

Guidelines for Diagnosis and Management of Cutaneous Graft-Versus-Host Disease

Following allogeneic stem cell transplantation, the commonest organs affected by graft-versus-host-disease (GVHD) are the skin and oral mucosa. The British Committee for Standards in Haematology GVHD guidelines recommend organ-specific management and supportive care (1) recognising that early input from a Dermatologist is likely to improve clinical outcomes (2). Clinical presentation of cutaneous GVHD is widely variable and a degree of GVHD is desirable for a graft-versus-malignancy effect. A dedicated GVHD clinic reported 13/30 referrals were made to Dermatologists with a specialist interest in GVHD (3). At Oxford University Hospitals NHS Foundation Trust, we demonstrated that Dermatology input was required in up to 40% patients in the BMT clinic over a nine-month period and a one-stop service initiated in 2015 has demonstrated excellent patient reported outcomes and experience(4). A dedicated Dermatology service enables accurate and early diagnosis of cutaneous and oral GVHD and allows diagnosis and management of a diverse range of skin diseases (other than GVHD) that affect patients post-transplantation.

This guideline focuses on the diverse clinical presentation and management of cutaneous GVHD. It focuses mainly on skin-directed therapies. See generic guidelines for systemic management of GVHD or when other organs are affected.

Acute cutaneous graft-versus-host disease

Acute GVHD is considered ‘classic’ if onset occurs within 100 days of allogeneic stem cell transplantation, ‘persistent’ if it lasts beyond 100 days, ‘recurrent’ if it resolves but reappears after 100 days, and ‘late-onset’ if symptoms start after 100 days. It can also occur following a rapid wean in dose of immunosuppressant agents or following donor lymphocyte infusions. The clinical signs and symptoms and underlying pathophysiological mechanisms are distinct to those seen in chronic cutaneous GVHD.

Acute cutaneous GVHD usually presents with sudden onset of a burning or pruritic morbilliform rash. This may be preceded by subtle peri-follicular prominence (erythema / scaling around the hair follicles on limbs). Initially there is macular blotchy erythema +/- dysaesthesia or oedema affecting palms & soles, and face, commonly also involving pinnae, cheeks, lateral neck, and upper back. The scalp is usually spared. If severe, the patient can become erythrodermic (erythema affecting more than 90% body surface area). Mucosal involvement is common, especially the conjunctivae and the oral cavity. Generalized erythema, blistering, and erosions simulate toxic epidermal necrolysis in severe acute GVHD and under these circumstances management of the skin should always be instigated in conjunction with Dermatology.

In most cases of acute cutaneous GVHD, the presence of other features confirms the diagnosis including fever (culture-negative), gastrointestinal symptoms e.g. abdominal pain, nausea, vomiting, and watery/bloody diarrhoea and abnormal liver function. Skin biopsies from a well-established peri-follicular lesion can sometimes help to distinguish between acute GVHD and other diagnoses e.g. drug eruptions, although this can prove challenging even for experienced dermatopathologists. Potent topical corticosteroids may control mild acute cutaneous GVHD, but severe cases require high-dose systemic corticosteroids. Other treatment options include immunosuppressant agents, anti-TNF antibodies and extracorporeal photopheresis (ECP). The main approach to acute GVHD management is prevention in the first place.

Chronic cutaneous graft-versus-host disease

Chronic GVHD can appear as an extension of acute GVHD (the progressive chronic form), or it can follow a disease free period (the quiescent form) or develop without prior GVHD signs (the de novo form). In chronic GVHD, the skin is affected in 75-100% of cases and the oral mucosa in 80-100% cases. It is important to remember that other mucosal surfaces can also be involved and should always be considered when examining patients [Box 1]. Photosensitivity is the one of the commonest reported skin disease post-transplant particularly for individuals who did not previously experience sensitivity when exposed to natural sunshine prior to their transplant. This manifests as erythema or skin disease that is accentuated in a UV-exposed distribution i.e. affecting face, neck, central 'V' of the chest. There are numerous skin manifestations of chronic cutaneous GVHD, with one form evolving into another or overlapping patterns co-existing within the same individual e.g. combination of lichenoid and sclerodermoid features.

