

BMJ Best Practice

Graft-versus-host disease

Straight to the point of care



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Summary

Graft-versus-host disease (GVHD) is a major cause of morbidity and mortality following allogeneic haematopoietic cell transplantation (HCT).

Occurs when donor T cells respond to histoincompatible antigens on the host tissues.

Clinical manifestations determine whether the signs and symptoms of GVHD are acute, chronic, or constitute an overlap syndrome.

Acute GVHD classically targets the skin, gastrointestinal tract, and liver. In contrast, chronic GVHD can involve almost any organ.

Standard GVHD prophylaxis comprises a calcineurin inhibitor combined with low-dose methotrexate or mycophenolate. Additional prophylactic agents may be considered in certain patients.

Treatment involves the use of systemic corticosteroids with additional immunosuppressants as clinically indicated.

Supportive care and monitoring are vital components of GVHD management with emphasis on infection prophylaxis, physiotherapy, nutritional status, pain control, and monitoring of drug-drug interactions and drug-related adverse effects.

Definition

GVHD is a serious and potentially life-threatening complication following allogeneic HCT. GVHD occurs when donor T cells respond to histoincompatible antigens on host tissues.

Clinical manifestations determine whether GVHD is acute or chronic.

Acute GVHD classically involves the skin, gastrointestinal tract, and liver and usually develops within 100 days post-HCT. However, acute GVHD may also develop or persist beyond 100 days post-HCT in some cases (i.e., late acute GVHD).

The clinical manifestations of chronic GVHD are variable, involving almost any organ, and may resemble those seen in autoimmune diseases. Chronic GVHD usually develops after 100 days post-HCT. It may emerge from acute GVHD (progressive type), following a period of resolution from acute GVHD (quiescent or interrupted type), or occur de novo.

Some patients may present with clinical manifestations of both acute and chronic GVHD (i.e., overlap syndrome).

Epidemiology

The number of allogeneic haematopoietic cell transplantations (HCTs) continues to increase.[14] Allogeneic HCT from unrelated donors in the US has surpassed the number from related donors.[15]

Acute graft-versus-host disease (GVHD)

Incidence ranges from 30% to 50%.[16] However, this varies depending on factors such as donor type (i.e., matched or unmatched; related or unrelated), type of malignant disease, and absent or suboptimal GVHD prophylaxis.[17] [18] The incidence is directly related to the degree of human leukocyte antigens (HLA) mismatch.[19]

The median time to onset of acute GVHD is typically 21-25 days after transplantation. Umbilical cord-blood transplantation has been associated with slower neutrophil recovery with lower incidence and later onset of acute GVHD.[20]

Chronic GVHD

Incidence ranges from 30% in recipients of fully histocompatible transplants to 60% to 70% in recipients of mismatched haematopoietic cells or haematopoietic cells from an unrelated donor.[21] Factors that increase the incidence include use of peripheral blood for the transplant and older recipient age.[21]

Evidence from the US suggests that the median time to diagnosis of chronic GVHD is 4.5 months after HLA-identical sibling transplantation and 4 months after unrelated donor transplantation.[22] De novo chronic GVHD almost never occurs ≥ 2 years post-allogeneic HCT.

Aetiology

Graft-versus-host disease (GVHD) is a serious and potentially life-threatening complication following allogeneic haematopoietic cell transplantation (HCT). GVHD occurs when donor T cells respond to histoincompatible antigens on the host tissues.

Several risk factors determine the development of GVHD, which may be acute or chronic.

Risk factors for the development of acute GVHD include:[18] [23][24] [25] [26] [27] [28] [29] [30] [31][32] [33] [34] [35] [36] [37][38][39] [40][41]

- Human leukocyte antigen (HLA) mismatch
- Older recipient or donor age
- Donor and recipient gender disparity (particularly a female donor with a male recipient)
- Parous female donor
- Type and stage of the underlying malignant condition
- Transplant conditioning regimen intensity
- ABO compatibility
- Performance score
- White/black race
- Cytomegalovirus serostatus
- Absent or suboptimal GVHD prophylaxis
- Splenectomy
- Low socio-economic status

Risk factors for the development of chronic GVHD include:[\[7\]\[8\]](#) [\[21\]](#) [\[39\]\[42\]](#) [\[43\]](#) [\[44\]\[45\]](#) [\[38\]](#) [\[46\]](#)

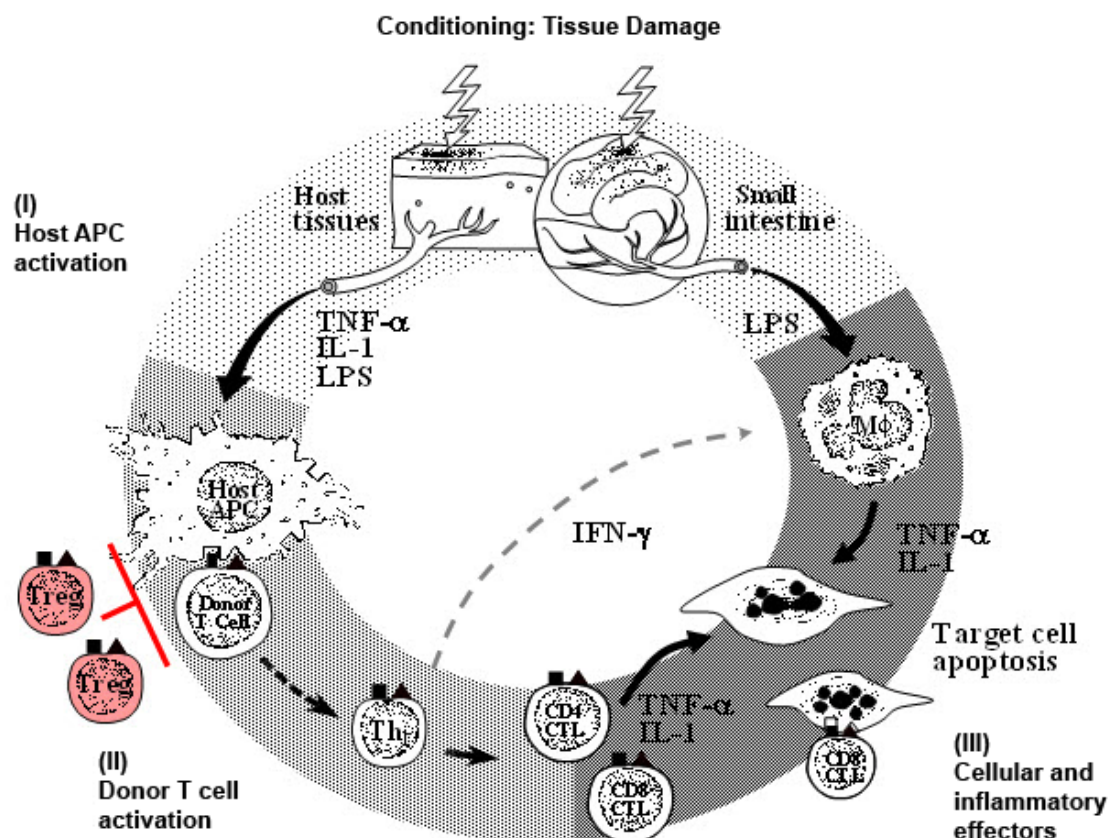
- Prior acute GVHD
- Older recipient age
- Female donor with male recipient
- Parous female donor
- Mismatched or unrelated donors
- Donor lymphocyte infusion (post-HCT)
- Use of peripheral blood stem cells
- Low socio-economic status

Pathophysiology

Acute GVHD

The pathophysiology of acute GVHD is complex, but can be conceptualised in three sequential steps or phases:

- Phase I: host activation of the antigen presenting cells (APCs). Initiated subsequent to the the profound damage caused by the underlying disease and consequent infections, exacerbated by the allogeneic HCT conditioning regimens (involving total body irradiation and/or chemotherapy) administered prior to the infusion of donor haematopoietic cells.
- Phase II: donor T-cell activation. Activated APCs interact with the infused donor T cells, leading to activation, proliferation, differentiation, and migration of alloreactive donor T cells.
- Phase III: cascade of multiple cellular and inflammatory effectors. Further modulate each other's responses, ultimately leading to the acute GVHD target organ damage. Effector mechanisms can be grouped into cellular effectors (e.g., cytotoxic T lymphocytes) and inflammatory effectors such as cytokines.



GVHD Pathophysiology. In Phase I, the recipient conditioning regimen damages host tissues and causes release of inflammatory cytokines such as $\text{TNF-}\alpha$, IL-1 and IL-6. Increased levels of these cytokines leads to activation of host antigen presenting cells (APCs). In Phase II, host APCs activate mature donor cells. The subsequent proliferation and differentiation of these activated T cells produces additional effectors that mediate the tissue damage, including Cytotoxic T Lymphocytes, natural killer (NK) cells, $\text{TNF-}\alpha$ and IL-1. Lipopolysaccharide (LPS) that has leaked through the damaged intestinal mucosa triggers additional $\text{TNF-}\alpha$ production. $\text{TNF-}\alpha$ can damage tissue directly by inducing necrosis and apoptosis in the skin and GI tract through either TNF receptors or the Fas pathway. $\text{TNF-}\alpha$ plays a direct role in intestinal GVHD damage, which further amplifies damage in the skin, liver and lung in a "cytokine storm."

GVHD pathophysiology

Courtesy of Dr James L.M. Ferrara, Professor, Blood and Marrow Transplantation Program, University of Michigan; used with permission

Chronic GVHD

In contrast to acute GVHD, the pathophysiology of chronic GVHD remains poorly understood.^[47] Alloreactive T cells have been implicated in the pathogenesis; however, the precise role of specific T-cell subsets, autoantigens, alloantigens, and B cells, as well as interactions of chemokines and cytokines has not been fully elucidated. The clinical manifestations of chronic GVHD are similar to an autoimmune process, suggesting similar pathophysiology.

Classification

National Institutes of Health (NIH) working group GVHD classification^[1]

Acute GVHD

- Classic acute GVHD
 - Clinical manifestations include: maculopapular rash, anorexia, profuse diarrhoea, nausea, vomiting, ileus, and cholestatic hepatitis
 - Occurs within 100 days post-allogeneic HCT or donor lymphocyte infusion
- Late onset acute GVHD
 - Clinical manifestations of classic acute GVHD occurring beyond 100 days post-allogeneic HCT or donor lymphocyte infusion
 - Often occurs during taper, or following withdrawal, of immunosuppressive drugs

Chronic GVHD

- Classic chronic GVHD
 - Clinical manifestations: variable and can involve any organ, including the mouth (e.g., oral lichen planus-like features), skin (e.g., poikiloderma), eyes (e.g., dry, gritty, painful), genitalia (e.g., lichen planus-like features), gastrointestinal tract (e.g., oesophageal web), lungs (e.g., bronchiolitis obliterans), and muscle, fascia, or joints (e.g., fasciitis)
 - No characteristic features of acute GVHD
 - No temporal relationship to allogeneic HCT or donor lymphocyte infusion
- Overlap syndrome
 - One or more features of acute GVHD in a patient with chronic GVHD
 - No temporal relationship to allogeneic HCT or donor lymphocyte infusion

Case history

Case history #1

A 50-year-old man with a history of Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) receives a human leukocyte antigen (HLA)-matched unrelated donor (MUD) haematopoietic cell transplantation (HCT). On day 16 post-transplant, the patient develops fever and diffuse maculopapular rash affecting >50% of his body surface area. By day 23 post-transplant, the patient starts developing nausea, abdominal pain, and profuse diarrhoea. On day 35, the patient begins showing signs of jaundice and hepatomegaly on physical examination.

Case history #2

A 30-year-old woman with a history of severe aplastic anaemia received an HLA-matched sibling donor haematopoietic cell transplant. Her transplant and immediate post-transplant course were unremarkable. Engraftment of donor white blood cells occurred on day +15 and full donor chimerism was achieved by day +30. Tacrolimus taper was initiated on day +56, slowly weaned over 4 months, and subsequently discontinued by day +180 as the patient did not display any signs or symptoms suggestive of acute graft-versus-host disease (GVHD). During a routine follow-up visit 1 month following discontinuation of tacrolimus, the patient presents with new-onset painful mouth sores; hyperpigmented skin lesions; and dry, gritty, and painful eyes. Physical examination is consistent with the patient's symptoms.

Other presentations

There may be delayed time to onset and variable frequency and severity of acute GVHD in a number of clinical scenarios.[\[2\]](#) [\[3\]](#) [\[4\]](#) [\[5\]](#) [\[6\]](#) [\[7\]](#)

- Following reduced-intensity or non-myeloablative HCT, time to onset of acute GVHD may be later and slower than conventional myeloablative HCT due to the slower engraftment of donor lymphocytes.
- Following umbilical cord-blood transplantation, acute GVHD generally occurs less frequently, at a later time point, and with decreased severity relative to unrelated donor HCT.
- Following donor lymphocyte infusion (DLI), the timing of GVHD may be delayed. DLI is generally performed in the setting of persistent or recurrent malignancy following myeloablative or non-myeloablative HCT, and most often administered without immunosuppressive prophylaxis, to take advantage of the graft-versus-tumour effect. The severity and manifestations of GVHD may differ following DLI, wherein diagnostic and/or distinctive features of acute and chronic GVHD appear together.

Chronic GVHD may develop and present in a number of ways:[\[8\]](#)

- de novo (which generally has a good prognosis),
- evolving directly from acute GVHD (progressive type, which has a poor prognosis), or
- following a period of GVHD resolution (quiescent or interrupted type, which has an intermediate prognosis).

GVHD may also present as idiopathic pneumonia syndrome (IPS, also known as non-infectious lung injury), a major complication of HCT that occurs in approximately 3% to 15% of allogeneic HCT recipients.[\[9\]](#) [\[10\]](#) Patients present with signs and symptoms of pneumonia, non-lobar radiographic infiltrates, abnormal pulmonary function, and absence of infectious organisms determined by bronchoalveolar lavage.[\[11\]](#) The median time to onset of IPS is 14-90 days post-transplant.[\[12\]](#) The role of GVHD and alloreactive donor T cells in the pathogenesis of IPS remains a topic of debate.

In the elderly, the development of acute GVHD may be severe and associated with significant morbidity and mortality.[\[13\]](#)

Approach

Early recognition of graft-versus-host disease (GVHD) is critical.

The diagnosis of GVHD is based primarily on clinical symptoms and manifestations.^{[79] [80]} Therefore, post-haematopoietic cell transplantation (HCT), all patients should undergo close monitoring and follow-up HCT comprising repeated physical examinations of all relevant organ systems, and interval history taking. The severity of involvement for each organ should be assessed and graded to inform prognosis and management.

Further investigations with laboratory tests, imaging studies, and tissue biopsies are recommended where indicated to support diagnosis and exclude other causes.^[81] Guidelines on monitoring and follow-up (including further testing) have been published.^{[80] [82]}

Acute GVHD

The median onset of acute GVHD is typically 21-25 days after allogeneic HCT (although it is now recognised that acute GVHD can occur beyond the 100 days post-transplant that historically defined the disease).^[1]

Factors in the history that may increase the likelihood of acute GVHD include: human leukocyte antigen (HLA) mismatch, older age of recipient or of donor, donor and recipient gender disparity (particularly a female donor with a male recipient), parous female donor, type and stage of the underlying malignant condition, transplant conditioning regimen intensity, absent or suboptimal GVHD prophylaxis. See Risk factors.

Commonly used scoring systems for grading acute GVHD include:

- Keystone (modified Glucksberg) criteria^{[83] [84]}
- Mount Sinai Acute GVHD International Consortium (MAGIC) criteria^[85]
- The University of Minnesota Refined Acute GVHD Risk Score^{[86] [87]}

See Diagnostic criteria .

Clinical manifestations of acute GVHD

The main organs affected in acute GVHD are the skin, gastrointestinal (GI) tract, and liver.^[1]

Skin

- The most commonly affected organ and generally the first to be affected. The presentation of skin involvement often coincides with donor cell engraftment and is characterised by an erythematous, maculopapular rash that is often pruritic.



Acute graft-versus-host disease (GVHD) of the skin (grade I)

Courtesy of Dr John Levine, Professor, Blood and Marrow

Transplantation Program, University of Michigan; used with permission

- In severe cases (stage 4), the skin may blister and ulcerate.

GI tract

- GI involvement of GVHD may present as nausea, vomiting, anorexia, diarrhoea and/or abdominal pain.[88] It is a pan-intestinal process, often with differences in severity between the upper and lower GI tracts.
- Diarrhoea is secretory and may be accompanied by significant GI blood loss as a result of mucosal ulceration, which is a prognostic factor for poor prognosis.[89] In advanced disease, diffuse, severe abdominal pain and distension is accompanied by voluminous diarrhoea.

Liver

- Jaundice or hepatomegaly may be noted. The presentation may be difficult to distinguish from other causes of liver dysfunction following HCT, such as veno-occlusive disease/sinusoidal obstructive syndrome, drug toxicity, viral infection, sepsis, total parenteral nutrition cholestasis, or iron overload.
- Isolated liver GVHD (i.e., with no other organs concurrently involved) is an uncommon finding.[90] Often a liver biopsy is required to establish the diagnosis. However, the increased risk of bleeding associated with thrombocytopenia in the immediate post-transplant period means that the diagnosis of isolated liver GVHD is often a diagnosis of exclusion.

Chronic GVHD

Classic chronic GVHD is not solely defined by any temporal relationship to HCT, although it usually occurs ≥ 100 days post-transplant. The reported median time to diagnosis is 4.5 months following HLA-identical sibling transplantation, and 4 months following unrelated donor transplantation.[22] De novo chronic GVHD almost never occurs ≥ 2 years post-allogeneic HCT.

Factors in the history that may increase the likelihood of chronic GVHD include: prior acute GVHD, older age of recipient or of donor, female donor with male recipient, parous female donor, use of peripheral blood stem cells, and donor lymphocyte infusion. See Risk factors.

Clinical manifestations of chronic GVHD

The potential clinical manifestations of chronic GVHD are many and varied, involving multiple organs and sites.

Clinical manifestations	Diagnostic for chronic GVHD	Distinctive for chronic GVHD (i.e., seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other features or unclassified entities (can be acknowledged as part of the chronic GVHD manifestations if diagnosis confirmed)	Features shared with acute GVHD
Skin	<ul style="list-style-type: none"> Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features 	<ul style="list-style-type: none"> Depigmentation Papulosquamous lesions 	<ul style="list-style-type: none"> Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation 	<ul style="list-style-type: none"> Erythema Maculopapular rash Pruritus
Nails		<ul style="list-style-type: none"> Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails) 		
Scalp and body hair		<ul style="list-style-type: none"> New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling 	<ul style="list-style-type: none"> Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair 	
Mouth	<ul style="list-style-type: none"> Lichen planus-like changes 	<ul style="list-style-type: none"> Xerostomia Mucocoeles Mucosal atrophy Ulcers Pseudomembranes 		<ul style="list-style-type: none"> Gingivitis Mucositis Erythema Pain
Eyes		<ul style="list-style-type: none"> New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctate keratopathy 	<ul style="list-style-type: none"> Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema) 	
Gastrointestinal tract	<ul style="list-style-type: none"> Esophageal web Strictures or stenosis in the upper to mid third of the oesophagus 		<ul style="list-style-type: none"> Exocrine pancreatic insufficiency 	<ul style="list-style-type: none"> Anorexia Nausea Vomiting Diarrhoea Weight loss Failure to thrive (infants and children)
Genitalia	<ul style="list-style-type: none"> Lichen planus-like features Lichen sclerosus-like features Female: vaginal scarring or clitoral/labial agglutination Male: phimosis or urethral/meatus scarring or stenosis 	<ul style="list-style-type: none"> Erosions Fissures Ulcers 		
Lung	<ul style="list-style-type: none"> Bronchiolitis obliterans diagnosed with lung biopsy Bronchiolitis obliterans syndrome (diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ) 	<ul style="list-style-type: none"> Air trapping and bronchiectasis on chest CT 	<ul style="list-style-type: none"> Cryptogenic organising pneumonia (pulmonary entities under investigation or unclassified) Restrictive lung disease (pulmonary entities under investigation or unclassified) 	
Liver				<ul style="list-style-type: none"> Total bilirubin, alkaline phosphatase >2 times upper limit of normal Alanine aminotransferase >2 times upper limit of normal
Muscles, fascia, joints	<ul style="list-style-type: none"> Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis 	<ul style="list-style-type: none"> Myositis or polymyositis (diagnosis of chronic GVHD requires biopsy) 	<ul style="list-style-type: none"> Oedema Muscle cramps Arthralgia or arthritis 	
Hematopoietic and immune			<ul style="list-style-type: none"> Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (autoimmune haemolytic anemia, immune thrombocytopenia) Raynaud's phenomenon 	
Other			<ul style="list-style-type: none"> Serositis (pericardial or pleural effusions, ascites) Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy 	

Clinical manifestations of chronic graft versus host disease from the National Institutes of Health

Created by BMJ Knowledge Centre

The National Institutes of Health (NIH) working group criteria recommend at least one diagnostic manifestation (e.g., oral or vaginal lichenoid findings, skin dyspigmentation, bronchiolitis obliterans), or one distinctive manifestation (e.g., ocular sicca, depigmentation, papulosquamous plaques) plus a

pertinent biopsy, laboratory, or other test (e.g., radiographic and/or pulmonary test), for a diagnosis of chronic GVHD.[1]

Definitive diagnosis of chronic GVHD necessitates excluding other possible diagnoses such as infection, drug effects, malignancies, and residual post-inflammatory damage and scarring.[1] See Diagnostic criteria .

Laboratory studies

Certain laboratory study findings may be suggestive of GVHD, or help to exclude other causes of GVHD.

Full blood cell count

- In the early post-transplant setting, cytopenia (particularly thrombocytopenia) may be associated with acute GVHD.
- Autoimmune cytopenias (leukopenia, anaemia, and thrombocytopenia) may be seen at a later stage with chronic GVHD.
- Eosinophilia may be present in acute or chronic GVHD.

Liver function tests

- Elevated transaminases, alkaline phosphatase, and/or bilirubin may be a manifestation of acute and/or chronic GVHD.

Serum electrolytes

- Acute and/or chronic GVHD affecting the GI tract (e.g., anorexia, nausea, vomiting, diarrhoea, weight loss, and failure to thrive [in infants and children]) can lead to a variety of electrolyte disturbances.

Urinalysis

- Proteinuria may be a manifestation of renal dysfunction seen with nephrotic syndrome associated with chronic GVHD.

Blood culture

- To exclude the possibility of bacteremia and/or sepsis.

Urine culture

- To exclude the possibility of urinary tract infection.

Stool culture

- Can help exclude potential infectious causes of diarrhoea that may closely resemble GVHD. However, positive stool studies and gastrointestinal GVHD can occur concurrently.

Viral polymerase chain reaction (PCR)

- To test for infection with cytomegalovirus, HHV-6, adenovirus, hepatitis virus (A, B, C, D, E), and parvovirus. Viral infection forms one of the differential diagnoses of GVHD.

Imaging studies

Certain radiographic study findings may be suggestive of GVHD, or help to exclude other causes of GVHD.

High-resolution CT chest

- Air trapping and bronchiectasis are distinctive features of chronic GVHD which may be evident on imaging.
- Bilateral patchy ground-glass opacities with air bronchograms (usually located peripherally) or a circular nodule in one lung (or 3-5 nodules across both lungs) suggest cryptogenic organising pneumonia (COP). The triangle sign (a triangular ground glass opacity with the base on the pleura and the apex towards the mediastinum) is characteristic for COP.

CT abdomen

- Luminal dilation with thickening of the small bowel wall (ribbon sign) and air-fluid levels suggestive of an ileus may be observed in GVHD affecting the GI tract.

Barium swallow

- May reveal characteristic features of chronic GVHD of the GI tract such as oesophageal web, stricture, or concentric rings.

Doppler ultrasonography of the liver

- Helpful to distinguish GVHD from other causes of liver dysfunction, such as cholecystitis and veno-occlusive disease/sinusoidal obstructive syndrome.
- Hepatomegaly and ascites may be noted in GVHD.

18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan

- FDG-PET scanning may be useful in localising GI tract GVHD, as well as predicting and monitoring treatment responsiveness.[\[91\]](#)

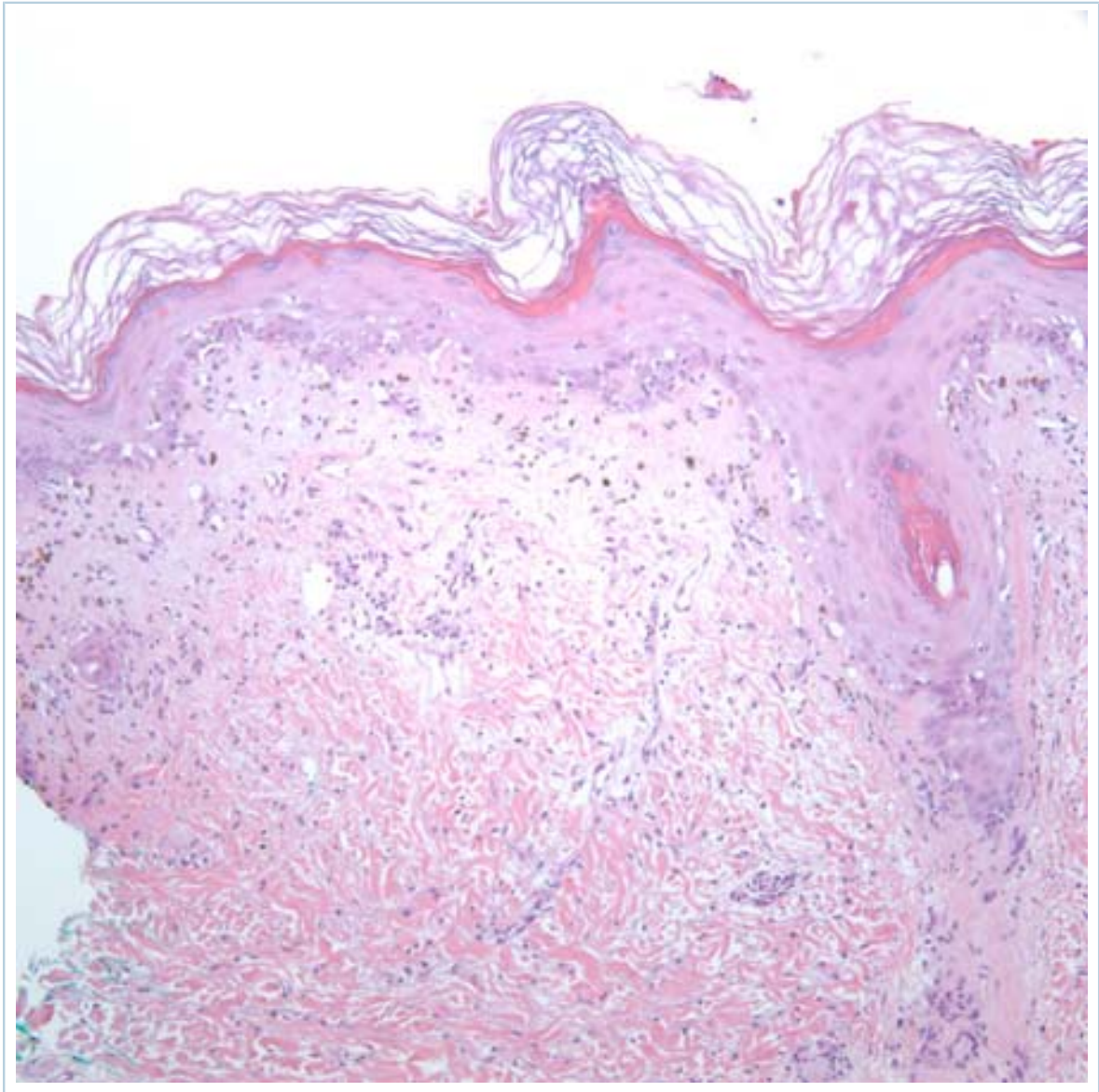
Biopsies

GVHD is a clinical diagnosis. A biopsy of the affected organ (e.g., skin, GI tract, liver, lung) may, however, be carried out to support or confirm a diagnosis, particularly if there is clinical uncertainty.[\[92\]](#)

Histopathological confirmation is also useful in excluding other conditions that may mimic GVHD.

