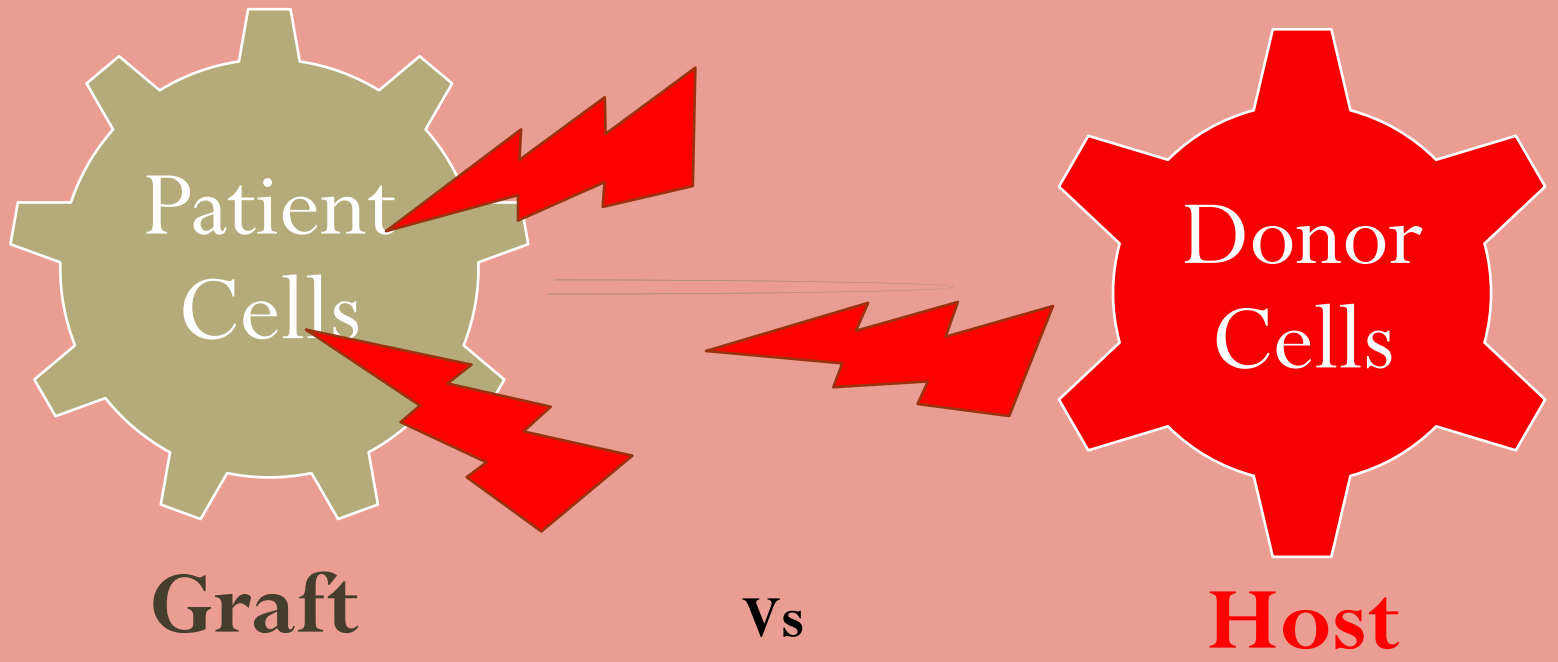

Graft Vs Host Disease

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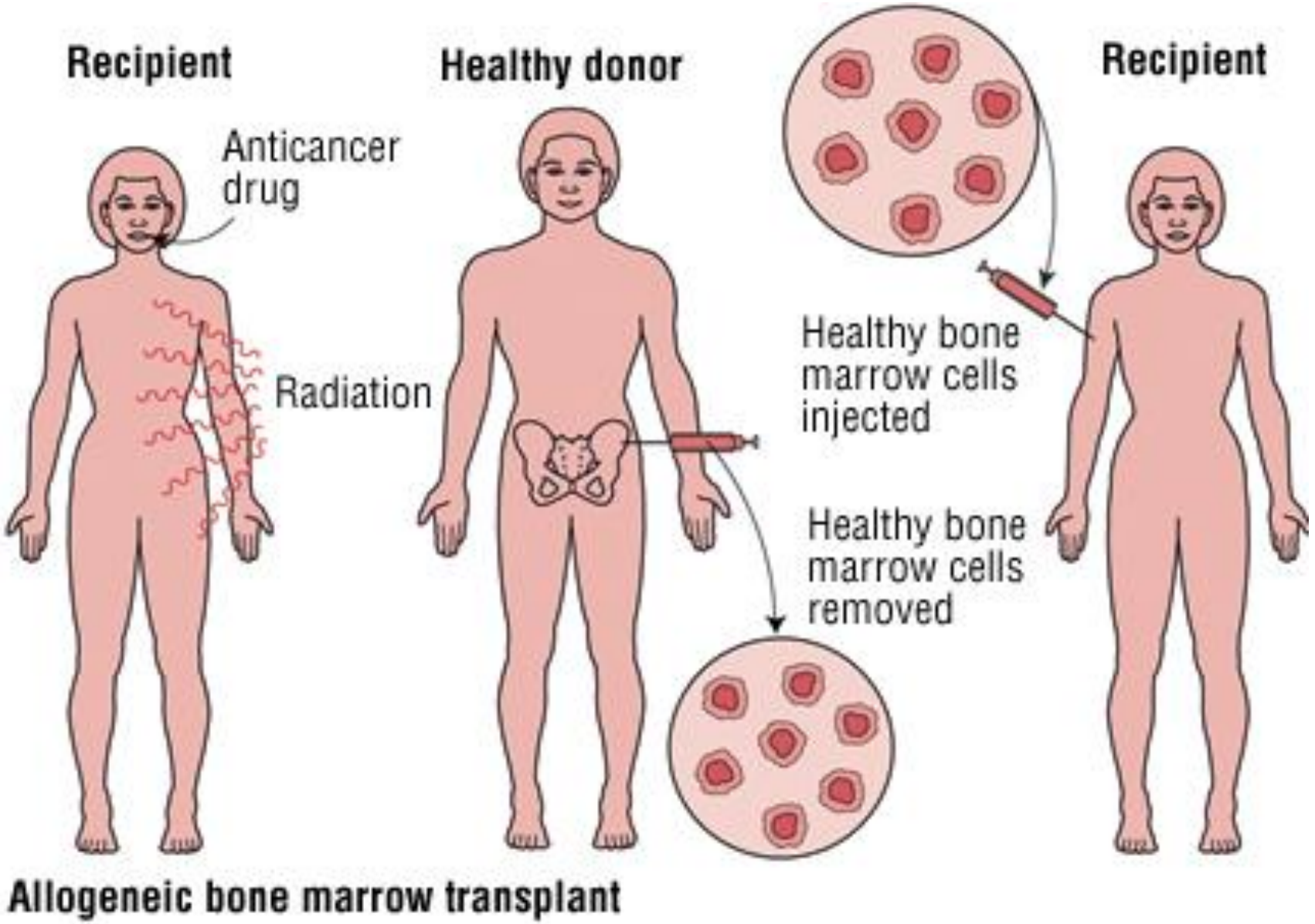
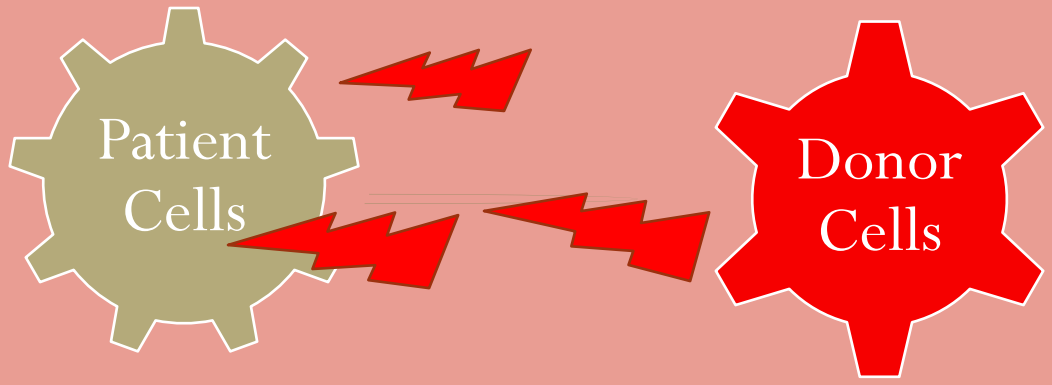
Outlines

- Definition
- Pathophysiology
- Risk factors
- Diagnosis
- Treatment
- Nursing care



http://www.drugs.com/health-guide/bone-marrow-transplant.html



Graft Vs Host Disease

GVHD occurs when immune cells transplanted froma donor (the **graft**) recognize the recipient (the **host**) as foreign, thereby initiating an immune reaction that causes disease.

Nelson J Chao, 2004 upto date

Classification

Acute vs Chronic based upon the time of onset using a cutoff of 100 days.

- ●**Classic acute GVHD** – Cases present within 100 days of (HCT) and display features of acute GVHD. Diagnostic and distinctive features of chronic GVHD are absent.

- ●**Persistent, recurrent, late onset acute GVHD** – Cases present greater than 100 days post-HCT with features of acute GVHD. Diagnostic and distinctive features of chronic GVHD are absent.