The major clinical categories of chronic cutaneous GVHD are detailed in Table 1. Use Chronic GVHD Diagnosis and Staging Tool to document clinical signs regularly.

- Sclerodermoid disease is the most serious form of cutaneous GVHD because if left untreated is irreversible. The superficial form is morphea-like and deep sclerotic disease is scleroderma-like. This form of GVHD demonstrates isomorphic response (localised to sites of minor skin injury or pressure e.g. waistband) and isotopic response (occurs at sites of previous skin damage e.g. varicella zoster infection and central line venepuncture sites).
- An early feature of sclerodermoid disease is whole body generalised oedema and/or loss of hair.
- Blistering and ulceration can occur in sites of active sclerodermoid disease and may confer a poorer prognosis.
 - Consider co-existing herpes viral infection if vesicles / erosions are present and if the skin is very painful. Swabs should always be sent to exclude primary or co-existing bacterial, viral or fungal infections.
- Potent topical steroids under hydrocolloid dressings can help with healing once infection has been excluded.
- Punched-out ulcers are commonly seen in sclerodermoid skin and healing can take weeks to months.
- Sclerotic disease over joints limits movement and can cause significant functional impairment.

Non-cutaneous sites

GVHD can affect any mucosal sites and enquire if there is cutaneous involvement [Box 1]. Many patients may be too embarrassed to discuss genital involvement until severe when scarring may be difficult to reverse. Consider using the Supplementary Genital GVHD form to record clinical signs.

Signs of GVHD affecting the hair can include brittle hair, premature greying and scarring alopecia. Loss of body hair and sweat glands can cause heat sensitivity. Nail involvement occurs in up to 50% of patients with chronic GVHD and includes nail dystrophy, longitudinal ridging, thinning, fragility, scarring (pterygium) & loss of nails (signs similar to those seen in patients with lichen planus).

Management of cutaneous GVHD

The evidence-base supporting treatment choice for cutaneous GVHD is limited for various reasons; the wide phenotypic spectrum of skin disease, lack of validated outcome measures, poorly designed / conducted RCTs means that studies are not sufficiently powered to measure responses according to disease subtype.

General Measures

See Box 2. Ichthyosis (very dry skin) is common and can be very symptomatic and itchy. Prescribe large quantities of emollient (500 grams) as effects are short-lived and encourage patients to apply these to all their skin regularly. A number of different emollients may need to be tried before the patient finds one that is tolerable. These are best applied after a shower or bath. Smear the emollient in the direction of hair growth and allow to soak into skin. Advise patients not to rub the emollient into the skin, to minimize irritation or blockage of hair follicles (folliculitis). Emollients should be applied to both affected and unaffected skin.

Topical corticosteroids

- Topical steroids are needed for active cutaneous GVHD.
- More than one topical steroid may need to be prescribed according to the body site affected; for the face / neck / genitals prescribe mild / moderate potency topical steroids in 30 gram tubes (sufficient for single application for 2 weeks); for the body, prescribe 100 gram tubes of moderate/ high potency topical steroids [Table 2].
- Refer to Dermatology if superpotent topical steroids or calcineurin inhibitors are required.
- Explain to patients how much to apply and where to apply the creams to maximise compliance.
- Specify the base on the prescription where possible i.e. cream, ointment, lotion etc – topical steroid ointments are preferred to creams because there is a greater risk of contact sensitisation from preservatives in cream formulations. Some patients may find ointments too greasy especially on the face.
- Topical steroids do not need to be applied more frequently than twice daily although once daily is often sufficient. Advise applying it 20-30 minutes before or after any emollient is applied.

Phototherapy

Phototherapy has been reported to be an effective treatment for chronic cutaneous GVHD (5). Psoralen plus ultraviolet A light (PUVA) and ultraviolet A-1 (UVA-1) are both effective options in sclerodermoid disease (6, 7). Narrowband UVB may be useful in lichenoid GVHD (5).

