

44.1 Introduction

Chronic GVHD (cGVHD) is the most relevant cause of late non-relapse morbidity and subsequent mortality (approximately 25%) following allo-HCT (Grube et al. 2016). Its incidence is approximately 50% among all patients following allo-HCT and has increased during the last two decades due to increasing patient age and increasing use of unrelated and/or mismatched donors, RIC regimens, PBSC with application of standard GVHD prophylaxis (calcineurin inhibitor [CNI] + MMF or MTX) only (Arai et al. 2015). While the incidence of cGVHD is lower (6–40%) in children, its incidence rises to 60% as age increases (Baird et al. 2010; Sobkowiak-Sobierajska et al. 2022).

The *pathophysiology* of cGVHD is different from aGVHD and mainly characterized by impaired immune tolerance mechanisms affecting innate and adaptive immunity. Both autoreactive and alloreactive donor-derived T and B cells play a role (Cooke et al. 2017). Other pathophysiological factors are indirect presentations of allo-antigens through antigen-presenting donor cells and mechanisms of chronic inflammation with subsequent scar formation and fibrosis. One important aspect of GVHD pathophysiology is the variability of immune reconstitution, which is age-related and dependent on thymic function and hormones (Sobkowiak-Sobierajska et al. 2022). This adds to the unpredictability of the effects of transplant procedures and complications in a very heterogenous cohort of children and adolescents with malignant and nonmalignant diseases.

Main *risk factors* for adult and pediatric cGVHD are unrelated and/or mismatched donor, PBSCs as donor source, older donor age, older patient age (>12 years), and female donor into male recipient combinations (Baird et al. 2010). By far the strongest predictor is the history and severity of acute GVHD and children below the age of 12 years rarely develop *de novo* cGVHD (Cuvelier et al. 2019).

In addition to the harm it causes, cGVHD also has a *protective effect*, as patients with cGVHD have lower rates of recurrence of their underlying malignant disease (Grube et al. 2016). Overall survival of patients transplanted for malignant

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diseases developing mild cGVHD is therefore better compared to patients without cGVHD. Even OS of patients with moderate cGVHD is not different from patients without cGVHD, as the slightly increased mortality associated with cGVHD is counterbalanced by lower disease-associated mortality (Kuzmina et al. 2012).

In contrast, the *long-term mortality* rate of patients with severe cGVHD is as high as 50% taking into account that the severity is less relevant compared to certain risk factors for mortality consisting of low platelets at diagnosis of cGVHD, the direct progression of acute GVHD into cGVHD (progressive onset), and certain organ manifestations (lung, gastrointestinal, and cholestatic liver involvement) (Grube et al. 2016). One important pediatric aspect involves the high proportion (up to 50%) of nonmalignant underlying diseases as HCT indication. While malignant diseases benefit from the graft-versus-malignancy effect induced by GVHD, it only offers harm for the nonmalignant diseases. In daily clinical routine, this fact influences GVHD prophylaxis and treatment both in regard to intensity and duration of immunosuppressants (Lawitschka et al. 2020).

44.2 Clinical Manifestations

cGVHD usually begins between 3 months and 2 years after HCT, but earlier onset (at least 1 month after transplantation) is possible (Jagasia et al. 2015).

While involvement of the organ systems mentioned below is regarded as NIH-defined classic cGVHD, almost every other organ can potentially be impaired by atypical forms of cGVHD or atypical manifestations can involve organs otherwise regarded as classic manifestation of cGVHD (restrictive forms of pulmonary cGVHD). The most frequent manifestations are immune-mediated cytopenias, polyserositis, renal manifestations, involvement of the central and peripheral nervous system, rheumatological including myositis, and autoimmune thyroiditis (Cuvelier et al. 2022). As cGVHD can affect a

number of organs, and patients often do not report changes until functional impairment is recognized, regular examination of all organs potentially affected is essential. The following section describes the most common clinical organ manifestations of cGVHD. In general, pediatric manifestations are similar to adult cGVHD; when indicated, specific aspects are shortly described.

44.2.1 Skin

The skin is the most frequently involved organ with different morphology, depending on the different skin layers (epidermis, cutis, subcutis, and fasciae) involved. Some manifestations may overlap with acute GVHD like erythema, maculopapular rash, and pruritus. Cutaneous cGVHD may show many different non-sclerotic and sclerotic phenotypes often simulating well-known chronic inflammatory and autoimmune diseases (Strong Rodrigues et al. 2018).

Diagnostic features of NIH-defined cGVHD include poikiloderma, lichen planus-like, lichen sclerosus-like, morphea-like, and deep sclerotic eruptions, and no biopsy is needed to confirm the diagnosis. Distinctive for cGVHD, other or common skin manifestations like depigmentation and papulosquamous lesions or ichthyosis, keratosis pilaris, pigmental changes, loss of skin appendages, and sweat impairment are not sufficient for diagnosis and require histopathological confirmation if no diagnostic signs in the skin or other organs are present (Jagasia et al. 2015).