- ●**Classic chronic GVHD** – Cases may present at any time post-HCT. Diagnostic and distinctive features of chronic GVHD are present. There are no features of acute GVHD.

- ●**Overlap syndrome** – Cases may present at any time post-HCT with features of both chronic GVHD and acute GVHD. On occasion, this is colloquially referred to as "acute on chronic" GVHD.

Acute vs Chronic GVHD

- Acute GVHD describes a distinctive syndrome of
  - dermatitis,
  - hepatitis,
  - enteritis developing within 100 days of allogeneic

- Chronic GVHD describes a more diverse syndrome developing after day 100.

(Mandanas et al, 2004)

Review of Chronic Graft-Versus-Host Disease in Children After Allogeneic Stem Cell Transplantation: Nursing Perspective CE

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Marilyn Hockenberry, PhD, RN-CS, PNP, FAAN[1]

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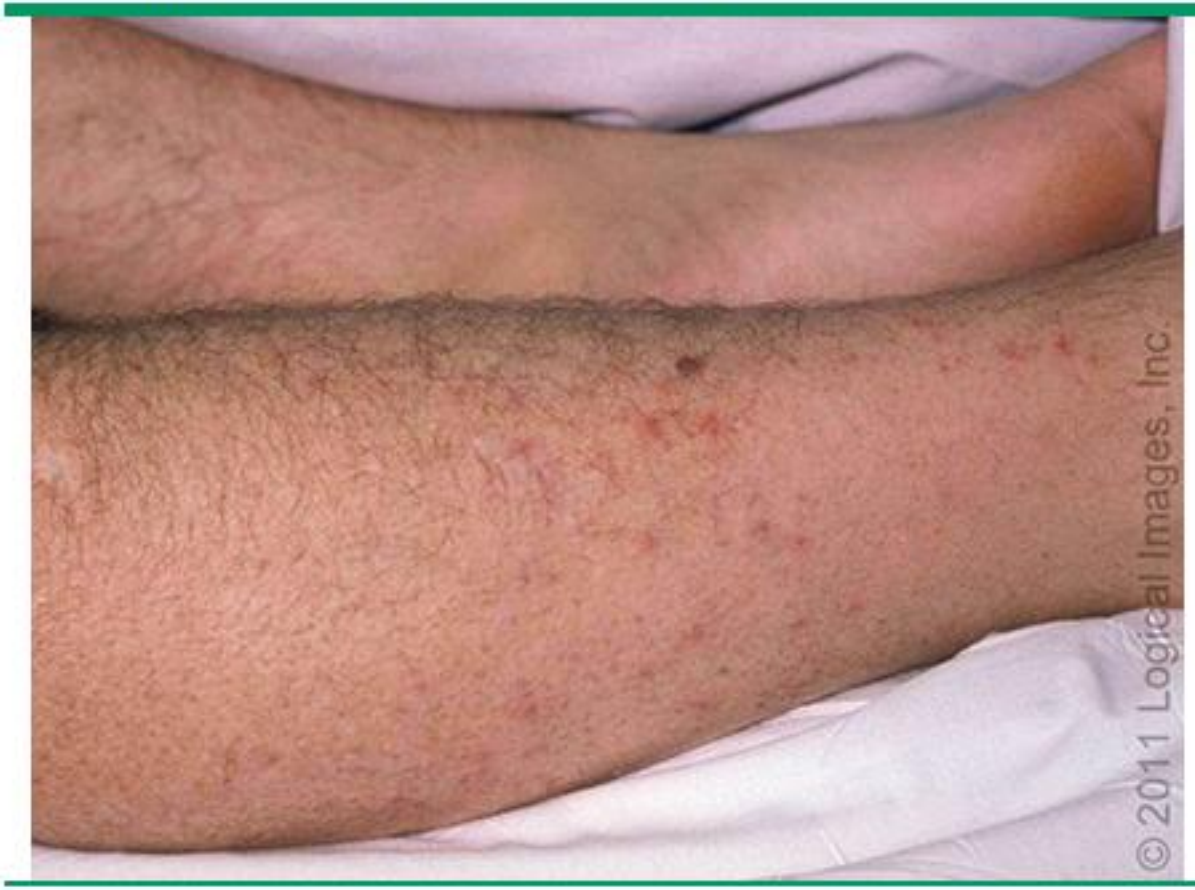
Table 1. Signs and Symptoms of Chronic GVHD[a]

