

Chronic graft-versus-host disease

Recommendations from the society for diagnosis and therapy of
haematological and oncological diseases

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DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
Bauhofstr. 12
D-10117 Berlin

Executive chairwoman: Prof. Dr. med. Claudia Baldus

Phone: +49 (0)30 27 87 60 89 - 0

info@dgho.de

www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

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- [Guideline](#)
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Authors: Daniel Wolff, Francis Ayuketang Ayuk, Gesine Bug, Johannes Clausen, Jörg Halter, Annkristin Heine, Thomas Luft, Olaf Penack, Christoph Scheid, Robert Zeiser

on behalf of the DAG-HSCT, German Working Group for Hematopoietic Stem Cell Transplantation and Cellular Therapy, e. V.

1 Summary

Chronic graft-versus-host disease (GvHD) is a protracted reaction of the donor's immune system against the recipient's tissue. It occurs in approximately 50% of patients following allogeneic hematopoietic stem cell transplantation and typically initially appears 2 to 18 months after transplantation.

A definitive diagnosis requires clinical diagnostic symptoms or manifestations, or histological confirmation.

Treatment depends on the severity of chronic GvHD and the affected organs. It consists of topical measures and systemic administration of corticosteroids, possibly in combination with other immunosuppressants.

Severe chronic GvHD, in particular, is a contributing factor in approximately 25% of deaths following allogeneic hematopoietic stem cell transplantation.

2 Basics

2.1 Definition

Chronic GvHD (cGvHD) is defined as a reaction of the donor's immune system against the recipient's tissues, which typically develops gradually as a result of impaired tolerance mechanisms following allogeneic hematopoietic stem cell transplantation (allo-HSCT). cGvHD typically initially appears between 2 and 18 months after allo-HSCT. The most commonly affected sites are the skin, eyes, oral mucosa, salivary glands, genital mucosa, intestines, liver, fascia, or lungs. In addition, cGvHD can affect virtually any organ. Clinically, symptoms resemble those of autoimmune diseases in the rheumatic spectrum, such as scleroderma, Sjögren's syndrome, systemic lupus erythematosus, primary biliary cholangitis, bronchiolitis obliterans, immune cytopenia, and chronic immunodeficiency. For the classification of the various forms of cGvHD, see chapter 5.3.

Overlap syndrome is a subtype of cGvHD (cGvHD with additional symptoms of acute GvHD such as nausea, vomiting, diarrhea, and diffuse erythema). It is distinguished from late acute GvHD, which is divided into 3 different subtypes. Persistent acute GvHD begins before day 100 and persists beyond that day; the *de novo* late form first appears after day 100; and the recurrent form of acute GvHD was initially treated successfully before day 100 and recurs after day 100. Late acute GvHD is also treated according to the guidelines for acute GvHD. The categories of acute and chronic GvHD are presented in [Table 1](#).

Table 1: Categories of acute and chronic GvHD according to the NIH Consensus

Category	Time of symptom onset after transplantation or DLI	Signs of acute GvHD	Signs of chronic GvHD
Acute GvHD			
Classic acute GvHD	≤ 100 days	yes	no
Persistent, recurrent, or <i>de novo</i> late acute GvHD	> 100 days	yes	no
Chronic GvHD			
classic chronic GvHD	No time limit	no	yes
Overlap syndrome (a combination of acute and chronic GvHD)	No time limit	yes	yes

Legend:

DLI: Donor Lymphocyte Infusion

2.2 Epidemiology

Chronic GvHD occurs in approximately 50% of patients following allogeneic hematopoietic stem cell transplantation [1] and is a contributing factor in approximately 25% of deaths [2]. While infections and acute GvHD primarily complicate the early phase following transplantation and are the main cause of early transplant-associated mortality, cGvHD represents the most significant long-term complication; severe cases also negatively impact long-term survival, whereas mild and moderate cases primarily impair quality of life. There is evidence that patients with cGvHD experience a stronger graft-versus-malignancy (GvM) effect, which reduces the likelihood of relapse of the underlying disease [3]. Therefore, mild and moderate cGvHD in particular are accepted as a means of achieving long-term disease control in patients at high risk for relapse of the underlying malignant hematologic disease. Systemic immunosuppression is indicated for moderate to severe cGvHD.

2.3 Pathogenesis

The pathogenesis of cGvHD is characterized by impaired tolerance mechanisms, in which both alloreactive and autoreactive T and B cells, as well as mechanisms of chronic inflammation leading to fibrosis, play a role [4, 5]. Disruptions in donor-mediated peripheral tolerance are reflected here in particular by a relative deficiency of antigen-specific regulatory T lymphocytes. Thus, host-reactive antibodies are detectable in cGvHD [5, 8]. In addition, GvHD leads to damage to the thymus and bone marrow stroma, which impedes the generation of T and B lymphocytes and, in the case of the thymus, also promotes the formation of autoreactive T cells through impaired T-cell selection. Increased collagen synthesis has been described in sclerotic connective tissue, indicating the involvement of macrophages and fibroblasts in cGvHD.