In pediatric patients, the incidence of viral reactivation and infection seems higher (although only proven for some viruses), and therefore, infection has to be ruled out. Viral skin infections can worsen or activate cGVHD (Jacobsohn 2010). Premature graying of the hair is even in small children common, possibly together with seborrheic scalp changes. Of note, if sweat glands are destroyed, this may be of importance for phototherapy because of the inability to sweat with consequent hyperthermia. Of note, long-lasting cutaneous cGVHD is a risk factor for secondary cutaneous malignancies.

44.2.2 Eyes

cGVHD of the eyes usually manifests as keratitis sicca. In addition to atrophy of the lacrimal gland with subsequent tear deficiency (sicca syndrome), the meibomian glands and eyelids are often affected by severe blepharitis which may initially present with tearing. Around the conjunctiva there are often not only fibrotic alterations but also chronic persistent inflammation with visible erythema of the conjunctiva. As dry eye symptoms are rarely communicated by children, light sensitivity is the predominant symptom, sometimes with excessive eye rubbing. Infections have to be ruled out. Referral to a pediatric experienced ophthalmologist is recommended.

44.2.3 Oral Mucosa

Oral manifestations may appear as erythema or lichenoid changes (the latter are regarded as diagnostic) of the oral mucosa as well as ulcers and mucocoeles. Sicca symptoms may result from destruction of the salivary glands. Long-term cGVHD may lead to gingivitis, periodontitis, increased tooth decay, tooth loss, and secondary malignancies of the oral mucosa. In children excessive drinking during eating may be the first symptom of oral involvement. Not only mucosal problems but abnormal teeth development (e.g., hypodontia, root malformation, enamel hypoplasia) and caries are often seen as secondary symptoms in infants.

44.2.4 Liver

Liver involvement manifests as cholestasis and may resemble primary biliary cirrhosis, but hepatic forms with high transaminases are also possible. Other factors, such as viral infections (hepatitis A, B, C, and E, CMV, EBV, ADV, and HHV6/7), drug toxicity, or total-parenteral nutrition-related cholestasis, should be excluded, but liver biopsy may be required to confirm the diagnosis, particularly in patients with no other symptoms of cGVHD and failure to respond to initial treatment of suspected GVHD (Stift et al. 2014).

44.2.5 Gastrointestinal Tract

GI manifestations can lead to dysphagia (esophagus), nausea and vomiting (stomach), or chronic diarrhea and malabsorption syndrome (intestines, pancreas). Occasionally, cGVHD may also manifest as immune-mediated pancreatitis. Of note, except esophageal involvement, intestinal involvement is regarded as manifestation of acute GVHD, and patients are therefore classified as suffering from overlap syndrome in which concomitant symptoms of chronic and acute GVHD occur.

Infections like ADV or CMV gastroenteritis, secondary gluten or lactose intolerance, pancreatic insufficiency, and drug-related side effects (e.g., mycophenolate mofetil) have to be ruled out.

Malnutrition and enteral fluid and protein loss in small children require regular laboratory monitoring.

44.2.6 Genitals

The symptoms of cGVHD are similar to those of genital lichen planus which may occur in males and females. Vaginal synechiae, ulceration, and fissures can subsequently occur. Genital manifestations are often associated with oral manifestations of cGVHD. As symptoms may not be reported spontaneously, females suffering from cGVHD require regular gynecological follow-up including screening for secondary malignancies. In girls cGVHD may manifest with vulvovaginitis, in boys with balanitis or balanoposthitis. Of note, healing may occur with fibrosis possibly leading to synechia with the risk of hematocolpos during puberty in females and of phimosis in males.

44.2.7 Lung

Pulmonary manifestations occur as progressive, irreversible obstruction (bronchiolitis obliterans syndrome) and less frequently as restrictive manifestation with bronchiolitis obliterans organizing pneumonia (BOOP) which may progress towards

fibrosis with nonspecific interstitial pneumonia pattern (see Chap. 52).

Since the onset of pulmonary symptoms may not be symptomatic and obstruction may be irreversible, regular evaluations of a serial pulmonary function test (PFT) with body plethysmography (from the age of 4–6 years on) and diffusion capacity (usually from 8 to 10 years of age on) are required in asymptomatic patients.

Patients require follow-up by a pediatric experienced pulmonologist. Of note, the possible overlap of (1) myopathy/hypotrophy of the respiratory muscles (glucocorticoid induced, \pm central obesity, and/or physical inactivity), (2) restriction of the chest wall in the context of dermal sclerosis, and (3) unproportional chest growth after TBI and/or local irradiation may contribute to a restrictive ventilator dysfunction leading to a mixed picture.

Finally, a thorough diagnostic evaluation includes a lung CT scan and a BAL to rule out viral, bacterial, fungal, and mycobacterial infections.

Coexisting IgA deficiency and chronic sinusitis or sinubronchial syndrome should be considered in the diagnostic workup (Hildebrandt et al. 2011).

44.2.8 Joints and Fasciae

cGVHD-associated fasciitis (diagnostic for cGVHD) can result in restricted mobility of joints. This can also be caused by deep cutaneous sclerosis. Moreover, rheumatoid complaints may

be associated with cGVHD. In children, myositis, muscle weakness, cramping, edema, and pain are quite common. However, iatrogenic glucocorticoid-induced myopathy may overlap with fasciitis. Photographic range-of-motion (P-ROM) examinations are recommended at baseline and at serial intervals with the P-ROM scale providing an easy-to-apply tool. (There is a pediatric adaption, ped P-ROM; see Addendum.)