Organ or Site	Diagnostic Sign	Distinctive Sign
Skin	Poikiloderma; lichen planus–like features; sclerotic features; morphea-like features; lichen sclerosus–like features	Depigmentation
Nails		Dystrophy; longitudinal ridging, splitting, or brittle features; onycholysis; pterygium unguis; nail loss (usually symmetric, affects most nails)
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy); scaling, papulosquamous lesions
Mouth	Lichen-type features; hyperkeratotic plaques; restriction of mouth opening from sclerosis	Xerostomia; mucocele; mucosal atrophy; pseudomembranes
Eyes		New onset dry, gritty, or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; confluent areas of punctate keratopathy
Genitalia	Lichen planus–like features; vaginal scarring or stenosis	Erosions; fissures; ulcers
GI tract	Esophageal web; strictures or stenosis in the upper to midthird of the esophagus	
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology
Muscles, fascia, joints	Fasciitis; joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis

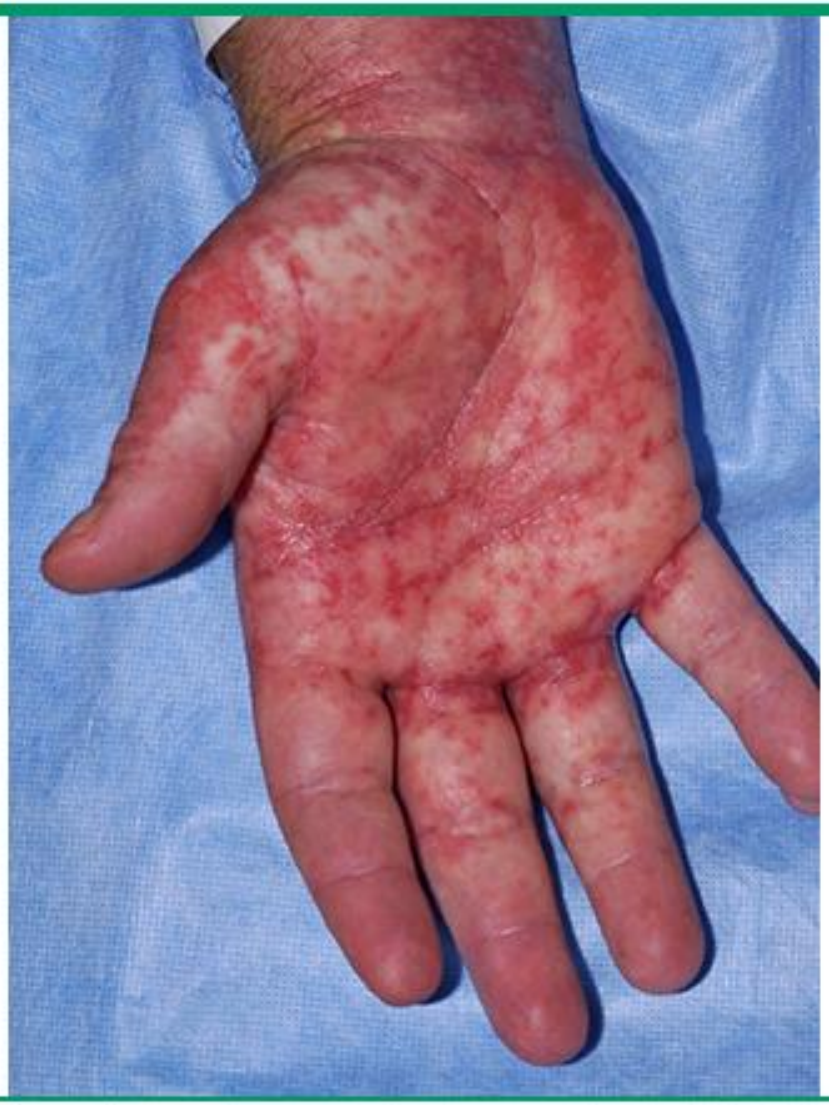
Abbreviations: GVHD, graft-versus-host disease; GI, gastrointestinal; PFTs: pulmonary function tests.
[a]Adapted from Filipovich et al. (2005).