Consider referral to Dermatology for phototherapy in patients whom additional systemic immunosuppression poses a high risk of infection or interferes with a graft versus tumour response. Dose modification is important in patients taking photosensitizing medications, and caution must be employed in patients with anti-nuclear autoantibodies. The potential benefit of phototherapy must be weighed against the elevated risk of cutaneous malignancy in immunocompromised patients (8), particularly those with actinic damage or a history of ionising radiation.

Phototherapy is given to patients in a dedicated suite in the Dermatology department (Churchill Hospital) and is given three times weekly (Narrowband UVB) or twice weekly (topical or oral PUVA). UVA1 is available through referral to Dr Ljuba Novakovic at St John's Institute, London.

Extracorporeal photopheresis (ECP)

ECP has demonstrated benefit in both sclerodermoid and non-sclerodermoid GVHD and is recommended for second line treatment of GVHD. UK Consensus statement (9) and recent guidelines have been published (10) providing more details. Indications for referral for ECP include:

- 1) Extensive chronic GVHD
- 2) Affecting skin +/- mucous membranes +/- liver
- 3) Requiring second / third line salvage therapy
 - a. Steroid refractory (minimal or no response to prednisolone 1mg/kg or equivalent after min 4 weeks treatment)
 - b. Steroid dependent (inability to reduce <10mg prednisolone or equivalent without GVHD flare)
 - c. Unable to tolerate steroids
- 4) Tissue biopsy confirmation of diagnosis

Patients should be provided with an ECP Patient Information Leaflet detailing the procedure.

Referral should be made using standardised NHS referral form (<http://hospital.blood.co.uk/patient-services/therapeutic-apheresis-services/how-to-make-patient-referrals-to-tas/>)

Initial treatment involves minimum 3 months of two consecutive treatments fortnightly administered in the NHS Blood and Transfusion Centre at the John Radcliffe Hospital. Prior to start of treatment a clinical assessment at baseline is required including:

- a) Chronic GVHD clinical assessment (NIHR Global score)
- b) Karnovskys score
- c) Chronic GVHD / ECP Symptom Score

Scoring should be undertaken on a three-monthly basis and will inform management decision which will be:

- a) Continue fortnightly treatments
- b) Reduce frequency of treatments to monthly (and subsequently six-weekly)
- c) Stop treatment

If patient experiences flare of GVHD whilst on ECP, consider increasing frequency of ECP to fortnightly treatment (if not already) and escalate oral steroids +/- immunosuppressants as per generic GVHD management.

Belumosudil

Belumosudil mesilate is an oral selective inhibitor of ROCK2 recommended **for treating chronic graft versus-host disease (GvHD)** in people 12 years and over, after 2 or more systemic treatments [NICE TA949]. For guide refer to: <http://nssg.oxford-haematology.org.uk/bmt/gvhd/B-84-belumosudil-mesilate-for-gvhd.pdf>

Other skin diseases

Skin disease has significant impact on quality of life and even in the context of severe extra-cutaneous GVHD, mucosal and cutaneous involvement can be devastating to patients. Patients who are concerned about dyspigmentation should be directed to Changing Faces [www.changingfaces.org.uk]. They can self-refer to discuss camouflage options. Ensure that active GVHD is aggressively treated as post-inflammatory changes in the skin will worsen if there is ongoing inflammation.

Refer patients with high levels of distress regarding their skin to Dermatology to assess whether onward referral for psychological input is needed. Use validated patient-reported outcome measures to monitor this where possible e.g. Dermatology Life Quality Index (DLQI) or Skindex-16.

Co-existing alternative common skin conditions e.g. seborrhoeic dermatitis, frequently occurs and if concerned refer to Dermatology for definitive diagnosis and management. Alopecia is common and often resolves spontaneously if non-scarring. If concerned (especially if there is scarring) refer for specialist opinion to Dermatology Hair Specialist (Dr Sanja Karanovic).