2.4 Risk Factors

The following risk factors, which increase the likelihood of developing cGvHD, have been described:

- Previous acute GvHD
- Degree of HLA mismatch between donor and recipient
- Peripheral blood stem cells as the stem cell source compared to bone marrow
- Older age of the recipient and the donor
- previous infection (pneumonia, gastroenteritis, CMV reactivation)
- adoptive transfer of donor lymphocytes (DLI)

- Female donor for a male recipient
- Omission of T-cell reduction in Graft-versus-Host Disease (GVHD) prophylaxis, particularly when using peripheral blood stem cell transplantation (ATG or post-transplant cyclophosphamide)

4 Clinical characteristics

4.1 Symptoms

According to the NIH consensus, a clear diagnostic manifestation or symptom must be present to diagnose cGVHD. In the absence of such a manifestation, the presence of a distinctive manifestation or symptom of cGVHD (a symptom that distinguishes between acute and chronic GVHD but is not, on its own, conclusive evidence of cGVHD—e.g., sicca syndrome affecting the eyes and/or oral mucosa) is required; in such cases, additional diagnostic measures, such as histological confirmation of the diagnosis, are necessary. In addition to the classic organ manifestations of cGVHD, atypical manifestations may also occur in other organs, which frequently present with symptoms of known autoimmune diseases (immune thrombocytopenia, autoimmune pancreatitis) [9]. The following manifestations have been defined; see [Table 2](#):

Table 2: Defined Manifestations of cGVHD

• Skin	Poikiloderma, lichen planus-like, sclerotic, morphea-like, and lichen sclerosus-like lesions
• Mucosa	Lichen planus-like and lichen sclerosus-like lesions, Lichen planus-like lesions on the genitals, vaginal scarring (women), phimosis, or urethral stricture (men)
• Muscles/fascia/joints	Fasciitis, joint stiffness, or contractures due to fasciitis or sclerosis
• Gastrointestinal tract	Strictures or stenoses in the upper or middle third of the esophagus
• Lungs	Bronchitis obliterans syndrome (BOS) with a decrease in FEV1 <75%, or ≥10% compared to the baseline value within 2 years, or an FEV1/FVC ratio <0.70 after ruling out other causes, including high-resolution CT (HR-CT) during exhalation and bronchoalveolar lavage (BAL). Histological confirmation should only be sought in situations involving a differential diagnosis relevant to treatment, e.g., evidence of an infection and a concurrent suspicion of BOS. A transthoracic biopsy is generally necessary, as trans-bronchial biopsies have low sensitivity.

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial Diagnosis

The NIH Consensus Criteria define 8 organ systems that are frequently affected [10], and to identify all of these organ manifestations, a detailed medical history and physical examination should be performed, including the following assessments [11]; see [Table 3](#):

Table 3: Physical Examination for cGvHD

Organ/Manifestation	Examination
Skin	Inspection of the skin for erythema (sign of active inflammation), dyspigmentation (sign of past inflammation), and ulcers, Palpation of the skin for induration (possible wrinkling, mobility)
Oral mucosa	Inspection of the oral mucosa for erythema, ulcers, and lichenoid changes
Muscles/Joints/Fascia	Joint range of motion: Buddha position, arm elevation and extension, dorsiflexion of the feet, knees, and ankles (PROM scale)
Eyes	Inspection of the eyes for erythema, increased tearing, and photophobia
External Genitalia	Inspection of the external genitalia for erythema, ulcers, and lichenoid changes

Since cutaneous and mucosal cGvHD is a risk factor for the development of squamous cell carcinomas, histological evaluation should always be performed if malignant changes are suspected. Furthermore, patients who have undergone allogeneic stem cell transplantation should be referred to skin cancer screening once a year. If the oral mucosa is affected, an annual follow-up with an oral and maxillofacial surgeon is necessary.

5.2.1.1 Assessment of the Severity of Organ Manifestations of Chronic GvHD

In a follow-up conference in 2014, the NIH Consensus Group made additions and clarifications, which were subsequently published [10].

The most important organ severity grades are presented in [Table 4](#). In clinical practice, an organ-specific assessment form for determining organ severity grades has proven effective; see [Appendix: cGvHD Assessment Form](#).

Table 4: Organ severity grades for chronic GVHD [10]