Acute graft-versus-host disease



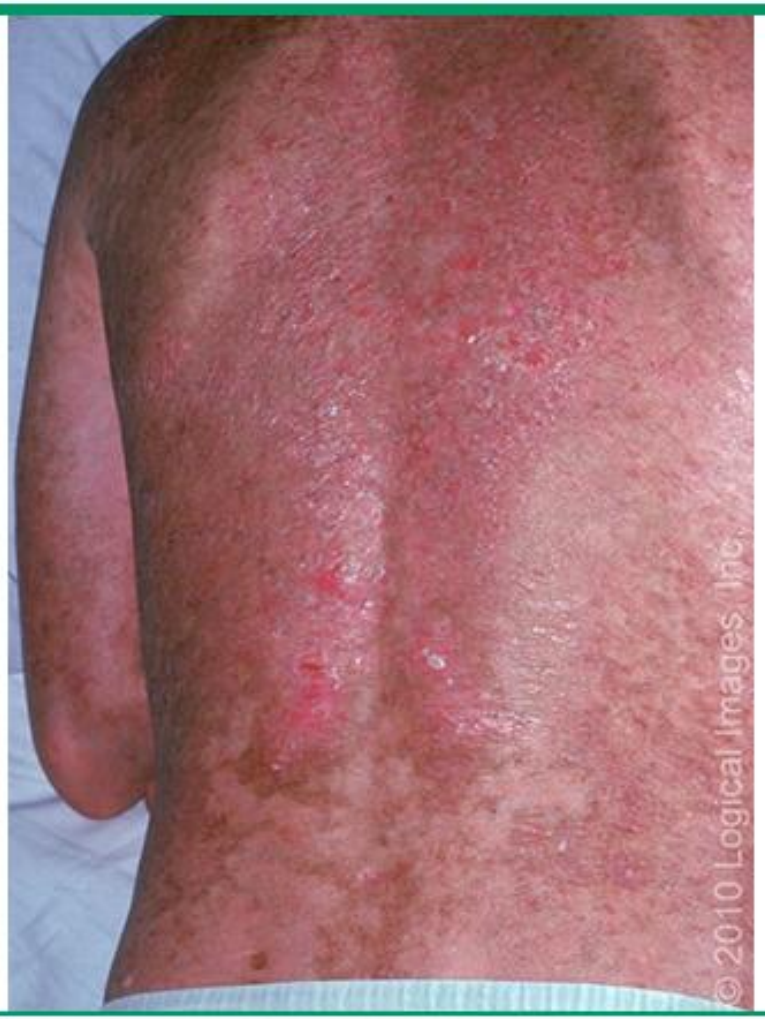
Small, erythematous, follicularly-based macules and papules are present on the distal lower extremities in this patient with acute graft-versus-host disease.

Palmar involvement in acute graft-versus-host disease



Numerous erythematous macules are present on the palm.

Acute graft-versus-host disease

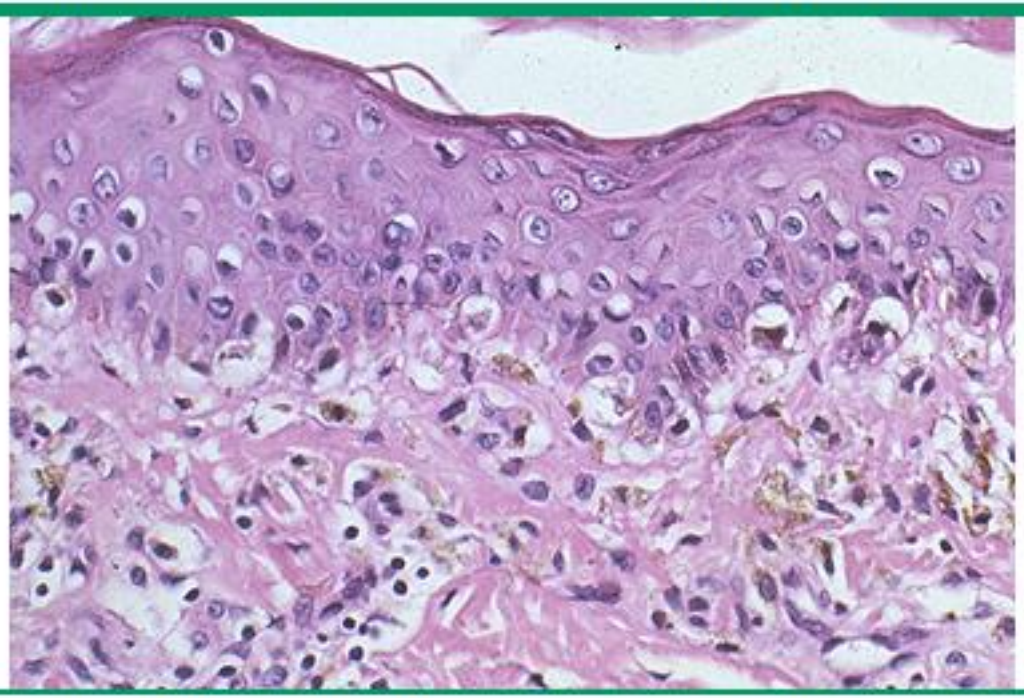


Widespread erythema, desquamation, and postinflammatory hyperpigmentation are evident in this patient with acute graft-versus-host disease.