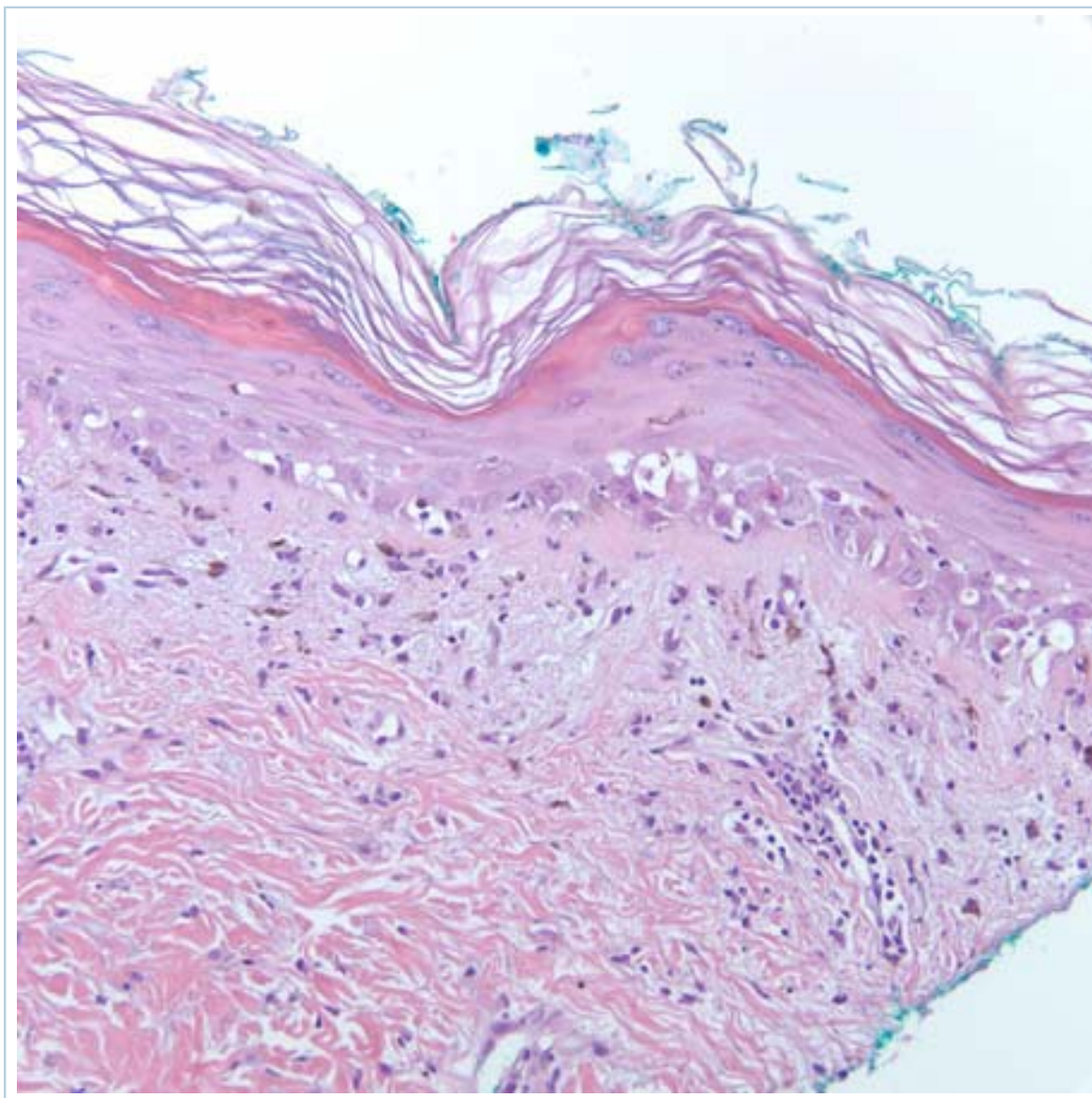
Skin

- The pathognomonic histopathological finding is apoptosis at the base of epidermal rete pegs. Other features include dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes, and a perivascular lymphocytic infiltration in the dermis.[\[93\]](#)
[\[94\]](#)



Histology of skin graft-versus-host disease (GVHD) (low power): Vacuolar interface dermatitis at the dermoepidermal junction with involvement of follicular epithelium (100x, haematoxylin and eosin)

Courtesy of Dr Lori Lowe, Professor, Dermatopathology, University of Michigan; used with permission

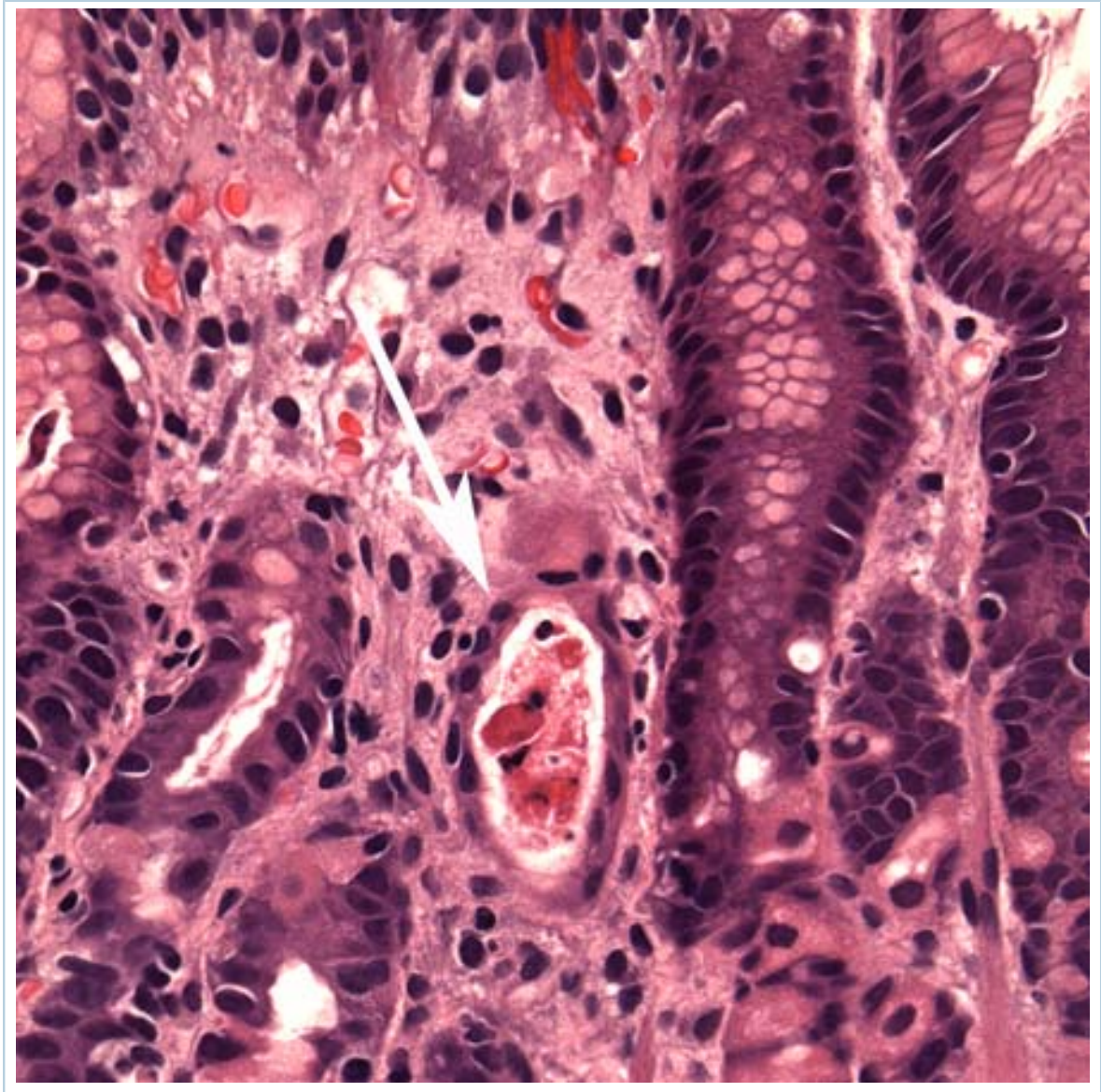


Histology of skin graft-versus-host disease (GVHD) (high power): Vacuolar interface dermatitis with rare necrotic keratinocytes (200x, haematoxylin and eosin)

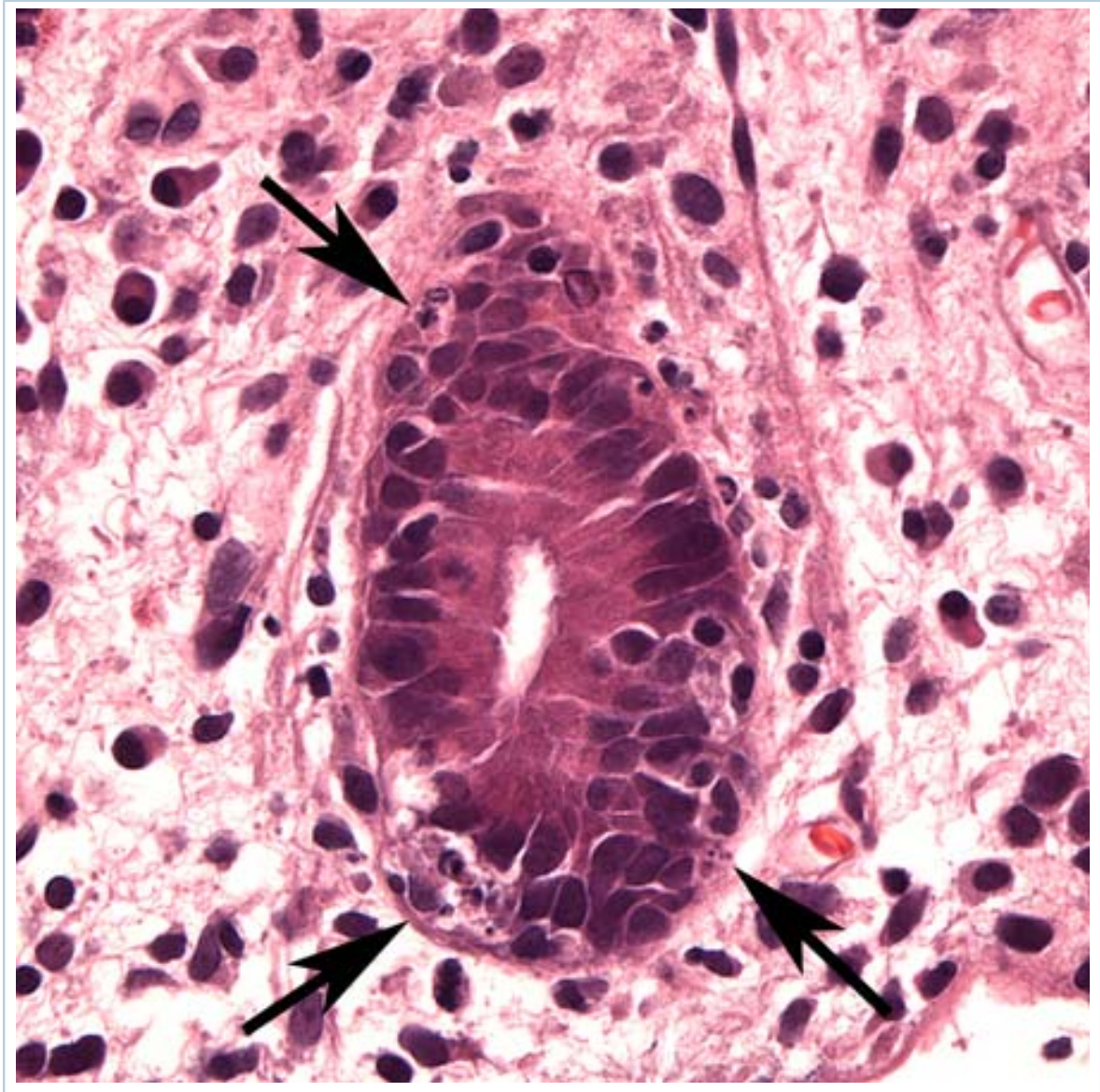
Courtesy of Dr Lori Lowe, Professor, Dermatopathology, University of Michigan; used with permission

GI tract

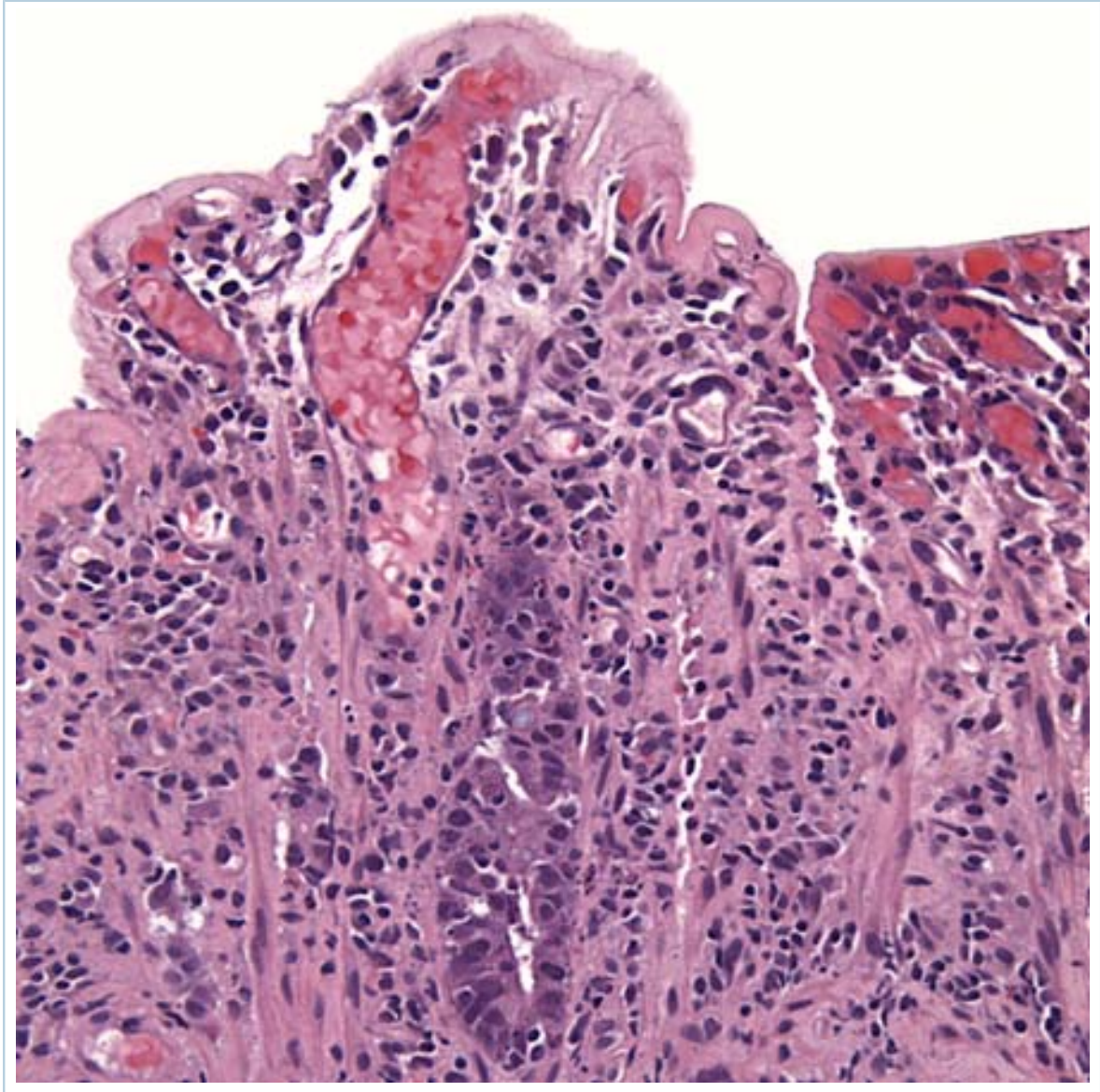
- Biopsy of the lower GI tract may be considered if there is diarrhoea.[92] An upper GI tract biopsy may be more appropriate if there is nausea and/or vomiting.[92]
- Histological features include patchy ulcerations, apoptotic bodies in the base of crypts, crypt abscesses, and loss as well as flattening of the epithelium surface.[95]



Histology of upper gastrointestinal graft-versus-host disease (GVHD) (medium-power photomicrograph of the stomach): Dilated gastric gland containing necrotic/apoptotic debris (arrow), typical of GVHD
Courtesy of Dr Joel Greenson, Professor, Pathology, University of Michigan; used with permission



Histology of lower gastrointestinal graft-versus-host disease (GVHD) (high-power photomicrograph of colon, mild disease): Numerous apoptotic bodies (arrows) indicative of GVHD involving the colon
Courtesy of Dr Joel Greenson, Professor, Pathology, University of Michigan; used with permission



*Histology of lower gastrointestinal graft-versus-host disease (GVHD)
(medium-power photomicrograph of colon, severe disease): Almost complete
denudation of the mucosa indicative of severe GVHD involving the colon*

Courtesy of Dr Joel Greenson, Professor, Pathology, University of Michigan; used with permission

Liver

- A liver biopsy may be considered to exclude other causes of liver dysfunction indicated (e.g., if liver function tests are abnormal).[92] The histological features supporting a diagnosis of acute liver GVHD include are endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis, and bile duct destruction.[96] [97] However, the increased risk of bleeding associated with thrombocytopenia in the immediate post-transplant period means that the diagnosis of liver GVHD is often a diagnosis of exclusion.

Lung

- Histological features of bronchiolitis obliterans include small airway inflammation with fibrinous obliteration of the bronchiolar lumen.[98]

Other investigations

The following investigations may also help to guide diagnosis.

Pulmonary function tests (PFTs)

- Used as a tool in identifying obstructive pulmonary disease (e.g., bronchiolitis obliterans) in chronic GVHD. Helpful in monitoring treatment response.

Bronchoscopy/bronchoalveolar lavage and culture

- Can be helpful in assessing and excluding infection as a potential differential diagnosis of GVHD.

Upper GI endoscopy

- May reveal features of gastrointestinal GVHD, such as oesophageal web, stricture, or concentric rings.

Echocardiogram

- Helpful to detect pericardial effusions or cardiomyopathy.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Factors that may increase the likelihood of acute graft-versus host disease (GVHD) include: human leukocyte antigen mismatch, older age of recipient or donor, donor and recipient gender disparity (particularly a female donor with a male recipient), parous female donor, type and stage of the underlying malignant condition, transplant conditioning regimen intensity, absent or suboptimal GVHD prophylaxis.
- Factors that may increase the likelihood of chronic GVHD include: prior acute GVHD, older age of recipient or donor, female donor with male recipient, parous female donor, use of peripheral blood stem cells, donor lymphocyte infusion.

allogeneic haematopoietic cell transplantation (HCT) recipient (common)

- Graft-versus-host disease (GVHD) occurs in the setting of allogeneic haematopoietic cell transplant.
- Distinguishing between acute and chronic GVHD depends on characteristic clinical manifestations and symptoms, and timing post-transplant.^[1]

new-onset painful mouth sores (common)

- The specific presence of lichen planus-like lesions in the mouth is a diagnostic feature of chronic graft-versus-host disease.^[1]

hyperpigmented skin lesions (common)

- The specific presence of poikiloderma and other skin features that are lichen planus-like, sclerotic, morphea-like, or lichen sclerosus-like are diagnostic features of chronic graft-versus-host disease.^[1]
- Generally, skin and mouth are the most commonly involved sites.

diffuse maculopapular rash (common)

- Maculopapular rash is one of the presenting clinical signs of acute skin graft-versus-host disease.
- In severe cases (stage 4), the skin may blister and ulcerate.



Acute graft-versus-host disease (GVHD) of the skin (grade I)

Courtesy of Dr John Levine, Professor, Blood and Marrow

Transplantation Program, University of Michigan; used with permission

genital signs and symptoms (common)

- Genital manifestations of chronic graft-versus-host disease include: lichenoid features, vaginal scarring or clitoral/labial agglutination, phimosis or urethral/meatus scarring or stenosis.^[1]

nausea, vomiting, abdominal pain, profuse diarrhoea, and anorexia (common)

- Classic gastrointestinal (GI) symptoms suggestive of acute GI graft-versus-host disease.

Other diagnostic factors**joint stiffness or tightness (common)**

- Joint stiffness and contractures secondary to fasciitis or sclerosis are diagnostic features of chronic graft-versus-host disease.^[1]

day +21 to day +25 after HCT (common)

- Median onset of acute graft-versus-host disease ranges between 21 and 25 days after transplantation.

dry, gritty, and painful eyes (common)

- Manifestation of chronic graft-versus-host disease (GVHD).
- Schirmer test can measure the degree of tear formation by the lacrimal glands. The test may be useful to monitor chronic GVHD and can be performed routinely in the office.

jaundice (uncommon)

- Jaundice is a sign of liver graft-versus-host disease (GVHD).
- Jaundice can also be commonly seen in other causes of liver dysfunction following haematopoietic cell transplantation (HCT), such as veno-occlusive disease/sinusoidal obstructive syndrome, drug toxicity, viral infection, sepsis, total parenteral nutrition cholestasis, or iron overload.

hepatomegaly (uncommon)

- May be noted in some patients with liver graft-versus-host disease.

scleroderma (uncommon)

- Sclerodermatous features are considered a high-risk feature in chronic graft-versus-host disease.
- May involve the skin, muscles, fascia, and joints.[1]

Risk factors

Strong

HLA mismatch and unrelated donor

- Human leukocyte antigen (HLA) mismatch is the greatest risk factor for acute GVHD. The greater the degree of HLA mismatch, regardless of the type, the higher the likelihood of developing acute GVHD.[31] [48] [49] [50]
- Incompatibility for HLA-A and HLA-C alleles between the donor and recipient of haematopoietic stem cells have been shown to be strong risk factors for the development of severe acute GVHD.[50] [51]
- Analysis of US National Marrow Donor Program (NMDP) data from 3857 allogeneic haematopoietic cell transplants between 1988 and 2003 found that high-resolution DNA matching for HLA-A, -B, -C, and -DRB1 (8/8 match) was the minimum level of matching associated with the highest survival. A single mismatch at HLA-A, -B, -C or -DRB1 (7/8 match) was associated with higher mortality.[52]
- The risk of developing acute GVHD following an unrelated donor transplant ranges from 60% to 80% depending on the human leukocyte antigen (HLA) mismatch.[53] [54]
- The risk of developing chronic GVHD is 60% to 70% in recipients of mismatched haematopoietic cells or haematopoietic cells from an unrelated donor.[21]
- The US National Marrow Donor Program and the Center for International Blood and Marrow Transplant provide matching guidelines and typing strategies for unrelated adult donor and cord blood selection.[55]

prior acute GVHD

- Prior acute GVHD has been consistently reported as a risk factor for chronic GVHD.[8] [46]

recipient or donor in older age group

- Older age of the recipient or of the donor have been shown to be associated with increased risk for GVHD.[24] [29] [31][36]

female donor with male recipient

- Studies have shown a female donor paired with male recipient to be a significant risk factor for GVHD.[32] [33] [34] [39]

parous female donor

- A parous female donor has been shown to be a significant risk factor for GVHD.[23] [32] [40]

type and stage of underlying malignant condition

- Patients with chronic myeloid leukaemia have a greater relative risk for developing grade II to IV acute GVHD compared with patients with acute myeloid leukaemia or acute lymphoblastic leukaemia patients.[24]
- Advanced malignant disease has been associated with increased risk for developing acute GVHD.[23]

high-intensity conditioning radiation regimen

- High doses of radiation are associated with increased GVHD severity.[35] [24]

peripheral blood stem cell transplant

- Significantly higher incidence of chronic GVHD has been reported with peripheral blood stem cell transplantation than with bone marrow transplantation (53% vs. 41%) in one randomised controlled trial of patients undergoing allogeneic transplant from unrelated donors.[42]

donor lymphocyte infusion (DLI)

- Chronic GVHD attributable to donor lymphocyte infusion is common.[7] [45]
- Risk-adapted donor lymphocyte infusion may reduce risk for GVHD.[56] [57]

absent or suboptimal GVHD prophylaxis

- The risk of developing GVHD is significant in patients who do not receive any acute GVHD prophylaxis.[58] Reduction of methotrexate and ciclosporin administration, primarily due to renal or hepatic dysfunction, is also associated with increased risk for acute GVHD.[23]

Weak

white or black race

- White and black people have been found to have an increased risk for acute GVHD compared with those of Asian or Hispanic ethnicity, although overall survival rates may be similar between ethnic groups.[24] [37]
- The association of ethnicity with acute GVHD is controversial.

cytomegalovirus (CMV) seropositive

- A significantly increased risk of grade II to IV acute GVHD in CMV-negative patients and a higher treatment-related mortality in CMV-positive recipients has been reported.[24] [59]

splenectomy

- Splenectomy has been reported to be a risk factor for GVHD.[60]
- Evidence is equivocal.[41] [60]

low performance status score

- Poor performance status has been found to correlate with increased risk for acute GVHD.[24]

low socio-economic status

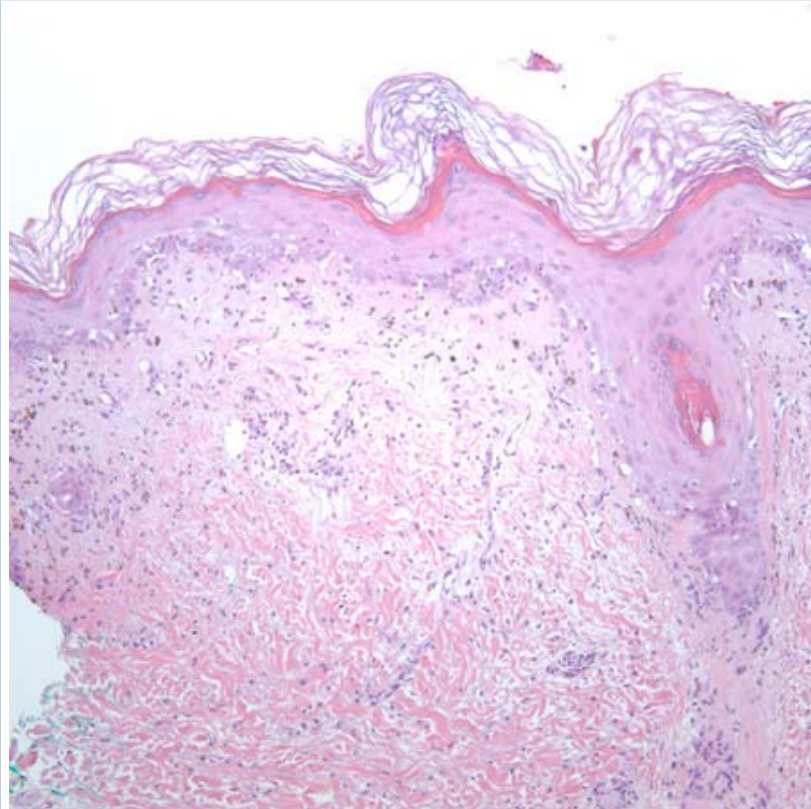
- Low socio-economic status has been associated with increased rates of acute and chronic GVHD, increased transplant-related complications within the first 100 days post haematopoietic cell transplant, and decreased overall survival.[38]

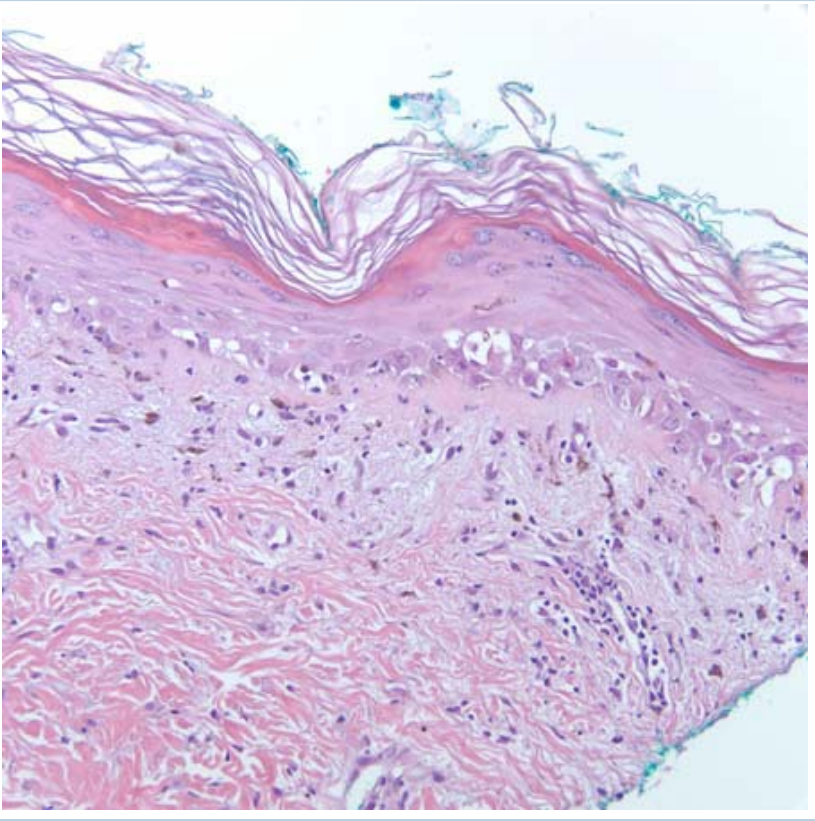
Investigations

1st test to order

Test	Result
FBC <ul style="list-style-type: none"> In the early post-transplant setting, cytopenia (particularly thrombocytopenia) may be associated with acute graft-versus-host disease (GVHD). Autoimmune cytopenias (leukopenia, anaemia, and thrombocytopenia) may be seen at a later stage with chronic GVHD. Eosinophilia may be present in acute or chronic GVHD. 	may show leukopenia, anaemia, thrombocytopenia, or eosinophilia
serum electrolytes <ul style="list-style-type: none"> Acute and/or chronic graft-versus-host disease affecting the gastrointestinal tract (e.g., anorexia, nausea, vomiting, diarrhoea, weight loss, and failure to thrive [in infants and children]) can lead to a variety of electrolyte disturbances. 	may show abnormal values
liver functions tests <ul style="list-style-type: none"> Elevated transaminases, alkaline phosphatase, and/or bilirubin may be a manifestation of acute and/or chronic graft-versus-host disease. 	may show elevated liver transaminases, alkaline phosphatase, and bilirubin
urinalysis <ul style="list-style-type: none"> Proteinuria may be a manifestation of renal dysfunction seen with nephrotic syndrome associated with chronic graft-versus-host disease. 	may show proteinuria
urine culture <ul style="list-style-type: none"> Useful in helping exclude the possibility of urinary tract infection. 	positive or negative for a pathogen
blood culture <ul style="list-style-type: none"> Important to exclude the possibility of bacteraemia and/or sepsis. 	positive or negative for a pathogen
stool culture <ul style="list-style-type: none"> Can help exclude potential infectious causes of diarrhoea that may closely resemble graft-versus-host disease (GVHD). Positive stool studies and gastrointestinal GVHD can occur concurrently. 	positive or negative for a pathogen
viral polymerase chain reaction (PCR) studies <ul style="list-style-type: none"> Can be used to test for infection with cytomegalovirus, HHV-6, adenovirus, hepatitis virus (A, B, C, D, E), and parvovirus. 	positive or a negative

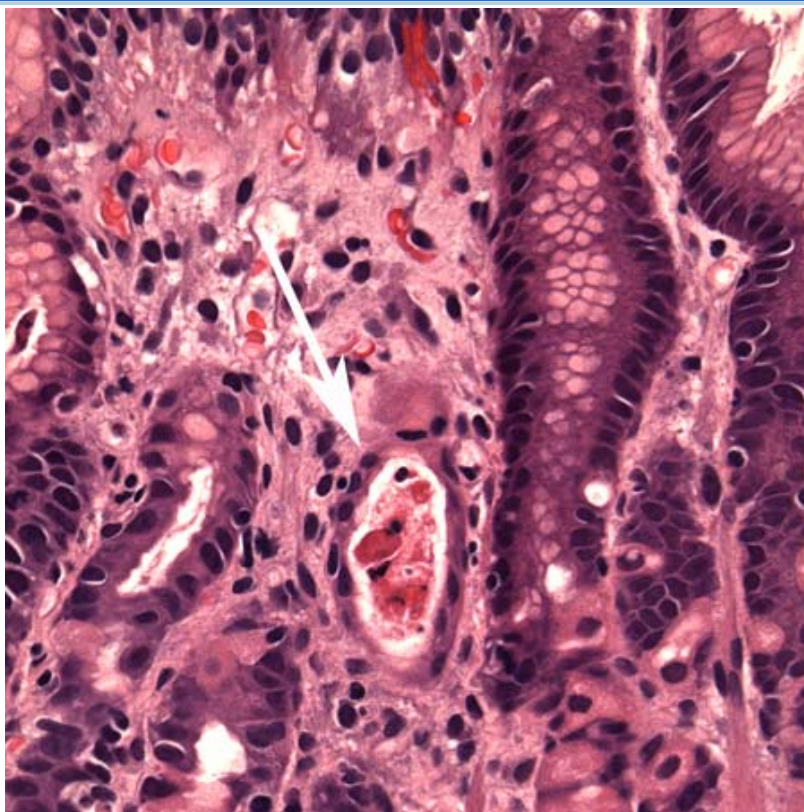
Other tests to consider

Test	Result
CT abdomen <ul style="list-style-type: none"> Important to obtain in patients presenting with symptoms suggestive of gastrointestinal graft-versus-host disease (GVHD; e.g., nausea, vomiting, diarrhoea, abdominal pain, anorexia). Ascites may be present; however, this is not diagnostic for GVHD. 	luminal dilatation with thickening of the small bowel wall (ribbon sign); air-fluid levels suggestive of an ileus; ascites
Doppler ultrasound of the liver <ul style="list-style-type: none"> To exclude other aetiologies of liver dysfunction in the post-transplant setting, such as veno-occlusive disease/sinusoidal obstructive syndrome or total parenteral nutrition cholestasis. 	hepatomegaly and ascites may be noted in graft-versus-host disease; no hepatic venous occlusion, calculi, or thickening of gall bladder seen
tissue biopsy (skin, gastrointestinal [GI] tract, liver, or lung) <ul style="list-style-type: none"> A biopsy of the affected organ (e.g., skin, GI tract, liver, lung) may, however, be carried out to support or confirm a diagnosis, particularly if there is clinical uncertainty.[92]  <p><i>Histology of skin graft-versus-host disease (GVHD) (low power): Vacuolar interface dermatitis at the dermoepidermal junction with involvement of follicular epithelium (100x, haematoxylin and eosin)</i> <i>Courtesy of Dr Lori Lowe, Professor, Dermatopathology, University of Michigan; used with permission</i></p>	histological features of graft-versus-host disease; skin: includes apoptosis at base of epidermal rete pegs, dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes, perivascular lymphocytic infiltration in the dermis; GI tract: includes patchy ulcerations, apoptotic bodies in the base of crypts, crypt abscesses and loss, flattening of the epithelium surface; liver: includes endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis, bile duct destruction; lung: includes small airway inflammation with fibrinous obliteration of the bronchiolar lumen