Organ Stage	0	I (mild)	II (moderate)	III (severe)
Skin • maculopapular rash • lichenoid rash • papular-squamous • ichthyotic (extreme scaling) • Keratosis pilaris • Erythema • superficial sclerosis • deep sclerosis	No changes	< 18% KOF	18-50% KOF	> 50% KOF
• Hyperpigmentation • Hypopigmentation • Poikiloderma • Ulcers • Severe pruritus • Hair loss • Nail changes		lichenoid or ichthyosis-like changes, no sclerodermi-form changes	sclerodermiiform changes with superficial sclerosis no "tethered skin" (folds can still be formed)	Deep sclerosis "shackled skin" (wrinkling not possible), limited mobility and/or ulcers
Joints/fascia	No contrac-tures	Mild stiffness of the arms and legs, mild restriction of movement without impairment of ATL*	Stiffness in the arms and legs or joint contractures or erythema due to fasciitis, moderate impairment of mobility, (mild impairment of ATL*)	Severe joint contrac-tures with impairment of ATL* (inability to tie shoes, unbutton but-tons, or get dressed)
Genital tract (male)	No changes or minimal non-specific changes	Erythema of the glans penis, "lichen planus-like" symptoms	Erythema of the glans penis and erosions, "lichen planus-like" symp-toms	Urethral stenosis, phi-mosis
Genital tract (female)	No symptoms, no changes, or minimal non-specific, changes	Symptoms with mild, typical changes but no effect on sexual intercourse and minimal discomfort during gynecological examina-tion	Symptoms with typical changes and pain during inter-course or gynecological examination	Symptoms with severe typical changes (stric-tures, labial adhesions, severe ulcerations, insertion of the specu-lum not possible)
Oral mucosa	No symptoms, no changes, or minimal non-specific changes	Mild symptoms with typical changes, but normal oral intake is possible	Moderate symp-toms and partial restriction of oral intake	Severe symptoms with typical changes, signifi-cant limitation of oral intake
Liver	Normal bilirubin and AP, and GPT (ALT) < 3 times the upper limit of normal	Bilirubin normal, GPT (ALT) ≥ 3 times the upper limit of normal and ≤ 5 times the upper limit of normal, and/or AP ≥ 3 times the upper limit of normal	Increased bilirubin but ≤ 3 mg/dL (51 µmol/L) or GPT > 5 times the upper limit of normal	Bilirubin > 3 mg/dL (51 µmol/L)
Lungs**	No symptoms FEV1 > 80%	Mild symptoms (e.g., shortness of breath when climbing stairs), FEV1 60-79%	Moderate symp-toms (e.g., short-ness of breath when walking on level ground) and/ or FEV1 40-59%	Resting dyspnea (O ₂ requirement) and/or FEV1 ≤ 39% or oxygen therapy required
Eyes	No changes	Mild dry eyes without impairment of overall quality of life, <3 times/day eye drops, asymptomatic keratoconjunctivitis sicca	Moderate symptomatic keratocon-junctivitis, >3 times per day eye drops or tear duct occlusion <u>without</u> impair-ment of vision	Severe impairment of vision due to pseudomembranes or corneal ulcers (up to vision loss), pain requiring special eyeglass lenses

Organ Stage	0	I (mild)	II (moderate)	III (severe)
Gastrointestinal tract	No symptoms	Difficulty swallowing, anorexia, nausea, vomiting, abdominal pain, diarrhea without significant weight loss and without relevant impairment (weight loss <5%)	Symptoms with weight loss of 5–15% or moderate diarrhea without significant impairment	Symptoms with weight loss >15% or parenteral supplemental nutrition required or esophageal dilation required or severe diarrhea with significant impairment

Legend:

* ADL = Activities of Daily Living.

** The severity of pulmonary involvement should always be assessed based on symptoms and pulmonary function tests (PFTs). In the event of a discrepancy between symptoms and PFT results, the higher of the two values should be used. The severity of pulmonary involvement should primarily be assessed using FEV1.

5.2.1.2 Assessment of the Overall Severity of Chronic GvHD

The overall severity of cGVHD is assessed according to the 2005 NIH Consensus Criteria and the 2014 follow-up conference [10, 12]; see Table 5. Mild cGVHD is present when no more than 2 organs are mildly affected and no pulmonary involvement is detectable. Moderate cGVHD is present when more than 2 organs and/or at least 1 organ is affected to a moderate degree (lungs only mildly affected). Severe cGVHD is present as soon as one organ shows severe changes (Grade III) or the lungs are moderately affected.

Table 5: Overall Severity Grades of Chronic GvHD [10, 12]

Overall Severity	Mild	Moderate	severe
Number of affected organs	1–2	>2	>2
Severity of organ involvement	mild (except lungs)	mild (>2 organs) – moderate (≥1 organ) Lungs: mild only	severe (≥1 organ) (Lungs: moderate-severe)

5.3 Classification

Three forms of cGVHD are distinguished:

- “De novo” onset without prior acute GvHD
- “Progressive” onset arising directly from acute GvHD or occurring during treatment of acute GvHD with a prednisolone dose of >0.5 mg/kg/day
- “quiescent” onset following resolution of a previous episode of acute GvHD and usually after reduction of immunosuppression.

In addition to the severity of cGVHD manifestations and the progressive onset of cGVHD, the presence of thrombocytopenia ($<100 \times 10^9/L$) at diagnosis has prognostic significance and is associated with an increased mortality of 10% [13]. When acute and cGVHD occur simultaneously, this is referred to as “overlap syndrome,” which is a subtype of cGVHD. Overlap syndrome is particularly present when, in addition to distinctive or diagnostic signs of cGVHD, diarrhea, vomiting, or nausea occur, or when there is diffuse erythema of the skin.