Toxic epidermal necrolysis

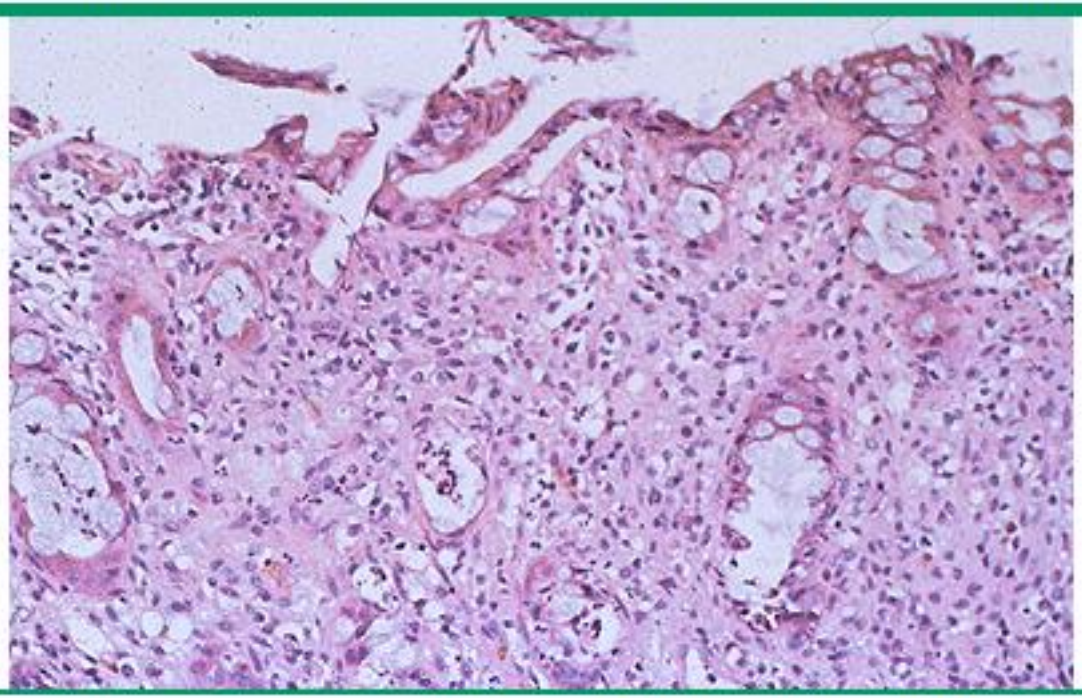
Multiple bullae and areas of denuded epidermis are present.

Acute graft-versus-host disease skin biopsy



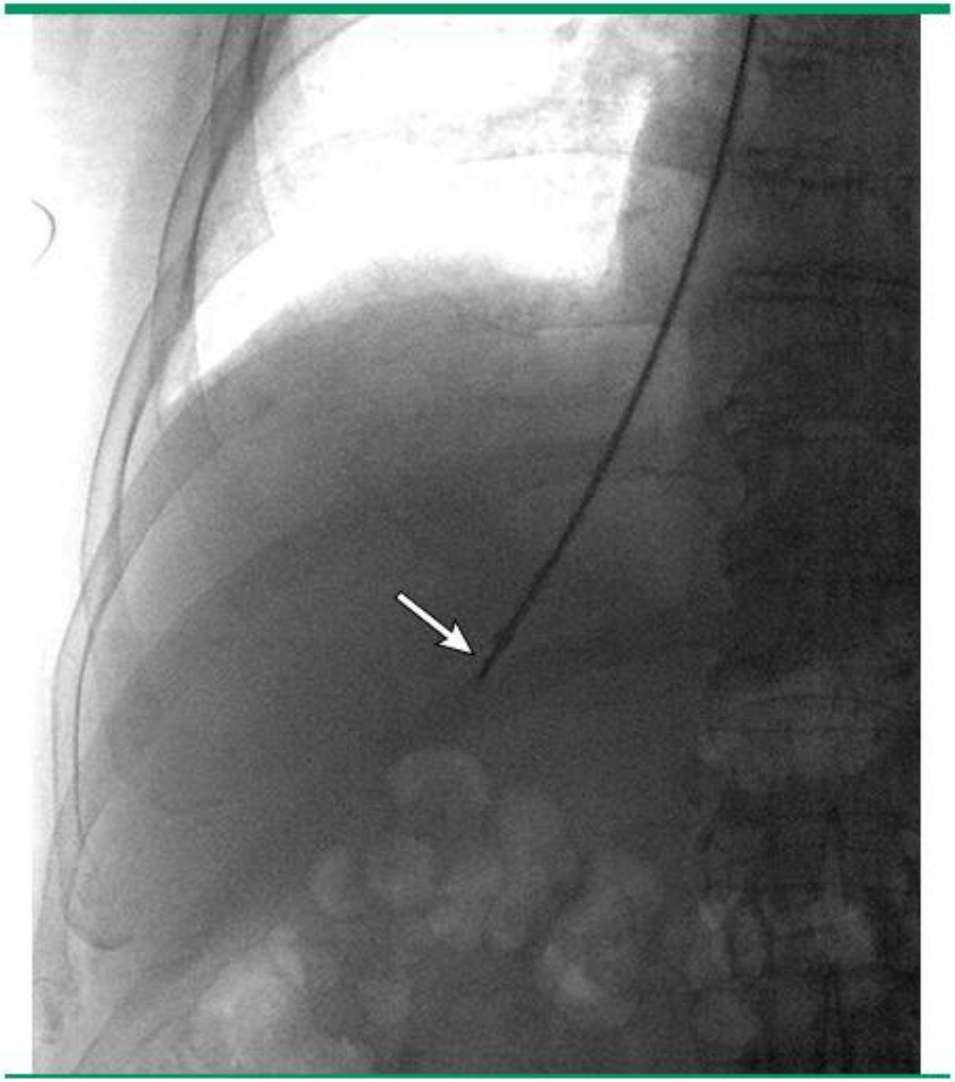
Skin biopsy from a patient with cutaneous manifestations of acute graft-versus-host disease reveals an interface dermatitis.