44.3 Diagnosis

cGVHD is diagnosed on the basis of cGVHD symptoms of eight organs, laboratory values (for hepatic manifestations), and PFTs. Each organ is graded between 0 and 3. The overall severity of cGVHD is classified as mild, moderate, or severe based on this organ-specific grading (number of organs and severity). Overall severity is calculated on the basis of the number of organs affected and the severity of their involvement. Only in case that functional involvement is solely due to none GVHD causes, the impairment is not scored (Jagasia et al. 2015). Biomarkers of cGVHD are currently explored but require validation before clinical use.

44.3.1 Organ Grading of cGVHD for Adults and Children (See Annex 1 and Addendum)

44.3.1.1 Grading of Overall Severity of cGVHD (Jagasia et al. 2015)

Overall severity	Mild	Moderate	Severe
Number of involved organs	1–2	>3	≥ 3
Severity of involved organs	Mild (excluding lung)	Mild–moderate (lung only mild)	Severe (lung moderate or severe)

If diagnostic symptoms of cGVHD are absent, histological confirmation of diagnosis may be required. This may be particularly the case in gastrointestinal, nonspecific cutaneous, hepatic, and pulmonary manifestations to rule out toxic or infectious causes or comorbidity. Clinicopathologic series indicate a significant risk for inappropriate diagnosis and subsequent treatment if diagnosis has been made solely by clinical manifestations (and lacking diagnostic symptoms) without histological confirmation.

44.4 Treatment

44.4.1 First-Line Therapy

First-line treatment (see Table 44.1) consists of steroids given alone or in combination with CNI and is based on randomized trials.

As *mild cGVHD* does not impair organ function, the use of topical IS (topical steroids, topical

CNI, or phototherapy) should be considered. If this is impossible, PRD treatment at an initial dose of 0.5–1 mg/kg body weight/day is recommended. Topical IS can be used in addition to systemic IS, to improve efficacy, or to reduce systemic IS, but lack systemic efficacy.

For *moderate or severe cGVHD*, systemic treatment with PRD or methylPRD at an initial dose of 1 mg/kg body weight/day should be used. In individual cases lower doses of 0.5–1 mg/kg may be used (Jacobsohn 2010). The combination of steroids with a CNI (CSA or TAC) is particularly worth considering for severe cGVHD. Rituximab has been explored in the first-line treatment of cGVHD in combination with steroids and CNI demonstrating an increased response rate on the expense of an increased risk for late infectious complications and delayed B-cell recovery. In addition, sirolimus may also be combined with prednisone showing identical response rates compared to CNI (Carpenter et al. 2018). Other combination partners like ECP, itaci-

Table 44.1 First-line treatment of cGVHD

Drug	Recommendation		Side effects in >25% patients	Response rate	Comment
	Grade	Evidence			
Steroids	A	I	Osteoporosis, osteonecrosis, diabetes mellitus	~30 to 50% CR	Main drug; strategies to reduce use due to SEs very important
CNI + steroids	C-1	II	Renal toxicity, hypertension	~30 to 50% RC	Reduces steroid use, reduced incidence of osteonecrosis
Rituximab + steroids/CNI	C-1	III-1	Increased risk for late infectious complications	~75%	Randomized data are lacking
Sirolimus + steroids	C-1	II	Hypercholesterinemia (Carpenter et al. 2018), cytopenia	~50%	Equal efficacy compared to combination with CNI within a randomized trial
MMF + CNI/steroids	D	II	GI complaints, infections		No increased efficacy compared to CNI and steroids, increased risk of relapse of malignancy
Azathioprine	D	II	Cytopenia, risk of infection		Increased mortality
Thalidomide	D	II	Neurotoxicity, drowsiness, constipation		Very little effect in first-line therapy

A, should always be used; C-1, use in first-line therapy justified; D, moderate evidence of lack of efficacy or unacceptably high risks, should generally not be offered; I, evidence from ≥ 1 properly randomized, controlled trials; II, evidence from more than one well-planned nonrandomized clinical trial, from cohort or case-controlled, analytic studies (preferably at several sites); III-1, only one noncontrolled study; III-2, only one retrospective, noncontrolled study or retrospective evaluation. (Evidence and recommendations graded according to the 2005 NIH Consensus)

SE side effect, NIH US National Institutes of Health, MMF mycophenolate mofetil

Adapted from Wolff et al. (2011)

tinib, and ibrutinib have been evaluated in the first-line treatment of cGVHD within randomized clinical trials but did not result in significantly higher response rates compared to steroids alone.

As cGVHD often takes time to respond to IS treatment, response should not be assessed until at least 8 weeks have elapsed or until 3–6 months have elapsed in the presence of deep cutaneous sclerosis. Long-term IS treatment lasting at least 3–6 months is often required. Dose reduction of IS agents should be performed stepwise. Depending on the patient population, first-line therapy achieves complete remission of cGVHD in approximately 20% (adults) to 50% (children) of cases. If symptoms progress during the first 4 weeks of first-line therapy or there is no improvement in symptoms within 8–12 weeks, second-line therapy should be initiated.