6 Treatment

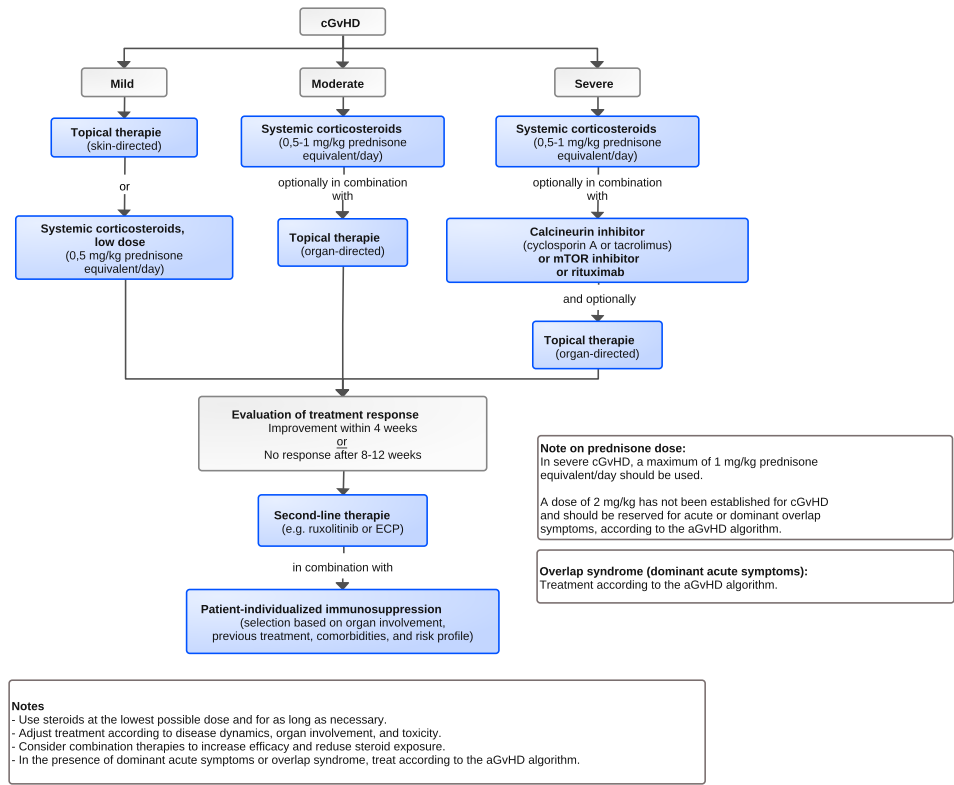
6.1 Treatment structure

Treatment of mild cGVHD is guided by the patient’s level of distress, the risk of recurrence of the underlying disease, and previous experience with the clinical course, and should be symptom-oriented, either topically or with low-dose steroids. An exception is made for patients with

a non-malignant underlying disease, for whom the indication for systemic immunosuppression should be applied more broadly (graft-versus-leukemia effect is not relevant).

The use of corticosteroids forms the basis of first-line therapy for moderate and severe cGvHD, leading to improvement in half of the patients. For patients with high-risk cGvHD (thrombocytopenia < 100/nl, overlap syndrome, pulmonary involvement), combination therapy (on-label with calcineurin inhibitors, off-label with mTOR inhibitors or rituximab) should be considered. Patients who are already receiving steroids >0.5 mg/kg at the onset of cGvHD due to aGvHD should primarily be treated with a combination including ruxolitinib (effectively second-line therapy). If cGvHD develops while the patient is being treated for aGvHD with steroids and ruxolitinib, the criteria for third-line therapy for cGvHD apply. The choice of therapeutic option is based on evidence, the spectrum of side effects, the severity of GvHD, the risk of recurrence, comorbidities, and availability. In general, it should be noted that the use of most immunosuppressants is associated with an increased susceptibility to infection, drug-specific side effects, and a potential reduction in the desired antitumor effect. Therapeutic options with no or only a slight increase in the risk of recurrence of the underlying disease include extracorporeal photopheresis (ECP), mTOR inhibitors, and topical therapies.

Figure 1: Guideline algorithm for the treatment of cGvHD



Legend:
Abbreviation: cGvHD = chronic graft-versus-host disease.
This figure reflects the state of knowledge as of May 2025.

6.1.1 First-line therapy

In cases of mild cGvHD, topical therapy should be administered; if this is not possible, systemic therapy with a low-dose steroid (prednisolone or methylprednisolone) once daily in the morning should be used [14].

6.1.1.1 Systemic therapy

In cases of moderate or severe cGvHD, systemic immunosuppression with a corticosteroid (prednisolone or methylprednisolone 1 mg/kg/day as a single dose in the morning) is necessary (Table 6). Particularly in cases of severe cGvHD, primary combination immunosuppression should also be considered to reduce steroid use in the medium to long term [15]. Both cyclosporine (target level 100–150 ng/mL) and tacrolimus (target level 4–6 ng/mL) can be used for this purpose. In a prospective, randomized pilot study, the use of ECP in combination with standard therapy consisting of a calcineurin inhibitor (cyclosporine or tacrolimus) and a corticosteroid in patients with newly diagnosed moderate or severe cGvHD showed high response rates of 74% at week 28 [16].

Combination therapy with more than two immunosuppressants is not indicated as first-line therapy. Topical therapy may be used as an adjunct to improve the local response. Patients with an overlap syndrome, in whom acute symptoms—particularly significant gastrointestinal symptoms (diarrhea)—predominate, should be treated according to the treatment recommendations for acute GVHD. Since, in cases of progressive cGVHD, symptoms typically begin while the patient is under significant immunosuppression, second-line therapy is generally necessary as soon as symptoms appear (see above).