Test	Result
	
<p><i>Histology of skin graft-versus-host disease (GVHD) (high power): Vacuolar interface dermatitis with rare necrotic keratinocytes (200x, haematoxylin and eosin) Courtesy of Dr Lori Lowe, Professor, Dermatopathology, University of Michigan; used with permission</i></p>	

Test

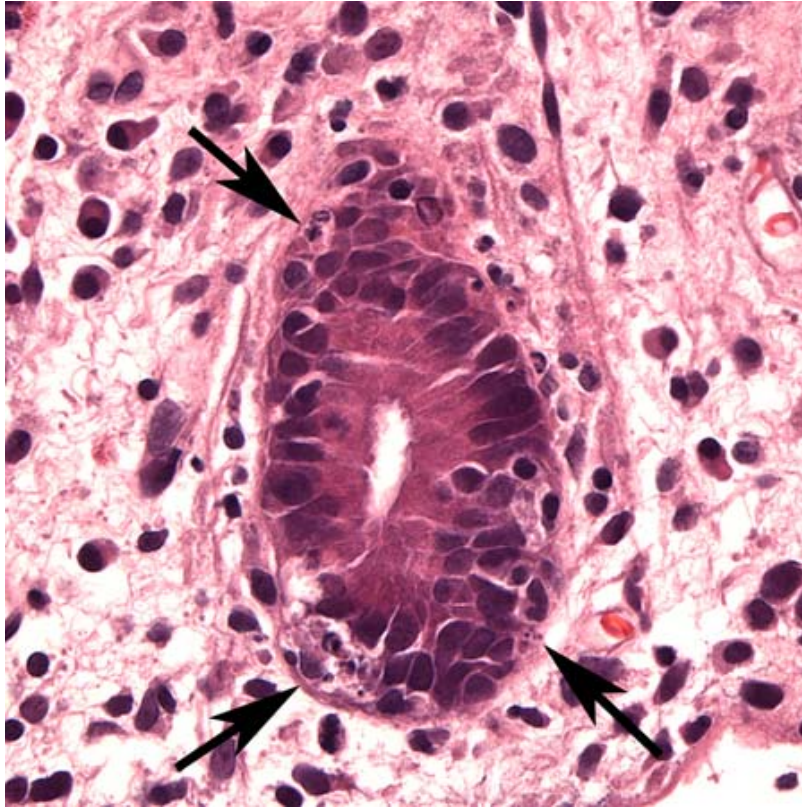
Result



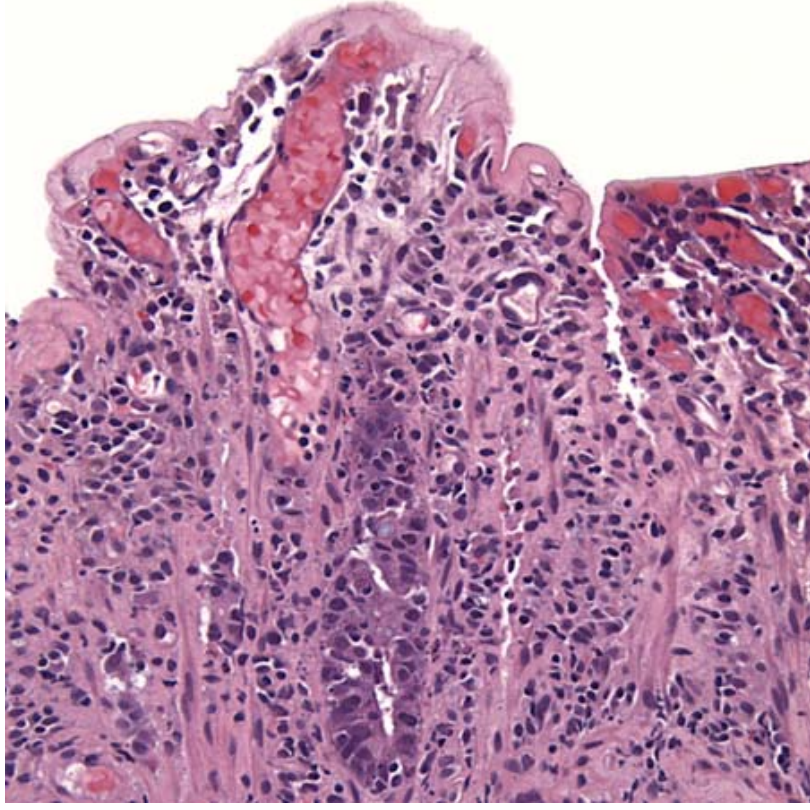
Histology of upper gastrointestinal graft-versus-host disease (GVHD) (medium-power photomicrograph of the stomach): Dilated gastric gland containing necrotic/apoptotic debris (arrow), typical of GVHD
Courtesy of Dr Joel Greenson, Professor, Pathology, University of Michigan; used with permission

Test

Result



*Histology of lower gastrointestinal graft-versus-host disease (GVHD) (high-power photomicrograph of colon, mild disease): Numerous apoptotic bodies (arrows) indicative of GVHD involving the colon
Courtesy of Dr Joel Greenson, Professor, Pathology, University of Michigan; used with permission*

Test	Result
 <p><i>Histology of lower gastrointestinal graft-versus-host disease (GVHD) (medium-power photomicrograph of colon, severe disease): Almost complete denudation of the mucosa indicative of severe GVHD involving the colon</i> <i>Courtesy of Dr Joel Greenson, Professor, Pathology, University of Michigan; used with permission</i></p>	
<p>pulmonary function tests</p> <ul style="list-style-type: none"> Used in identifying obstructive pulmonary disease (e.g., bronchiolitis obliterans) in chronic graft-versus-host disease (GVHD). 	<p>FEV1/FVC ratio may be <0.7 and FEV1 <75% of predicted in chronic GVHD involving the lungs</p>
<p>high-resolution CT chest</p> <ul style="list-style-type: none"> Used in establishing the diagnosis of chronic graft-versus-host disease affecting the lungs. 	<p>air trapping and bronchiectasis; bilateral patchy ground-glass opacities with air bronchograms (usually located peripherally) or a circular nodule in one lung (or 3-5 nodules across both lungs) suggest cryptogenic organising pneumonia (COP); the triangle sign (a triangular ground glass opacity with the base on the pleura and the apex towards the mediastinum) is characteristic for COP</p>

Test	Result
bronchoalveolar lavage (BAL) and culture <ul style="list-style-type: none"> Can be helpful in assessing and excluding infection as a potential differential diagnosis of graft-versus-host disease. 	positive or negative culture
echocardiogram <ul style="list-style-type: none"> Helpful to detect pericardial effusions or cardiomyopathy in chronic graft-versus-host disease. 	may show pericardial effusion or cardiomyopathy
barium swallow or upper gastrointestinal endoscopy <ul style="list-style-type: none"> Useful in identifying features of chronic graft-versus-host disease (GVHD) of the gastrointestinal (GI) tract. 	characteristic features of chronic GVHD of the GI tract include oesophageal web, stricture, or concentric rings
18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan <ul style="list-style-type: none"> May be useful in localising gastrointestinal tract (GI) graft-versus-host disease (GVHD), as well as predicting and monitoring treatment responsiveness.^[91] 	may show hot spots of GVHD activity in the GI tract

Emerging tests

Test	Result
serum biomarkers <ul style="list-style-type: none"> Serum biomarkers (e.g., REG3a and ST2) are being investigated for risk assessment and prognostication for acute graft-versus-host disease.^{[99] [100] [101]} 	elevated; can indicate risk for severe disease

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Drug rash	<ul style="list-style-type: none"> • May be clinically indistinguishable from acute GVHD of the skin. • Can occur with use of any drug. 	<ul style="list-style-type: none"> • If the rash does not improve with removing the offending drug, skin biopsy may reveal infiltration of eosinophilic polymorphonuclear leukocytes suggestive of a drug-induced lesion.
Radiation or chemotherapy-induced rash	<ul style="list-style-type: none"> • May be clinically indistinguishable from acute GVHD of the skin. • Rash may coincide with the timing of recent radiotherapy or chemotherapy. 	<ul style="list-style-type: none"> • Clinical diagnosis. No differentiating tests.
Bacterial gastroenteritis	<ul style="list-style-type: none"> • May be clinically indistinguishable from gastrointestinal GVHD. • May coincide with contact with contaminated food or water, or contact with infected person. 	<ul style="list-style-type: none"> • Stool cultures are recommended in order to rule out an infectious cause for the enteritis symptoms that may mimic gastrointestinal GVHD.
Viral gastroenteritis	<ul style="list-style-type: none"> • May be clinically indistinguishable from gastrointestinal GVHD. • May coincide with contact with contaminated food or water, or contact with infected person. 	<ul style="list-style-type: none"> • Stool rapid antigen testing: may detect rotavirus or calicivirus. • Stool reverse transcriptase polymerase chain reaction: may detect rotavirus, norovirus, astrovirus, or adenovirus. • Stool viral culture and electron microscopy: may detect and identify viral cause.
Neutropenic colitis	<ul style="list-style-type: none"> • May be clinically indistinguishable from gastrointestinal GVHD. 	<ul style="list-style-type: none"> • Abdominal x-ray or abdominal CT scan: may reveal thickening of the colon with fat stranding (an appearance of stranding in peritoneal fat due to inflammation).
Pseudomembranous colitis	<ul style="list-style-type: none"> • May be clinically indistinguishable from gastrointestinal GVHD. • May coincide with recent antibiotic use. 	<ul style="list-style-type: none"> • Stool testing for <i>Clostridioides difficile</i>. If negative, colonoscopy or sigmoidoscopy may be warranted.
Drug-induced enterocolitis	<ul style="list-style-type: none"> • May be clinically indistinguishable from gastrointestinal GVHD. 	<ul style="list-style-type: none"> • Trial withdrawal of drug known to affect the gastrointestinal tract may

Condition	Differentiating signs / symptoms	Differentiating tests
	<ul style="list-style-type: none"> May coincide with introduction of new drug. 	lead to improvement or resolution of abdominal symptoms.
Drug-induced hepatotoxicity	<ul style="list-style-type: none"> May be clinically indistinguishable from liver GVHD. Drug history includes drugs with known hepatotoxicity. Clinical presentation may include pruritus, arthralgia, headache, and anorexia. 	<ul style="list-style-type: none"> Trial withdrawal of drug known to be hepatotoxic may lead to improvement or resolution of liver function abnormalities.
Viral hepatitis	<ul style="list-style-type: none"> Presence of key risk factors (e.g., blood transfusion, intravenous drug use, overseas travel, exposure to infected individuals). 	<ul style="list-style-type: none"> Polymerase chain reaction (PCR) may detect hepatitis virus (A, B, C, D, E).
Veno-occlusive disease (VOD)/sinusoidal obstructive syndrome	<ul style="list-style-type: none"> The classic triad for VOD includes hepatomegaly, right upper quadrant (RUQ) pain, and ascites (or unexplained weight gain). 	<ul style="list-style-type: none"> Doppler ultrasound of the liver shows increased phasicity of portal veins with eventual development of portal flow reversal. The liver is usually enlarged but maintains normal echogenicity. Liver biopsy is required for a definitive diagnosis.
Total parenteral nutrition (TPN) associated cholestasis	<ul style="list-style-type: none"> Current treatment with TPN is a key differentiating factor. Pale stools and/or dark urine are non-specific findings with cholestasis. Anorexia and decreased appetite may also be present. 	<ul style="list-style-type: none"> Abdominal ultrasound may reveal gall bladder sludge with mild thickening. Serum triglycerides and cholesterol may also be elevated. Trial withdrawal of TPN may lead to improvement of liver function abnormalities.
Acalculous cholecystitis	<ul style="list-style-type: none"> Pain often localised to RUQ or jaundice may be presenting signs for acute or chronic cholecystitis. 	<ul style="list-style-type: none"> Abdominal ultrasound may reveal echogenic sludge within a moderately distended gall bladder with no discrete gallstones. The gall bladder wall is not thickened. No biliary ductal dilation seen. Abdominal CT scan: sludge may be present; no gallstones. Hepatobiliary scintigraphy is highly sensitive and specific for diagnosing acute cholecystitis. Serial images show normal hepatic uptake

Condition	Differentiating signs / symptoms	Differentiating tests
		of radiotracer with normal visualisation of common duct and bowel at 30 minutes after injection. In acalculous cholecystitis, the gall bladder is not visualised at 1 hour despite an intravenously administered dose of morphine sulfate.

Criteria

Acute graft-versus-host disease (GVHD): staging and grading criteria

Acute GVHD is graded on the extent of involvement (stage) of each of the target organs, namely the skin, gastrointestinal (GI) tract, and liver. Several criteria are commonly used for staging and grading acute GVHD.

Keystone (modified Glucksberg) criteria^[83]

Widely used at transplant centres.^[83] The skin is staged based on percent of body surface area (BSA) involvement of maculopapular rash. The gastrointestinal tract is staged based on the volume of stool output, and the liver is staged based on degree of bilirubinaemia. In children, stool output is measured per kilogram body weight.^[84]

An overall grade is assigned based on the individual stages of the organs involved, which reflects the actual extent of GVHD. Grade I GVHD is characterised as mild disease, grade II GVHD as moderate disease, grade III as severe disease, and grade IV as very severe and life-threatening disease.

MAGIC criteria^[85]

International expert consensus criteria developed to standardise the inclusion of acute GVHD symptoms of the GI tract as part of clinical staging and grading.

Staging is based on clinical manifestations of the skin, GI tract (upper and lower), and liver, with an overall grade assigned based on the most severe target organ involvement.

Acute GVHD stage

- Stage 0
 - Skin (active erythema only): no active (erythematous) GVHD rash
 - Liver (bilirubin): <2 mg/dL
 - Upper GI: no or intermittent nausea, vomiting, or anorexia
 - Lower GI (stool output/day): adults <500 mL/day or <3 episodes/days; children <10 mL/kg/day or <4 episodes/day
- Stage 1
 - Skin (active erythema only): maculopapular rash <25% BSA
 - Liver (bilirubin): 2-3 mg/dL
 - Upper GI: persistent nausea, vomiting, or anorexia

- Lower GI (stool output/day): adults: 500-999 mL/day or 3-4 episodes/day; children: 10.0 to 19.9 mL/kg/day or 4-6 episodes/day
- Stage 2
 - Skin (active erythema only): maculopapular rash 25% to 50% BSA
 - Liver (bilirubin): 3.1 to 6.0 mg/dL
 - Lower GI (stool output/day): adults: 1000-1500 mL/day or 5-7 episodes/day; children: 20-30 mL/kg/day or 7-10 episodes/day
- Stage 3
 - Skin (active erythema only): maculopapular rash >50% BSA
 - Liver (bilirubin): 6.1 to 15.0 mg/dL
 - Lower GI (stool output/day): adults: >1500 mL/day or >7 episodes/day; children: >30 mL/kg/day or >10 episodes/day
- Stage 4
 - Skin (active erythema only): generalised erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA
 - Liver (bilirubin): >15 mg/dL
 - Lower GI (stool output/day): severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Acute GVHD grade

- Grade 0
 - No stage 1-4 of any organ
- Grade I
 - Stage 1-2 skin without liver, upper GI, or lower GI involvement
- Grade II
 - Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
- Grade III
 - Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI
- Grade IV
 - Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI

Minnesota refined acute GVHD risk score

Stratifies patients as either standard risk or high risk depending on stage and grade.^{[86] [87]}

Chronic GVHD: staging and grading criteria

The National Institutes of Health (NIH) working group scoring system for chronic GVHD^[1] [National Institutes of Health: organ scoring of chronic GVHD] (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329079/figure/F1>)

Can be used to assess disease severity and prognosis based on specific signs, degree of organ involvement (mild, moderate, severe), and laboratory data.

The NIH working group scoring system recommends:

- at least one diagnostic manifestation (e.g., oral or vaginal lichenoid findings, skin dyspigmentation, bronchiolitis obliterans), or
- one distinctive manifestation (e.g., ocular sicca, depigmentation, papulosquamous plaques) plus a pertinent biopsy, laboratory, or other test for the diagnosis of chronic GVHD.

Approach

Optimal management of graft-versus-host disease (GVHD) requires a multidisciplinary team approach, comprising infectious disease specialists, dermatologists, gastroenterologists, nutritionists, physiotherapist, cardiologists, pulmonologists, ophthalmologists, dentists, gynaecologists, rheumatologists, and urologists. Appropriate specialists should be involved at diagnosis and throughout treatment and follow-up.

Optimal prophylaxis, prompt treatment, appropriate monitoring of treatment response, and supportive care reduce risk of complications and disability.^{[63] [92]} Other factors that may influence the management of GVHD include local practices and guidelines, availability of therapies, and the preferences and experience of treating physicians.

GVHD prophylaxis

Prophylaxis with immunosuppressants is the main preventive strategy for patients undergoing allogeneic haematopoietic cell transplantation (HCT).^{[62] [63]} Standard prophylactic regimens are calcineurin inhibitor-based. Corticosteroids are not routinely recommended for GVHD prophylaxis.

Standard GVHD prophylactic regimens

The standard regimens for GVHD prophylaxis in patients undergoing matched related or unrelated donor HCT comprise a calcineurin inhibitor (e.g., ciclosporin or tacrolimus) plus low-dose methotrexate or mycophenolate.^{[63] [102] [103]}

A therapeutic regimen comprising calcineurin inhibitor plus methotrexate has been shown to be superior to either agent alone in the reduction of GVHD incidence and improvement in survival.^{[65] [104]} One meta-analysis found no difference in all-cause mortality between tacrolimus plus methotrexate and ciclosporin plus methotrexate.^[103] However, the former regimen was superior with respect to reducing acute GVHD incidence.^[103]

One Cochrane review examining the effect of mycophenolate versus methotrexate for acute GVHD prevention found no significant differences in overall survival, median time to neutrophil engraftment, or the incidence of acute GVHD, relapse, non-relapse mortality, and chronic GVHD.^[102] However, mycophenolate was associated with less mucositis, less use of parenteral nutrition, and less use of analgesia, suggesting a more favourable toxicity profile.^[102]

Tacrolimus plus sirolimus has been suggested as an alternative regimen for GVHD prophylaxis.^{[75] [76] [77] [78]} Incidence of acute GVHD (by day +114) is similar between tacrolimus plus sirolimus and tacrolimus plus methotrexate in patients who have undergone allogeneic HCT from a matched related donor.^[78]

Evidence continues to influence the management of GVHD prophylaxis, and alternative prophylactic treatment strategies may be considered for specific patient populations.

Abatacept

A selective T-cell costimulation modulator, abatacept is approved by the US Food and Drug Administration (FDA), in combination with a calcineurin inhibitor and methotrexate, for the prevention of acute GVHD in patients undergoing allogeneic HCT from a matched or 1 allele-mismatched unrelated donor.

In one phase 2 randomised trial, the addition of abatacept to standard prophylaxis (calcineurin inhibitor plus methotrexate) numerically reduced rates of severe (grade III or IV) acute GVHD (6.8% vs. 14.8%), and significantly improved severe acute GVHD-free survival (93.2% vs. 82.0%), in patients with haematological malignancies who had undergone HCT from an HLA-matched (8/8) unrelated donor.[66]

Post-transplant cyclophosphamide (combined with standard prophylaxis of tacrolimus plus mycophenolate)

Increasingly favoured for primary GVHD prevention based on results from large-scale, multi-site clinical trials.[63] [67] [68] In one phase 3 trial of patients undergoing allogeneic HLA-matched HCT with reduced-intensity conditioning, GVHD-free, relapse-free survival at 1 year was significantly more common in patients randomised to cyclophosphamide-based prophylaxis (cyclophosphamide, tacrolimus, and mycophenolate) than those assigned to standard prophylaxis (52.7% vs. 34.9%).[67] Post-transplant cyclophosphamide-based prophylaxis is commonly used in patients who have undergone allogeneic HCT from an HLA-haploidentical (i.e., half-matched) donor or unrelated donor.[69] [70]

Rabbit antithymocyte immunoglobulin

A polyclonal immunoglobulin G, rabbit antithymocyte immunoglobulin reduces the cumulative incidence of both acute and chronic GVHD in patients undergoing HCT from unrelated donors. In one randomised phase 3 trial, the addition of rabbit antithymocyte immunoglobulin to standard prophylaxis (ciclosporin or tacrolimus plus methotrexate or mycophenolate) reduced acute GVHD incidence at 30 and 100 days compared with standard prophylaxis (30 days: 22% vs. 37%; 100 days: 50% vs. 65%).[71] At 24 months, this regimen reduced incidence of chronic GVHD (26.3% vs. 41.3%), and led to improved survival (70.6% vs. 53.3%) and reduced use of immunosuppressive therapy.[72] Rabbit antithymocyte immunoglobulin effectively reduces GVHD incidence after HLA-matched sibling donor HCT.[73]

Sirolimus combined with standard prophylaxis (ciclosporin plus mycophenolate)

Lowers the incidence of grade II to IV acute GVHD (at day 100) compared with standard ciclosporin plus and mycophenolate alone in patients who have undergone allogeneic HCT from an HLA-matched unrelated donor with non-myeloablative conditioning.[74]

Treatment of acute GVHD

Treatment of acute GVHD is complex and multiple factors (e.g., risk of relapse, organ function, performance status, and presence or risk of infections) play an important role in treatment decisions. Furthermore, the optimal drug combination is not well defined.

Mild skin GVHD (grade I) is primarily treated with topical corticosteroids.[63] If the patient is asymptomatic or if the rash is stable, a period of observation without any interventional treatment may be appropriate.[92]

Systemic corticosteroids are initiated for more severe and/or symptomatic skin GVHD and/or any visceral GVHD involvement (grade II-IV).[63] [92] [105][106] Methylprednisolone is the standard initial treatment, given in combination with therapeutic dosing of the calcineurin inhibitor used for GVHD prophylaxis (i.e., tacrolimus or ciclosporin).[92] Patients with grade II-IV acute GVHD should be considered for enrolment in a clinical trial wherever available.[92]

With clinical response, immunosuppressive drugs should be tapered as appropriate.[63] [92] Generally, taper schedules are influenced by the patient's clinical response and circumstances (e.g., risk for relapse,

presence or absence of infection, or other corticosteroid-related complications). A commonly reported taper schedule is over 8-12 weeks.

Acute gastrointestinal GVHD: oral-topical corticosteroids

Topically active corticosteroids taken orally (oral-topical corticosteroids, e.g., budesonide, beclometasone) may be used for confirmed cases of acute gastrointestinal GVHD in combination with a systemic corticosteroid.^{[92] [107] [108] [109]} The systemic corticosteroid can be tapered in patients who show a clinical response.

Oral-topical corticosteroid formulations have high first-pass metabolism, facilitating local effects while reducing systemic absorption. However, some systemic effects do occur.

An oral proprietary formulation of beclometasone is not currently available in the US. However, selected pharmacies may be able to compound this formulation. Budesonide may be less effective at treating the GVHD of the upper GI tract.^[92]

Corticosteroid-refractory acute GVHD

If there is disease progression or lack of response following 3-7 days treatment, additional immunosuppressive therapy is required.^[92] Further immunosuppression will, however, increase the risk of life-threatening infections (due to immunosuppression and lymphopenia) and/or multi-organ dysfunction.

There is no standard approach for the treatment of corticosteroid-refractory acute GVHD.^[106] A variety of agents have been used, and varying response rates have been reported.^[110] Entry into a clinical trial may be appropriate.^[92]

Alternative immunosuppressive agents should be considered if a patient develops an unacceptable level of toxicity (i.e., corticosteroid intolerance).^{[92] [106]}

Acute GVHD: alternative or additional immunosuppressive treatments

Consideration should be given to an alternative or additional immunosuppressive agent in the presence of corticosteroid-refractory acute GVHD or corticosteroid intolerance, respectively.^{[63] [92]}

Ruxolitinib

Approved by the FDA and European Medicines Agency (EMA) for patients with corticosteroid-refractory acute GVHD.^[111] Ruxolitinib is recommended as a primary treatment option for corticosteroid-refractory acute GVHD by the National Comprehensive Cancer Network (NCCN) and the European Society for Blood and Marrow Transplantation (ESBMT).^{[63] [92]}

Day-28 overall response rate was 54.9% among 39 patients treated with ruxolitinib for corticosteroid-refractory acute GVHD grades II-IV (occurring after allogeneic hematopoietic stem cell transplantation) in an open-label, phase 2 multicenter study (REACH 1).^[112] The median duration of response was 345 days.

In the REACH 2 open-label phase 3 trial of patients with corticosteroid-refractory acute GVHD after allogeneic stem cell transplantation, day 28 overall response rate was 62% in patients randomised to ruxolitinib compared with 39% in the control group (investigator's choice of commonly used therapy).^[113]

Antithymocyte immunoglobulin (ATG)

ATG is an infusion of horse- or rabbit-derived antibodies against human T cells that can lead to prolonged immunosuppression. The response rates following ATG have been reported to be highest in patients with skin involvement and lowest in those with liver involvement.^{[114] [115]} Its use has been limited primarily due to severe life-threatening opportunistic infections from prolonged immunosuppression.^[114]

There are many different horse- and rabbit-derived ATG antisera available. To date, a standard dose and schedule for ATG in the treatment for GVHD has not been established.^[116]

Sirolimus

Sirolimus is efficacious in the treatment of acute and chronic GVHD.^{[117] [118]} However, in these studies, significant toxicity was observed, including thrombocytopenia, hypertriglyceridaemia, neutropenia, haemolytic uraemic syndrome, and hypercholesterolaemia.

Etanercept

One trial reported that the combination of etanercept plus a corticosteroid (as initial treatment for grade II-IV acute GVHD) resulted in significantly better complete response rates 4 weeks following treatment compared with a historical control group of corticosteroids alone.^[119]

Alemtuzumab

Alemtuzumab lowered incidence of acute GVHD in case report series.^{[120] [121]} However, the delayed immune reconstitution has led to higher incidences of life-threatening infections.^{[122] [123]}

Pentostatin

In a four-arm, phase 2 trial (BMT CTN 0302) investigating etanercept, mycophenolate, denileukin diftitox, and pentostatin (all combined with corticosteroids) as initial therapy for acute GVHD, the day 28 complete response rate for pentostatin was 38%, and 9-month overall survival was 47%.^[124] Infectious complications remain one of the most significant toxicities with this agent.

Extracorporeal photopheresis (ECP)

ECP exposes peripheral blood mononuclear cells to photoactivated methoxsalen and ultraviolet A (UV-A) radiation. Upon photoactivation, methoxsalen covalently binds and cross links DNA, initiating apoptosis. ECP has become an increasingly common adjunct therapy in efforts to minimise corticosteroid exposure and allow for more rapid corticosteroid tapers.^[125]

One systematic review of prospective studies concluded that ECP demonstrated encouraging responses in corticosteroid-refractory acute GVHD, and is more likely to be beneficial in patients with skin involvement.^[126] Further studies are required to evaluate the efficacy of ECP in children and adolescents.^[127]

Acute GVHD: withdrawal of corticosteroid therapy

The prognosis for patients who develop severe acute GVHD, especially those not responding to corticosteroids, is generally poor.^[128]

Withdrawal of corticosteroid therapy can lead to a flare of acute GVHD and/or the onset of chronic GVHD. There is no standard taper schedule; it will depend on the patient, clinical picture, and physician preference and experience.

Enrolment in a clinical trial is encouraged for patients with corticosteroid-refractory disease.^[92]

Treatment of chronic GVHD

The recommended first-line therapy for patients with chronic GVHD is a systemic corticosteroid (methylprednisolone).^[92] National Institutes of Health (NIH) guidelines recommend systemic corticosteroid therapy if three or more organs are involved, or any single organ with a severity score of more than 2.^[1] Alternative immunosuppressive agents should be considered if a patient develops an unacceptable level of toxicity (i.e., corticosteroid intolerance).^[92]

Therapeutic choice is informed by agents used for prophylaxis and/or treatment of acute GVHD, specific patient characteristics, and preference of the treating physician and center. Treatment for chronic GVHD is generally less intense and less aggressive than for acute GVHD. It may, however, require prolonged duration of therapy.

Patients should be considered for enrollment in a clinical trial whenever available.^[92]

Chronic GVHD: inadequate response to initial therapy

If there is an inadequate response to initial therapy with a systemic corticosteroid, additional immunosuppressants may be required.^[92] The NIH working group define failure of initial therapy or requirement of additional secondary therapy as:^[1] ^[129]

- progression of chronic GVHD despite optimal first line therapy, or
- no improvement after 4-8 weeks of sustained therapy, or
- inability to taper corticosteroid dose.

Alternative or additional immunosuppressive treatments for the management of chronic GVHD have been described.^[63] ^[92]

Ruxolitinib

FDA-approved for chronic GVHD after failure of one or two lines of systemic therapy.^[130] Ruxolitinib is recommended as a primary treatment option for corticosteroid-refractory chronic GVHD by the NCCN and the European Society for Blood and Marrow Transplantation ESBMT.^[63] ^[92]

In one phase 3 open-label randomised trial of patients aged 12 years or older with moderate or severe corticosteroid-refractory or corticosteroid-dependent chronic GVHD (REACH3 trial), ruxolitinib improved overall response rate compared with best available therapy (investigator choice) at 24 weeks.^[131]

Ibrutinib

A Bruton tyrosine kinase inhibitor approved by the FDA for second-line therapy of chronic GVHD (after failure of one or more lines of systemic therapy).^[132]

Ibrutinib is associated with an increased risk for serious cardiac events including arrhythmias and heart failure. Recommended risk minimisation measures include performing a clinical evaluation of cardiac history and function prior to starting treatment, careful monitoring for signs of cardiac deterioration during

treatment, and treatment interruption and/or dose modification if any new-onset or worsening cardiac events are observed.[133] [134]

Belumosudil

Approved by the FDA for chronic GVHD after failure of at least two prior lines of systemic therapy. In one phase 2 open-label randomised trial of patients with chronic GVHD who had received between 2 and 5 prior lines of therapy, the overall response rate with belumosudil was 77% (median follow-up of 14 months).[135] Pneumonia was the most commonly reported serious adverse event.

