVHD. The standard approach for the past two decades has been combination therapy consisting of a CI and methotrexate due to the lower incidence of acute GVHD when compared to a single agent [44–46]. A survey conducted by the European society for blood and marrow transplantation found that there are different protocols in use for GVHD prophylaxis with most centers using a CI (cyclosporine or tacrolimus) and a mini-dose regimen of methotrexate [47].

Cyclosporine and tacrolimus, both inhibit interleukin-2 activation on the T-cell receptor, and have similar clinical efficacy and side effects [13]. Adverse effects of these medications occur as a result of calcineurin inhibition in other organs resulting in hypertension, electrolyte imbalance, hirsuitism, gingival hyperplasia and renal insufficiency [48]. Serious post transplant complications such as thrombotic microangiopathy and posterior reversible encephalopathy syndrome might lead to early discontinuation of CI therapy [10].

In contrast to the CIs, methotrexate interferes with DNA synthesis. Adverse side effects of methotrexate include mucositis, delayed neutrophil and platelet recovery and hepatic toxicity [49]. In an effort to reduce toxicities, a mini-dose methotrexate regimen is often administered consisting of 5 mg/m^2 on day 1, 3, 6, and 11 or 10 mg/m^2 on day 3, 6 and 11 [49]. In recent years, methotrexate has been replaced by MMF. MMF inhibits purine synthesis leading to impaired proliferation of both B and T-lymphocytes [50, 51]. Studies comparing cyclosporine with MMF to the standard cyclosporine with methotrexate regimen reported neutrophil engraftment occurring approximately 1 wk earlier, reduced mucositis and no increased incidence of acute GVHD occurring in those who received the MMF [51, 52].

Alternative approaches in combination with immunosuppressive medications include reduced intensity conditioning which decreases the “cytokine storm” emanating from tissue damaged by the preparation regimen [53, 54] as well as T-cell depletion of the graft [13]. The lower incidence of GVHD with T-cell depletion is offset by higher rates of graft failure, relapse of malignancy, infection and Epstein-Barr virus associated lymphoproliferative disorders.

Preparative regimens consisting of alemtuzumab have lower rates of GVHD, but more infectious complications and may contribute to graft failure. Pre-transplant anti-thymocyte globulin (ATG) has been extensively studied and provides protection against extensive cGVHD [13]. Post-transplant cyclophosphamide may reduce GVHD by eliminating rapidly dividing T-cells [10]. This therapy is currently undergoing study.

7. Management of GVHD

Historically, much of the published data and clinical trials pertaining to the management of GVHD has focused on its prevention. In fact, currently there is no United States Food and Drug Administration approved medications for the treatment of GVHD and all therapy is used off label.

7.1. Acute GVHD management

Grade I acute skin GVHD can often be treated with topical steroids and by optimizing the current CI dosing to achieve therapeutic levels [55]. Upper gastrointestinal tract GVHD typified by symptoms of nausea, vomiting, anorexia and dyspepsia can be treated well with lower dose methylprednisolone (1 mg/kg/d) and local medications such as oral beclomethasone [56, 57]. For grades II–IV acute GVHD systemic corticosteroids remain the gold standard of first line therapy, although the dosing and length of therapy continues to be variable between institutions and clinicians [58–60]. The initiation of methylprednisolone at 2 mg/kg/d is considered standard of care and is the most common management strategy [57]. There appears to be no benefit to higher dose steroid therapy [57, 61]. An early clinical response to steroid therapy is a significant predictor of overall post-transplant survival [57, 62]. About half of all patients treated with steroid therapy respond either partially or completely to first line therapy, with higher response rates in skin versus liver or gut GVHD [63, 64]. Side effects of prolonged high dose glucocorticoid therapy are significant including immunosuppression and subsequent infections, hyperglycemia, psychosis, osteopenia, hypertension, dyspepsia, delayed wound healing, avascular necrosis and myopathy. Therefore, an important management goal of GVHD therapy is to minimize these complications [65]. The optimal taper is not defined in the literature, and there does not appear to be a significant benefit to either a rapid versus a slow taper [66]. The steroid taper should begin when there are noteworthy improvements in GVHD signs and symptoms. Typically, a 10% wean (0.2 mg/kg/d) every 3–5 d is appropriate followed by slow taper after reaching 20 mg per d in adults [57].

The decision to start second line therapy is made based on the severity and progression of GVHD. Steroid refractory GVHD has been defined as progression of symptoms after 3 consecutive days of steroid therapy at 1-2 mg/kg/d or 5–7 d of therapy with no response [65, 67–69]. Second line therapy is known to have high failure rates, significant toxicities, and overall poor survival [57, 65, 70]. On average, half of all patients respond either completely or partially to second line therapy [10, 65]. A comprehensive review determined that there is no significant evidence to support that one particular therapy should be used, and there is no evidence that any particular therapeutic agent should be avoided [67, 71]. It is left to the clinician to use their clinical expertise taking into account any effects from previous treatment, GVHD prophylaxis, toxicity and drug interactions. Some of the common second line agents in use are MMF, denileukin diffitox, sirolimus, methotrexate, basiliximab, infliximab, etanercept, pentostatin, horse ATG, rabbit ATG, alemtuzumab and ECP. Corticosteroid therapy should be continued with the initiation of second line treatment [72].