Acute graft-versus-host disease (GVHD) rectal biopsy



Rectal biopsy in a patient with acute graft-versus-host disease (GVHD) shows crypt cell necrosis with the accumulation of degenerative material in the dead crypts.

Transjugular liver biopsy



Fluoroscopic image of the right upper quadrant of the abdomen showing a catheter with a metallic cannula (arrow) rotated away from the center of the vein pointing toward the liver parenchyma.

Grading of acute graft-versus-host disease

Organ	Stage	Description
Skin	1	Maculopapular rash over <25 percent of body area
	2	Maculopapular rash over 25 to 50 percent of body area
	3	Generalized erythroderma
	4	Generalized erythroderma with bullous formation and often with desquamation
Liver	1	Bilirubin 2.0 to 3.0 mg/dL; SGOT 150 to 750 international units
	2	Bilirubin 3.1 to 6.0 mg/dL
	3	Bilirubin 6.1 to 15.0 mg/dL
	4	Bilirubin >15.0 mg/dL
Gut	1	Diarrhea >30 mL/kg or >500 mL/day
	2	Diarrhea >60 mL/kg or >1000 mL/day
	3	Diarrhea >90 mL/kg or >1500 mL/day
	4	Diarrhea >90 mL/kg or >2000 mL/day; or severe abdominal pain with or without ileus
Glucksberg grade		
I – Stage 1 or 2 skin involvement; no liver or gut involvement; ECOG PS 0		
II – Stage 1 to 3 skin involvement; Grade 1 liver or gut involvement; ECOG PS 1		
III – Stage 2 or 3 skin, liver, or gut involvement; ECOG PS 2		
IV – Stage 1 to 4 skin involvement; Stage 2 to 4 liver or gut involvement; ECOG PS 3		
International Bone Marrow Transplant Registry Severity Index		
A – Stage 1 skin involvement; no liver or gut involvement		
B – Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement		
C – Stage 3 skin, liver, or gut involvement		
D – Stage 4 skin, liver, or gut involvement		

SGOT: serum glutamic oxaloacetic transaminase; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Chronic GVHD

Diagnostic and distinctive clinical manifestations of chronic graft-versus-host disease

Organ or site	Diagnostic (sufficient to establish the diagnosis of chronic GVHD)	Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation
Nails		• Dystrophy • Longitudinal ridging, splitting, or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric; affects most nails)*
Scalp and body hair		• New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) • Scaling, papulosquamous lesions
Mouth	• Lichen-type features • Hyperkeratotic plaques • Restriction of mouth opening from sclerosis	• Xerostomia • Mucocele • Mucosal atrophy • Pseudomembranes* • Ulcers*
Eyes		• New onset dry, gritty, or painful eyes$^{\Delta}$ • Cicatricial conjunctivitis • Keratoconjunctivitis sicca$^{\Delta}$ • Confluent areas of punctate keratopathy
Genitalia	• Lichen planus-like features • Vaginal scarring or stenosis	• Erosions* • Fissures* • Ulcers*
GI tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus*	
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy	• Bronchiolitis obliterans diagnosed with PFTs and radiology$^{\Delta}$
Muscles, fascia, joints	• Fasciitis • Joint stiffness or contractures secondary to sclerosis	• Myositis or polymyositis$^{\Delta}$

Diagnosis of chronic GVHD requires the presence of at least one diagnostic clinical sign of chronic GVHD or the presence of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests in the same or another organ. Furthermore, other possible diagnoses for clinical symptoms must be excluded. No time limit is set for the diagnosis of chronic GVHD.

GVHD: graft-versus-host disease; PFTs: pulmonary function tests.

* In all cases, infection, drug effects, malignancy, or other causes must be excluded.