Table 1: Clinical presentation of chronic cutaneous GVHD

Clinical findings	Description	Skin-directed therapies
Xerosis / ichthyosis	Dry skin Very common	Emollients ++ Consider 50:50 WSP / LP or Epaderm ointment
Keratosis pilaris-like	Follicular prominence, peri-follicular erythema, 'hedgehog' appearance of skin	Emollients containing urea or salicylic acid (e.g. Flexitol [®] , Eucerin lotion [®] , Calmurid lotion [®] -community prescription)
Lichen planus-like*	Purple / hyperpigmented papules / plaques often on extensor surfaces, acral predisposition	Potent topical steroids, topical tacrolimus, phototherapy (psoralen plus UVA)
Poikiloderma*	Telangiectasia + dyspigmentation + epidermal atrophy	Often asymptomatic – no specific treatment required, consider potent topical steroids
Dyspigmentation	Post-inflammatory hyperpigmentation or vitiligo-like hypopigmentation	Use topical steroids if erythema co-exists suggesting active GVHD. Low threshold for skin biopsy.
Acral erythema	Erythema, oedema, pain (can appear out of proportion to clinical signs) +/- hyperkeratosis	Superpotent topical steroids +/- salicylic acid if hyperkeratosis. Consider oral steroids.
Morphoea / Sclerodermoid*	Superficial or deep sclerotic patches / plaques	If superficial consider PUVA or UVA1 phototherapy, if deeper +/- other organ involvement, consider increased immunosuppression or extracorporeal photopheresis.

		Consider referral to physiotherapist / podiatry / orthotics.
--	--	--

* Diagnostic criteria according to NIH

Table 2: Examples of topical steroids according to potency

Potency of topical steroid	Examples
Mild	Hydrocortisone 1% / 2.5% Hydrocortisone with antifungal [Daktacort®] (used for inflamed flexural rashes when candidiasis may complicate treatment with corticosteroid).
Moderate	Clobetasone butyrate 0.05% [Eumovate®] Moderate with antibacterials and antifungals (clobetasone butyrate 0.05%, oxytetracycline 3% [as calcium salt], nystatin 100 000 units) [Trimovate cream®]
Potent	Betamethasone valerate 0.1% [Betnovate®], Mometasone furoate 0.1% [Elocon®] Potent with salicylic acid, e.g. betamethasone 0.05% with salicylic acid 3%.
Superpotent	Clobetasol propionate 0.05% [Dermovate®]

BOX 1: Mucosal involvement in GVHD

- Oral cavity - with lichen planus-like lacy white buccal involvement (early diagnostic sign), ulceration, mucocelles, hyperkeratosis, sclerosis and fibrosis (late – patients report difficulty moving tongue when chewing). When the salivary glands are involved patients may report pain, dryness, abnormal taste sensations, hypersensitivity, and dental caries. Viral or fungal infections especially oral candidiasis are common. See Oral GVHD guidelines for more details.
- Eyes with burning, irritation, dryness, and photophobia.
- Vulvovaginal dryness, pain, erythema, lichen planus-like changes (diagnostic), lichen sclerosus-like changes, and strictures – many patients will not report these symptoms unless directly asked.
- Penile irritation, soreness, erythematous plaques on penile head, lichen-sclerosus-like changes, difficulty retracting the foreskin

BOX 2: Skin management advice to all allograft transplant recipients.

1) General advice

Most patients report that their skin is much drier post-transplant so they should use:

- a) Emollients – applied regularly and liberally at least 2 – 3 times daily
- b) Use soap substitutes (e.g. Dermol lotion®) or bath additives (Oilatium® or Balneum® range) when bathing / showering to improve hydration of the skin

2) Photoprotection

Ultraviolet light exposure can trigger a flare of GVHD and can prolong or worsen cutaneous GVHD. UV light can also trigger phototoxic drug eruptions e.g. Voriconazole, non-steroidal anti-inflammatory drugs. The risk of skin cancer is higher in patients with GVHD (8); this risk is already elevated by immunosuppressive agents and/or prior phototherapy treatment. Advice should include

- a) Avoiding the peak hours of sunshine (11am – 3pm)
- b) Using a broad spectrum sun screen SPF 30+ regularly
- c) Using broad-brimmed hats, long sleeves, trousers or UV-protective clothing (physical methods of sun protection are more effective than relying on sunscreens)