44.4.2 Topical Therapy and Supportive Care

In principle, there is no difference between cGVHD treatment for children and adults. However, long-term steroid therapy in children causes major side effects in terms of growth, bone density, osteonecrosis, and organ development, making agents that reduce steroid use, entailing the use of topical drugs, particularly important. Age-based ancillary supportive care is essential in the management of pediatric cGVHD with the chance of sparing systemic therapy, often supported by highly compliant parents and/or family members as caregivers (Carpenter et al. 2015; Sobkowiak-Sobierajska et al. 2022). In small children, the risk of systemic effects of topical steroid and CNI treatment must be considered. cGVHD is by itself remarkably immunosuppressive intensified by its treatment (especially high-dose corticosteroids) leading to a high risk for infections: (a) for viral reactivation like CMV, ADV, and EBV and (b) for fungal infection like candida and aspergillosis. Functional asplenia with occurrence of Howell-Jolly bodies and a higher incidence of pneumococcal sepsis has to be considered also. Breakdown of skin and mucosal barriers adds to this risk.

Revaccinations (see Chap. 29) with inactivated vaccines are strongly recommended after

consolidation of cGVHD (Hilgendorf et al. 2011). Live vaccines should be avoided in this patient population. Ursodeoxycholic acid reduced liver GVHD and improved survival (Ruutu et al. 2014). Supplemental IG replacement is recommended in cGVHD patients with IgG <400 mg/dL or recurrent infections which is of special importance in children but does also apply to adults.

44.4.3 Second-Line Therapy

While first-line therapy is based on randomized trials, second-line treatment is mostly based on phase II trials and retrospective analyses taking into account that ruxolitinib has been recently evaluated within a phase III trial and additional randomized trials evaluated ECP, rituximab, and imatinib (see Table 44.2). In addition, because the data on disease severity and patient populations are very heterogeneous (in terms of age, treatment line, conditioning, and stem cell source), the published response rates cannot be fully extrapolated to the majority of patients currently treated for cGVHD. Moreover, many substances have been used almost exclusively in combination with steroids.

In general, no more than three IS agents should be combined, as combinations of more drugs often does not lead to improved efficacy but results in a significantly increased risk of side effects and infections. Because of the substantial toxicity of long-term steroid treatment, strategies for dose reduction are very important. Since no predictors of response for a single agent in individual patients are yet available, the choice of agent depends mainly on side effect profiles, availability including approval status, evidence, biology of the disease (overlap vs. classic), and patients' medical history. The response rates for specific agents range between 20 and 70%.

Response is assessed as for first-line therapy. Administration of drugs that have been shown to be ineffective should be stopped. As a rule, drugs shown to be ineffective should be tapered off stepwise with no more than one drug to be changed at a time in order to be able to evaluate their efficacy.

Table 44.2 Second-line treatment of cGVHD (Wolff et al. 2021)

Drug	Recommendation		Response rate	Side effects in >25% of patients	Comments
	Grade	Evidence			
Steroids	B	III-1	n.a.	Osteoporosis, osteonecrosis, diabetes mellitus	Main drug, strategies to reduce use due to SEs very important
Ruxolitinib	C-1	II	~50%	Infections, cytopenia	FDA and EMA approved in second-line treatment
Ibrutinib	C-1	III-1	~50 to 75% ~16 to 25% CR	Bruising, diarrhea, infections	FDA approved in second-line treatment of cGVHD
Photopheresis	C-1	II	~30 to 70% ~60% CR	Infections of the CVC (if applicable)	Venous access required, steroid-saving effect, good tolerability
mTOR-inh (sirolimus, everolimus)	C-1	III-1	~60% ~20% CR	TMA, hyperlipidemia, cytopenia	Increased risk of TMA when combined with CNI, regular blood levels required
MMF	C-1	III-1	~50% ~10% CR	GI SEs, risk of infection (viral) and increased risk of relapse	Steroid-sparing activity
CNI	C-1	III-1	n.a.	Renal toxicity, hypertension	Reduces steroid use, regular blood levels required
Belumosudil	C-2	III-1	~75%	Liver toxicity	FDA approved in third-line treatment
MTX	C-2	III-1	~50% ~10 to 20% CR	Cytopenia, mucositis	Best results in mucocutaneous cGVHD, reduces steroid use, contraindicated in the presence of pleural effusions or ascites
IL-2	C-2	III-1	~65% (only PR)	Fever, malaise, and fatigue	Applied in sclerodermoid skin disease
Ixazomib	C-2	III-2	~40%	Nausea, infection, cytopenia	Evaluated in advanced cGVHD
Bortezomib	C-2	III-1	n.a. for second-line Tx	Cytopenia, neuropathy	Trial was performed in first-line treatment
High-dose steroids	C-2	III-2	50–75% (only PR)	Infections	Rapid control of cGVHD
Total nodal irradiation	C-2	III-2	~50% ~25% CR	Cytopenia	Best results for fasciitis and mucocutaneous cGVHD
Abatacept	C-2	III-1	~45%	Airway infection	Best results in lung and mucocutaneous cGVHD
Hydroxychloroquine	C-2	III-2	~25% ~10% CR	GI side effects	Best results for mucocutaneous and hepatic cGVHD
Pentostatin	C-2	II	~50% ~10% CR	Cytopenia, risk of infection	Best results in children
Rituximab	C-2	II	~50% ~10% CR	Risk of infection	Effective in manifestations associated with autoAb and sclerodermoid cutaneous involvement
Imatinib	C-2	III-1	~50% ~20% CR	Fluid retention	Efficacy demonstrated mainly in sclerodermoid cGVHD and bronchiolitis obliterans
Pomalidomid	C-2	III-1	~60%	Cytopenia	Evaluated in late cGVHD only