Axatilimab

Approved by the FDA for chronic GVHD after failure with at least two prior lines of systemic therapy. One phase 2 multinational randomised trial of patients with recurrent or refractory chronic GVHD reported an overall response rate (ORR) of 74% in the lower axatilimab dose group; an ORR of 67% and 50% was reported for higher-dose groups.[136]

Calcineurin inhibitors (ciclosporin or tacrolimus)

May be combined with systemic corticosteroids in patients with corticosteroid-refractory chronic GVHD, particularly if calcineurin inhibitors have not been used previously (e.g., for GVHD prophylaxis).[92]

Rituximab

An anti-CD20 chimeric monoclonal antibody. One retrospective study reported on 38 patients (a median age of 48 years) who received rituximab for refractory chronic GVHD. The overall response rate was 65%.[137] These findings were similar to those from a phase 1/2 study, where the clinical response rate was 70%.[138] Rituximab was well-tolerated in the latter study, and toxicity was limited primarily to infectious events.[138]

Sirolimus

In one phase 2/3 trial, sirolimus plus prednisolone demonstrated similar long-term outcomes to sirolimus plus a calcineurin inhibitor plus prednisolone in patients with chronic GVHD (treatment-naïve or early inadequate responders).[139] Sirolimus plus prednisone was easier to administer and was better tolerated.[139]

Pentostatin

Pentostatin has been studied in a phase 2 trial of patients with corticosteroid-refractory chronic GVHD. Of the 58 heavily pretreated patients enrolled, 32 (55 %) had an objective response.[140] Infectious complications remain one of the most significant toxicities with this agent.

ECP

An increasingly common adjunct therapy to minimise corticosteroid exposure and allow for more rapid corticosteroid taper.[125] One systematic review of prospective studies reported an overall response rate of 69% (pooled data from six studies of patients with corticosteroid-refractory or corticosteroid-dependent acute or chronic GVHD).[126] ECP is more likely to be beneficial in patients with skin involvement.[126] Further studies are required to evaluate the efficacy of ECP in children and adolescents.[141]

Organ systems affected by chronic GVHD: monitoring and treatment

Close serial monitoring of all organ systems is recommended to promote early detection and intervention directed towards reversing or preventing progression of chronic GVHD manifestations.[142]

Ancillary therapies are commonly employed in addition to systemic GVHD treatment, and in some cases their use may circumvent the need for systemic treatment or allow doses of systemic agents to be decreased.

Immunological and infectious diseases

- Immunisations and prophylaxis against *Pneumocystis carinii*, varicella zoster virus, and encapsulated bacteria should be guideline-based.[143]
- Antibacterial prophylaxis is given to all patients with chronic GVHD as long as systemic immunosuppressives are being administered. *Pneumocystis* pneumonia <6 months after HCT is strongly associated with chronic GVHD. All patients who receive immunosuppression after allogeneic HCT should receive *Pneumocystis* prophylaxis.
- Most experts advocate the use of *Haemophilus influenzae* type b vaccine and influenza vaccine (not live-attenuated). No live virus, including the live attenuated influenza vaccine and measles-mumps-rubella (MMR), should be given.
- Consider intravenous immunoglobulin (IVIG) replacement based on levels and recurrent infections. Universal administration of IVIG after HCT has not been shown to confer clinical benefit and should be avoided.
- No current evidence supports the use of mould-active agents.
- Surveillance for infection (viral, bacterial, fungal, and atypical).
- Empiric parenteral broad-spectrum antibacterial coverage for fever.
- Organism-specific antimicrobial agents.

Skin and appendages

- Photoprotection
- Surveillance for malignancy
- For intact skin:
 - Emollients
 - Topical corticosteroids. Non-sclerotic skin lesions without erosions or ulcerations (e.g., lichen planus-like or papulosquamous plaques) may respond well to topical corticosteroids and emollients. Long-term use of topical corticosteroids may be complicated by local skin atrophy and development of striae.
 - Antipruritic agents.
 - PUVA (psoralen-UV-A)
 - Calcineurin inhibitors
- For erosions/ulcerations:
 - Microbiological cultures
 - Topical antimicrobials
 - Protective films or other dressings
 - Debridement
 - Hyperbaric oxygen
 - Wound care specialist consultation

Mouth and oral cavity^[144]

- Maintain good oral/dental hygiene
- Consider routine dental cleaning and endocarditis prophylaxis
- Surveillance for infection and malignancy
- Topical high and ultra-high potency corticosteroids and analgesics
- Systemic and intralesional corticosteroid in sclerotic disease
- Stretching exercises
- Therapy for oral dryness

Salivary gland involvement:

- Frequent water sipping
- Salivary gland substitute and/or stimulant
- Home fluoride therapy

Eyes

- Photoprotection
- Surveillance for infection, cataract formation, and increased intraocular pressure
- Artificial tears
- Ocular ointments
- Topical corticosteroids or ciclosporin
- Punctal occlusion
- Humidified environment
- Occlusive or moisture chamber eyewear
- Cevimeline or pilocarpine
- Tarsorrhaphy
- Gas-permeable scleral contact lens
- Autologous serum, microbiological cultures
- Topical antimicrobials

Vulva and vagina

- Surveillance for oestrogen deficiency, infection (e.g., herpes simplex virus, human papillomavirus, yeast, bacteria), malignancy
- Water-based lubricants
- Topical oestrogens
- Topical corticosteroids or calcineurin inhibitors
- Dilators
- Surgery for extensive synechiae/obliteration
- Early gynaecological consultation

Gastrointestinal tract and liver

- Surveillance for infection (e.g., viral, fungal)
- Eliminate other potential aetiologies
- Dietary modification, enzyme supplementation for malabsorption, gastrointestinal reflux management, oesophageal dilation, ursodeoxycholic acid

Lungs

- Surveillance for infection (e.g., *Pneumocystis carinii*, viral, fungal, bacterial)
- Eliminate other potential aetiologies (e.g., infection, gastrointestinal reflux)

- Inhaled corticosteroids and/or bronchodilators and/or leukotriene receptor antagonists
- Supplementary oxygen
- Pulmonary rehabilitation
- Consideration of lung transplantation in appropriate candidates

Haematopoietic

- Surveillance for infection (e.g., cytomegalovirus, parvovirus)
- Eliminate other potential aetiologies (e.g., drug toxicity, infection)
- Haematopoietic growth factors, intravenous immunoglobulin for immune cytopenias

Neurological

- Calcineurin drug-level monitoring
- Seizure prophylaxis including blood pressure control, electrolyte replacement, anticonvulsants
- Occupational and physical therapies
- Treatment of neuropathic syndromes with tricyclic antidepressants, selective serotonin-reuptake inhibitors (SSRIs), or anticonvulsants

Musculoskeletal

- Bone mineral metabolism is disturbed after allogeneic HCT, even at >6 years. The abnormalities include increased bone resorption, decreased bone formation, osteopenia and osteoporosis. After HCT, bone mineral density (BMD) of the femoral neck may be more affected than the vertebrae, unlike postmenopausal osteoporosis.
- Management should include surveillance for decreased range of motion, measurement of bone density, calcium levels, and 25-OH vitamin D.
- Appropriate treatments may include physiotherapy, calcium and vitamin D supplements, and bisphosphonates for osteopenia and osteoporosis.

Supportive care and monitoring

Infection prophylaxis, physiotherapy, nutritional status, pain control, and monitoring of drug-drug interactions and drug-related adverse effects are vital components of GVHD management.

Patients often require close follow-up, which should include an assessment of signs and symptoms of disease progression, treatment response, and adverse effects of treatment.^[145] Treatment plans may be adapted accordingly to improve treatment response, manage symptoms, and improve quality of life.

Early recognition of high-risk features, such as thrombocytopenia, progressive onset chronic GVHD, extensive skin involvement with sclerodermatous features, and multi-organ involvement, and appropriate early intervention are also important considerations in the overall management.^{[1] [8]}

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: [see disclaimer](#)

Initial (summary)		
haematopoietic cell transplantation (HCT) recipient		
	1st	GVHD standard prophylaxis
	adjunct	abatacept or cyclophosphamide or rabbit antithymocyte immunoglobulin or sirolimus
Acute (summary)		
acute: grade I		
	1st	topical corticosteroid
	plus	calcineurin inhibitor
acute: grade II-IV		
	1st	systemic corticosteroid
	plus	calcineurin inhibitor
	adjunct	topical or oral-topical corticosteroid
<div> <div></div> <div> lack of response or disease progression or corticosteroid toxicity </div> </div>	adjunct	alternative or additional immunosuppressive agent ± trial entry

Ongoing		(summary)
chronic		
	1st	systemic corticosteroid
	plus	antibacterial prophylaxis
	plus	Pneumocystis prophylaxis
	plus	vaccinations
	plus	nutritional support
	adjunct	alternative or additional immunosuppressive agent
	adjunct	antiviral prophylaxis
	adjunct	antifungal therapy
	adjunct	intravenous immunoglobulin
	adjunct	trial entry
■ intact skin involvement	adjunct	emollient
	adjunct	topical corticosteroid
	adjunct	antipruritic
	adjunct	topical calcineurin inhibitor
	adjunct	PUVA
	adjunct	topical bleaching agent
■ non-intact skin involvement	adjunct	specialist wound dressings
	adjunct	topical antimicrobial
	adjunct	specialist skin therapies
	adjunct	hyperbaric oxygen therapy
■ mucosal involvement of mouth or oral cavity	adjunct	topical corticosteroid or tacrolimus
	adjunct	mouth rinse
	adjunct	topical analgesia
■ salivary gland involvement	adjunct	frequent water sipping + saliva substitute
	adjunct	saliva stimulant
	adjunct	home fluoride therapy
■ sclerotic oral disease	adjunct	systemic and intralesional corticosteroid
	adjunct	stretching exercises
■ eye involvement	adjunct	artificial tears or tear stimulant

Ongoing

(summary)

	adjunct	corticosteroid, ciclosporin, or autologous serum eye drops
	adjunct	evaporation control
	adjunct	tear duct occlusion
	adjunct	scleral contact lens
	adjunct	tarsorrhaphy
■ vulval and vaginal involvement	adjunct	hygiene measures
	adjunct	topical oestrogen with/without dilator
	adjunct	topical corticosteroid or calcineurin inhibitor
	adjunct	surgical lysis
■ gastrointestinal tract involvement: odynophagia and dysphagia	adjunct	oral lubricant
	adjunct	oesophageal dilation
■ gastrointestinal tract involvement: diarrhoea	adjunct	pancreatic enzyme supplementation
■ liver involvement	adjunct	ursodeoxycholic acid
■ lung involvement	adjunct	inhaled bronchodilator
	adjunct	inhaled corticosteroid
	adjunct	montelukast
	adjunct	pulmonary rehabilitation
	adjunct	supplementary oxygen
	adjunct	lung transplantation
■ haematopoietic involvement: cytopenias	adjunct	intravenous immunoglobulin
	adjunct	growth factor
■ neurological involvement	adjunct	antidepressant or anticonvulsant
	adjunct	opioid analgesics
	adjunct	physical and occupational therapy
■ musculoskeletal involvement: fasciitis or contractures	adjunct	physical and occupational therapy
	adjunct	surgical release

Ongoing (summary)		
	■ musculoskeletal involvement: osteopenia and osteoporosis	adjunct osteoporosis therapy

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: [see disclaimer](#)

Initial

haematopoietic cell transplantation (HCT) recipient

1st

GVHD standard prophylaxis

Primary options

- » [methotrexate](#): children and adults: consult specialist for guidance on dose
- or-**
- » [mycophenolate mofetil](#): children and adults: consult specialist for guidance on dose

--AND--

- » [ciclosporin](#): consult specialist for guidance on dose
- or-**
- » [tacrolimus](#): children and adults: consult specialist for guidance on dose

Secondary options

- » [sirolimus](#): children and adults: consult specialist for guidance on dose
- and-**
- » [tacrolimus](#): children and adults: consult specialist for guidance on dose

» The standard regimens for GVHD prophylaxis in patients undergoing matched related or unrelated donor HCT comprise a calcineurin inhibitor (e.g., ciclosporin or tacrolimus) plus low-dose methotrexate or mycophenolate.[63] [102] [103]

» The results of one meta-analysis found no difference in all-cause mortality between tacrolimus plus methotrexate and ciclosporin plus methotrexate.[103] However, the former regimen was superior with respect to reducing acute GVHD.[103]

» One Cochrane review found mycophenolate and methotrexate to be similarly efficacious for acute GVHD prevention.[102] However, mycophenolate may have a more favourable toxicity profile than methotrexate.[102]

» An alternative regimen for GVHD prophylaxis is tacrolimus plus sirolimus.[75] [76] [77] [78] A phase 3 trial (Bone Marrow Transplant Clinical Trials Network [BMT CTN] 0402) found no significant difference in incidence of acute GVHD

Initial

(by day 114) between tacrolimus plus sirolimus and tacrolimus plus methotrexate in patients who had undergone allogeneic HCT from a matched related donor.[78]

adjunct

abatacept or cyclophosphamide or rabbit antithymocyte immunoglobulin or sirolimus

Treatment recommended for SOME patients in selected patient group

Primary options

» **abatacept**: children 2 to <6 years of age: 15 mg/kg intravenous infusion on the day before transplant, followed by 12 mg/kg on days 5, 14, and 28 after transplant; children ≥6 years of age and adults: 10 mg/kg intravenous infusion on the day before transplant, followed by 10 mg/kg on days 5, 14, and 28 after transplant, maximum 1000 mg/dose

Secondary options

» **cyclophosphamide**: consult specialist for guidance on dose

OR

» **antithymocyte immunoglobulin (rabbit)**: consult specialist for guidance on dose

OR

» **sirolimus**: consult specialist for guidance on dose

» Evidence continues to influence the management of GVHD prophylaxis, and alternative prophylactic treatment strategies may be considered for specific patient populations.

» Abatacept (a selective T-cell costimulation modulator) is approved by the US Food and Drug Administration (FDA), in combination with a calcineurin inhibitor and methotrexate, for the prevention of acute GVHD in patients undergoing allogeneic HCT from a matched or 1 allele-mismatched unrelated donor. In one phase 2 randomised trial, the addition of abatacept to standard prophylaxis with a calcineurin inhibitor and methotrexate numerically reduced rates of severe (grade III or IV) acute GVHD, and significantly improved severe acute GVHD-free survival, in patients with haematological malignancies who had undergone HCT from

Initial

an HLA-matched (8/8) unrelated donor.[66]

Screen for latent tuberculosis infection and hepatitis prior to starting abatacept. Patients who test positive for tuberculosis should be treated prior to starting treatment. Serious infections have been reported. Patients with a history of recurrent infections or underlying conditions predisposing to infections may be at higher risk. Discontinue abatacept if a serious infection develops. Update vaccinations prior to starting treatment (live vaccines are contraindicated). Consider starting prophylaxis therapy for Epstein-Barr virus and cytomegalovirus infection/reactivation before transplant.

» Post-transplant cyclophosphamide, combined with tacrolimus plus mycophenolate, is increasingly favoured for primary GVHD prevention based on results from large-scale, multi-site clinical trials.[63] [67] [68] In one phase 3 trial of patients undergoing allogeneic HLA-matched HCT with reduced-intensity conditioning, GVHD-free, relapse-free survival at 1 year was significantly more common in patients randomised to cyclophosphamide-based prophylaxis (cyclophosphamide, tacrolimus, and mycophenolate) than those assigned to standard prophylaxis (52.7% vs. 34.9%).[67] Post-transplant cyclophosphamide-based prophylaxis is commonly used in patients who have undergone allogeneic HCT from an HLA-haploidentical (i.e., half-matched) donor or unrelated donor.[69] [70]

» Rabbit antithymocyte immunoglobulin (a polyclonal immunoglobulin G) reduces the cumulative incidence of both acute and chronic GVHD in patients undergoing HCT from unrelated donors. In one randomised phase 3 trial, the addition of rabbit antithymocyte immunoglobulin to standard prophylaxis (cyclosporin or tacrolimus plus methotrexate or mycophenolate) reduced acute GVHD incidence at 30 and 100 days compared with standard prophylaxis (30 days: 22% vs. 37%; 100 days: 50% vs. 65%).[71] At 24 months, this regimen reduced incidence of chronic GVHD (26.3% vs. 41.3%), and led to improved survival (70.6% vs. 53.3%) and reduced use of immunosuppressive therapy.[72] Rabbit antithymocyte immunoglobulin effectively reduces GVHD incidence after HLA-matched sibling donor HCT.[73]

» Sirolimus combined with standard prophylaxis (cyclosporin plus mycophenolate) has been reported to lower the incidence of grade II to

Initial

IV acute GVHD (at day 100) compared with ciclosporin plus mycophenolate alone in patients who have undergone allogeneic HCT from an HLA-matched unrelated donor with non-myeloablative conditioning.[74]

Acute

acute: grade I

1st topical corticosteroid

Primary options

» **triamcinolone topical**: (0.1%) children and adults: apply to the affected area(s) on body twice or three times daily when required

OR

» **hydrocortisone topical**: (0.5%) children and adults: apply to the affected area(s) on face twice or three times daily when required

» Topical corticosteroids are the standard of care treatment for stage 1 or 2 (overall grade I) skin only GVHD with <50% body surface area rash involvement.

» Hydrocortisone should be used on the face, whereas triamcinolone is reserved for use on the body.

» If the patient is asymptomatic or if the rash is stable, a period of observation without any interventional treatment may be appropriate.^[92]

plus calcineurin inhibitor

Treatment recommended for ALL patients in selected patient group

Primary options

» **tacrolimus**: children and adults: consult specialist for guidance on dose

OR

» **ciclosporin**: children and adults: consult specialist for guidance on dose

» Patients continue on calcineurin therapy during the treatment of acute GVHD, usually at the same dose as the prophylactic regimen.^[92]

» If a patient has already been tapered off their prophylactic calcineurin inhibitor or it has been discontinued due to toxicities, then it is generally reintroduced (depending on physician discretion and the degree of toxicity).

» Doses should be tapered according to response and serum drug levels. These drugs are usually given for a period of several weeks, depending on the institutional protocol and patient response.

Acute

acute: grade II-IV

1st systemic corticosteroid

Primary options

» **methylprednisolone**: children and adults: 0.5 to 2 mg/kg/day intravenously
Lower doses (e.g., 0.5 to 1 mg/kg/day) are recommended for upper gastrointestinal involvement only. Higher doses (e.g., 1-2 mg/kg/day) are recommended for lower gastrointestinal/skin/liver involvement.[92]

» Systemic corticosteroids are initiated for severe and/or symptomatic skin GVHD and/or any visceral GVHD involvement (grade II-IV).[63] [92] [105][106] Methylprednisolone is the standard initial treatment.

» Depending on the clinical status of the patient, methylprednisolone may be administered intravenously or orally. If a patient is started on the intravenous route, they will generally be transitioned to oral therapy as soon as possible.

» There are no standard corticosteroid tapering schedules. Generally, taper schedules are influenced by the patient's clinical response as well as circumstances (e.g., risk for relapse, presence or absence of infection, or other corticosteroid-related complications). A commonly reported taper schedule is over 8-12 weeks.

plus calcineurin inhibitor

Treatment recommended for ALL patients in selected patient group

Primary options

» **tacrolimus**: children and adults: consult specialist for guidance on dose

OR

» **ciclosporin**: children and adults: consult specialist for guidance on dose

» Patients continue on calcineurin therapy during the treatment of acute GVHD; this should be at the therapeutic dose rather than the prophylactic dose.[92]

» If a patient has already been tapered off their prophylactic calcineurin inhibitor or it has been discontinued due to toxicities, then it is

Acute

generally reintroduced (depending on discretion of physician and the degree of toxicity).

» Doses should be tapered according to clinical response and serum drug levels. These drugs are usually given for a period of several weeks, depending on the institutional protocol and patient response.

adjunct topical or oral-topical corticosteroid

Treatment recommended for SOME patients in selected patient group

Primary options

» **triamcinolone topical**: (0.1%) children and adults: apply to the affected area(s) on body twice or three times daily when required

OR

» **hydrocortisone topical**: (0.5%) children and adults: apply to the affected area(s) on face twice or three times daily when required

OR

» **budesonide**: children: consult specialist for guidance on dose; adults: 9 mg orally once daily

OR

» **beclometasone dipropionate**: adults: 5 mg orally once daily in the morning

» Adjuvant topical corticosteroids are used if there is any skin involvement present. Hydrocortisone should be used on the face, whereas triamcinolone is reserved for use on the body.

» Topically active corticosteroids taken orally (oral-topical corticosteroids) may be used for confirmed cases of acute gastrointestinal GVHD.^{[108] [109]} The systemic corticosteroid can be tapered in patients who show a clinical response.

» Oral-topical corticosteroid formulations have high first-pass metabolism, facilitating local effects while reducing systemic absorption. However, some systemic effects do still occur.

■ **lack of response or disease progression or corticosteroid toxicity**

adjunct alternative or additional immunosuppressive agent ± trial entry

Acute

Treatment recommended for SOME patients in selected patient group

Primary options

» **ruxolitinib**: children ≥ 12 years and adults: 5 mg orally twice daily initially, may increase to 10 mg twice daily after 3 days depending on blood counts

May be approved for use in children < 12 years in some countries.

OR

» **antithymocyte immunoglobulin (rabbit)**: children and adults: consult specialist for guidance on dose

OR

» **lymphocyte immunoglobulin, anti-thymocyte globulin (equine)**: children and adults: consult specialist for guidance on dose

OR

» **sirolimus**: children and adults: consult specialist for guidance on dose

OR

» **etanercept**: children and adults: consult specialist for guidance on dose

OR

» **pentostatin**: children and adults: consult specialist for guidance on dose

OR

» **alemtuzumab**: children and adults: consult specialist for guidance on dose

» If there is disease progression or lack of response following 3-7 days treatment, additional immunosuppressive therapy is required.^[92] Further immunosuppression will, however, increase the risk of life-threatening infections (due to immunosuppression and lymphopenia) and/or multi-organ dysfunction.

» There is no standard approach for the treatment of corticosteroid-refractory acute GVHD.^[106] A variety of agents have been

Acute

used, and varying response rates have been reported.^[110] Entry into a clinical trial may be appropriate.^[92]

» Alternative immunosuppressive agents should also be considered if a patient develops an unacceptable level of toxicity (i.e., corticosteroid intolerance).^[92] ^[106]

» Agents that may be considered for additional immunosuppressive therapy include: ruxolitinib, antithymocyte immunoglobulin (ATG), sirolimus, etanercept, alemtuzumab, and pentostatin.^[111] ^[114] ^[115] ^[116] ^[117] ^[118] ^[119] ^[120] ^[121] ^[122] ^[123] ^[124] ^[146]

» Extracorporeal photopheresis is being increasingly used as an adjunct treatment to minimise corticosteroid exposure and allow for more rapid corticosteroid tapers.^[125] It involves peripheral blood mononuclear cells being exposed to photoactivated methoxsalen and ultraviolet-A radiation.

Ongoing

chronic

1st **systemic corticosteroid****Primary options**

» **methylprednisolone**: children and adults: consult specialist for guidance on dose; initial dose may vary depending on organs involved and disease severity

» The recommended first-line therapy for patients with chronic GVHD is a systemic corticosteroid.[92]

» National Institutes of Health (NIH) guidelines recommend systemic corticosteroid therapy if three or more organs are involved, or a single organ with a severity score of more than 2.[1] However, close serial monitoring of all organ systems is recommended to promote early detection and intervention directed toward reversing or preventing progression of chronic GVHD manifestations and treatment-associated toxicities.

» Ancillary and supportive care therapies are employed in addition to systemic GVHD treatment, and in some cases, their use may circumvent the need for systemic treatment or allow doses of systemic agents to be decreased.

plus antibacterial prophylaxis

Treatment recommended for ALL patients in selected patient group

Primary options

» **phenoxymethylpenicillin**: children <5 years of age: 125 mg orally twice daily; children ≥5 years of age: 250 mg orally twice daily; adults: 250-750 mg orally twice daily

OR

» **azithromycin**: adults: 250 mg orally once daily or three times weekly

OR

» **trimethoprim/sulfamethoxazole**: children >2 months of age: 2 mg/kg orally once daily; adults: 160/800 mg orally once daily
Paediatric dose refers to trimethoprim component.

Ongoing

» Requires coverage against encapsulated bacteria, in particular *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides*.

» Phenoxyethylpenicillin is the prophylactic agent of choice when the frequency of penicillin-resistant *S pneumoniae* is low. Alternatives include azithromycin (particularly for lung involvement) or other macrolides, and newer-generation fluoroquinolones, although drug interactions can cause problems.^[92] Daily use of trimethoprim/sulfamethoxazole has also been used for this indication, but its efficacy has not been demonstrated.

» Antibiotic prophylaxis before dental and other invasive procedures in these patients has not been studied and consensus has not been reached.

plus

Pneumocystis prophylaxis

Treatment recommended for ALL patients in selected patient group

Primary options

» **trimethoprim/sulfamethoxazole**: children >2 months of age: 150 mg/square metre of body surface area orally three times weekly, daily dose given in divided doses every 12 hours; adults: 160/800 mg orally once daily or three times weekly

OR

» **dapsone**: children >1 month of age: 2 mg/kg/day orally, maximum 100 mg/day; adults: 100 mg orally once daily

OR

» **pentamidine inhaled**: children >4 years of age and adults: 300 mg inhaled every 4 weeks

OR

» **atovaquone**: children >13 years of age and adults: 1500 mg orally once daily

» *Pneumocystis pneumonia* <6 months after allogeneic haematopoietic cell transplantation (HCT) is strongly associated with chronic GVHD. All patients who receive immunosuppression after allogeneic HCT should receive *Pneumocystis* prophylaxis.

Ongoing

» It is unknown how long prophylaxis should be continued after stopping immunosuppression and practices vary widely across centres.

» Agents used include trimethoprim/sulfamethoxazole, pentamidine, dapsone, and atovaquone. Trimethoprim/sulfamethoxazole also provides prophylaxis against toxoplasmosis and nocardia.

plus vaccinations

Treatment recommended for ALL patients in selected patient group

» Most experts advocate the use of *Haemophilus influenzae* type b vaccine and influenza vaccine (not live-attenuated).

» No live virus, including the live-attenuated influenza vaccine and MMR, should be given.

» Household contacts should not be given oral polio vaccine.

» Other vaccines that may be considered include diphtheria tetanus toxoid, pneumococcus, and hepatitis B, hepatitis A, meningococcal and human papillomavirus (HPV).

plus nutritional support

Treatment recommended for ALL patients in selected patient group

» In patients with extensive chronic GVHD, weight loss may result from increased action of glucagon and noradrenaline (norepinephrine), which causes an increase in resting energy expenditure and alteration in fat and carbohydrate oxidation rates.

» More than 40% of patients with GVHD are malnourished, so nutritional advice and support is extremely important.

adjunct alternative or additional immunosuppressive agent

Treatment recommended for SOME patients in selected patient group

Primary options

» **ruxolitinib**: children ≥ 12 years of age and adults: 10 mg orally twice daily
May be approved for use in children < 12 years in some countries.

OR

Ongoing

» **ibrutinib**: children <12 years of age: 240 mg/square metre of body surface orally once daily, maximum 420 mg/dose; children ≥12 years of age and adults: 420 mg orally once daily

OR

» **belumosudil**: children ≥12 years of age and adults: 200 mg orally once daily

OR

» **axatilimab**: children and adults ≥40 kg body weight: 0.3 mg/kg intravenously every 2 weeks, maximum 35 mg/dose

OR

» **tacrolimus**: children and adults: consult specialist for guidance on dose

OR

» **ciclosporin**: children and adults: consult specialist for guidance on dose

OR

» **rituximab**: children and adults: consult specialist for guidance on dose

OR

» **sirolimus**: children and adults: consult specialist for guidance on dose

OR

» **pentostatin**: children and adults: consult specialist for guidance on dose

» Alternative immunosuppressive agents should be considered if a patient develops an unacceptable level of toxicity (i.e., corticosteroid intolerance).[92] If there is an inadequate response to initial therapy with a systemic corticosteroid, additional immunosuppression may be required.[92]

» Therapeutic choice is informed by agents used for prophylaxis and/or treatment of acute GVHD, specific patient characteristics, and preference of the treating physician and centre.

Ongoing

» The NIH working group define failure of initial immunosuppressive therapy or requirement of secondary therapy as follows: progression of chronic GVHD despite optimal first-line therapy; or no improvement after 4-8 weeks of sustained therapy; or inability to taper corticosteroid dosage.[1] [129]

» Immunosuppressive therapies used in chronic GVHD vary by institutional practice and may include ruxolitinib, ibrutinib, belumosudil, axatilimab, a calcineurin inhibitor (cyclosporin or tacrolimus), rituximab, sirolimus, and pentostatin.[130] [131] [132] [135] [136][137] [138] [139] [140]

» Ibrutinib is associated with an increased risk for serious cardiac events including arrhythmias and heart failure. Recommended risk minimisation measures include performing a clinical evaluation of cardiac history and function prior to starting treatment, careful monitoring for signs of cardiac deterioration during treatment, and treatment interruption and/or dose modification if any new-onset or worsening cardiac events are observed.[133] [134]

» Extracorporeal photopheresis is being increasingly used as an adjunct treatment to minimise corticosteroid exposure and allow for more rapid corticosteroid tapers.[125] It involves peripheral blood mononuclear cells being exposed to photoactivated methoxsalen and ultraviolet-A radiation.

adjunct antiviral prophylaxis

Treatment recommended for SOME patients in selected patient group

Primary options

» **aciclovir**: children and adults: consult specialist for guidance on dose

OR

» **valaciclovir**: children and adults: consult specialist for guidance on dose

Secondary options

» **ganciclovir**: children: consult specialist for guidance on dose; adults: 5 mg/kg intravenously twice daily or 1000 mg orally three times daily

OR

Ongoing

» **foscarnet**: children and adults: 90 mg/kg intravenously once daily

» Approximately, 30% to 60% of patients develop an episode of zoster during the first year after discontinuing post-transplant prophylaxis. Some experts use long-term antiviral prophylaxis to prevent recurrent herpes simplex virus (HSV) and varicella zoster virus (VZV) infection among allogeneic haematopoietic cell transplantation (HCT) recipients with severe, long-term immunodeficiency, but current evidence does not support routine administration of antiviral prophylaxis for HSV in patients with chronic GVHD. If VZV-seronegative patients with chronic GVHD are exposed to varicella (primary or post-vaccination illness), VZV immunoglobulin should be given within 96 hours.

» Cytomegalovirus (CMV) disease after day 100 has become more common. The best strategy to monitor and treat CMV after day 100 has not been defined. Patients with active GVHD, a history of CMV reactivation during the first 3 months, and lymphopenia are at higher risk of CMV reactivation and death. Some centres continue to monitor for CMV infection after day 100 by pp65 anti-genaemia or PCR tests, followed by pre-emptive therapy, based on the individual risk as determined by donor and recipient serology, as follows:

» 1) CMV seronegative (donor and recipient): No prophylaxis, no anti-genaemia (or PCR) checks.

» 2) CMV seropositive (donor or recipient): No history of CMV infection: CMV surveillance testing (anti-genaemia or PCR) every 1 to 4 weeks.

» 3) History of CMV infection or disease: Weekly CMV surveillance testing (anti-genaemia or PCR) and pre-emptive treatment as during the first 100 days.

» Some investigators have advocated early empirical treatment of influenza with neuraminidase inhibitors during influenza outbreaks by using prediction rules based on symptoms and signs, although there is no evidence to support this practice.