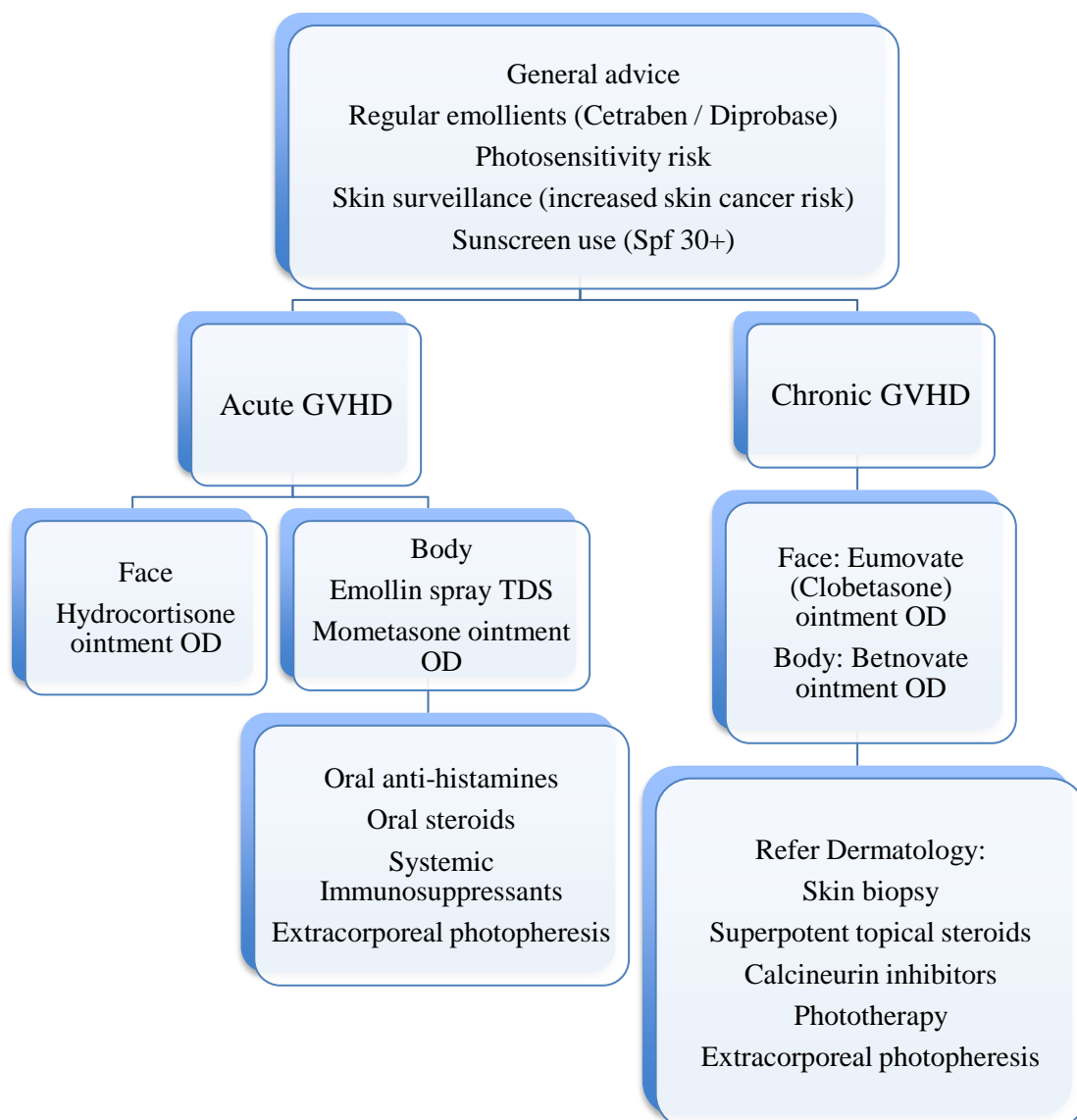
3) Advise patients about self-skin examination

- a) Erythematous rashes may not be symptomatic in the early stages
- b) Advise patients about identifying early signs of sclerotic chronic GVHD e.g. darkening or tightening of skin – commonly occurs at the waistband or under breasts, thickening of skin, rippling/dimpling of the skin, restricted range of motion and joints e.g. wrists, shoulders or ankles.
- c) Advise patients to contact us if they notice any new or rapidly growing lump on the skin or any skin lesion, which is slow to heal as this may indicate a new skin cancer.