(continued)

Table 44.2 (continued)

Drug	Recommendation		Response rate	Side effects in >25% of patients	Comments
	Grade	Evidence			
Axatilimab	C-3	III-1	~50%	Elevated liver enzymes, periorbital edema	Available in clinical trials only
Fostamatinib	C-3	III-2	~70%	Risk of infection	Phase I trial only
Thalidomide	C-3	II	~20 to 30% (only PR)	Neurotoxicity, drowsiness, constipation	Treatment for simultaneous cGVHD and recurrent multiple myeloma
Azathioprine	C-3	III-1	n.a.	Cytopenia, risk of infection, secondary malignancies	Increased risk of malignant disease of the oral mucosa
Retinoids	C-3	III-2	~60% (only PR)	Skin toxicity, hyperlipidemia	Effective in sclerodermoid cutaneous involvement
Tocilizumab	C-3	III-2	n.a.	Cytopenia, lack of acute phase reaction	Effective in sclerosing skin involvement
Regulatory T cells	C-4			None	Currently explored in several clinical trials
Mesenchymal stem cells	C-4	III-2	~50%	None	Repetitive application required
Alemtuzumab	C-4	III-3	n.a.	Infectious risks	Last resort for refractory cGVHD
Etanercept	C-4	III-3	n.a.	Infectious risks	May be used to treat mixed acute and chronic GVHD or pulmonary or GI manifestations of cGVHD

B, should generally be used; C-1, use in second-line therapy justified; C-2, use after failure of second-line therapy justified; C-3, should only be used in specific circumstances, due to unfavorable risk profile; C-4, experimental, should only be used in clinical trials and individual cases; II, evidence from >1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from >1 center) or from multiple time series; III-1, several reports from retrospective evaluations or small uncontrolled clinical trials; III-2, only one report from small uncontrolled clinical trial or retrospective evaluations; III-3, only case reports available
SE side effect, *n.a.* not available
 Adapted from Wolff et al. (2011)

Appendix A

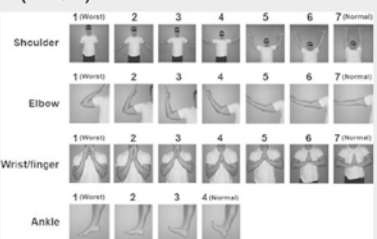
Annex 1 - Organ Scoring of Chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: KPS ECOG LPS	<input type="checkbox"/> Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	<input type="checkbox"/> Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	<input type="checkbox"/> Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	<input type="checkbox"/> Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† SCORE %BSA				
<u>GVHD features to be scored by BSA:</u> Check all that applies: <input type="checkbox"/> Maculopapular rash/erythema <input type="checkbox"/> Lichen planus-like features <input type="checkbox"/> Sclerotic features <input type="checkbox"/> Papulosquamous lesions or ichthyosis <input type="checkbox"/> Keratosis pilaris-like GVHD	<input type="checkbox"/> No BSA involved	<input type="checkbox"/> 1-18% BSA	<input type="checkbox"/> 19-50% BSA	<input type="checkbox"/> >50% BSA
SKIN FEATURES SCORE:	<input type="checkbox"/> No sclerotic features		<input type="checkbox"/> Superficial sclerotic features "not hidebound" (able to pinch)	Check all that applies: <input type="checkbox"/> Deep sclerotic features <input type="checkbox"/> "Hidebound" (unable to pinch) <input type="checkbox"/> Impaired mobility <input type="checkbox"/> Ulceration
<u>Other skin GVHD features (NOT scored by BSA)</u> Check all that applies: <input type="checkbox"/> Hyperpigmentation <input type="checkbox"/> Hypopigmentation <input type="checkbox"/> Poikiloderma <input type="checkbox"/> Severe or generalized pruritus <input type="checkbox"/> Hair involvement <input type="checkbox"/> Nail involvement				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
MOUTH <i>Lichen planus-like features present:</i> <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms with disease signs but not limiting oral intake significantly	<input type="checkbox"/> Moderate symptoms with disease signs with partial limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination with major limitation of oral intake
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				