Table 6: Corticosteroids for the Treatment of Chronic GVHD

	Dexamethasone	Methylprednisolone	Prednisone	Prednisolone
Dose (mg/day)	0.5–12	0.5–1 mg/kg/day	0.5–1 mg/kg/day	0.5–1.0 mg/kg/day
Duration of action in hours	36–72	12–36	12–36	12–36
Cushing's threshold (mg/day)	1.5–2	6–8	7.5–10	7.5–10
- times greater anti-inflammatory effect relative to hydrocortisone	25–30	5	4	4
- times the mineralocorticoid effect	<0.1	0.5	0.6–0.8	0.6–0.8
Special feature	Poor efficacy in GVHD but good CNS penetration—used for CNS manifestations of GVHD	Rare occurrence of myopathies; frequent occurrence of euphoria	None	Levels are independent of albumin

In general, for cGvHD, a single dose of corticosteroids should be administered in the morning. An exception is patients with overlap syndrome, who have concurrent symptoms of both acute and chronic GVHD.

6.1.1.2 Topical Therapy

The following local treatment options are available (Table 7).

Table 7: Organ-specific treatment measures for chronic GvHD

Organ	Drug	Response Rate %	Side Effects	Comments
Skin	Steroids	N/A	Skin atrophy	Trunk and extremities: moderate- and high-potency steroids Face: Hydrocortisone 1%
	Tacrolimus / Pimecrolimus	~70	Long-term risk of cutaneous malignancies	Application twice daily
	PUVA	~75	Phototoxicity, long-term risk of skin cancer	Do not combine with phototoxic medications
	UVA	~60-70	Phototoxicity, long-term risk of skin cancer	No UV protection required after treatment; do not combine with phototoxic medications
	UVA1	~50-90	Phototoxicity, long-term risk of skin cancer	Particularly useful for deep sclerosis that cannot be adequately treated with other light therapies
	UVB	~60	Phototoxicity, long-term risk of skin cancer	Ineffective for sclerosis of the skin
Gastrointestinal tract	Steroids	~60-70		Budesonide or Beclomethasone
Lungs	Inhaled steroids	~50		Can be combined with beta-agonists
Oral mucosa	Tacrolimus / Cyclosporine	~60	Potential long-term risk of oral mucosal malignancies	Systemic levels possible; use with caution in renal insufficiency
	Steroids	~60-80	Risk of local infections (fungi, viruses)	Best results with budesonide and clobetasol
	PUVA	~60-70	Phototoxicity, long-term risk of skin cancer	Important option for refractory oral cGVHD
Eyes	Steroids	~60-75	Risk of corneal atrophy, infectious keratitis, and glaucoma	Better short-term tolerability; not suitable for long-term therapy
	Cyclosporine	~60	Local burning and stinging	Fewer long-term side effects, higher long-term efficacy than steroids
Vaginal	Steroids	N/A	Increased risk of local infections and atrophy	Topical estrogen therapy and antifungal prophylaxis recommended
	Tacrolimus / Cyclosporine / Pimecrolimus	N/A	Burning	is less well tolerated but has greater long-term effectiveness

Legend:

n.a. – not available, PUVA – psoralen plus ultraviolet A radiation, UVA – ultraviolet A radiation, UVB – ultraviolet B radiation;

6.2 Second-line therapy

If symptoms progress during the first 4 weeks of first-line therapy, or if there is no improvement in symptoms within 8 to 12 weeks, second-line therapy must be initiated. Ruxolitinib is approved for this purpose in the EU. Alternatively, treatment should be administered as part of prospective clinical trials whenever possible. Even after failure of first-line therapy, the use of steroids remains important due to their broad anti-inflammatory effect. Given the numerous side effects, the primary goal should therefore be to achieve the lowest possible dose of corticosteroids through a combination of corticosteroids with another immunosuppressant and, in the event of remission of cGVHD, to discontinue corticosteroids. Regarding the choice of corti-

costeroid, there is no evidence of a benefit when comparing methylprednisolone, prednisone, and prednisolone, although prednisone and prednisolone were almost always used in studies on cGvHD. Given the complete lack of evidence supporting the use of dexamethasone for the treatment of cGvHD and clinical indications of reduced efficacy, it should be used only in patients with suspected CNS manifestations of GvHD.

In general, no more than three immunosuppressive drugs should be combined, as this often does not lead to improved efficacy but does result in a significantly increased risk of side effects and infection. To date, there is little evidence regarding the expected efficacy of these medications for individual patients; therefore, drug selection is primarily based on the evidence, approval status, side effect profile, and medical history. Relevant information on the available medications is summarized in [Table 8](#). The choice of second-line therapeutic option is based on the evidence, the spectrum of side effects, the severity of cGvHD, the risk of recurrence, comorbidities, the patient's current clinically relevant side effects, and the availability of the medication. In second-line therapy, ruxolitinib is currently approved based on the results of the REACH 3 study and is therefore the first-line treatment. If ruxolitinib is contraindicated (e.g., due to infections or cytopenia), another therapy (e.g., an ECP) should be considered based on the adverse effect profile. Starting with the third line of therapy, belumosudil is approved in the EU for the treatment of cGvHD based on the ROCKStar study (see [Figure 2](#)). It is not yet approved in Switzerland.

In general, cellular therapies should also be explored within the context of clinical trials (mesenchymal stromal cells, regulatory immune cells, CAR-T cells, etc.).