» A randomised trial of pre-emptive therapy for the prevention of CMV disease after allogeneic HCT suggests that low-dose ganciclovir can be as effective as standard-dose ganciclovir in

Ongoing

adjunct

these patients.^[147] However, further studies are needed to validate these findings.

antifungal therapy

Treatment recommended for SOME patients in selected patient group

Primary options

» **fluconazole**: children: 3-12 mg/kg orally/intravenously once daily; adults: 100 mg orally/intravenously once daily

OR

» **voriconazole**: children and adults: consult specialist for guidance on dose

OR

» **micafungin**: children: consult specialist for guidance on dose; adults: 50 mg intravenously once daily

» Invasive mould infections are a significant concern in patients who receive immunosuppressives for GVHD.^{[148] [149]}

» There is no evidence to support the use of antifungal prophylaxis >75 days after allogeneic haematopoietic cell transplantation (HCT).

» Some centres prescribe prophylactic antifungals for patients with chronic GVHD, but this approach remains investigational.

adjunct

intravenous immunoglobulin

Treatment recommended for SOME patients in selected patient group

Primary options

» **normal immunoglobulin human**: children and adults: consult specialist for guidance on dose

» Universal administration of intravenous immunoglobulin (IVIG) after allogeneic haematopoietic cell transplantation (HCT) has not been shown to confer clinical benefit and should be avoided.

» In patients with hypogammaglobulinaemia caused by other disorders, administration of IVIG to maintain IgG levels >400 mg/dL has been associated with a decreased incidence of severe bacterial infections.

Ongoing

■ intact skin involvement

adjunct

» IVIG may be considered for patients >90 days after HCT who have recurrent sinopulmonary infections and serum IgG levels <400 mg/dL.

» Some experts recommend monitoring IgG levels and administering IVIG routinely in chronic GVHD, but there are no data demonstrating that this approach improves outcomes.

» Treatment course depends on serum IgG levels.

trial entry

Treatment recommended for SOME patients in selected patient group

» Patients should be considered for enrollment in a clinical trial where available.^[92]

adjunct

emollient

Treatment recommended for SOME patients in selected patient group

» Regular lubrication of dry but intact skin with emollients may decrease pruritus and maintain skin.

adjunct

topical corticosteroid

Treatment recommended for SOME patients in selected patient group

Primary options

» **desonide topical**: (0.05%) children and adults: apply to the affected area(s) twice daily when required

OR

» **hydrocortisone topical**: (0.5%) children and adults: apply to the affected area(s) twice daily when required

OR

» **triamcinolone topical**: (0.1%) children and adults: apply to the affected area(s) twice daily when required

Secondary options

» **fluocinonide topical**: (0.05%) children and adults: apply to the affected area(s) twice daily when required

Tertiary options

Ongoing

» **clobetasol topical**: (0.05%) children and adults: apply to the affected area(s) twice daily when required, maximum 14 days use

» For lesions from the neck down, treatment should begin with low- or mid-strength formulation (e.g., desonide, hydrocortisone, triamcinolone). In unresponsive cases, short-term occlusion of mid-strength corticosteroids with damp towels (wet wraps) increases skin hydration and drug penetration. When this is impractical, higher potency corticosteroids such as fluocinonide may be helpful. The most potent topical corticosteroids (e.g., clobetasol) should not be used under occlusion. The use of wet wraps and mid-strength potency corticosteroids should be limited to 14 consecutive days, if possible.

» On the face, axillae and groin, lower-potency corticosteroids (hydrocortisone and desonide) are preferable for long-term use. Emollients may be applied after application, and being occlusive may increase the potency of the corticosteroid.

adjunct antipruritic

Treatment recommended for SOME patients in selected patient group

Primary options

» **hydrocortisone/pramocaine topical**: children and adults: apply to the affected area(s) three to four times daily when required

Secondary options

» **diphenhydramine**: children 2-5 years of age: 6.25 mg orally every 4-6 hours when required, maximum 37.5 mg/day; children 6-11 years of age: 12.5 to 25 mg orally every 4-6 hours when required, maximum 150 mg/day; children >11 years of age and adults: 25-50 mg orally every 4-6 hours when required, maximum 300 mg/day

OR

» **hydroxyzine**: children ≤40 kg: 2 mg/kg/day orally given in divided doses every 6-8 hours when required; children >40 kg and adults: 25 mg orally every 6-8 hours when required, maximum 100 mg/day

OR

Ongoing

» **doxepin**: children: consult specialist for guidance on dose; adults: 10-25 mg orally once daily at bedtime when required

» Pruritus related to GVHD generally responds to immunosuppressive therapy; however, other adjuvant treatments may be useful.

adjunct topical calcineurin inhibitor

Treatment recommended for SOME patients in selected patient group

Primary options

» **tacrolimus topical**: (0.03%) children >2 years of age and adults: apply to the affected area(s) twice daily; (0.1%) adults: apply to the affected area(s) twice daily

OR

» **pimecrolimus topical**: (1%) children >2 years of age and adults: apply to the affected area(s) twice daily

» Reported to improve erythema and pruritus in some patients.

adjunct PUVA

Treatment recommended for SOME patients in selected patient group

» Can be effective, especially if sclerosis is not present. Phototherapy may be administered 2 to 3 times per week. A history of skin cancer, aphakia, or photosensitivity would normally contraindicate this therapy due to the increased risk of skin cancer.

adjunct topical bleaching agent

Treatment recommended for SOME patients in selected patient group

Primary options

» **hydroquinone topical**: (4%) children >12 years of age and adults: apply to the affected area(s) twice daily

OR

» **tretinoin topical**: (0.025 to 0.05%) children >12 years of age and adults: apply to the affected area(s) once daily at bedtime

» May be used to treat post-inflammatory hyperpigmentation in the setting of inactive disease.

Ongoing

■ non-intact skin involvement

adjunct **specialist wound dressings**

Treatment recommended for SOME patients in selected patient group

» On denuded skin, specialist dressings and protective films can be used to maintain a moist environment that enhances repair of the epithelium, lysis of necrotic tissue, and phagocytosis of necrotic debris.

adjunct **topical antimicrobial**

Treatment recommended for SOME patients in selected patient group

Primary options

» **mupirocin topical**: (2%) apply to the affected area(s) three times daily

» If indicated, topical antimicrobials such as mupirocin may be useful.

adjunct **specialist skin therapies**

Treatment recommended for SOME patients in selected patient group

» Difficult wounds are best treated in consultation with a plastic surgeon.

» Slow-healing wounds may be treated with hyaluronic acid products, collagen products, or fibroblast and keratinocyte products.

» Non-healing wounds that involve the dermis may benefit from platelet-derived growth factor products.

adjunct **hyperbaric oxygen therapy**

Treatment recommended for SOME patients in selected patient group

» This specialist treatment has been used to treat hypoxic wounds, but may not be widely available.

■ mucosal involvement of mouth or oral cavity

adjunct **topical corticosteroid or tacrolimus**

Treatment recommended for SOME patients in selected patient group

Primary options

» **triamcinolone acetonide topical**: (0.1% oral paste) apply to the affected area(s) two to three times daily

OR

Ongoing

» **fluocinonide topical**: (0.05% gel) children and adults: apply to the affected area(s) two to three times daily

OR

» **clobetasol topical**: (0.05% gel) children and adults: apply to the affected area(s) two to three times daily

OR

» **betamethasone dipropionate topical**: (0.05% gel) children and adults: apply to the affected area(s) two to three times daily

OR

» **tacrolimus topical**: (0.03%) children >2 years of age and adults: apply to the affected area(s) twice daily; (0.1%) adults: apply to the affected area(s) twice daily

» There are three possible components to this type of disease: mucosal involvement, salivary gland involvement, and sclerotic involvement of mouth and surrounding tissues. Before initiating treatment, infection with HSV, HPV, *Candida* need to be ruled out. This may require use of viral and bacterial cultures, and/or biopsies.

» Persistent or new oral lesions occurring >3 years after allogeneic haematopoietic cell transplantation (HCT) need assessment for secondary cancer (especially squamous cell cancer).

» Mainstay of therapy of localised and symptomatic disease is high-potency topical corticosteroid gel used orally. Tacrolimus ointment is an alternative.

» Vaseline-based ointments such as topical tacrolimus are generally less effective in the mouth than are alcohol-based corticosteroid gels but are preferable for the treatment of chapped lips caused by GVHD, because high-potency corticosteroids cause irreversible atrophy when applied to the vermilion border of the lips.

» Prolonged use of high-potency corticosteroids should be avoided in the very young child because of the potential for greater systemic effects.

Ongoing

adjunct

» Affected area(s) must be dried before treatment is applied, and no food or drink should be consumed for 30 minutes after application.

mouth rinse

Treatment recommended for SOME patients in selected patient group

» Mouth rinses may be used when there is more extensive involvement of the entire oral cavity.

» Corticosteroid rinses are a good first-line option. Oral manifestations in children generally respond well to dexamethasone rinses. Prolonged use of high-potency corticosteroids should be avoided in the very young child because of the potential for greater systemic effects.

» Ciclosporin or azathioprine rinses may be useful in cases refractory to corticosteroids rinses.

» These solutions are held and swished in the mouth for 4 to 6 minutes and then spat out. This is repeated 4 to 6 times daily. Food or drink should not be consumed for 30 minutes after.

» Mouth washes may need to be compounded by the pharmacy department if the drug is not available in a proprietary liquid formulation.

adjunct

topical analgesia

Treatment recommended for SOME patients in selected patient group

Primary options

» **lidocaine topical**: (2% viscous solution) 15 mL every 3 hours when required (swish around in mouth and spit out), maximum 8 doses/day

OR

» **aluminium hydroxide/magnesium hydroxide/simethicone**: 10-20 mL orally four times daily, maximum 500 mg/day of simethicone

» May be helpful when symptomatic mucosal GVHD impairs nutrition.

» A mixture of lidocaine with either kaolin/pectin or aluminium hydroxide/magnesium hydroxide/simethicone and diphenhydramine may be used as a mouthwash.

■ **salivary gland involvement**

adjunct

frequent water sipping + saliva substitute

Ongoing

Treatment recommended for SOME patients in selected patient group

» This type of involvement usually manifests as dry mouth, mucocoeles, and variable oral sensitivity to hot, cold, spicy, and acidic food; mint flavours such as toothpaste; and carbonated drinks.

» Frequent sipping of water and use of sugar-free chewing gum may be sufficient.

» Oral moisturisers and saliva stimulants made be used if simple measures are inadequate.

adjunct saliva stimulant

Treatment recommended for SOME patients in selected patient group

Primary options

» **cevimeline**: children: consult specialist for guidance on dose; adults: 30 mg orally three times daily

OR

» **pilocarpine**: children: consult specialist for guidance on dose; adults: 5-10 mg orally three times daily

» In the absence of contraindications (e.g., glaucoma, heart disease, or asthma), treatment with cholinergic agonists may produce a significant increase in salivary secretion.

adjunct home fluoride therapy

Treatment recommended for SOME patients in selected patient group

» Even if there is not subjective oral dryness, mild salivary gland dysfunction can increase the risk of tooth decay, and topical fluorides should be offered as a decay prevention strategy.

■ sclerotic oral disease

adjunct systemic and intralesional corticosteroid

Treatment recommended for SOME patients in selected patient group

Primary options

» **methylprednisolone**: children and adults: 1-2 mg/kg/day intravenously

-and-

» **triamcinolone acetonide**: (40 mg/mL) children and adults: 0.3 to 0.4 mL intralesionally per square centimetre of lesion

Ongoing

■ eye involvement

» Topical therapy alone is insufficient to treat sclerosis of the perioral skin and surrounding tissues.

» In this situation, systemic treatment is required.

» Adjunctive intralesional corticosteroid injections may be helpful, but long-term therapy is often required to maintain the response.

adjunct stretching exercises

Treatment recommended for SOME patients in selected patient group

» Stretching exercises to increase range of motion of the mouth may be helpful in order to counteract the sclerotic disease.

adjunct artificial tears or tear stimulant

Treatment recommended for SOME patients in selected patient group

Primary options

» **carmellose ophthalmic**: 1-2 drops into the affected eye(s) when required

OR

» **hydroxypropylcellulose ophthalmic**: insert 5 mg pellet into affected eye(s) once or twice daily when required

Secondary options

» **cevimeline**: children: consult specialist for guidance on dose; adults: 30 mg orally three times daily

OR

» **pilocarpine**: children: consult specialist for guidance on dose; adults: 5-10 mg orally three times daily

» The use of preservative-free artificial tears reduces superficial punctate keratopathy, decreases ocular symptoms, and improves the quality of vision. Certain brands may be better tolerated than others, so patients should test different brands to identify the one that provides the most benefit. Thicker formulations may be recommended for patients who need frequent use of artificial tears; ointment may be recommended at bedtime.

Ongoing

» For patients who require application of artificial tears more than once every hour, pellets of hydroxypropylcellulose may be more convenient.

» Orally administered tear stimulants may be useful but drug interactions, toxicities, and contraindications (glaucoma, heart disease, and asthma) must be reviewed.

adjunct corticosteroid, ciclosporin, or autologous serum eye drops

Treatment recommended for SOME patients in selected patient group

Primary options

» **prednisolone ophthalmic**: (1%) children and adults: 1 drop in both eyes two to four times daily

OR

» **fluorometholone ophthalmic**: (0.1%) children >2 years of age and adults: 1 drop in both eyes two to four times daily

OR

» **loteprednol ophthalmic**: (0.5%) adults: 1-2 drops in both eyes four times daily

OR

» **ciclosporin ophthalmic**: (0.05%) adults: 1 drop in both eyes twice daily

» Used to reduce ocular surface inflammation and usually reserved for control of ocular GVHD exacerbations during tapering of systemic immunosuppression. Consult a specialist for guidance on the use of autologous serum eye drops.

» Treatment should be carefully supervised by an ophthalmologist.

adjunct evaporation control

Treatment recommended for SOME patients in selected patient group

» To decrease evaporation, patients should be encouraged to use warm compresses and lid care to maximise the output of the meibomian glands that produce the outer oil layer of tear film that protects against evaporation.

Ongoing

■ vulval and vaginal involvement

» Avoidance of low humidity environments and use of moisture chamber goggles may also decrease evaporation.

» Scleral contact lenses may be available in some centres and surgery (tarsorrhaphy) may be necessary in severe cases.

adjunct tear duct occlusion

Treatment recommended for SOME patients in selected patient group

» Temporary (silicone plugs) or permanent (thermal cautery) occlusion of the tear-duct punta may provide benefit in patients with severe sicca syndrome.

adjunct scleral contact lens

Treatment recommended for SOME patients in selected patient group

» Fluid-ventilated, gas permeable scleral contact lenses can be used to protect the corneal surface, reducing hyperosmolarity, dessication, and shear forces from the eyelids.

adjunct tarsorrhaphy

Treatment recommended for SOME patients in selected patient group

» In cases that cannot be managed adequately by medical means, tarsorrhaphy may have a useful role.

adjunct hygiene measures

Treatment recommended for SOME patients in selected patient group

» Reported in 3% of bone marrow recipients and 15% of peripheral blood recipients. Oestrogen deficiency and infections (HPV, HSV, yeast, bacteria, or other gynaecological pathogens) must be ruled out at initial diagnosis and periodically during management of this type of GVHD.

» Mechanical and chemical irritants should be avoided. Wash with water rather than soap or feminine wash products. Area should be air-dried and advice given on wiping from front to back. Small amounts of emollients or lanolin cream applied to the vulva (not vagina) may provide some relief from itching or irritation. Water-based vaginal lubricants may also be of benefit.

adjunct topical oestrogen with/without dilator

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» **oestrogens, conjugated vaginal:** (cream) apply 0.5 to 2 g once daily for 3 weeks then stop for 1 week, repeat cycle

OR

» **estradiol vaginal:** (intravaginal ring) 50-100 micrograms/day ring inserted and replaced every 3 months
Dose refers to estradiol acetate formulation.

OR

» **estradiol vaginal:** (intravaginal tablet) 25 micrograms inserted once daily for 2 weeks, then twice weekly thereafter

» If vulvovaginal symptoms are accompanied by low estradiol levels, topical oestrogen therapy with or without the use of a vaginal dilator should be initiated unless there are absolute contraindications such as increased risk of breast cancer or cardiovascular events.

adjunct

topical corticosteroid or calcineurin inhibitor

Treatment recommended for SOME patients in selected patient group

Primary options

» **clobetasol topical:** (0.05%) adults: apply sparingly to the affected area(s) up to twice daily; consult specialist for further guidance on dose

OR

» **betamethasone dipropionate topical:** (0.05%) adults: apply sparingly to the affected area(s) up to twice daily; consult specialist for further guidance on dose

Secondary options

» **tacrolimus topical:** (0.1%) adults: apply sparingly to the affected area(s) up to twice daily; consult specialist for further guidance on dose

» If the vulvovaginal region is the only clinical manifestation of chronic GVHD, topical immunosuppressive agents may constitute an

Ongoing

		adequate primary therapy for controlling mild manifestations.
		» High-potency corticosteroids are the mainstay of such therapy, although topical calcineurin inhibitors have also been used.
		» Patients should be advised to monitor for signs or symptoms of candidiasis, HSV, or HPV during treatment.
	adjunct	surgical lysis
		Treatment recommended for SOME patients in selected patient group
		» If there are extensive vaginal synechiae and complete obliteration of the vaginal canal, surgical lysis with or without vaginal reconstruction may be necessary.
■ gastrointestinal tract involvement: odynophagia and dysphagia	adjunct	oral lubricant
		Treatment recommended for SOME patients in selected patient group
		» Oral lubricants such as hydroxyethyl cellulose solutions can be considered.
	adjunct	oesophageal dilation
		Treatment recommended for SOME patients in selected patient group
		» If a patient has oesophageal webs or strictures confirmed by endoscopy, dilation may be of benefit though this should be done by an experienced gastroenterologist due to the risk of perforation.
■ gastrointestinal tract involvement: diarrhoea	adjunct	pancreatic enzyme supplementation
		Treatment recommended for SOME patients in selected patient group
		Primary options
		» pancreatin : children and adults: dose depends on brand, consult product literature for guidance on dose
		» If a patient has chronic diarrhoea symptoms, in certain cases, pancreatic enzyme supplementation may be beneficial. Its use is primarily physician- and institution-dependent.
■ liver involvement	adjunct	ursodeoxycholic acid
		Treatment recommended for SOME patients in selected patient group
		Primary options

Ongoing

■ lung involvement

» **ursodeoxycholic acid**: children: 10-15 mg/kg/day orally given in 3 divided doses; adults: 250-300 mg orally three to four times daily

» Use of ursodeoxycholic acid (ursodiol) can help improve biochemical abnormalities and pruritus in some patients with hepatic chronic GVHD.

adjunct inhaled bronchodilator

Treatment recommended for SOME patients in selected patient group

Primary options

» **salbutamol inhaled**: (100 micrograms/dose metered dose inhaler) children and adults: 1-2 puffs (100-200 micrograms) every 4-6 hours when required

OR

» **salbutamol inhaled**: (0.63 mg/3 mL or 1.25 mg/3 mL nebulisation solution) children 2-12 years of age: 0.63 to 1.25 mg nebulised every 4-6 hours when required; children >12 years of age and adults: 2.5 to 5 mg nebulised every 4-6 hours when required

» Can be used prior to and in conjunction with inhaled corticosteroids in cases of lung involvement.

adjunct inhaled corticosteroid

Treatment recommended for SOME patients in selected patient group

Primary options

» **beclometasone inhaled**: children 5-11 years of age: 40-80 micrograms twice daily; children ≥12 years of age and adults: 40-320 micrograms twice daily

OR

» **fluticasone propionate inhaled**: children 4-11 years of age: 50-100 micrograms twice daily; children ≥12 years of age and adults: 100-500 micrograms twice daily

» Used in addition to systemic corticosteroids in cases where CT scanning reveals lung involvement.^[92] Usually used after inhaled bronchodilators.

adjunct montelukast

Ongoing

Treatment recommended for SOME patients in selected patient group

Primary options

» **montelukast**: children 12 months to 5 years of age: 4 mg orally once daily; children 6-14 years of age: 5 mg orally once daily; children ≥15 years of age and adults: 10 mg orally once daily

» The leukotriene receptor antagonist (LTRA) montelukast may be added to antibiotic prophylaxis and inhaled corticosteroids to improve respiratory symptoms.[92]

» In 2020, the US Food and Drug Administration mandated a boxed warning for montelukast because of the risk of serious behaviour- and mood-related adverse effects.[150]

adjunct pulmonary rehabilitation

Treatment recommended for SOME patients in selected patient group

» A properly structured and supervised pulmonary rehabilitation programme may be of benefit in some patients.

adjunct supplementary oxygen

Treatment recommended for SOME patients in selected patient group

» If there is a need for supplemental oxygen (i.e., saturation of oxyhaemoglobin <87% while breathing room air) then the amount of supplementary oxygen should be titrated with the use of a 6-minute walk test conducted according to American Thoracic Society guidelines.[151]

adjunct lung transplantation

Treatment recommended for SOME patients in selected patient group

» Should be considered in appropriate candidates if there is progression or worsening of lung involvement following 2-3 lines of therapy.[92]

■ haematopoietic involvement: cytopenias

adjunct intravenous immunoglobulin

Treatment recommended for SOME patients in selected patient group

Primary options

» **normal immunoglobulin human**: children and adults: consult specialist for guidance on dose

Ongoing

» Cytopenia may result from stromal damage, graft failure, drug toxicity, infection, relapse of underlying disease, cytomegalovirus infection, haemolysis, anaemia of chronic disease, and autoimmune processes.

» Intravenous immunoglobulin may be effective in certain cytopenias that are not improved after corticosteroid treatment.

adjunct growth factor

Treatment recommended for SOME patients in selected patient group

Primary options

» **filgrastim**: children and adults: consult specialist for guidance on dose

OR

» **sargramostim**: children and adults: consult specialist for guidance on dose

» Growth factor use has not been formally evaluated in patients with chronic GHVD.

» Used as needed if patient's absolute neutrophil count falls below $0.5 \times 10^9/L$ (500/microlitre).

■ **neurological involvement** **adjunct antidepressant or anticonvulsant**

Treatment recommended for SOME patients in selected patient group

Primary options

» **amitriptyline**: children >5 years of age: 0.1 to 2 mg/kg orally once daily at bedtime; adults: 25-150 mg/day orally

OR

» **paroxetine**: children: consult specialist for guidance on dose; adults: 10-50 mg/day orally

OR

» **gabapentin**: children >12 years of age and adults: 300 mg orally once daily on day 1, followed by 300 mg twice daily on day 2, followed by 300 mg three times daily on day 3, then increase dose according to response, maximum 3600 mg/day

» Although rare, it can present as polyneuropathy, myositis, and myasthenia.

Ongoing

■ **musculoskeletal involvement: fasciitis or contractures**

» Interventions for painful peripheral neuropathies may include use of tricyclic antidepressants, selective serotonin-reuptake inhibitors (SSRIs), or anticonvulsants.

» Doses may need to be titrated up every 1 to 2 weeks until symptoms are adequately controlled.

adjunct opioid analgesics

Treatment recommended for SOME patients in selected patient group

» Opioid analgesics are poorly effective when used alone, but may provide some relief and can be an important adjunctive treatment when used in combination with antidepressants or anticonvulsants.

» Local protocols should be followed for opioid selection and administration.

adjunct physical and occupational therapy

Treatment recommended for SOME patients in selected patient group

» Appropriate for all patients who have a decreased ability to perform activities of daily living or impaired quality of life because of pain or muscle weakness.

» Physiotherapy evaluation may be needed every 1 to 3 months.

adjunct physical and occupational therapy

Treatment recommended for SOME patients in selected patient group

» Joint contractures, limb swelling, and muscle weakness and atrophy are often seen in chronic GVHD.

» Physiotherapy incorporates comprehensive neuromuscular examination, testing strength, range of movement in affected joints, limb girth, mobility, stamina, and activities of daily living.

» Physical and occupational therapies are then directed at improving these parameters via an outpatient and home-based programme of exercises, stretches, and activities.

adjunct surgical release

Treatment recommended for SOME patients in selected patient group

» If contractures are severe and unresponsive to physiotherapy, consideration can be given to surgical intervention to improve range of movement.

Ongoing

■ **musculoskeletal involvement: osteopenia and osteoporosis**

adjunct

osteoporosis therapy

Treatment recommended for SOME patients in selected patient group

Primary options

» **calcium carbonate**: adults: 1000-1500 mg/day orally
Dose expressed as elemental calcium.

-and-

» **ergocalciferol**: adults: 400-800 units orally once daily

-and-

» **alendronic acid**: adults (prevention): 5 mg orally once daily, or 35 mg orally once weekly; adults (treatment): 10 mg orally once daily, or 70 mg orally once weekly

Secondary options

» **calcium carbonate**: adults: 1000-1500 mg/day orally
Dose expressed as elemental calcium.

-and-

» **ergocalciferol**: adults: 400-800 units orally once daily

-and-

» **raloxifene**: adults: 60 mg orally once daily

» When bone mineral density testing indicates osteopenia or osteoporosis, management consists of calcium and vitamin D (as ergocalciferol) supplementation and anti-resorptive therapy. Calcium and vitamin D replacement is justified in deficient states or when patients are post-menopausal or at high risk of developing deficiency, but is not adequate alone in patients with osteoporosis.

» If corticosteroid therapy is expected to last >3 months, bone mineral density (BMD) should be measured and antiresorptive therapy started regardless of the results. Preferred agents include hormonal replacement or bisphosphonates. Raloxifene is a secondary option.

Emerging

Itacitinib

A selective Janus kinase-1 (JAK-1) inhibitor. One phase 3 trial of patients with grades II to IV acute GVHD failed to demonstrate a significant difference in overall response rate between itacitinib plus systemic corticosteroids versus placebo (standard treatment with systemic corticosteroids only).^[152]

Vorinostat

A histone deacetylase (HDAC) inhibitor, vorinostat has been studied in combination with tacrolimus and methotrexate for the prevention of GVHD in patients undergoing HCT.^{[153] [154]} A phase 1/2 multicentre trial of vorinostat for GVHD prevention in children, adolescents, and young adults undergoing allogeneic blood and marrow transplantation is recruiting.^[155]

Corticosteroid prophylaxis

One randomised open-label trial found that low-dose corticosteroid prophylaxis effectively reduced acute GVHD in high-risk patients (based on bone marrow allogeneic graft CD4:CD8 ratio).^[156] More evidence is required on the role of corticosteroids for GVHD prophylaxis.

Basiliximab

A chimeric murine/human monoclonal antibody specific for the alpha subunit (CD 25) interleukin-2-alpha receptor.^[157] Basiliximab, in conjunction with a corticosteroid, may be considered as an alternative to ruxolitinib for corticosteroid-refractory GVHD.^{[92] [157]} The role of basiliximab in the management of GVHD continues to be explored.^{[158] [159][160]} Further studies are required.

Itolizumab

Itolizumab, a monoclonal antibody that selectively targets CD6, is under investigation as a first-line treatment for acute GVHD in combination with corticosteroids.^{[161] [162]} It has been granted orphan drug designation by the European Medicines Agency (EMA) and fast track designation by the US Food and Drug Administration (FDA).

Remestemcel-L

The European Medicines Agency (EMA) has granted orphan drug designation to the mesenchymal stem cell (MSC) product remestemcel-L for acute GVHD. Remestemcel-L is currently approved in Canada and New Zealand for the management of acute GVHD in children and is available for adults and children in eight countries including the US, under an Expanded Access Program. It has also been granted approval by the FDA for use in children with corticosteroid-refractory acute GVHD.

BPX-501

BPX-501, a T-cell therapy using donor-derived T cells transduced with an iC9 suicide gene, attempts to improve upon the delayed recovery of adaptive T-cell immunity that occurs post HCT. Clinical studies are ongoing.^{[163] [164]} The FDA has granted orphan drug designation to BPX-501 for the treatment of immunodeficiency and GVHD following stem cell transplant.

LP-310

A proprietary liposomal tacrolimus oral rinse formulation, LP-310 has received orphan drug designation by the FDA for the treatment of oral GVHD.

Primary prevention

Prolonged use of immunosuppressive drugs has not been shown to prevent chronic to prevent acute graft-versus-host disease (GVHD).[61] There is currently no effective prophylaxis for chronic GVHD. Nonetheless, early intervention guided by a multidisciplinary approach to treatment, including appropriate immunosuppressive drugs medications and aggressive supportive care, is critical in the management of chronic GVHD.

Prophylaxis is the primary strategy to prevent acute GVHD.[62] [63]

The most commonly used drug combination for acute GVHD prophylaxis includes a calcineurin inhibitor (ciclosporin or tacrolimus, which act to block T-cell activation) and low-dose methotrexate or mycophenolate.[64] [65]

Evidence continues to influence the management of GVHD prophylaxis, and alternative prophylactic treatment strategies may be considered for specific patient populations.

Abatacept

A selective T-cell costimulation modulator, abatacept is approved by the US Food and Drug Administration (FDA), in combination with a calcineurin inhibitor and methotrexate, for the prevention of acute GVHD in patients undergoing allogeneic haematopoietic cell transplantation (HCT) from a matched or 1 allele-mismatched unrelated donor.

In one phase 2 randomised trial, the addition of abatacept to standard prophylaxis with a calcineurin inhibitor and methotrexate numerically reduced rates of severe (grade III or IV) acute GVHD (6.8% vs. 14.8%), and significantly improved severe acute GVHD-free survival (93.2% vs. 82%), in patients with haematological malignancies who had undergone HCT from an HLA-matched (8/8) unrelated donor.[66]

Post-transplant cyclophosphamide (combined with standard prophylaxis of tacrolimus plus mycophenolate)

Increasingly favoured for primary GVHD prevention based on results from large-scale, multi-site clinical trials.[63] [67][68] In one phase 3 trial of patients undergoing allogeneic HLA-matched HCT with reduced-intensity conditioning, GVHD-free, relapse-free survival at 1 year was significantly more common in patients randomised to cyclophosphamide-based prophylaxis (cyclophosphamide, tacrolimus, and mycophenolate) than those assigned to standard prophylaxis (52.7% vs. 34.9%).[67] Post-transplant cyclophosphamide-based prophylaxis is commonly used in patients who have undergone allogeneic HCT from an HLA-haploidentical (i.e., half-matched) donor or unrelated donor.[69] [70]

Rabbit antithymocyte immunoglobulin

A polyclonal immunoglobulin G, rabbit antithymocyte immunoglobulin reduces the cumulative incidence of both acute and chronic GVHD in patients undergoing HCT from unrelated donors. In one randomised phase 3 trial, the addition of rabbit antithymocyte immunoglobulin to standard prophylaxis (ciclosporin or tacrolimus plus methotrexate or mycophenolate) reduced acute GVHD incidence at 30 and 100 days compared with standard prophylaxis (30 days: 22% vs. 37%; 100 days: 50% vs. 65%).[71] At 24 months, this regimen reduced incidence of chronic GVHD (26.3% vs. 41.3%), and lead to improved survival (70.6% vs. 53.3%) and reduced use of immunosuppressive therapy.[72] Rabbit antithymocyte immunoglobulin effectively reduces GVHD incidence after HLA-matched sibling donor HCT.[73]

Sirolimus combined with standard prophylaxis (ciclosporin plus mycophenolate)

Lowers the incidence of grade II to IV acute GVHD (at day 100) compared with ciclosporin plus mycophenolate alone in patients who have undergone allogeneic HCT from an HLA-matched unrelated donor with non-myeloablative conditioning.[74]

Tacrolimus plus sirolimus

Suggested as an alternative regimen to standard GVHD prophylaxis.[75] [76] [77] [78] Incidence of acute GVHD (by day +114) is similar between tacrolimus plus sirolimus and tacrolimus plus methotrexate in patients who have undergone allogeneic HCT from a matched related donor.[78]

Secondary prevention

A critical component in the management of GVHD is its early recognition and prompt, effective intervention that may ultimately prevent the progression to severe disease.[79]

Routine monitoring and open communication between the patient and physician guide the duration and intensity of immunosuppressive drugs. Preventive actions include infection prophylaxis (antibacterial, viral, and fungal), vaccinations, general hygiene, and involvement of necessary consultants (dental, ophthalmology, gynecology, physiotherapy, psychosocial therapy).