Annex 1 - Organ Scoring of Chronic GVHD (continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES <i>Keratoconjunctivitis sicca (KCS) confirmed by Ophthalmologist:</i> <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not examined	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): <hr/>				
GI TRACT Check all that applies: <input type="checkbox"/> Esophageal web/proximal stricture or ring <input type="checkbox"/> Dysphagia <input type="checkbox"/> Anorexia <input type="checkbox"/> Nausea <input type="checkbox"/> Vomiting <input type="checkbox"/> Diarrhea <input type="checkbox"/> Weight loss* <input type="checkbox"/> Failure to thrive	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Symptoms without significant weight loss* ($< 5\%$)	<input type="checkbox"/> Symptoms associated with mild to moderate weight loss* (5-15%) OR moderate diarrhea without significant interference of daily living	<input type="checkbox"/> Symptoms associated with significant weight loss* $> 15\%$, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference of daily living
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): <hr/>				
LIVER	<input type="checkbox"/> Normal total bilirubin and ALT or AP < 3 x ULN	<input type="checkbox"/> Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP > 3 x ULN	<input type="checkbox"/> Elevated total bilirubin but ≤ 3 mg/dL or ALT > 5 ULN	<input type="checkbox"/> Elevated total bilirubin > 3 mg/dL
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): <hr/>				
LUNGS** Symptoms score:	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms (shortness of breath after climbing one flight of steps)	<input type="checkbox"/> Moderate symptoms (shortness of breath after walking on flat ground)	<input type="checkbox"/> Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score: FEV1 <input type="text"/>	<input type="checkbox"/> FEV1 $\geq 80\%$	<input type="checkbox"/> FEV1 60-79	<input type="checkbox"/> FEV1 40-59%	<input type="checkbox"/> FEV1 $\leq 39\%$
Pulmonary function tests <input type="checkbox"/> Not performed				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): <hr/>				

Annex 1. Organ scoring of chronic GVHD (continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA <input type="checkbox"/> No symptoms <u>P-ROM score</u> <i>(see below)</i> Shoulder (1-7): ____ Elbow (1-7): ____ Wrist/finger (1-7): ____ Ankle (1-4): ____	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	<input type="checkbox"/> Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	<input type="checkbox"/> Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
GENITAL TRACT <i>(See Supplemental figure†)</i> Check all that applies <input type="checkbox"/> Not examined Currently sexually active <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> No signs	<input type="checkbox"/> Mild signs‡ and females with or without discomfort on exam	<input type="checkbox"/> Moderate signs‡ and may have symptoms* with discomfort on exam	<input type="checkbox"/> Severe signs‡ with or without symptoms
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable none –0, mild -1, moderate -2, severe -3).				
<input type="checkbox"/> Ascites (serositis) ____		<input type="checkbox"/> Myasthenia Gravis ____		
<input type="checkbox"/> Pericardial Effusion ____		<input type="checkbox"/> Peripheral Neuropathy ____		<input type="checkbox"/> Eosinophilia > 500/ μ l ____
<input type="checkbox"/> Pleural Effusion(s) ____		<input type="checkbox"/> Polymyositis ____		<input type="checkbox"/> Platelets <100,000/ μ l ____
<input type="checkbox"/> Nephrotic syndrome ____		<input type="checkbox"/> Weight loss* without GI symptoms ____		<input type="checkbox"/> Others (specify): _____
Overall GVHD Severity <i>(Opinion of the evaluator)</i>	<input type="checkbox"/> No GVHD	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe
Photographic Range of Motion (P-ROM) 				

Adapted from Jagasia, 2015.

† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, **OR** if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

** Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.
Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); NUL (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

Appendix B

Diagnosis and staging cGVHD in children

Jagasia et al BBMT 2015

pediatric adaptation A. Lawitschka 11/2015

patient name

date:

patient name

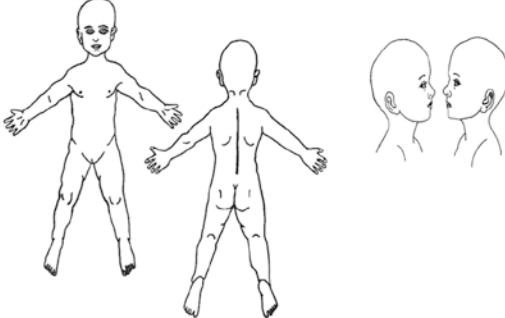
► please score/check the worst manifestation

► diagnostic features are marked **bold****classification:actual**

- ☐ feat. of acute GVHD
☐ feat. of classic cGVHD
☐ both

onset type ONLY at diagn.:

- ☐ de novo
☐ quiescent
☐ progressive

symptoms/features	Score 0	Score 1	Score 2	Score 3
KPS/LPS: %	<input type="checkbox"/> asymptomatic and fully active (KPS/LPS 100%)	<input type="checkbox"/> sympt., fully amb., restricted only in physically strenuous activity (KPS/LPS 80-90%)	<input type="checkbox"/> sympt., amb., capable of self-care, >50% of waking hours out of bed (KPS/LPS 60-70%)	<input type="checkbox"/> sympt., limited self-care >50% of waking hours in bed (KPS/LPS < 60%)
SKIN				
Feat. scored by BSA:	no BSA involved	1-18% BSA	19-50% BSA	> 50% BSA
<input type="checkbox"/> maculopapular rash/erythema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> lichen planus-like features	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> sclerotic features:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> lichen sclerosus-like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> morphea-like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> papulosquamous lesions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> ichthyosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> keratosis pilaris-like GVHD	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feat. not scored by BSA:				
<input type="checkbox"/> hyperpigmentation				
<input type="checkbox"/> hypopigmentation/ depigmentation				
<input type="checkbox"/> poikiloderma				
<input type="checkbox"/> severe pruritus				
<input type="checkbox"/> hair involvement				
<input type="checkbox"/> nail involvement				
<input type="checkbox"/> sweat impairment				
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				
► feature decisive for diagnosis /scoring:				
sclerotic features:	<input type="checkbox"/> no sclerotic features	<input type="checkbox"/> superficial sclerotic features "not hidebound" (able to pinch)	<input type="checkbox"/> deep sclerotic features "hidebound" (unable to pinch)	<input type="checkbox"/> impaired mobility
			<input type="checkbox"/> ulceration	
MOUTH				
<input type="checkbox"/> erythema	<input type="checkbox"/> no symptoms	<input type="checkbox"/> mild sympt with disease signs but not limiting oral intake significantly	<input type="checkbox"/> moderate sympt. with disease signs with partial limitation of oral intake	<input type="checkbox"/> severe sympt. with disease signs on examination with major limitation of oral intake
<input type="checkbox"/> lichen planus-like features				
<input type="checkbox"/> hyperkeratot. plaques				
<input type="checkbox"/> mucocels <input type="checkbox"/> pseudomembranes				
<input type="checkbox"/> ulcers <input type="checkbox"/> mucosal atrophy				
<input type="checkbox"/> dryness <input type="checkbox"/> pain				
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				
► feature decisive for diagnosis /scoring:				

%BSA:

child: head front/back 9 / 9
back 18, chest 18,
arm left 9, arm right 9
leg left 13,5, leg right 13,5
adult: head front/back 4,5 / 4,5
back 18, chest 18
arm left 9, arm right 9
leg left 18, leg right 18

palm: 1,5

Appendix 2 - Diagnosis and staging cGVHD in children (continued)





symptoms/features	Score 0	Score 1	Score 2	Score 3
EYES				
<input type="checkbox"/> keratokonjunktivitis sicca (KCS)	<input type="checkbox"/> no symptoms	<input type="checkbox"/> mild dry eye sympt.	<input type="checkbox"/> moderate dry eye sympt.	<input type="checkbox"/> severe dry eye sympt.
<input type="checkbox"/> confirmed by ophthalmologist		not affecting ADL	partially affecting ADL	significantly affecting ADL
<input type="checkbox"/> dryness <input type="checkbox"/> pain		(requirement of	(lubricant eye drops	(special eyewear to relieve pain) or
<input type="checkbox"/> photophobia <input type="checkbox"/> blepharitis		lubricant eye drops	>3 x/d or punctual plugs)	unable to work because of ocular
<input type="checkbox"/> pseudomembranes <input type="checkbox"/> ulcers		≤ 3 x per day)	without new vision	sympt or loss of vision due to KCS
			impairment due to KCS	
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				
▶ feature decisive for diagnosis /scoring:				
GI TRACT				
<input type="checkbox"/> esophageal web/ prox stricture or ring	<input type="checkbox"/> no symptoms	<input type="checkbox"/> symptoms without significant weight loss (5%)	<input type="checkbox"/> sympt. associated with mild to moderate weight loss (5-15%) or moderate diarrhea without significant interference with daily living	<input type="checkbox"/> symptoms associated with significant weight loss (> 15%) requires nutritional supplement for most calorie needs or esophageal dilatation or severe diarrhea with signif. Interference with daily living
<input type="checkbox"/> dysphagia <input type="checkbox"/> abdominal pain				
<input type="checkbox"/> anorexia <input type="checkbox"/> failure to thrive				
<input type="checkbox"/> nausea <input type="checkbox"/> vomiting				
<input type="checkbox"/> diarrhea <input type="checkbox"/> weight loss ≥ 5%				
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				height:
▶ feature decisive for diagnosis /scoring:				weight:
LIVER				
<input type="checkbox"/> hepatic pattern	<input type="checkbox"/> normal total bili	<input type="checkbox"/> normal total bili	<input type="checkbox"/> elevated total bili	<input type="checkbox"/> elevated total bili > 3 mg/dl
Bili: _____ AST: _____ ALT: _____	and ALT or AP	with ALT ≥ 3-5x ULN	but ≤ 3 mg/dl or	
GGT: _____ AP: _____	< 3 ULN	or AP ≥ 3 x ULN	ALT > 5 ULN	
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				
▶ feature decisive for diagnosis /scoring:				
LUNGS				
FEV1: _____ % MEF25: _____ %	<input type="checkbox"/> no symptoms	<input type="checkbox"/> mild symptoms	<input type="checkbox"/> moderate symptoms	<input type="checkbox"/> severe symptoms
FVC: _____ % MEF50: _____ %	FEV1 ≥ 80%	(shortness of breath	(shortness of breath	(shortness of breath at rest;
DLCO: _____ % MEF75: _____ %		after climbing one	after walking on	requiring O2)
RV: _____ <input type="checkbox"/> RV/TLC > 120%		flight of steps)	flat ground)	FEV1 ≤ 39%
CT: _____		FEV1 60-79%	FEV1 40-59%	
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				
▶ feature decisive for diagnosis /scoring:				
JOINTS AND FASCIA				
ped P-ROM score (see below)	<input type="checkbox"/> no symptoms	<input type="checkbox"/> mild tightness,	<input type="checkbox"/> tightness or joint	<input type="checkbox"/> contractures, fasciitis
<input type="checkbox"/> edema <input type="checkbox"/> fasciitis		normal or mild ↓ of	contractures, fasciitis,	significant ↓ of ROM,
<input type="checkbox"/> muscle cramps <input type="checkbox"/> athralgia		range of motion (ROM)	moderate ↓ of ROM,	significant ↓ of ADL
			mild - moderate ↓ of ADL	
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				
▶ feature decisive for diagnosis /scoring:				
GENITAL TRACT				
<input type="checkbox"/> erosions, fissures	<input type="checkbox"/> no signs	<input type="checkbox"/> mild signs	<input type="checkbox"/> moderate signs	<input type="checkbox"/> severe signs with or without symptoms
<input type="checkbox"/> lichen planus-like features				
<input type="checkbox"/> lichen sclerosus-like features				
<input type="checkbox"/> labial/ vaginal scarring <input type="checkbox"/> phimosis				
<input type="checkbox"/> abnormality present but explained entirely by non-GVHD cause (specify):				
▶ feature decisive for diagnosis /scoring:				
Overall GVHD severity				
<input type="checkbox"/> no cGVHD				
<input type="checkbox"/> mild:	max. score of 1 in any affected organ, max. 2 organs affected, no lung involvement			
<input type="checkbox"/> moderate:	≥3 organ with max score 1 or max. score of 2 in any affected organ, lung score max 1			
<input type="checkbox"/> severe:	score 3 in any affected organ, lung score 2-3			