7.2. cGVHD management

Limited cGVHD of the skin may be managed successfully with topical corticosteroid or CI creams and ointments alone [73]. For more extensive disease, systemic therapy is required. The standard of care for the treatment of moderate to extensive cGVHD and for those with high-risk disease (i.e. platelets <100 K) is methylprednisolone 1 mg/kg/d with or without a CI [72–74]. Approximately 33% of these patients will have a response to first line therapy [75]. However, 90% of those who do respond to primary therapy will do so within 3 mo. At that time, they can begin a slow steroid taper with the goal of achieving a sustained response on low dose alternate day dosing [76]. If there is a flare of GVHD while weaning or discontinuation of immunosuppression, increased dosing may be required to achieve therapeutic levels or restarting of the drug with a slower taper when a response has been obtained [67, 73].

Steroid refractory cGVHD is most commonly described as having progressive symptoms for one month after initiation of 1-2 mg/kg/d of steroid therapy, or an incomplete response after 2 mo of treatment. There is no consensus second line therapy although various immunosuppressive agents have been found to improve symptoms or facilitate the tapering and discontinuation of steroids [67]. Multiple agents are often required and depend on clinician preference, expertise, involved organs, comorbidities, toxicity profile and financial and logistical considerations [73, 77]. Common therapeutic agents include MMF, ECP, sirolimus, methotrexate, pentostatin, imatinib, rituximab and mesenchymal stem cells [78]. Once cGVHD symptoms are quiescent, the corticosteroids are generally tapered first due to their toxicity followed by other agents, one at a time, over a 3 to 9 mo period depending on the clinical response. The mean time until discontinuation of immunosuppressive therapy for cGVHD is highly variable, but ranges from 2-3 yr depending on multiple factors [29, 73].

8. Supportive care

A multidisciplinary approach in collaboration with a HSCT specialist is essential to managing complex, multi-organ involvement of both acute and cGVHD, as well as toxicities from the therapy itself. Infection is the leading cause of non-relapse related mortality in HSCT patients with GVHD due to the immunosuppressive effects of GVHD and its treatment [27]. It is essential to monitor the patent closely for infection in combination with antimicrobial prophylaxis and prompt intervention when infection is suspected [13]. All patients with GVHD are at risk for fungal infections and those on prolonged steroids are particularly at risk for invasive mold infections including aspergillosis. Patients with GVHD should be on a minimum of fluconazole prophylaxis, and the more highly immunosuppressed patients and those in the early post-transplant period, benefit from a more broad spectrum azole (e.g. voriconazole or posaconazole) or echinocandin (e.g. micafungin or caspofungin) coverage [79, 80]. Patients with GVHD are also at high risk for viral infections, both primary and the reactivation of latent viruses such as cytomegalovirus (CMV), Ebstein-Barr virus, varicella zoster virus and human herpes virus 6 [81]. Antiviral prophylaxis with acyclovir or ganciclovir is recommended for these patients as well as frequent CMV monitoring using polymerase chain reaction. Pre-emptive therapy with ganciclovir or foscarnet should be initiated quickly when a significant viral load is detected and before it develops into organ disease [80, 82]. CMV can be a cause of interstitial pneumonia and gastritis [13]. Immunosuppressed patients are also at risk for opportunistic infection with *Pneumocystis jirovecii* and should receive trimethoprim sulfamethoxazole or pentamidine prophylaxis [80]. AHSCT patients with GVHD, and particularly those with implanted central venous access devices, are at high risk for bacterial infection and the rapid onset of sepsis. Therefore, any patients with signs or symptoms of bacterial infection such as fever, chills, hypotension or erythema at the catheter sites should have blood cultures drawn and broad spectrum antibiotics including anti-pseudomonal coverage started immediately [13]. Patients with GVHD are also at risk for infection with encapsulated organisms (such as streptococcal pneumonia) and may benefit from antibiotic prophylaxis for the same with penicillin or its equivalent [61]. Despite limited evidence of routine prophylaxis, intravenous immunoglobulin is administered by many centers for significant hypogammaglobulinemia as a means to prevent infection [83, 84]. Patients and their caregivers should receive vaccinations against influenza and treatment with neuraminidase inhibitors in the event of an infection [13].

In conclusion, as the population of patients with GVHD has grown with the number of allogeneic transplants performed and their associated intensive care admissions, it is important for the pediatric intensivist to recognize GVHD and understand the sequel of the disease and its treatment. The medical management of these children is complex and requires cooperation between the transplant and intensive care teams. A major barrier to GVHD treatment is life-threatening infectious complications. Given that the symptoms of GVHD often mimic other common complications of transplant, more precise and less invasive diagnostic tools are desirable. Current promising research is that of plasma biomarkers [10]. There has been increased interest in measuring plasma biomarkers not only to help diagnose disease, but also to help identify patients at higher risk for developing more severe disease [85, 86]. These biomarkers may also be useful in monitoring response to therapy [10]. Plasma biomarkers are not yet widely used, but current studies suggest that they may be both a promising diagnostic and prognostic tool [85, 86].

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