Table 8: Salvage Therapy for Chronic GvHD

Treatment	Recommendation ¹	Evidence ²	Response rate %	Adverse effects in >25% of treated patients	Comments
Corticosteroids	B	III-1	n/a [13]	Osteoporosis, osteonecrosis, infections, diabetes mellitus	Of central importance
Ruxolitinib [17]	B	Ib	~60	Hematotoxicity, infections, hepatotoxicity	FDA and EMA approval for steroid-refractory cGvHD starting in the second-line setting (based on a randomized Phase III trial)
Belumosudil [34]	C-1	II	65% (Best ORR)	Liver toxicity Diarrhea Infections	EMA approval for third-line treatment of cGvHD. No direct comparison with BAT to date
Photopheresis [18]	C-1	II	~ 60-70 ~ (30% CR)	Infections associated with central venous catheters	Venous access required, steroid-sparing effect, good tolerability
mTOR inhibitors (sirolimus, everolimus) [19]	C-1	III-1	~ 60 ~ (20% CR)	TAM, hyperlipidemia, hematotoxicity	Increased risk of microangiopathy when used in combination with calcineurin inhibitors; monitoring of levels is required
Mycophenolate mofetil (MMF) [20]	C-1	III-1	~ 50 ~ (10% CR)	Gastrointestinal side effects, increased risk of infection (viral) and recurrence	Steroid-sparing effect
Calcineurin inhibitors (cyclosporine, tacrolimus) [21]	C-1	III-1	n/a	renal toxicity, hypertension, increased risk of recurrence	Steroid-sparing effect; monitoring of drug levels required
Ibrutinib [22]	C-1	III-1	~60%	Infections Tendency to bleed (skin)	FDA approval for steroid-refractory cGvHD
Methotrexate	C-2	III-1	~50 ~ (10-20% CR)	Hematotoxicity, mucositis	Option for mucocutaneous cGvHD, steroid-sparing effect; not recommended for pleural effusion, ascites, renal insufficiency, cytopenia, or oral GvHD > Grade 1
High-dose corticosteroids	C-2	III-2	50-75 (PR3 only)	Increased risk of infection	Rapid control of cGvHD symptoms
Thoracoabdominal radiation therapy	C-2	III-2	~ 50 ~ (25% CR)	Hematotoxicity	Best results for fasciitis and mucocutaneous cGvHD
Hydroxychloroquine	C-2	III-2	~ 25 ~ (10% CR)	GI side effects	Best results for mucocutaneous and hepatic cGvHD
Clofazimine	C-2	III-2	~ 50 (PR only)	GI side effects, hyperpigmentation	Best results in mucocutaneous cGvHD
Pentostatin	C-2	II	~ 50 ~ (10% CR)	Hematotoxicity, risk of infection	Best results in children
Rituximab [24]	C-2	II	~ 50 ~ (10% CR)	Increased risk of infection	Effective for autoantibody-mediated manifestations

Treatment	Recommendation ¹	Evidence ²	Response rate %	Adverse effects in >25% of treated patients	Comments
Imatinib	C-2	II	~ 50 ~ (20% CR)	Fluid retention	Efficacy demonstrated primarily in sclerodermoid cGVHD and bronchiolitis obliterans
Bortezomib [25] (Reported to date only as a first-line therapy in combination with cortisone)	C-2	III-1	~ 70 10 CR (combination effect of prednisone + bortezomib)	Polyneuropathy, hematotoxicity	Particularly in cases of concurrent cGVHD and relapse in multiple myeloma
Pomalidomide [26]	C-2	III-1	~60	Infection, fatigue	May cause cutaneous inflammation if used early after treatment
Ixazomib [27]	C-2	III-2	~40	Hematotoxicity, gastrointestinal toxicity	
Tocilizumab [28]	C-3	III-3	~40%	Suppression of the acute-phase response	Efficacy in fibrosing mucocutaneous GVHD
Abatacept [29, 30]	C-3	III-2	~40%	Infections, intolerance	Efficacy in mucocutaneous and pulmonary cGVHD
Interleukin 2 [31]	C-3	III-1	~ 50 (PR only)	Fever, arthralgia	In sclerodermoid cGVHD
Cyclophosphamide [32]	C-3	III-3		Hematotoxicity	For the vasculitic form and/or renal involvement
Axatilimab [35]	C-2	III-1	~70%	Increased transaminases and lipase	FDA approval for third-line treatment of cGVHD
Azathioprine	C-3	III-1	n/a	Hematotoxicity, increased risk of infection	Increased risk of oral mucosal malignancies
Retinoids	C-3	III-2	~ 60 (PR only)	Skin toxicity, hyperlipidemia	Effective for sclerodermoid skin involvement
Alemtuzumab	C-4	III-3	n/a	Increased risk of infection	Last resort for refractory cGVHD
Etanercept	C-4	III-3	n/a	Increased risk of infection	May be used in cases of a mixed presentation of acute and chronic GVHD or gastrointestinal manifestations of chronic GVHD

Legend:

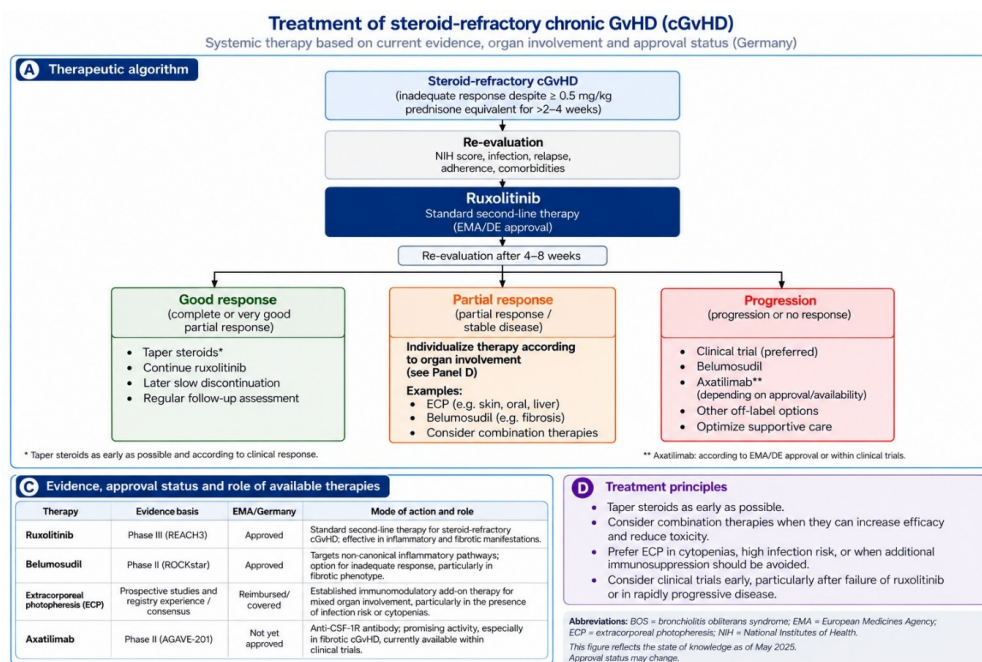
¹ Recommendation: B: Should generally be used; C-1: Use justified after failure of first-line therapy; C-2: Use justified starting with third-line therapy; C-3: Use justified only under specific circumstances due to an unfavorable risk profile; C-4: Experimental; should only be used within clinical trials and in individual cases;

² Evidence: III-1: multiple case reports from retrospective evaluations or small, uncontrolled clinical trials; III-2: only one retrospective, uncontrolled study or retrospective evaluation; III-3: exclusively individual case reports [33].

³ Abbreviations: CR – complete remission, n.a. – not specified, PR – partial remission

Response is assessed in the same manner as for first-line therapy; see [the Appendix cGVHD Assessment Form](#). Medications that have proven ineffective should be discontinued accordingly; as a general rule, only one medication should be changed at a time to better assess the efficacy of the therapeutic measures implemented.

Figure 2: Treatment of Steroid-Refractory Chronic GvHD (cGvHD) – Systemic Therapy Based on Current Evidence, Organ Manifestation, and Approval Status (Germany)



6.3 Specific Treatment of Affected Organ Systems

6.3.1 Oral

- First, rule out infections; then start with budesonide mouthwash (if the affected area is extensive; otherwise, use triamcinolone acetonide adhesive ointment if the condition is localized; only then use tacrolimus ointment)
- Budesonide nasal spray
- Tacrolimus monohydrate 0.1% on a gauze pad
- Triamcinolone
- Black tea mouthwash
- Xerostomia: drink frequently, sugar-free candies, chewing gum,
- Budesonide lozenges
- Saliva substitute, mouthwash (contains, among other ingredients, carboxymethylcellulose)
- A lack of saliva increases susceptibility to tooth decay. Regular dental checkups are recommended
- Rhubarb root, salicylic acid for mucocoeles

6.3.2 Neuromuscular

- Polyneuropathy: Carbamazepine, gabapentin, pregabalin
- Muscle cramps: Try high-dose magnesium, quinine sulfate, or gamma-aminobutyric acid (GABA)
- Steroid myopathy / contractures: intensive physical therapy

6.3.3 Liver

- Urodeoxycholic acid, dose 3 × 250 mg for cholestasis
- Budesonide 3 × 3 mg (for elevated transaminases)

6.3.4 Lungs

- Azithromycin 250 mg 0-1-0 Mon, Wed, Fri
- High-dose steroid inhalation in combination with a long-acting beta-2 agonist
- Use of montelukast
- Immunoglobulin replacement therapy for IgG deficiency (IgG < 4 g/L or IgG2 deficiency) and infections
- Consistent immunosuppressive therapy with monitoring of lung function (preferred medications: steroids, CNI [tacrolimus], ECP, mTOR inhibitors, MMF, imatinib, abatacept, belumosudil)
- If applicable, lung transplant outpatient clinic when a lung transplant is being considered. A lung transplant is only possible after 2 years of being recurrence-free from the underlying malignant disease.
- Respiratory Therapy
- For respiratory failure: Home oxygen therapy

6.3.5 Gastrointestinal tract

- Budesonide 3x3 mg
- Exclusion and treatment of differential diagnoses (viral/bacterial gastroenteritis, exocrine pancreatic insufficiency)

6.3.6 Eye

- Use preservative-free and phosphate-free eye drops; due to the increased risk of infection, preferably in single-use vials (EDO)
- Cyclosporine eye drops for long-term topical therapy
- Cortisone-containing eye drops should be used only for short-term therapy under the supervision of an ophthalmologist
- Always under the care of an ophthalmologist

6.3.7 Genital

Women:

- Care with oil-based ointments, water-based cream (may cause a burning sensation)
- If necessary, local estrogen therapy—prescribed by a gynecologist
- Anti-inflammatory therapy with topical steroids or calcineurin inhibitors
- For stenosis: vaginal dilation, surgical removal of synechiae.