Appendix 2 - Diagnosis and staging cGVHD in children (continued)

Other indicators, clinical features or complications related to cGVHD			biopsy:
check all that apply and assign a severity score (0-3) based on functional impact			organ:
<input type="checkbox"/> ascites (serositis)	<input type="checkbox"/> myasthenia gravis	<input type="checkbox"/> eosinophilia >500 /ul	GVHD confirmed?
<input type="checkbox"/> pericardial effusion	<input type="checkbox"/> peripheral neuropathy	<input type="checkbox"/> platelets <100 000/ul	
<input type="checkbox"/> pleural effusion	<input type="checkbox"/> polymyositis	<input type="checkbox"/> hypo/hyperglobulinemia	
<input type="checkbox"/> nephrotic syndrome	<input type="checkbox"/> weight loss >5% without GI sympt	<input type="checkbox"/> auto-antibodies	
<input type="checkbox"/> others (specify)	<input type="checkbox"/> diabetes		

pediatric photographic range of motion (adapted ped P-ROM):

please mark appropriate number

shoulder:	1 (worst)	2	3	4	5 (normal)
					
elbow:	1 (worst)	2	3	4 (normal)	
					
wrist / finger:	1 (worst)	2	3	4 (normal)	
					
global flexion:	1 (worst)	2	3	4 (normal)	
					
ankle:	1 (worst)	2	3 (normal)		
					

Appendix C

Genital Tract GVHD Assessment and Scoring Form

Name: _____ Date of birth: _____

Assessment date: _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GENITAL TRACT (male or female)	<input type="checkbox"/> No signs	<input type="checkbox"/> Mild signs and females may have symptoms* WITH discomfort on exam	<input type="checkbox"/> Moderate signs and may have symptoms* with discomfort on exam	<input type="checkbox"/> Severe signs with or without symptoms*
<p>Currently sexually active: <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Check all signs that applies:</p> <p> <input type="checkbox"/> Lichen planus -like features <input type="checkbox"/> Lichen sclerosis-like features <input type="checkbox"/> Vaginal scarring (female) <input type="checkbox"/> Clitoral/labial agglutination (female) <input type="checkbox"/> Labial resorption (female) <input type="checkbox"/> Erosions <input type="checkbox"/> Fissures <input type="checkbox"/> Ulcers <input type="checkbox"/> Phimosis (male) <input type="checkbox"/> Urethral meatuusscarring/ stenosis (male) </p> <p><input type="checkbox"/> Abnormality present but <u>NOT</u> thought to represent GVHD (specify cause): _____</p> <p><input type="checkbox"/> Abnormality thought to represent GVHD <u>PLUS</u> other causes (specify cause): _____</p>				

* Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection.

If a gynecologist is unavailable, external examination may be performed to determine "discomfort on exam" as follows:

- Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene's and Bartholin's), labia minora and majora gently with a qtip. Vulvar pain elicited by the gentle touch of a qtip is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.
- If the woman is sexually active, determine whether qtip palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

Female genitalia: Severity of signs:

- Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis.
- Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds.
- Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis.

Male genitalia: Diagnostic features include lichen planus-like or lichen sclerosis-like features and phimosis or urethral scarring or stenosis. Severity of signs:

- Mild: lichen planus-like feature;
- Moderate: lichen sclerosis-like feature or moderate erythema;
- Severe: phimosis or urethral/meatal scarring.

Biopsy obtained:	<input type="checkbox"/> Yes <input type="checkbox"/> No	Site biopsied: _____	GVHD confirmed by histology:	<input type="checkbox"/> Yes <input type="checkbox"/> No
Change from previous evaluation:	<input type="checkbox"/> No prior or current GVHD <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Worse <input type="checkbox"/> N/A (baseline)			

Completed by (spell out name): _____

Date form completed: _____

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