Recommendations regarding screening and preventive practices for long-term survivors after haematopoietic cell transplantation are available.[80] [172] [174] [Children's Oncology Services] (<http://www.onestepcamp.org>) [National Marrow Donor Program] (<http://www.marrow.org>) [European Society for Blood and Marrow Transplantation] (<http://www.ebmt.org>) [Center for International Blood and Marrow Transplant Research] (<http://www.cibmtr.org>) [American Society for Transplantation and Cellular Therapy] (<https://www.astct.org>)

Patient discussions

Patients and carer should be educated regarding relevant signs and symptoms of acute and chronic GVHD, as well as any evidence of progressive disease, and to notify their physician and treating team urgently in such cases.

Adherence to routine follow-up and treatment recommendations, including drugs, nutritional support, and physiotherapy, is critical.

Monitoring

Monitoring

Because treatment of graft-versus-host disease (GVHD) involves the use of aggressive, multimodal, immunosuppressive regimens that can quickly lead to potentially life-threatening complications, close monitoring is essential to allow early recognition and intervention, and to optimise the overall care delivered to patients.

The frequency of monitoring and follow-up in the outpatient setting can range between once weekly to daily. Diagnosis of GVHD is based on clinical manifestations; therefore, follow-up should include regular and repeated physical examination, covering all relevant organ systems, and interval history.

Recommendations regarding monitoring, and ancillary and supportive therapies, have been published.[\[80\]](#) [\[82\]](#) [\[172\]](#)[\[173\]](#)

The NIH recommends that all organ systems potentially affected by chronic GVHD or its treatment should be monitored serially in individuals at risk at least annually for 5 years after haematopoietic cell transplantation (HCT).[\[172\]](#) Scope and frequency of monitoring should be individualised as clinically indicated, with more frequent monitoring strongly advised for those with active GVHD, especially during high-risk periods (e.g., treatment taper or escalation), and for those who are participating in clinical trials.[\[172\]](#)

Specific NIH recommendations include:[\[172\]](#)

- Interval history with symptom assessment (including psychosocial symptoms) and a drug medication review (minimal every 3 months)
- Physical examination (minimal every 3 months)
 - Weight (adults: every 3 months; children: every 1-3 months)
 - Height (adults: every 12 months; children and adolescents: every 3-6 months)
 - Nutritional assessment (adults: every 3-6 months; children: every 1-6 months)
 - Tanner staging sexual maturity score (children and adolescents: every 6-12 months)
 - Developmental assessment (children and adolescents: every 3-6 months)
- Laboratory monitoring
 - Full blood cell counts with differential (every 3 months)
 - Chemistry panel including renal and liver function tests (every 3 months)
 - Therapeutic drug monitoring (every 3 months)
 - IgG level (every 1-3 months until normal and independent of replacement)
 - Lipid profile (every 6 months during treatment with corticosteroids or sirolimus)
 - Iron indices (every 6-12 months if red blood cell transfusions are required or if iron overload has been documented previously)
 - Pulmonary function tests (every 3-6 months)
 - Endocrine function evaluation, for example, thyroid function tests, bone densitometry, calcium levels, 25-OH vitamin D (every 12 months).
- Subspecialty evaluations
 - Ophthalmology (every 3-12 months)
 - Dental evaluation and oral cancer surveillance with comprehensive soft and hard tissue examination (radiographs as indicated), culture, biopsy, or photographs of lesions (as clinically indicated), and professional dental hygiene (every 6 months)

- Dermatology with assessment of extent and type of skin involvement, biopsy, or photographs (as clinically indicated)
- Gynaecology for vulvar or vaginal involvement (as clinically indicated)
- Physical therapy with assessment of range of motion (every 3-12 months if sclerotic features are present)
- Neuropsychological testing (every 12 months as clinically indicated)

Complications

Complications	Timeframe	Likelihood
opportunistic infections	variable	high
Continued treatment for graft-versus-host disease leads to additional drug-induced complications. Address risk of infection, provide appropriate infection prophylaxis, monitor potential drug-drug interactions, and limit intensity of immunosuppressive therapy as clinically possible.		
secondary malignancies	variable	high
<p>The risks of cancers following allogeneic haematopoietic cell transplantation (HCT) include the involvement of the skin (squamous-cell carcinoma, basal-cell carcinoma, and melanoma), oral mucosa (squamous-cell carcinoma), thyroid, bone, or connective tissue, and central nervous system. There is also an increased risk of lymphoproliferative disorders due to Epstein-Barr virus infection, generally within the first year post-transplant.</p> <p>One study suggests that new solid cancers develop at twice the rate post-HCT compared with the general population.^[171] Appropriate monitoring, early recognition, and prompt initiation of treatment are important in successful management.</p>		
corticosteroid-related complications	variable	high
Includes immunological dysfunction, hyperglycaemia, hypertension, deconditioning, muscle wasting avascular necrosis, compression fractures, and cataracts.		
malnutrition/wasting syndrome	variable	high
The clinical syndrome of GVHD can lead to a wasting or malnutrition syndrome. Referral to a dietician/nutritionist for advice is recommended to minimise the risk of this occurring.		
endocrine dysfunction	variable	high
There is an increased risk for thyroid dysfunction, gonadal dysfunction, osteoporosis, and decreased growth rates and growth hormone deficiency following allogeneic haematopoietic cell transplantation. Corticosteroid therapy can also lead to secondary adrenal dysfunction. Monitoring, early recognition, and prompt initiation of treatment are important in successful management. Endocrine consultation is recommended.		

Prognosis

Acute graft-versus-host disease (GVHD)

Using the Minnesota acute GVHD risk score to categorise a relatively recent patient cohort (2007-2016), overall response rates (complete response plus partial response) for patients with standard risk acute GVHD and high-risk acute GVHD were 68% and 49% at day 56, respectively.^[87] Patients with high-risk acute GVHD were at increased risk for 2 year transplant-related mortality and overall mortality compared with patients with a standard risk GVHD. Of note, the Minnesota GvHD Risk Score is intended to explore GVHD risk, inform upfront acute GVHD therapy, and to improve risk stratification in clinical trials.

Once acute GVHD occurs, the most important predictor of long-term survival is the primary response to therapy. In patients who do not respond completely to initial therapy, the risk of morbidity and mortality increases significantly.^{[165] [166]} Lack of response or lack of improvement following 3-7 days of corticosteroid therapy is associated with poor prognosis, primarily due to life-threatening opportunistic infections and/or multi-organ dysfunction.^[167] For severe grade III-IV GVHD, survival rates beyond 1 year are approximately 10% to 15%.

In some cases, withdrawal of corticosteroid therapy can lead to a flare of acute GVHD and/or evolve into chronic GVHD. The exact rate of flares is unpredictable, but it is higher in mismatched or unrelated donor haematopoietic cell transplantations (HCTs).

The outlook for patients who require second-line treatments is poor, and new approaches to prophylaxis, initial and salvage therapy are needed. Furthermore, it is difficult to predict which patients will respond to certain therapeutic modalities.

Chronic GVHD

The overall prognosis for patients with chronic GVHD is primarily dependent on the appropriate diagnosis, treatment, prevention of treatment-associated complications, and long-term care of organs affected. The leading cause of death is treatment-associated complications, particularly life-threatening opportunistic infections.

Despite aggressive management, overall survival following diagnosis and treatment has not improved significantly during the past 30 years.^{[8] [168] [169]} In an analysis of 668 patients treated for chronic GVHD, the cumulative incidence of non-relapse mortality at 2 years was 16% and overall survival at 2 years was 74%.^[170]

Treatment-related complications

Prolonged exposure to systemic corticosteroids in the treatment of acute and chronic GVHD can lead to numerous toxicities and potentially irreversible adverse effects in many organs, including hypertension, hyperglycaemia, anxiety, altered mood behaviours, avascular necrosis, osteopenia, vertebral fractures, poor wound healing, central obesity, myopathy, and skin atrophy with local depigmentation and telangiectasias. In addition, GVHD-mediated organ damage also contributes to significant morbidity and mortality.

Diagnostic guidelines

United Kingdom

Diagnosis and management of acute graft-versus-host disease (<https://onlinelibrary.wiley.com/toc/13652141/2012/158/1>)

Published by: British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation

Last published: 2012

Diagnosis and management of chronic graft-versus-host disease (<https://onlinelibrary.wiley.com/toc/13652141/2012/158/1>)

Published by: British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation

Last published: 2012

International

IBMTR severity index for grading acute graft versus host disease (<https://cibmtr.org/CIBMTR/Resources/Publications>)

Published by: International Bone Marrow Transplant Registry

Last published: 1997

North America

NCCN clinical practice guidelines in oncology: hematopoietic cell transplantation (https://www.nccn.org/guidelines/category_3)

Published by: National Comprehensive Cancer Network

Last published: 2024

Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. Pathology working group report ([https://www.astctjournal.org/issue/S1083-8791\(14\)X0015-7](https://www.astctjournal.org/issue/S1083-8791(14)X0015-7))

Published by: National Institutes of Health

Last published: 2015

National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report ([https://www.astctjournal.org/issue/S1083-8791\(14\)X0014-5](https://www.astctjournal.org/issue/S1083-8791(14)X0014-5))

Published by: National Institutes of Health

Last published: 2015

National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: IIa. The 2020 clinical implementation and early diagnosis working group report (<https://www.sciencedirect.com/science/article/pii/S2666636721008241?via%3Dihub>)

Published by: National Institutes of Health

Last published: 2021

The 1994 consensus conference on acute GVHD grading (<https://pubmed.ncbi.nlm.nih.gov/7581076>)

Published by: 1994 Consensus Conference on Acute GVHD Grading

Last published: 1995

Treatment guidelines

United Kingdom

The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection (<https://onlinelibrary.wiley.com/toc/13652141/2017/177/2>)

Published by: UK Photopheresis Society

Last published: 2017

Transfusion guidelines for fetuses, neonates and older children (<https://b-s-h.org.uk/guidelines/?category=Transfusion>)

Published by: British Committee for Standards in Haematology Transfusion Task Force

Last published: 2016

Diagnosis and management of acute graft-versus-host disease (<https://onlinelibrary.wiley.com/toc/13652141/2012/158/1>)

Published by: British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation

Last published: 2012

Diagnosis and management of chronic graft-versus-host disease (<https://onlinelibrary.wiley.com/toc/13652141/2012/158/1>)

Published by: British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation

Last published: 2012

International

Recommended screening and preventative practices for long-term survivors after hematopoietic cell transplantation (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3393084>)

Published by: Center for International Blood and Marrow Transplant Research; American Society for Blood and Marrow Transplantation; European Group for Blood and Marrow Transplantation; Asia-Pacific Blood and Marrow Transplantation Group; Bone Marrow Transplant Society of Australia and New Zealand; East Mediterranean Blood and Marrow Transplantation Group; Sociedade Brasileira de Transplante de Medula Ossea

Last published: 2012

Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations ([https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026\(23\)00342-3/abstract](https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(23)00342-3/abstract))

Published by: European Society for Blood and Marrow Transplantation

Last published: 2024

North America

NCCN clinical practice guidelines in oncology: hematopoietic cell transplantation (https://www.nccn.org/guidelines/category_3)

Published by: National Comprehensive Cancer Network

Last published: 2024

Dental management of pediatric patients receiving immunosuppressive therapy and/or head and neck radiation (<https://www.aapd.org/research/oral-health-policies--recommendations>)

Published by: American Academy of Pediatric Dentistry

Last published: 2022

Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers (<http://www.survivorshipguidelines.org>)

Published by: Children's Oncology Group

Last published: 2023

Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report ([https://www.astctjournal.org/article/S1083-8791\(15\)00155-X/fulltext](https://www.astctjournal.org/article/S1083-8791(15)00155-X/fulltext))

Published by: National Institutes of Health

Last published: 2015

National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group report ([https://www.astctjournal.org/issue/S1083-8791\(14\)X0018-2](https://www.astctjournal.org/issue/S1083-8791(14)X0018-2))

Published by: American Society for Blood and Marrow Transplantation

Last published: 2015

A perspective on the selection of unrelated donors and cord blood units for transplantation (<https://cibmtr.org/CIBMTR/Resources/Publications>)

Published by: National Marrow Donor Program; Center for International Blood and Marrow Transplant Research

Last published: 2012

Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective ([https://www.astctjournal.org/issue/S1083-8791\(09\)X0009-1](https://www.astctjournal.org/issue/S1083-8791(09)X0009-1))

Published by: American Society for Blood and Marrow Transplantation

Last published: 2009

Online resources

1. National Institutes of Health: organ scoring of chronic GVHD (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329079/figure/F1>) (*external link*)
2. Children's Oncology Services (<http://www.onestepcamp.org>) (*external link*)
3. National Marrow Donor Program (<http://www.marrow.org>) (*external link*)
4. European Society for Blood and Marrow Transplantation (<http://www.ebmt.org>) (*external link*)
5. Center for International Blood and Marrow Transplant Research (<http://www.cibmtr.org>) (*external link*)
6. American Society for Transplantation and Cellular Therapy (<https://www.astct.org>) (*external link*)

Key articles

- Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015 Mar;21(3):389-401.e1. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329079\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329079) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/25529383?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/25529383?tool=bestpractice.bmj.com)
- Penack O, Marchetti M, Aljurf M, et al. Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol*. 2024 Feb;11(2):e147-59. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/38184001?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/38184001?tool=bestpractice.bmj.com)
- Dignan FL, Amrolia P, Clark A, et al. Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol*. 2012 Jul;158(1):46-61. [Full text \(https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09128.x\)](https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09128.x) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/22533811?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/22533811?tool=bestpractice.bmj.com)
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: hematopoietic cell transplantation [internet publication]. [Full text \(https://www.nccn.org/guidelines/category_3\)](https://www.nccn.org/guidelines/category_3)
- Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol*. 2012 Jul;158(1):30-45. [Full text \(https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09129.x\)](https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09129.x) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/22533831?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/22533831?tool=bestpractice.bmj.com)
- Carpenter PA, Kitko CL, Elad S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group report. *Biol Blood Marrow Transplant*. 2015 Jul;21(7):1167-87. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821166\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821166) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/25838185?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/25838185?tool=bestpractice.bmj.com)

References

1. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015 Mar;21(3):389-401.e1. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329079\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329079) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/25529383?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/25529383?tool=bestpractice.bmj.com)
2. Mielcarek M, Martin PJ, Leisenring W, et al. Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood*. 2003 Jul 15;102(2):756-62. [Full text](#)

- (<http://bloodjournal.hematologylibrary.org/cgi/reprint/102/2/756>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/12663454?tool=bestpractice.bmj.com>)
3. Couriel DR, Saliba RM, Giralt S, et al. Acute and chronic graft-versus-host disease after ablative and nonmyeloablative conditioning for allogeneic hematopoietic transplantation. *Biol Blood Marrow Transplant.* 2004 Mar;10(3):178-85. Full text ([http://www.bbmt.org/article/S1083-8791\(03\)00419-1/fulltext](http://www.bbmt.org/article/S1083-8791(03)00419-1/fulltext)) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/14993883?tool=bestpractice.bmj.com>)
 4. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. *N Engl J Med.* 1997 Aug 7;337(6):373-81. Full text (<http://www.nejm.org/doi/full/10.1056/NEJM199708073370602#t=article>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/9241126?tool=bestpractice.bmj.com>)
 5. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Engl J Med.* 1998 Nov 26;339(22):1565-77. Full text (<http://www.nejm.org/doi/full/10.1056/NEJM199811263392201#t=article>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/9828244?tool=bestpractice.bmj.com>)
 6. Eapen M, Rubinstein P, Zhang MJ, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet.* 2007 Jun 9;369(9577):1947-54. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17560447?tool=bestpractice.bmj.com>)
 7. Frey NV, Porter DL. Graft-versus-host disease after donor leukocyte infusions: presentation and management. *Best Pract Res Clin Haematol.* 2008 Jun;21(2):205-22. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/18503987?tool=bestpractice.bmj.com>)
 8. Lee SJ, Vogelsang G, Flowers MED. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2003 Apr;9(4):215-33. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/12720215?tool=bestpractice.bmj.com>)
 9. Wenger DS, Triplette M, Crothers K, et al. Incidence, risk factors, and outcomes of idiopathic pneumonia syndrome after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2020 Feb;26(2):413-20. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC7035790>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/31605819?tool=bestpractice.bmj.com>)
 10. Panoskaltsis-Mortari A, Griesse M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *Am J Respir Crit Care Med.* 2011 May 1;183(9):1262-79. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC3266140>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/21531955?tool=bestpractice.bmj.com>)
 11. Crawford SW, Hackman RC. Clinical course of idiopathic pneumonia after bone marrow transplantation. *Am Rev Respir Dis.* 1993 Jun;147(6 Pt 1):1393-400. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/8503550?tool=bestpractice.bmj.com>)

12. Clark JG, Hansen JA, Hertz MI, et al. NHLBI workshop summary. Idiopathic pneumonia syndrome after bone marrow transplantation. *Am Rev Respir Dis*. 1993 Jun;147(6 Pt 1):1601-6. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/8503576?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/8503576?tool=bestpractice.bmj.com)
13. Sullivan KM, Storb R, Buckner CD, et al. Graft-versus-host disease as adoptive immunotherapy in patients with advanced hematologic neoplasms. *N Engl J Med*. 1989 Mar 30;320(13):828-34. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/2648143?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/2648143?tool=bestpractice.bmj.com)
14. Rocha V, Fatobene G, Niederwieser D, et al. Increasing access to allogeneic hematopoietic cell transplant: an international perspective. *Hematology Am Soc Hematol Educ Program*. 2021 Dec 10;2021(1):264-74. [Full text \(https://ashpublications.org/hematology/article/2021/1/264/482965/Increasing-access-to-allogeneic-hematopoietic-cell\)](https://ashpublications.org/hematology/article/2021/1/264/482965/Increasing-access-to-allogeneic-hematopoietic-cell) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/34889391?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/34889391?tool=bestpractice.bmj.com)
15. Auletta JJ, Kou J, Chen M, et al. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021 [internet publication]. [Full text \(https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports\)](https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports)
16. Zeiser R, Blazar BR. Acute graft-versus-host disease - biologic process, prevention, and therapy. *N Engl J Med*. 2017 Nov 30;377(22):2167-79. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/29171820?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/29171820?tool=bestpractice.bmj.com)
17. Ringden O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood*. 2009 Mar 26;113(13):3110-8. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/19059878?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/19059878?tool=bestpractice.bmj.com)
18. Wojnar J, Giebel S, Krawczyk-Kulis M, et al. Acute graft-versus-host disease. The incidence and risk factors. *Ann Transplant*. 2006;11(1):16-23. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/17025025?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/17025025?tool=bestpractice.bmj.com)
19. Kanda J. Effect of HLA mismatch on acute graft-versus-host disease. *Int J Hematol*. 2013 Sep;98(3):300-8. [Full text \(https://link.springer.com/article/10.1007/s12185-013-1405-x\)](https://link.springer.com/article/10.1007/s12185-013-1405-x) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/23893313?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/23893313?tool=bestpractice.bmj.com)
20. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med*. 2004 Nov 25;351(22):2276-85. [Full text \(http://www.nejm.org/doi/full/10.1056/NEJMoa041469#t=article\)](http://www.nejm.org/doi/full/10.1056/NEJMoa041469#t=article) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/15564544?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/15564544?tool=bestpractice.bmj.com)
21. Antin JH. Clinical practice. Long-term care after hematopoietic-cell transplantation in adults. *N Engl J Med*. 2002 Jul 4;347(1):36-42. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/12097539?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/12097539?tool=bestpractice.bmj.com)
22. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft versus-host disease: association with treatment-related mortality and relapse. *Blood*. 2002 Jul 15;100(2):406-14. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/reprint/100/2/406\)](http://bloodjournal.hematologylibrary.org/cgi/reprint/100/2/406) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/12091329?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/12091329?tool=bestpractice.bmj.com)

23. Nash RA, Pepe MS, Storb R, et al. Acute graft-versus-host disease: analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. *Blood*. 1992 Oct 1;80(7):1838-45. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/reprint/80/7/1838\)](http://bloodjournal.hematologylibrary.org/cgi/reprint/80/7/1838) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/1391947?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/1391947?tool=bestpractice.bmj.com)
24. Hahn T, McCarthy PL Jr, Zhang MJ, et al. Risk factors for acute graft-versus-host disease after human leukocyte antigen-identical sibling transplants for adults with leukemia. *J Clin Oncol*. 2008 Dec 10;26(35):5728-34. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/18981462?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/18981462?tool=bestpractice.bmj.com)
25. Storb R, Prentice RL, Buckner CD, et al. Graft-versus-host disease and survival in patients with aplastic anemia treated by marrow grafts from HLA-identical siblings. Beneficial effect of a protective environment. *N Engl J Med*. 1983 Feb 10;308(6):302-7. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/6337323?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/6337323?tool=bestpractice.bmj.com)
26. Anasetti C, Beatty PG, Storb R, et al. Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. *Hum Immunol*. 1990 Oct;29(2):79-91. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/2249952?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/2249952?tool=bestpractice.bmj.com)
27. Weisdorf D, Hakke R, Blazar B, et al. Risk factors for acute graft-versus-host disease in histocompatible donor bone marrow transplantation. *Transplant*. 1991 Jun;51(6):1197-203. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/2048196?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/2048196?tool=bestpractice.bmj.com)
28. Hagglund H, Bostrom L, Remberger M, et al. Risk factors for acute graft-versus-host disease in 291 consecutive HLA-identical bone marrow transplant recipients. *Bone Marrow Transplant*. 1995 Dec;16(6):747-53. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/8750264?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/8750264?tool=bestpractice.bmj.com)
29. Eisner MD, August CS. Impact of donor and recipient characteristics on the development of acute and chronic graft-versus-host disease following pediatric bone marrow transplantation. *Bone Marrow Transplant*. 1995 May;15(5):663-8. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/7670393?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/7670393?tool=bestpractice.bmj.com)
30. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. *Blood*. 2006 Oct 15;108(8):2509-19. [Full text \(http://bloodjournal.org/content/108/8/2509.full\)](http://bloodjournal.org/content/108/8/2509.full) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16778145?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16778145?tool=bestpractice.bmj.com)
31. Martin P, Bleyzac N, Souillet G, et al. Clinical and pharmacological risk factors for acute graft-versus-host disease after paediatric bone marrow transplantation from matched-sibling or unrelated donors. *Bone Marrow Transplant*. 2003 Nov;32(9):881-7. [Full text \(https://www.nature.com/articles/1704239\)](https://www.nature.com/articles/1704239) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/14561988?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/14561988?tool=bestpractice.bmj.com)
32. Gale RP, Bortin MM, van Bekkum DW, et al. Risk factors for acute graft-versus-host disease. *Br J Haematol*. 1987 Dec;67(4):397-406. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/3322360?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/3322360?tool=bestpractice.bmj.com)
33. Atkinson K, Farrell C, Chapman G, et al. Female marrow donors increase the risk of acute graft-versus-host disease: effect of donor age and parity and analysis of cell subpopulations in the donor

- marrow inoculum. *Br J Haematol*. 1986 Jun;63(2):231-9. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/3521713?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/3521713?tool=bestpractice.bmj.com)
34. Bross DS, Tutschka PJ, Farmer ER, et al. Predictive factors for acute graft-versus-host disease in patients transplanted with HLA-identical bone marrow. *Blood*. 1984 Jun;63(6):1265-70. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/reprint/63/6/1265\)](http://bloodjournal.hematologylibrary.org/cgi/reprint/63/6/1265) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/6372895?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/6372895?tool=bestpractice.bmj.com)
35. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of 2 irradiation regimens. *Blood*. 1990 Nov 1;76(9):1867-71. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/reprint/76/9/1867\)](http://bloodjournal.hematologylibrary.org/cgi/reprint/76/9/1867) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/2224134?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/2224134?tool=bestpractice.bmj.com)
36. Finke J, Schmoor C, Bethge WA, et al; ATG-Fresenius Trial Group. Prognostic factors affecting outcome after allogeneic transplantation for hematological malignancies from unrelated donors: results from a randomized trial. *Biol Blood Marrow Transplant*. 2012 Nov;18(11):1716-26. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/22713691?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/22713691?tool=bestpractice.bmj.com)
37. Oh H, Loberiza FR, Zhang MJ, et al. Comparison of graft-versus-host-disease and survival after HLA-identical sibling bone marrow transplantation in ethnic populations. *Blood*. 2005 Feb 15;105(4):1408-16. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/105/4/1408\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/105/4/1408) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/15486071?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/15486071?tool=bestpractice.bmj.com)
38. Silla L, Fischer GB, Paz A, et al. Patient's socioeconomic status as a prognostic factor for allo-SCT. *Bone Marrow Transplant*. 2009 Apr;43(7):571-7. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/18978820?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/18978820?tool=bestpractice.bmj.com)
39. Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011 Mar 17;117(11):3214-9. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC3062319\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC3062319) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/21263156?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/21263156?tool=bestpractice.bmj.com)
40. Azari M, Barkhordar M, Bahri T, et al. Determining the predictive impact of donor parity on the outcomes of human leukocyte antigen matched hematopoietic stem cell transplants: a retrospective, single-center study. *Front Oncol*. 2024;14:1339605. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC10918844\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC10918844) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/38454927?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/38454927?tool=bestpractice.bmj.com)
41. Kalhs P, Schwarzingner I, Anderson G, et al. A retrospective analysis of the long-term effect of splenectomy on late infections, graft-versus-host disease, relapse, and survival after allogeneic marrow transplantation for chronic myelogenous leukemia. *Blood*. 1995 Sep 1;86(5):2028-32. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/7655031?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/7655031?tool=bestpractice.bmj.com)
42. Anasetti C, Logan BR, Lee SJ, et al; Blood and Marrow Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012 Oct 18;367(16):1487-96. [Full text \(http://www.nejm.org/doi/full/10.1056/NEJMoa1203517#t=article\)](http://www.nejm.org/doi/full/10.1056/NEJMoa1203517#t=article) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/23075175?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/23075175?tool=bestpractice.bmj.com)

43. Cutler C, Giri S, Jeyapalan S, et al. Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: a meta-analysis. *J Clin Oncol*. 2001 Aug 15;19(16):3685-91. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/11504750?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/11504750?tool=bestpractice.bmj.com)
44. Loren AW, Bunin GR, Boudreau C, et al. Impact of donor and recipient sex and parity on outcomes of HLA-identical sibling allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2006 Jul;12(7):758-69. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16785065?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16785065?tool=bestpractice.bmj.com)
45. Koster EAS, von dem Borne PA, van Balen P, et al. Risk factors for graft-versus-host-disease after donor lymphocyte infusion following T-cell depleted allogeneic stem cell transplantation. *Front Immunol*. 2024;15:1335341. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC10966113\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC10966113) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/38545096?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/38545096?tool=bestpractice.bmj.com)
46. Lazaryan A, Weisdorf DJ, DeFor T, et al. Risk factors for acute and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation with umbilical cord blood and matched sibling donors. *Biol Blood Marrow Transplant*. 2016 Jan;22(1):134-40. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC4787268\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC4787268) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/26365153?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/26365153?tool=bestpractice.bmj.com)
47. Lee SJ. New approaches for preventing and treating chronic graft-versus-host disease. *Blood*. 2005 Jun 1;105(11):4200-6. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/105/11/4200\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/105/11/4200) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/15701727?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/15701727?tool=bestpractice.bmj.com)
48. Beatty P, Clift R, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. *N Engl J Med*. 1985 Sep 26;313(13):765-71. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/3897863?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/3897863?tool=bestpractice.bmj.com)
49. Kernan NA, Bartsch G, Ash RC, et al. Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. *N Engl J Med*. 1993 Mar 4;328(9):593-602. [Full text \(http://www.nejm.org/doi/full/10.1056/NEJM199303043280901#t=article\)](http://www.nejm.org/doi/full/10.1056/NEJM199303043280901#t=article) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/8429851?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/8429851?tool=bestpractice.bmj.com)
50. Flomenberg N, Baxter-Lowe LA, Confer D, et al. Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. *Blood*. 2004 Oct 1;104(7):1923-30. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/104/7/1923\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/104/7/1923) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/15191952?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/15191952?tool=bestpractice.bmj.com)
51. Sasazuki T, Juji T, Morishima Y, et al; Japan Marrow Donor Program. Effect of matching of class I HLA alleles on clinical outcome after transplantation of hematopoietic stem cells from an unrelated donor. *N Engl J Med*. 1998 Oct 22;339(17):1177-85. [Full text \(http://www.nejm.org/doi/full/10.1056/NEJM199810223391701#t=article\)](http://www.nejm.org/doi/full/10.1056/NEJM199810223391701#t=article) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/9780337?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/9780337?tool=bestpractice.bmj.com)
52. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*. 2007 Dec 15;110(13):4576-83.