BOX 3: When to refer to a Dermatologist:

- a) Diagnosis is not clear e.g. drug eruption versus GVHD or suspect alternative skin condition
- b) Early superficial / evolving sclerodermoid skin disease
- c) Suspected new skin cancer
- d) Skin disease unresponsive to potent topical steroids for > 3 weeks
- e) Skin ulceration
- f) Skin disease impacting significantly on patient quality of life
- g) Using topical calcineurin inhibitors (tacrolimus or pimecrolimus)

Figure 1: Flow chart for initial management of acute / chronic GVHD



References

1. Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, et al. Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol.* 2012;158(1):46-61.
2. Dignan FL, Scarisbrick JJ, Cornish J, Clark A, Amrolia P, Jackson G, et al. Organ-specific management and supportive care in chronic graft-versus-host disease. *Br J Haematol.* 2012;158(1):62-78.
3. Dignan FL, Manwani R, Potter MN, Ethell ME, Leonard H, Brennan J, et al. A dedicated GvHD clinic may improve the quality of life for allogeneic stem cell transplant survivors. *Clin Transplant.* 2013;27(1):E1-2.
4. Matin RN, Danby R, Gibbons E, Venning V, Rowley L, Barton D, et al. Developing a dedicated Dermatology Service for allogeneic bone marrow transplant recipients. *Br J Dermatol.* 2017.
5. Garbutcheon-Singh KB, Fernandez-Penas P. Phototherapy for the treatment of cutaneous graft versus host disease. *Australas J Dermatol.* 2015;56(2):93-9.
6. Kroft EB, Berkhof NJ, van de Kerkhof PC, Gerritsen RM, de Jong EM. Ultraviolet A phototherapy for sclerotic skin diseases: a systematic review. *J Am Acad Dermatol.* 2008;59(6):1017-30.
7. York NR, Jacobe HT. UVA1 phototherapy: a review of mechanism and therapeutic application. *Int J Dermatol.* 2010;49(6):623-30.
8. DePry JL, Vyas R, Lazarus HM, Caimi PF, Gerstenblith MR, Bordeaux JS. Cutaneous Malignant Neoplasms in Hematopoietic Cell Transplant Recipients: A Systematic Review. *JAMA Dermatol.* 2015;151(7):775-82.
9. Scarisbrick JJ, Taylor P, Holtick U, Makar Y, Douglas K, Berlin G, et al. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol.* 2008;158(4):659-78.
10. Alfred A, Taylor PC, Dignan F, El-Ghariani K, Griffin J, Gennery AR, et al. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. *Br J Haematol.* 2017.
11. Belumosudil for treating chronic graft-versus-host disease after 2 or more systemic treatments in people 12 years or over. National Institute for Healthy and Care Excellence Technology appraisal guidance TA949, accessed 25-3-2024
12. Sanofi. Belumosudil. (REZUROCK) Summary of Product Characteristics. Updated 02.01.2024

Author

Dr Rubeta Matin, Consultant Dermatologist

Audit

These processes are subject to the OxBMT audit programme

Circulation

NSSG Haematology Website

Review

Department of Clinical Haematology
Oxford BMT Programme

Name	Revision	Date	Version	Review date
Guidelines for Diagnosis and Management of Cutaneous Graft-Versus-Host Disease	New document	Feb 2017	1.0	Feb 2019
Dr Rubeta N Matin, Consultant Dermatologist, Cristina Ovas, BMT Quality and Data Manager	Minor formatting changes	July 2019	1.1	July 2021
Dr Rubeta N Matin, Consultant Dermatologist	Minor changes	April 2022	1.2	April 2024
Eva Anguita (specialist haematology pharmacist)	Adding Belumosudil for treatment of chronic GvHD	Oct 2024	1.3	Oct 2026