Men:

- Treatment with dexpanthenol ointment, black tea compresses, topical calcineurin inhibitors—especially for erosions; use topical steroids only for a short time, ideally combined with a topical antifungal
- Circumcision if necessary in cases of phimosis

6.3.8 Bones

- Patients with chronic GvHD have a high risk of osteoporosis and an increased risk of aseptic bone necrosis. 25OH-vitamin D supplementation is urgently required (in combination with calcium if calcium intake is insufficient).
- Annual bone densitometry is recommended unless antiresorptive therapy (bisphosphonates or denosumab) is already being administered.

6.4 Physical Therapy

The following supportive measures should be implemented over an extended period to improve the patient's overall well-being:

- Physical therapy for the prevention and treatment of steroid myopathy
- Connective tissue techniques (following prior heat application) and manual therapy, particularly in cases of fibrotic changes
- Lymphatic drainage
- Respiratory therapy, reflexive breathing exercises in cases of pulmonary involvement and indurations in the trunk region

6.5 Supportive care

- Inhalation therapies
- Antiinfectives (PjP prophylaxis is always required during immunosuppression; in addition, at least one “standby” antibiotic effective against pneumococci should be prescribed; HSV/VZV prophylaxis should be considered during the first 2 years after transplantation or in patients with a relevant medical history. Under combination immunosuppression and steroids > 0.5 mg/kg/day, prophylactic antifungal therapy effective against *Aspergillus* should also be considered.)
- Vaccinations may be administered while on immunosuppression with controlled GVHD and steroids < 0.5 mg/kg/day. Following B-cell depletion and ibrutinib treatment, no immune response to conjugate vaccines is expected.
- Skincare products
- Supplemental nutrition
- Psychological support for distressed patients and their families

6.6 Response Assessment

Assessment of response according to the criteria listed in [the cGvHD assessment form](#) in [the appendix](#).

7 Rehabilitation

In addition to supportive physical therapy, inpatient or outpatient rehabilitation may be beneficial following management of cGvHD, with the goal of improving functional status and overall performance. Due to the immunodeficiency associated with cGvHD and the often complex medication regimen, expertise at the rehabilitation facility—including collaboration with a transplant center—is urgently required for the care of patients following allogeneic hematopoietic stem cell transplantation.

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10 Assessment Form

[Appendix - Chronic GvHD Staging Form](#) (current version)

14 Authors' Affiliations

Prof. Dr. med. Francis Ayuketang Ayuk

Universitätsklinikum Hamburg-Eppendorf
Klinik für Stammzelltransplantation
Martinistr. 52
20246 Hamburg
ayuketang@uke.de

PD Dr. med. Gesine Bug

Universitätsklinikum Frankfurt
Medizinische Klinik II
Abteilung Hämatologie / Onkologie
Theodor-Stern-Kai 7
60590 Frankfurt/M.
g.bug@em.uni-frankfurt.de

PD Dr. Johannes Clausen

Ordensklinikum Linz Elisabethinen
Abteilung Interne 1 Hämatologie mit
Stammzelltransplantation,
Hämostaseologie und medizinische Onkologie
Fadingerstr. 1
A-4020 Linz
johannes.clausen@elisabethinen.or.at

Prof. Dr. Jörg Halter

Klinik für Hämatologie
Universitätsspital Basel
Spitalstr. 21/ Petersgraben 4
CH-4031 Basel
joerg.halter@usb.ch

Univ. Prof. Dr. med. Annkristin Heine

Medizinische Universität Graz
Klinische Abteilung für Hämatologie
Auenbruggerplatz 38
A-8036 Graz
annkristin.heine@medunigraz.at

Prof. Dr. med. Thomas Luft

Universitätsklinikum Heidelberg
Medizinische Klinik und Poliklinik V
Im Neuenheimer Feld 410
69120 Heidelberg
thomas.luft@med.uni-heidelberg.de

Prof. Dr. med. Olaf Penack

Charité - Universitätsmedizin Berlin
CVK: Campus Virchow-Klinikum
CC 14: Tumormedizin
Augustenburger Platz 1
13353 Berlin
olaf.penack@charite.de

Prof. Dr. med. Dr. h.c. Christoph Scheid

Universitätsklinikum Köln
Klinik I für Innere Medizin
Kerpener Str. 62
50937 Köln
christoph.scheid@uk-koeln.de

Prof. Dr. med. Daniel Wolff

Universitätsklinikum Regensburg
Klinik für Innere Medizin III
Franz-Josef-Strauß-Allee 11
93053 Regensburg
daniel.wolff@ukr.de

Univ.-Prof. Dr. Robert Zeiser

Universitätsklinikum Freiburg
Klinik für Innere Medizin 1
Schwerpunkt Hämatologie und Onkologie
Hugstetter Str. 55
79106 Freiburg
robert.zeiser@uniklinik-freiburg.de

15 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.