Full text (<http://bloodjournal.hematologylibrary.org/cgi/content/full/110/13/4576>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17785583?tool=bestpractice.bmj.com>)

53. Petersdorf EW, Longton GM, Anasetti C, et al. The significance of HLA-DRB1 matching on clinical outcome after HLA-A, B, DR identical unrelated donor marrow transplantation. *Blood*. 1995 Aug 15;86(4):1606-13. Full text (<http://www.bloodjournal.org/content/86/4/1606.full-text.pdf>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/7632970?tool=bestpractice.bmj.com>)
54. Loiseau P, Busson M, Balere ML, et al. HLA association with hematopoietic stem cell transplantation outcome: the number of mismatches at HLA-A, -B, -C, -DRB1, or -DQB1 is strongly associated with overall survival. *Biol Blood Marrow Transplant*. 2007 Aug;13(8):965-74. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17640601?tool=bestpractice.bmj.com>)
55. Spellman SR, Eapen M, Logan BR, et al; National Marrow Donor Program; Center for International Blood and Marrow Transplant Research. A perspective on the selection of unrelated donors and cord blood units for transplantation. *Blood*. 2012 Jul 12;120(2):259-65. Full text (<http://bloodjournal.hematologylibrary.org/content/120/2/259.long>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/22596257?tool=bestpractice.bmj.com>)
56. Rujkijyanont P, Morris C, Kang G, et al. Risk-adapted donor lymphocyte infusion based on chimerism and donor source in pediatric leukemia. *Blood Cancer J*. 2013 Aug 30;3(8):e137. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC3763390>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/23995046?tool=bestpractice.bmj.com>)
57. Suryaprakash S, Sun Y, Tang L, et al. Risk-adapted donor lymphocyte infusion after hematopoietic cell transplant in pediatric and young adult patients is associated with low risk of graft versus host disease. *Blood*;142:7042. Full text (<https://ashpublications.org/blood/article/142/Supplement%201/7042/505721/Risk-Adapted-Donor-Lymphocyte-Infusion-after>)
58. Sullivan KM, Deeg HJ, Sanders J, et al. Hyperacute graft-v-host disease in patients not given immunosuppression after allogeneic marrow transplantation. *Blood*. 1986 Apr;67(4):1172-5. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/3513869?tool=bestpractice.bmj.com>)
59. Yakoub-Agha I, Mesnil F, Kuentz M, et al. Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. *J Clin Oncol*. 2006 Dec 20;24(36):5695-702. Full text (<http://jco.ascopubs.org/cgi/content/full/24/36/5695>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17116940?tool=bestpractice.bmj.com>)
60. Michallet M, Corront B, Bosson JL, et al. Role of splenectomy in incidence and severity of acute graft-versus-host disease: a multicenter study of 157 patients. *Bone Marrow Transplant*. 1991 Jul;8(1):13-7. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/1912953?tool=bestpractice.bmj.com>)
61. Kansu E, Gooley T, Flowers ME, et al. Administration of cyclosporine for 24 months compared with 6 months for prevention of chronic graft-versus-host disease: a prospective randomized clinical trial. *Blood*. 2001 Dec 15;98(13):3868-70. Full text (<http://bloodjournal.hematologylibrary.org/cgi/content/full/98/13/3868>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/11739201?tool=bestpractice.bmj.com>)

62. Choi SW, Reddy P. Current and emerging strategies for the prevention of graft-versus-host disease. *Nat Rev Clin Oncol*. 2014 Sep;11(9):536-47. [Full text \(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151470\)](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151470) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/24958183?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/24958183?tool=bestpractice.bmj.com)
63. Penack O, Marchetti M, Aljurf M, et al. Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol*. 2024 Feb;11(2):e147-59. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/38184001?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/38184001?tool=bestpractice.bmj.com)
64. Vogelsang GB, Arai S. Mycophenolate mofetil for the prevention and treatment of graft-versus-host disease following stem cell transplantation: preliminary findings. *Bone Marrow Transplant*. 2001 Jun;27(12):1255-62. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/11548843?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/11548843?tool=bestpractice.bmj.com)
65. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. *N Engl J Med*. 1986 Mar 20;314(12):729-35. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/3513012?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/3513012?tool=bestpractice.bmj.com)
66. Watkins B, Qayed M, McCracken C, et al. Phase II trial of costimulation blockade with abatacept for prevention of acute GVHD. *J Clin Oncol*. 2021 Jun 10;39(17):1865-77. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/33449816?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/33449816?tool=bestpractice.bmj.com)
67. Bolaños-Meade J, Hamadani M, Wu J, et al. Post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis. *N Engl J Med*. 2023 Jun 22;388(25):2338-2348. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC10575613\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC10575613) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/37342922?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/37342922?tool=bestpractice.bmj.com)
68. Bolaños-Meade J, Reshef R, Fraser R, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). *Lancet Haematol*. 2019 Mar;6(3):e132-43. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6503965\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6503965) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/30824040?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/30824040?tool=bestpractice.bmj.com)
69. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008 Jun;14(6):641-50. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC2633246\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC2633246) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/18489989?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/18489989?tool=bestpractice.bmj.com)
70. Gooptu M, Antin JH. GVHD Prophylaxis 2020. *Front Immunol*. 2021;12:605726. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC8059368\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC8059368) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/33897681?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/33897681?tool=bestpractice.bmj.com)
71. Walker I, Panzarella T, Couban S, et al. Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell

- transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial. *Lancet Oncol.* 2016 Feb;17(2):164-73. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/26723083?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/26723083?tool=bestpractice.bmj.com)
72. Walker I, Panzarella T, Couban S, et al. Addition of anti-thymocyte globulin to standard graft-versus-host disease prophylaxis versus standard treatment alone in patients with haematological malignancies undergoing transplantation from unrelated donors: final analysis of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol.* 2020 Feb;7(2):e100-11. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/31958417?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/31958417?tool=bestpractice.bmj.com)
73. Chang YJ, Wu DP, Lai YR, et al. Antithymocyte globulin for matched sibling donor transplantation in patients with hematologic malignancies: a multicenter, open-label, randomized controlled study. *J Clin Oncol.* 2020 Oct 10;38(29):3367-76. [Full text \(https://ascopubs.org/doi/10.1200/JCO.20.00150?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed\)](https://ascopubs.org/doi/10.1200/JCO.20.00150?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/32650683?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/32650683?tool=bestpractice.bmj.com)
74. Sandmaier BM, Kornblit B, Storer BE, et al. Addition of sirolimus to standard cyclosporine plus mycophenolate mofetil-based graft-versus-host disease prophylaxis for patients after unrelated non-myeloablative haemopoietic stem cell transplantation: a multicentre, randomised, phase 3 trial. *Lancet Haematol.* 2019 Aug;6(8):e409-18. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC6686903\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC6686903) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/31248843?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/31248843?tool=bestpractice.bmj.com)
75. Antin JH, Kim HT, Cutler C, et al. Sirolimus, tacrolimus, and low-dose methotrexate for graft-versus-host disease prophylaxis in mismatched related donor or unrelated donor transplantation. *Blood.* 2003 Sep 1;102(5):1601-5. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/102/5/1601\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/102/5/1601) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/12730113?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/12730113?tool=bestpractice.bmj.com)
76. Cutler C, Li S, Ho VT, et al. Extended follow-up of methotrexate-free immunosuppression using sirolimus and tacrolimus in related and unrelated donor peripheral blood stem cell transplantation. *Blood.* 2007 Apr 1;109(7):3108-14. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/109/7/3108\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/109/7/3108) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/17138818?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/17138818?tool=bestpractice.bmj.com)
77. Törlén J, Ringdén O, Garming-Legert K, et al. A prospective randomized trial comparing cyclosporine/methotrexate and tacrolimus/sirolimus as graft-versus-host disease prophylaxis after allogeneic hematopoietic stem cell transplantation. *Haematologica.* 2016 Nov;101(11):1417-25. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5394879\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5394879) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/27662016?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/27662016?tool=bestpractice.bmj.com)
78. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood.* 2014 Aug 21;124(8):1372-7. [Full text \(http://www.bloodjournal.org/content/124/8/1372.long?sso-checked=true\)](http://www.bloodjournal.org/content/124/8/1372.long?sso-checked=true) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/24982504?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/24982504?tool=bestpractice.bmj.com)
79. Kitko CL, Pidala J, Schoemans HM, et al. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: IIa. The 2020 Clinical Implementation and Early Diagnosis Working Group Report. *Transplant Cell Ther.* 2021 Jul;27(7):545-557. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC8803210\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC8803210) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/33839317?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/33839317?tool=bestpractice.bmj.com)

80. Rotz SJ, Bhatt NS, Hamilton BK, et al. International recommendations for screening and preventative practices for onlg-term survivors of transplantation and cellular therapy: a 2023 update. *Transplant Cell Ther.* 2024 Apr;30(4):349-85. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC11181337\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC11181337) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/38413247?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/38413247?tool=bestpractice.bmj.com)
81. Dignan FL, Amrolia P, Clark A, et al. Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol.* 2012 Jul;158(1):46-61. [Full text \(https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09128.x\)](https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09128.x) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/22533811?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/22533811?tool=bestpractice.bmj.com)
82. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, Version 6.0. Oct 2023 [internet publication]. [Full text \(http://www.survivorshipguidelines.org\)](http://www.survivorshipguidelines.org)
83. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant.* 1995 Jun;15(6):825-8. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/7581076?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/7581076?tool=bestpractice.bmj.com)
84. Jacobsohn DA. Acute graft versus-host disease in children. *Bone Marrow Transplant.* 2008 Jan;41(2):215-21. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/17934526?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/17934526?tool=bestpractice.bmj.com)
85. Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant.* 2016 Jan;22(1):4-10. [Full text \(https://www.astctjournal.org/article/S1083-8791\(15\)00602-3/fulltext\)](https://www.astctjournal.org/article/S1083-8791(15)00602-3/fulltext) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/26386318?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/26386318?tool=bestpractice.bmj.com)
86. MacMillan ML, DeFor TE, Weisdorf DJ. What predicts high risk acute graft-versus-host disease (GVHD) at onset? Identification of those at highest risk by a novel acute GVHD risk score. *Br J Haematol.* 2012 Jun;157(6):732-41. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC3654854\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC3654854) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/22486355?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/22486355?tool=bestpractice.bmj.com)
87. MacMillan ML, DeFor TE, Holtan SG, et al. Validation of Minnesota acute graft-versus-host disease risk score. *Haematologica.* 2020;105(2):519-24. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC7012472\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC7012472) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/31320554?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/31320554?tool=bestpractice.bmj.com)
88. Naymagon S, Naymagon L, Wong SY, et al. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. *Nat Rev Gastroenterol Hepatol.* 2017 Dec;14(12):711-26. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC6240460\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC6240460) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/28951581?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/28951581?tool=bestpractice.bmj.com)
89. Nevo S, Enger C, Swan V, et al. Acute bleeding after allogeneic bone marrow transplantation: association with graft versus host disease and effect on survival. *Transplantation.* 1999 Mar 15;67(5):681-9. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/10096522?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/10096522?tool=bestpractice.bmj.com)
90. Modi D, Ye JC, Surapaneni M, et al. Liver graft-versus-host disease is associated with poor survival among allogeneic hematopoietic stem cell transplant recipients. *Am J Hematol.* 2019

Oct;94(10):1072-80. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC8422561>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/31292984?tool=bestpractice.bmj.com>)

91. Stelljes M, Hermann S, Albring J, et al. Clinical molecular imaging in intestinal graft-versus-host disease: mapping of disease activity, prediction, and monitoring of treatment efficiency by positron emission tomography. *Blood*. 2008 Mar 1;111(5):2909-18. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/18057227?tool=bestpractice.bmj.com>)
92. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: hematopoietic cell transplantation [internet publication]. Full text (https://www.nccn.org/guidelines/category_3)
93. Ferrara JL, Deeg HJ. Graft-versus-host disease. *N Engl J Med*. 1991 Mar 7;324(10):667-74. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/1994250?tool=bestpractice.bmj.com>)
94. Goker H, Haznedaroglu IC, Chao NJ. Acute graft-vs-host disease: pathobiology and management. *Exp Hematol*. 2001 Mar;29(3):259-77. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/11274753?tool=bestpractice.bmj.com>)
95. Snover DC, Weisdorf SA, Vercellotti GM, et al. A histopathologic study of gastric and small intestinal graft-versus-host disease following allogeneic bone marrow transplantation. *Hum Pathol*. 1985 Apr;16(4):387-92. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/3884482?tool=bestpractice.bmj.com>)
96. Snover DC, Weisdorf SA, Ramsay NK, et al. Hepatic graft versus host disease: a study of the predictive value of liver biopsy in diagnosis. *Hepatology*. 1984 Jan-Feb;4(1):123-30. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/6363248?tool=bestpractice.bmj.com>)
97. Fujii N, Takenaka K, Shinagawa K, et al. Hepatic graft-versus-host disease presenting as an acute hepatitis after allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2001 May;27(9):1007-10. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/11436113?tool=bestpractice.bmj.com>)
98. Urbanski SJ, Kossakowska AE, Curtis J, et al. Idiopathic small airways pathology in patients with graft-versus-host disease following allogeneic bone marrow transplantation. *Am J Surg Pathol*. 1987 Dec;11(12):965-71. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/3318513?tool=bestpractice.bmj.com>)
99. Srinagesh HK, Levine JE, Ferrara JLM. Biomarkers in acute graft-versus-host disease: new insights. *Ther Adv Hematol*. 2019;10:2040620719891358. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC6893923>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/31839920?tool=bestpractice.bmj.com>)
100. Srinagesh HK, Özbek U, Kapoor U, et al. The MAGIC algorithm probability is a validated response biomarker of treatment of acute graft-versus-host disease. *Blood Adv*. 2019 Dec 10;3(23):4034-42. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC6963240>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/31816061?tool=bestpractice.bmj.com>)
101. Levine JE, Braun TM, Harris AC, et al. A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study. *Lancet Haematol*. 2015 Jan;2(1):e21-9. Full text

- (<https://pmc.ncbi.nlm.nih.gov/articles/PMC4340092>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/26687425?tool=bestpractice.bmj.com>)
102. Kharfan-Dabaja M, Mhaskar R, Reljic T, et al. Mycophenolate mofetil versus methotrexate for prevention of graft-versus-host disease in people receiving allogeneic hematopoietic stem cell transplantation. *Cochrane Database Syst Rev.* 2014 Jul 25;(7):CD010280. Full text (<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010280.pub2/full>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/25061777?tool=bestpractice.bmj.com>)
 103. Ram R, Gafter-Gvili A, Yeshurun M, et al. Prophylaxis regimens for GVHD: systematic review and meta-analysis. *Bone Marrow Transplant.* 2009 Apr;43(8):643-53. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/18997826?tool=bestpractice.bmj.com>)
 104. Storb R, Deeg HJ, Pepe M, et al. Graft-versus-host disease prevention by methotrexate combined with cyclosporin compared to methotrexate alone in patients given marrow grafts for severe aplastic anaemia: long-term follow-up of a controlled trial. *Br J Haematol.* 1989 Aug;72(4):567-72. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/2673331?tool=bestpractice.bmj.com>)
 105. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol.* 2012 Jul;158(1):30-45. Full text (<https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09129.x>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/22533831?tool=bestpractice.bmj.com>)
 106. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2012 Aug;18(8):1150-63. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC3404151>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/22510384?tool=bestpractice.bmj.com>)
 107. Mielcarek M, Furlong T, Storer BE, et al. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. *Haematologica.* 2015 Jun;100(6):842-8. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC4450631>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/25682602?tool=bestpractice.bmj.com>)
 108. Hockenbery DM, Cruickshank S, Rodell TC, et al. A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. *Blood.* 2007 May 15;109(10):4557-63. Full text (<http://bloodjournal.hematologylibrary.org/cgi/content/full/109/10/4557>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17244684?tool=bestpractice.bmj.com>)
 109. Bertz H, Afting M, Kreisel W, et al. Feasibility and response to budesonide as topical corticosteroid therapy for acute intestinal GVHD. *Bone Marrow Transplant.* 1999 Dec;24(11):1185-9. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/10642806?tool=bestpractice.bmj.com>)
 110. Kim SS. Treatment options in steroid-refractory acute graft-versus-host disease following hematopoietic stem cell transplantation. *Ann Pharmacother.* 2007 Sep;41(9):1436-44. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17684033?tool=bestpractice.bmj.com>)

111. Przepiorka D, Luo L, Subramaniam S, et al. FDA approval summary: ruxolitinib for treatment of steroid-refractory acute graft-versus-host disease. *Oncologist*. 2020 Feb;25(2):e328-e334. [Full text \(https://www.doi.org/10.1634/theoncologist.2019-0627\)](https://www.doi.org/10.1634/theoncologist.2019-0627) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/32043777?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/32043777?tool=bestpractice.bmj.com)
112. Jagasia M, Perales MA, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. *Blood*. 2020 May 14;135(20):1739-49. [Full text \(https://ashpublications.org/blood/article/135/20/1739/452638/Ruxolitinib-for-the-treatment-of-steroid\)](https://ashpublications.org/blood/article/135/20/1739/452638/Ruxolitinib-for-the-treatment-of-steroid) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/32160294?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/32160294?tool=bestpractice.bmj.com)
113. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. *N Engl J Med*. 2020 May 7;382(19):1800-10. [Full text \(https://www.nejm.org/doi/10.1056/NEJMoa1917635\)](https://www.nejm.org/doi/10.1056/NEJMoa1917635) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/32320566?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/32320566?tool=bestpractice.bmj.com)
114. Arai S, Margolis J, Zahurak M, et al. Poor outcome in steroid-refractory graft-versus-host disease with antithymocyte globulin treatment. *Biol Blood Marrow Transplant*. 2002;8(3):155-60. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/11939605?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/11939605?tool=bestpractice.bmj.com)
115. McCaul KG, Nevill TJ, Barnett MJ, et al. Treatment of steroid-resistant acute graft-versus-host disease with rabbit antithymocyte globulin. *J Hematother Stem Cell Res*. 2000 Jun;9(3):367-74. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/10894358?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/10894358?tool=bestpractice.bmj.com)
116. Hsu B, May R, Carrum G, et al. Use of antithymocyte globulin for treatment of steroid-refractory acute graft-versus-host disease: an international practice survey. *Bone Marrow Transplant*. 2001 Nov;28(10):945-50. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/11753549?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/11753549?tool=bestpractice.bmj.com)
117. Benito AI, Furlong T, Martin PJ, et al. Sirolimus (rapamycin) for the treatment of steroid-refractory acute graft-versus-host disease. *Transplantation*. 2001 Dec 27;72(12):1924-9. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/11773890?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/11773890?tool=bestpractice.bmj.com)
118. Couriel DR, Saliba R, Escalón MP, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. *Br J Haematol*. 2005 Aug;130(3):409-17. [Full text \(http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2005.05616.x/full\)](http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2005.05616.x/full) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16042691?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16042691?tool=bestpractice.bmj.com)
119. Levine JE, Paczesny S, Mineishi S, et al. Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. *Blood*. 2008 Feb 15;111(4):2470-5. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/18042798?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/18042798?tool=bestpractice.bmj.com)
120. Carella AM, Beltrami G, Scalzulli PR, et al. Alemtuzumab can successfully treat steroid-refractory acute graft-versus-host disease (aGVHD). *Bone Marrow Transplant*. 2004 Jan;33(1):131-2. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/14566330?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/14566330?tool=bestpractice.bmj.com)
121. Wandroo F, Auguston B, Cook M, et al. Successful use of Campath-1H in the treatment of steroid refractory liver GvHD. *Bone Marrow Transplant*. 2004 Aug;34(3):285-7. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/15170160?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/15170160?tool=bestpractice.bmj.com)

122. Chakrabarti S, Mackinnon S, Chopra R, et al. High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. *Blood*. 2002 Jun 15;99(12):4357-63. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/99/12/4357\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/99/12/4357) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/12036862?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/12036862?tool=bestpractice.bmj.com)
123. Chakrabarti S, Mautner V, Osman H, et al. Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. *Blood*. 2002 Sep 1;100(5):1619-27. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/100/5/1619\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/100/5/1619) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/12176880?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/12176880?tool=bestpractice.bmj.com)
124. Alousi AM, Weisdorf DJ, Logan BR, et al; Blood and Marrow Transplant Clinical Trials Network. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. *Blood*. 2009 Jul 16;114(3):511-7. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713466\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713466) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/19443659?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/19443659?tool=bestpractice.bmj.com)
125. Greinix HT, Ayuk F, Zeiser R. Extracorporeal photopheresis in acute and chronic steroid-refractory graft-versus-host disease: an evolving treatment landscape. *Leukemia*. 2022 Nov;36(11):2558-66. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC9613461\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC9613461) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/36153436?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/36153436?tool=bestpractice.bmj.com)
126. Abu-Dalle I, Reljic T, Nishihori T, et al. Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies. *Biol Blood Marrow Transplant*. 2014 Nov;20(11):1677-86. [Full text \(https://www.astctjournal.org/article/S1083-8791\(14\)00315-2/fulltext\)](https://www.astctjournal.org/article/S1083-8791(14)00315-2/fulltext) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/24867779?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/24867779?tool=bestpractice.bmj.com)
127. Buder K, Zirngibl M, Bapistella S, et al. Extracorporeal photopheresis versus standard treatment for acute graft-versus-host disease after haematopoietic stem cell transplantation in children and adolescents. *Cochrane Database Syst Rev*. 2022 Sep 27;9(9):CD009759. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC9514720\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC9514720) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/36166494?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/36166494?tool=bestpractice.bmj.com)
128. Malard F, Huang XJ, Sim JPY. Treatment and unmet needs in steroid-refractory acute graft-versus-host disease. *Leukemia*. 2020 May;34(5):1229-40. [Full text \(https://pmc.ncbi.nlm.nih.gov/articles/PMC7192843\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC7192843) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/32242050?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/32242050?tool=bestpractice.bmj.com)
129. Martin PJ, Weisdorf D, Przepiorka D, et al; Design of Clinical Trials Working Group. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: VI. Design of Clinical Trials Working Group report. *Biol Blood Marrow Transplant*. 2006 May;12(5):491-505. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16635784?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16635784?tool=bestpractice.bmj.com)
130. Le RQ, Wang X, Zhang H, et al. FDA approval summary: ruxolitinib for treatment of chronic graft-versus-host disease after failure of one or two lines of systemic therapy. *Oncologist*. 2022 Jun

- 8;27(6):493-500. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC9177119>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/35363318?tool=bestpractice.bmj.com>)
131. Zeiser R, Poverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med*. 2021 Jul 15;385(3):228-38. Full text (<https://www.nejm.org/doi/10.1056/NEJMoa2033122>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/34260836?tool=bestpractice.bmj.com>)
 132. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood*. 2017 Nov 23;130(21):2243-50. Full text (<http://www.bloodjournal.org/content/130/21/2243.long>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/28924018?tool=bestpractice.bmj.com>)
 133. European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 26-29 September 2022. Sep 2022 [internet publication]. Full text (<https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-26-29-september-2022>)
 134. Tang CPS, Lip GYH, McCormack T, et al. Management of cardiovascular complications of bruton tyrosine kinase inhibitors. *Br J Haematol*. 2022 Jan;196(1):70-8. Full text (<https://onlinelibrary.wiley.com/doi/10.1111/bjh.17788>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/34498258?tool=bestpractice.bmj.com>)
 135. Cutler C, Lee SJ, Arai S, et al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. *Blood*. 2021 Dec 2;138(22):2278-89. Full text (<https://ashpublications.org/blood/article/138/22/2278/476399/Belumosedil-for-chronic-graft-versus-host-disease>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/34265047?tool=bestpractice.bmj.com>)
 136. Wolff D, Cutler C, Lee SJ, et al. Axatilimab in recurrent or refractory chronic graft-versus-host disease. *N Engl J Med*. 2024 Sep 19;391(11):1002-14. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/39292927?tool=bestpractice.bmj.com>)
 137. Zaja F, Bacigalupo A, Patriarca F, et al. Treatment of refractory chronic GVHD with rituximab: a GITMO study. *Bone Marrow Transplant*. 2007 Aug;40(3):273-7. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17549053?tool=bestpractice.bmj.com>)
 138. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood*. 2006 Jul 15;108(2):756-62. Full text (<http://bloodjournal.hematologylibrary.org/cgi/reprint/108/2/756>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/16551963?tool=bestpractice.bmj.com>)
 139. Carpenter PA, Logan BR, Lee SJ, et al; BMT CTN. A phase II/III randomized, multicenter trial of prednisone/sirolimus versus prednisone/ sirolimus/calcineurin inhibitor for the treatment of chronic graft-versus-host disease: BMT CTN 0801. *Haematologica*. 2018 Nov;103(11):1915-24. Full text (<http://www.haematologica.org/content/103/11/1915.long>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/29954931?tool=bestpractice.bmj.com>)
 140. Jacobsohn DA, Chen AR, Zahurak M, et al. Phase II study of pentostatin in patients with corticosteroid-refractory chronic graft-versus-host disease. *J Clin Oncol*. 2007 Sep 20;25(27):4255-61.

Full text (<http://jco.ascopubs.org/cgi/content/full/25/27/4255>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/17878478?tool=bestpractice.bmj.com>)

141. Buder K, Zirngibl M, Bapistella S, et al. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in children and adolescents. *Cochrane Database Syst Rev*. 2022 Jun 9;6(6):CD009898. Full text (<https://pmc.ncbi.nlm.nih.gov/articles/PMC9181448>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/35679154?tool=bestpractice.bmj.com>)
142. Dignan FL, Scarisbrick JJ, Cornish J, et al. Organ-specific management and supportive care in chronic graft-versus-host disease. *Br J Haematol*. 2012 Jul;158(1):62-78. Full text (<https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2141.2012.09131.x?sid=nlm%3Apubmed>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/22533889?tool=bestpractice.bmj.com>)
143. Tomblyn M, Chiller T, Einsele H, et al; Center for International Blood and Marrow Research; National Marrow Donor program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Disease Canada; Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009 Oct;15(10):1143-238. Full text (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3103296>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/19747629?tool=bestpractice.bmj.com>)
144. Epstein JB, Raber-Drulacher JE, Wilkins A, et al. Advances in hematologic stem cell transplant: an update for oral health care providers. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009 Mar;107(3):301-12. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/19217013?tool=bestpractice.bmj.com>)
145. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2015 Jun;21(6):984-99. Full text ([https://www.astctjournal.org/article/S1083-8791\(15\)00155-X/fulltext](https://www.astctjournal.org/article/S1083-8791(15)00155-X/fulltext)) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/25796139?tool=bestpractice.bmj.com>)
146. Bolanos-Meade J, Jacobsohn DA, Margolis J, et al. Pentostatin in steroid-refractory acute graft-versus-host disease. *J Clin Oncol*. 2005 Apr 20;23(12):2661-8. Full text (<http://jco.ascopubs.org/cgi/content/full/23/12/2661>) Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/15837980?tool=bestpractice.bmj.com>)
147. Kim ST, Lee MH, Kim SY, et al. A randomized trial of preemptive therapy for prevention of cytomegalovirus disease after allogeneic hematopoietic stem cell transplantation. *Int J Hematol*. 2010 Jun;91(5):886-91. Abstract (<http://www.ncbi.nlm.nih.gov/pubmed/20454943?tool=bestpractice.bmj.com>)
148. Maertens J, Marchetti O, Herbrecht. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3 - 2009. *Bone Marrow*

Transplant. 2011 May;46(5):709-18. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/20661235?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/20661235?tool=bestpractice.bmj.com)

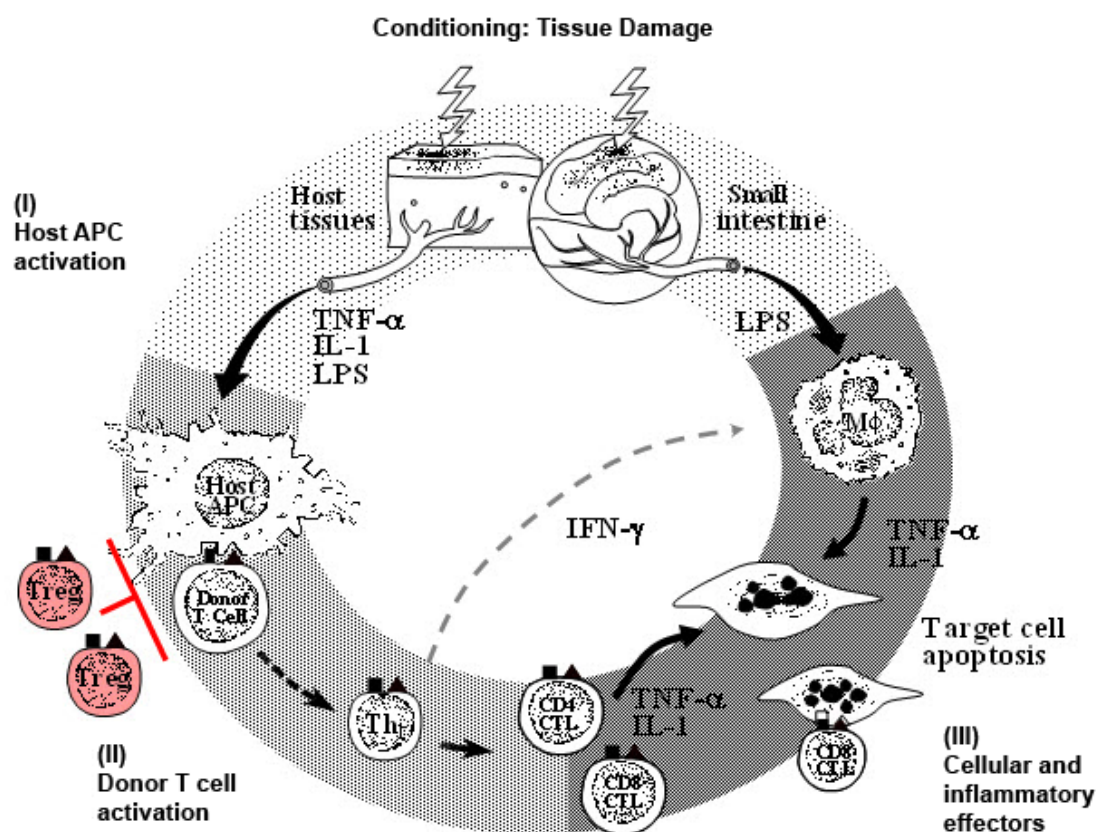
149. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010 Dec 9;116(24):5111-8. [Full text \(http://bloodjournal.hematologylibrary.org/content/116/24/5111.long\)](http://bloodjournal.hematologylibrary.org/content/116/24/5111.long) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/20826719?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/20826719?tool=bestpractice.bmj.com)
150. Food and Drug Administration. FDA requires boxed warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. Mar 2020 [internet publication]. [Full text \(https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug\)](https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug)
151. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002 Jul 1;166(1):111-7. [Full text \(http://www.atsjournals.org/doi/full/10.1164/ajrccm.166.1.at1102#.UkATT9pggZk\)](http://www.atsjournals.org/doi/full/10.1164/ajrccm.166.1.at1102#.UkATT9pggZk) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/12091180?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/12091180?tool=bestpractice.bmj.com)
152. Zeiser R, Socié G, Schroeder MA, et al. Efficacy and safety of itacitinib versus placebo in combination with corticosteroids for initial treatment of acute graft-versus-host disease (GRAVITAS-301): a randomised, multicentre, double-blind, phase 3 trial. *Lancet Haematol*. 2022 Jan;9(1):e14-e25. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/34971577?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/34971577?tool=bestpractice.bmj.com)
153. Choi SW, Braun T, Chang L, et al. Vorinostat plus tacrolimus and mycophenolate to prevent graft-versus-host disease after related-donor reduced-intensity conditioning allogeneic haemopoietic stem-cell transplantation: a phase 1/2 trial. *Lancet Oncol*. 2014 Jan;15(1):87-95. [Full text \(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103793\)](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103793) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/24295572?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/24295572?tool=bestpractice.bmj.com)
154. Choi SW, Braun T, Henig I, et al. Vorinostat plus tacrolimus/methotrexate to prevent GVHD after myeloablative conditioning, unrelated donor HCT. *Blood*. 2017 Oct 12;130(15):1760-7. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639486\)](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639486) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/28784598?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/28784598?tool=bestpractice.bmj.com)
155. ClinicalTrials.gov. Vorinostat for graft vs host disease prevention in children, adolescents and young adults undergoing allogeneic blood and marrow transplantation. 2024 [internet publication]. [Full text \(https://clinicaltrials.gov/study/NCT03842696?cond=GVHD&intr=vorinostat&rank=1\)](https://clinicaltrials.gov/study/NCT03842696?cond=GVHD&intr=vorinostat&rank=1)
156. Chang YJ, Xu LP, Wang Y, et al. Controlled, randomized, open-label trial of risk-stratified corticosteroid prevention of acute graft-versus-host disease after haploidentical transplantation. *J Clin Oncol*. 2016 Jun 1;34(16):1855-63. [Full text \(http://jco.ascopubs.org/content/34/16/1855.long\)](http://jco.ascopubs.org/content/34/16/1855.long) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/27091717?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/27091717?tool=bestpractice.bmj.com)
157. Schmidt-Hieber M, Fietz T, Knauf W, et al. Efficacy of the interleukin-2 receptor antagonist basiliximab in steroid-refractory acute graft-versus-host disease. *Br J Haematol*. 2005 Aug;130(4):568-74. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16098072?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16098072?tool=bestpractice.bmj.com)

158. Podichetty JT, Brinda BJ, Nelson RP, et al. Pharmacokinetics of basiliximab for the prevention of graft-versus-host disease in patients undergoing hematopoietic cell transplantation with minimal-intensity cyclophosphamide and fludarabine. *Pharmacotherapy*. 2020 Jan;40(1):26-32. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/31742732?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/31742732?tool=bestpractice.bmj.com)
159. Freyer CW, Gier S, Carulli A, et al. Salvage therapy with basiliximab and etanercept for severe steroid-refractory acute graft-versus-host disease. *Am J Hematol*. 2022 Jul;97(7):E273-6. [Full text \(https://onlinelibrary.wiley.com/doi/10.1002/ajh.26568\)](https://onlinelibrary.wiley.com/doi/10.1002/ajh.26568) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/35413140?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/35413140?tool=bestpractice.bmj.com)
160. Mo XD, Hong SD, Zhao YL, et al. Basiliximab for steroid-refractory acute graft-versus-host disease: a real-world analysis. *Am J Hematol*. 2022 Apr;97(4):458-69. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/35064928?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/35064928?tool=bestpractice.bmj.com)
161. Koreth J, Chhabra S, Pidala J, et al. Equate, a phase 1b/2 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical activity of a novel targeted anti-CD6 therapy, itolizumab, in subjects with newly diagnosed acute graft versus host disease. *Blood*. 2019;134:4516. [Full text \(https://ashpublications.org/blood/article/134/Supplement_1/4516/424498/Equate-a-Phase-1b-2-Study-Evaluating-the-Safety\)](https://ashpublications.org/blood/article/134/Supplement_1/4516/424498/Equate-a-Phase-1b-2-Study-Evaluating-the-Safety)
162. Nagai H, Shimizu K, Shikata J, et al. Chylous leakage after circumferential thoracolumbar fusion for correction of kyphosis resulting from fracture. Report of three cases. *Spine (Phila Pa 1976)*. 1997 Dec 1;22(23):2766-9. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/9431612?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/9431612?tool=bestpractice.bmj.com)
163. ClinicalTrials.gov. Safety study of gene modified donor T-cells following TCRαβ+ depleted stem cell transplant. Jan 2023 [internet publication]. [Full text \(https://clinicaltrials.gov/ct2/show/NCT02065869\)](https://clinicaltrials.gov/ct2/show/NCT02065869)
164. ClinicalTrials.gov. Long term follow-up study for patients enrolled on the BP-004 clinical study. Jul 2022 [internet publication]. [Full text \(https://clinicaltrials.gov/ct2/show/NCT03733249\)](https://clinicaltrials.gov/ct2/show/NCT03733249)
165. Leisenring WM, Martin PJ, Petersdorf EW, et al. An acute graft-versus-host disease activity index to predict survival after hematopoietic cell transplantation with myeloablative conditioning regimens. *Blood*. 2006 Jul 15;108(2):749-55. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/108/2/749\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/108/2/749) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16537799?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16537799?tool=bestpractice.bmj.com)
166. Van Lint MT, Milone G, Leotta S, et al. Treatment of acute graft-versus-host disease with prednisolone: significant survival advantage for day +5 responders and no advantage for nonresponders receiving anti-thymocyte globulin. *Blood*. 2006 May 15;107(10):4177-81. [Full text \(http://bloodjournal.hematologylibrary.org/cgi/content/full/107/10/4177\)](http://bloodjournal.hematologylibrary.org/cgi/content/full/107/10/4177) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16449522?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16449522?tool=bestpractice.bmj.com)
167. Bolanos-Meade J, Vogelsang GB. Novel strategies for steroid-refractory acute graft-versus-host disease. *Curr Opin Hematol*. 2005 Jan;12(1):40-4. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/15604890?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/15604890?tool=bestpractice.bmj.com)
168. Goerner M, Gooley T, Flowers ME, et al. Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory

anemias. Biol Blood Marrow Transplant. 2002;8(1):47-56. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/11858190?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/11858190?tool=bestpractice.bmj.com)

169. Baird K, Pavletic SZ. Chronic graft versus host disease. Curr Opin Hematol. 2006 Nov;13(6):426-35. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/17053454?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/17053454?tool=bestpractice.bmj.com)
170. Flowers MED, Storer B, Carpenter P, et al. Treatment change as a predictor of outcome among patients with classic chronic GVHD. Biol Blood Marrow Transplant. 2008 Dec;14(12):1380-4. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/19041060?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/19041060?tool=bestpractice.bmj.com)
171. Rizzo JD, Curtis RE, Socie G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. Blood. 2009 Jan 29;113(5):1175-83. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/18971419?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/18971419?tool=bestpractice.bmj.com)
172. Carpenter PA, Kitko CL, Elad S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group report. Biol Blood Marrow Transplant. 2015 Jul;21(7):1167-87. [Full text \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821166\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821166) [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/25838185?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/25838185?tool=bestpractice.bmj.com)
173. National Marrow Donor Program. Post-transplant care guideline: long-term care recommendations. 2023 [internet publication]. [Full text \(https://network.nmdp.org/-/media/project/nmdp/networkresourcecenter/pdfs/services-support/hematology-oncology/post-transplant-care/np23070-posttransplantcareguidelines-11x85-2024-08-27-digitalversion.pdf?rev=becc1a5035cd4723ae097805cf5599da&hash=17E46BBDA99FE0AD90E8804BF95FCD1\)](https://network.nmdp.org/-/media/project/nmdp/networkresourcecenter/pdfs/services-support/hematology-oncology/post-transplant-care/np23070-posttransplantcareguidelines-11x85-2024-08-27-digitalversion.pdf?rev=becc1a5035cd4723ae097805cf5599da&hash=17E46BBDA99FE0AD90E8804BF95FCD1)
174. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and the American Society for Blood and Marrow Transplantation (EBMT/CIBMTR/ASBMT). Bone Marrow Transplant. 2006 Feb;37(3):249-61. [Abstract \(http://www.ncbi.nlm.nih.gov/pubmed/16435004?tool=bestpractice.bmj.com\)](http://www.ncbi.nlm.nih.gov/pubmed/16435004?tool=bestpractice.bmj.com)

Images



GVHD Pathophysiology. In Phase I, the recipient conditioning regimen damages host tissues and causes release of inflammatory cytokines such as $\text{TNF}\alpha$, IL-1 and IL-6 . Increased levels of these cytokines leads to activation of host antigen presenting cells (APCs). In Phase II, host APCs activate mature donor cells. The subsequent proliferation and differentiation of these activated T cells produces additional effectors that mediate the tissue damage, including Cytotoxic T Lymphocytes, natural killer (NK) cells, $\text{TNF}\alpha$ and IL-1 . Lipopolysaccharide (LPS) that has leaked through the damaged intestinal mucosa triggers additional $\text{TNF}\alpha$ production. $\text{TNF}\alpha$ can damage tissue directly by inducing necrosis and apoptosis in the skin and GI tract through either TNF receptors or the Fas pathway. $\text{TNF}\alpha$ plays a direct role in intestinal GVHD damage, which further amplifies damage in the skin, liver and lung in a "cytokine storm."

Figure 1: GVHD pathophysiology

Courtesy of Dr James L.M. Ferrara, Professor, Blood and Marrow Transplantation Program, University of Michigan; used with permission



Figure 2: Acute graft-versus-host disease (GVHD) of the skin (grade I)

Courtesy of Dr John Levine, Professor, Blood and Marrow Transplantation Program, University of Michigan; used with permission

Clinical manifestations	Diagnostic for chronic GVHD	Distinctive for chronic GVHD (i.e., seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other features or unclassified entities (can be acknowledged as part of the chronic GVHD manifestations if diagnosis confirmed)	Features shared with acute GVHD
Skin	<ul style="list-style-type: none"> • Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features 	<ul style="list-style-type: none"> • Depigmentation • Papulosquamous lesions 	<ul style="list-style-type: none"> • Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation 	<ul style="list-style-type: none"> • Erythema • Maculopapular rash • Pruritus
Nails		<ul style="list-style-type: none"> • Dystrophy • Longitudinal ridging, splitting, or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails) 		
Scalp and body hair		<ul style="list-style-type: none"> • New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling 	<ul style="list-style-type: none"> • Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) • Premature gray hair 	
Mouth	<ul style="list-style-type: none"> • Lichen planus-like changes 	<ul style="list-style-type: none"> • Xerostomia • Mucocoeles • Mucosal atrophy • Ulcers • Pseudomembranes 		<ul style="list-style-type: none"> • Gingivitis • Mucositis • Erythema • Pain
Eyes		<ul style="list-style-type: none"> • New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy 	<ul style="list-style-type: none"> • Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eyelids with edema) 	
Gastrointestinal tract	<ul style="list-style-type: none"> • Esophageal web • Strictures or stenosis in the upper to mid third of the oesophagus 		<ul style="list-style-type: none"> • Exocrine pancreatic insufficiency 	<ul style="list-style-type: none"> • Anorexia • Nausea • Vomiting • Diarrhoea • Weight loss • Failure to thrive (infants and children)
Genitalia	<ul style="list-style-type: none"> • Lichen planus-like features • Lichen sclerosus-like features • Female: vaginal scarring or clitorallabial agglutination • Male: phimosis or urethral/meatus scarring or stenosis 	<ul style="list-style-type: none"> • Erosions • Fissures • Ulcers 		
Lung	<ul style="list-style-type: none"> • Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ) 	<ul style="list-style-type: none"> • Air trapping and bronchiectasis on chest CT 	<ul style="list-style-type: none"> • Cryptogenic organising pneumonia (pulmonary entities under investigation or unclassified) • Restrictive lung disease (pulmonary entities under investigation or unclassified) 	
Liver				<ul style="list-style-type: none"> • Total bilirubin, alkaline phosphatase >2 times upper limit of normal • Alanine aminotransferase >2 times upper limit of normal
Muscles, fascia, joints	<ul style="list-style-type: none"> • Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis 	<ul style="list-style-type: none"> • Myositis or polymyositis (diagnosis of chronic GVHD requires biopsy) 	<ul style="list-style-type: none"> • Oedema • Muscle cramps • Arthralgia or arthritis 	
Hematopoietic and immune			<ul style="list-style-type: none"> • Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (autoimmune haemolytic anemia, immune thrombocytopenia) • Raynaud's phenomenon 	
Other			<ul style="list-style-type: none"> • Serositis (pericardial or pleural effusions, ascites) • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy 	

Figure 3: Clinical manifestations of chronic graft versus host disease from the National Institutes of Health

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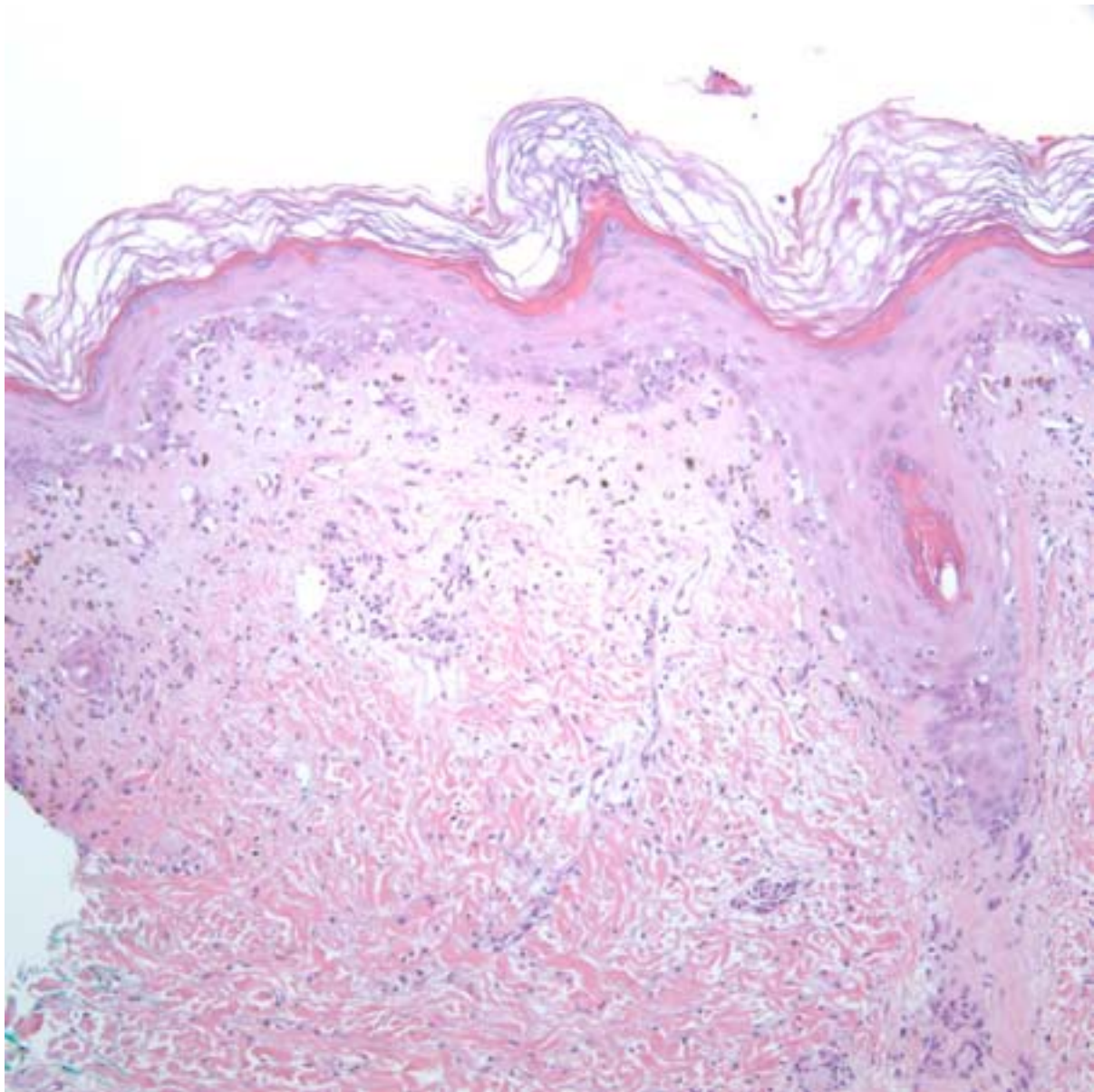


Figure 4: Histology of skin graft-versus-host disease (GVHD) (low power): Vacuolar interface dermatitis at the dermoepidermal junction with involvement of follicular epithelium (100x, haematoxylin and eosin)

Courtesy of Dr Lori Lowe, Professor, Dermatopathology, University of Michigan; used with permission

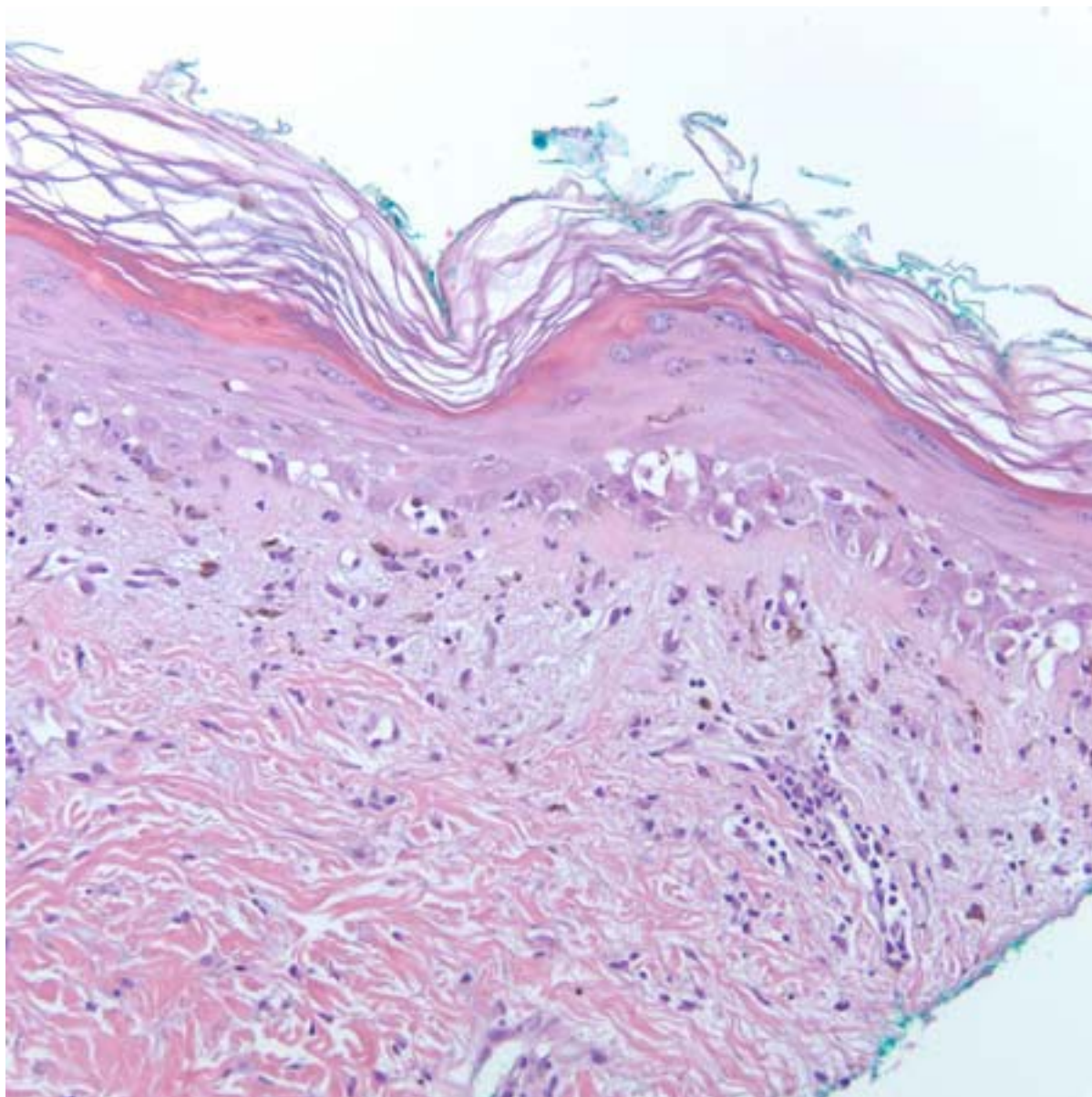


Figure 5: Histology of skin graft-versus-host disease (GVHD) (high power): Vacuolar interface dermatitis with rare necrotic keratinocytes (200x, haematoxylin and eosin)

Courtesy of Dr Lori Lowe, Professor, Dermatopathology, University of Michigan; used with permission

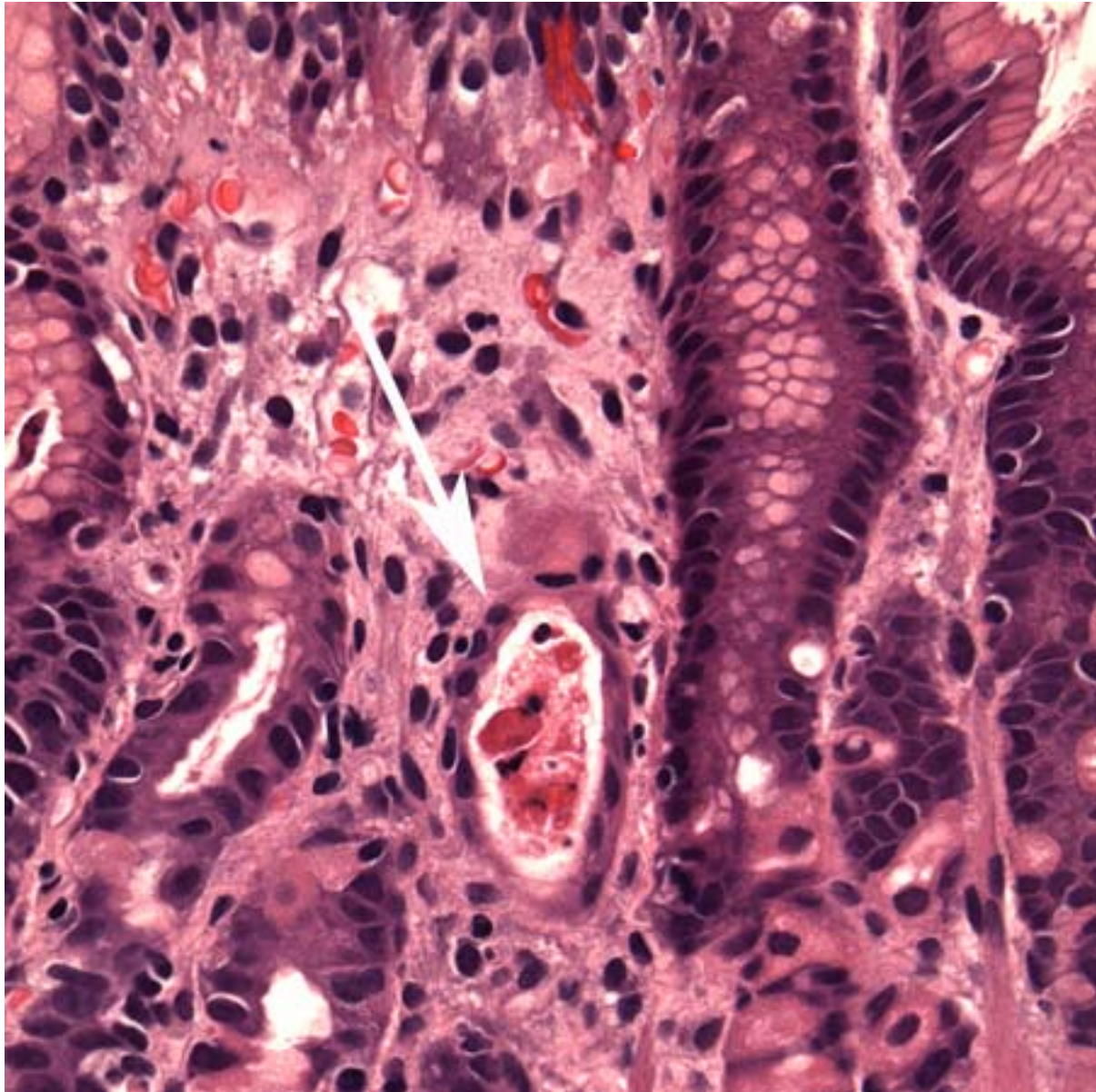


Figure 6: Histology of upper gastrointestinal graft-versus-host disease (GVHD) (medium-power photomicrograph of the stomach): Dilated gastric gland containing necrotic/apoptotic debris (arrow), typical of GVHD

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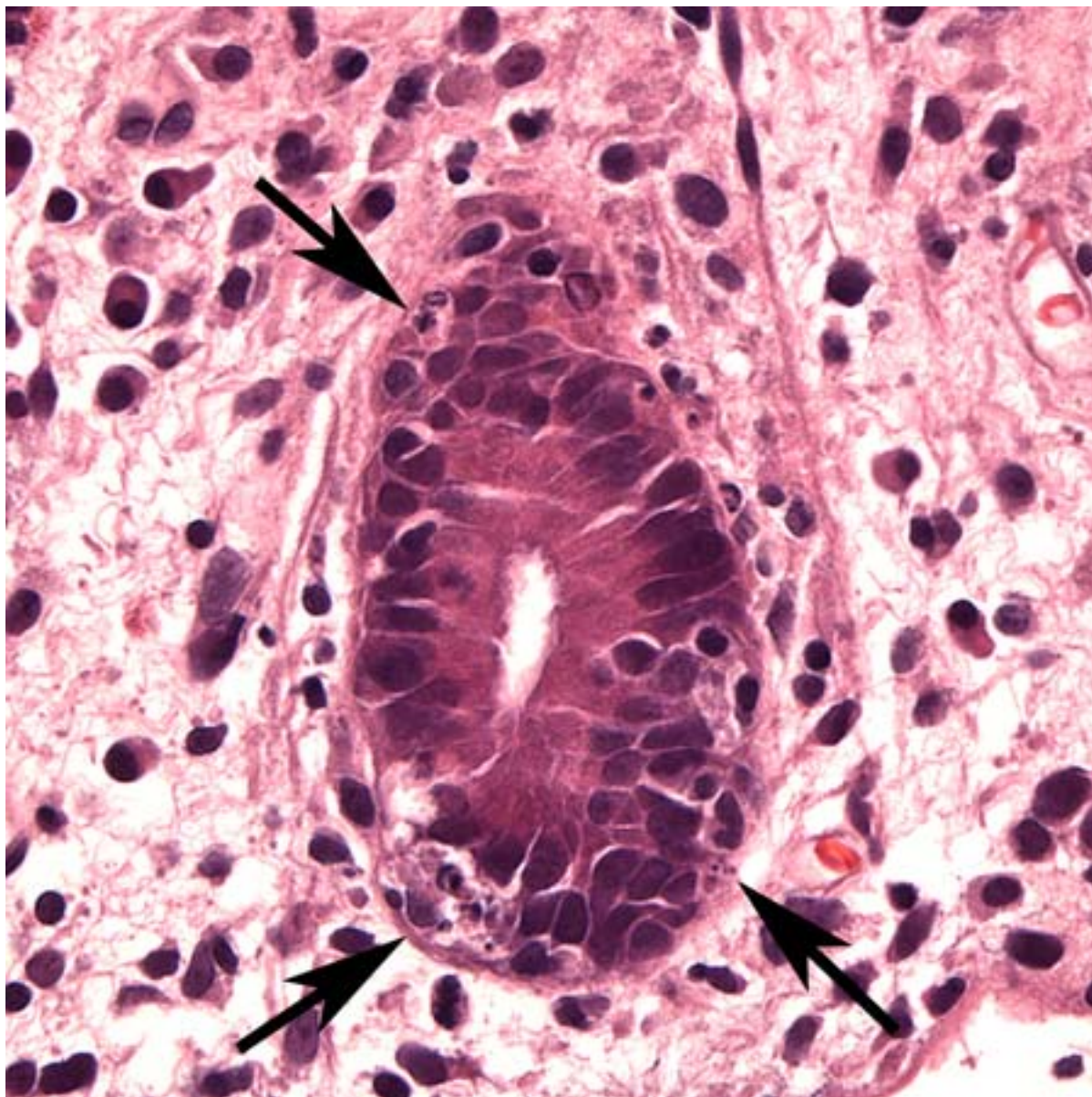


Figure 7: Histology of lower gastrointestinal graft-versus-host disease (GVHD) (high-power photomicrograph of colon, mild disease): Numerous apoptotic bodies (arrows) indicative of GVHD involving the colon

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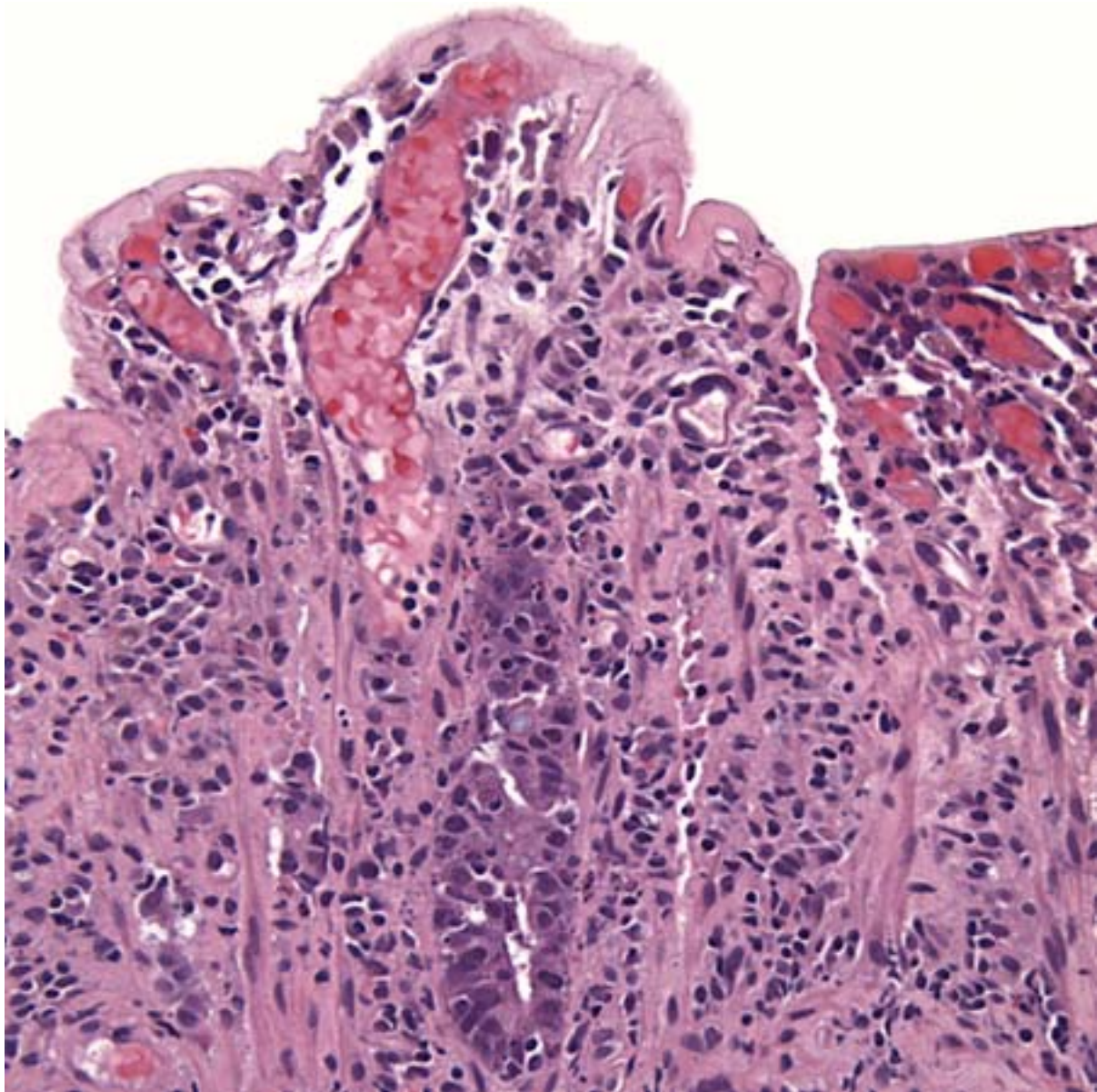


Figure 8: Histology of lower gastrointestinal graft-versus-host disease (GVHD) (medium-power photomicrograph of colon, severe disease): Almost complete denudation of the mucosa indicative of severe GVHD involving the colon

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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numerals < 1: 0.25

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