Δ Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

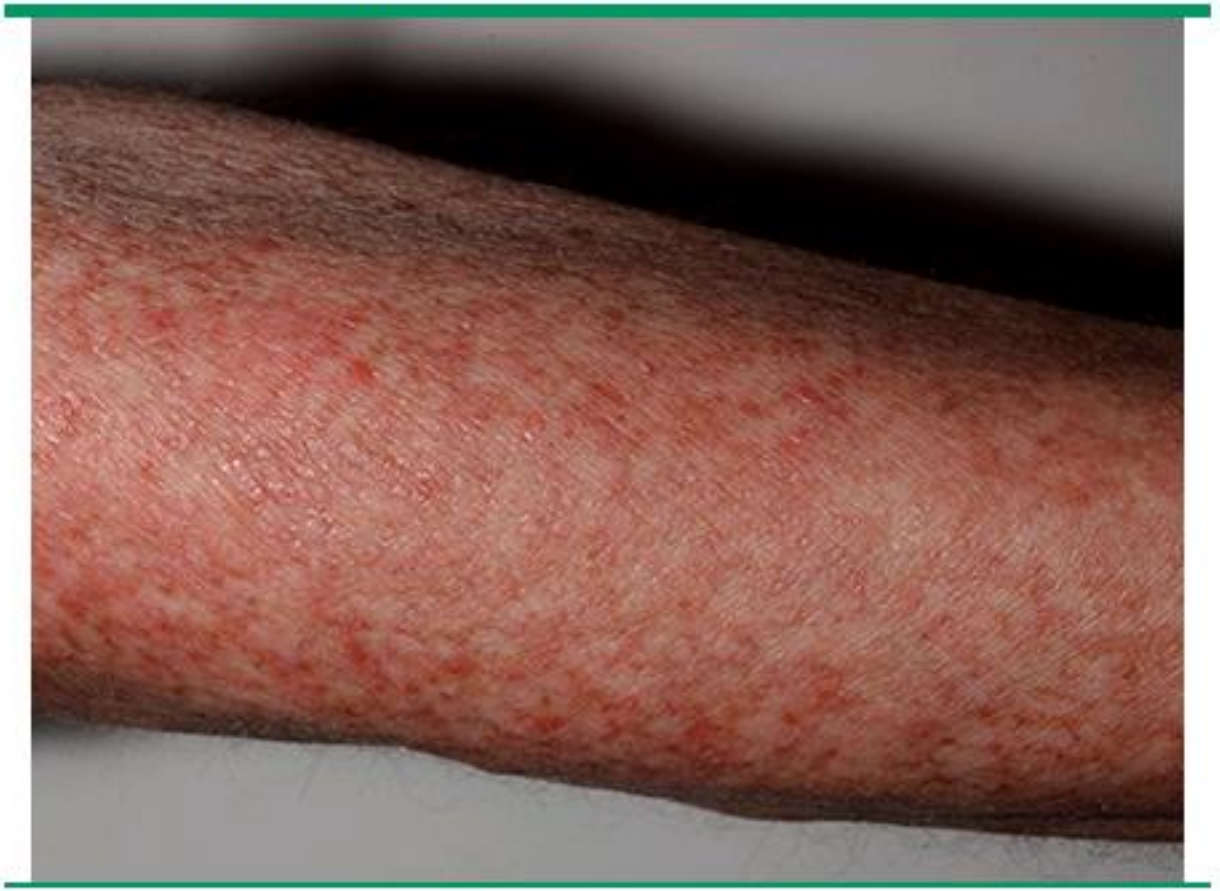
Original figure modified for this publication. Filipovitch AH, Weisdorf D, Pavletic S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: 1. Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2005; 11:945. Table used with the permission of Elsevier Inc. All rights reserved.

Table 2. Teaching Physical Signs and Symptoms of Chronic GVHD to Children and Parents

Sites	Signs and Symptoms to Observe
Skin	Check for skin changes: skin color may deepen and the texture becomes very hard or thick; a rash and itching may occur; the skin may become scaly; the skin may heal by scarring; hair loss may accompany the skin injury
Eyes and mouth	Look for dry eyes: no tears, constant rubbing and blinking; sensitivity to light; difficulty seeing clearly; the inside of the mouth may become excessively dry and sensitive with sores; ulcers may occur
Breathing	Look for chronic cough; colored sputum; feeling short of breath with either exercise or rest
Eating and digestion	Watch for difficulty swallowing or a sensation that food becomes caught in the throat; nausea/vomiting; diarrhea; poor appetite; abdominal pain; unexplained weight loss
Muscles and joints	Look for joint and muscle aches; the motion of nearby joints may be restricted; muscle cramps; weak muscles
Energy	Watch for being easily fatigued; needs to sleep more

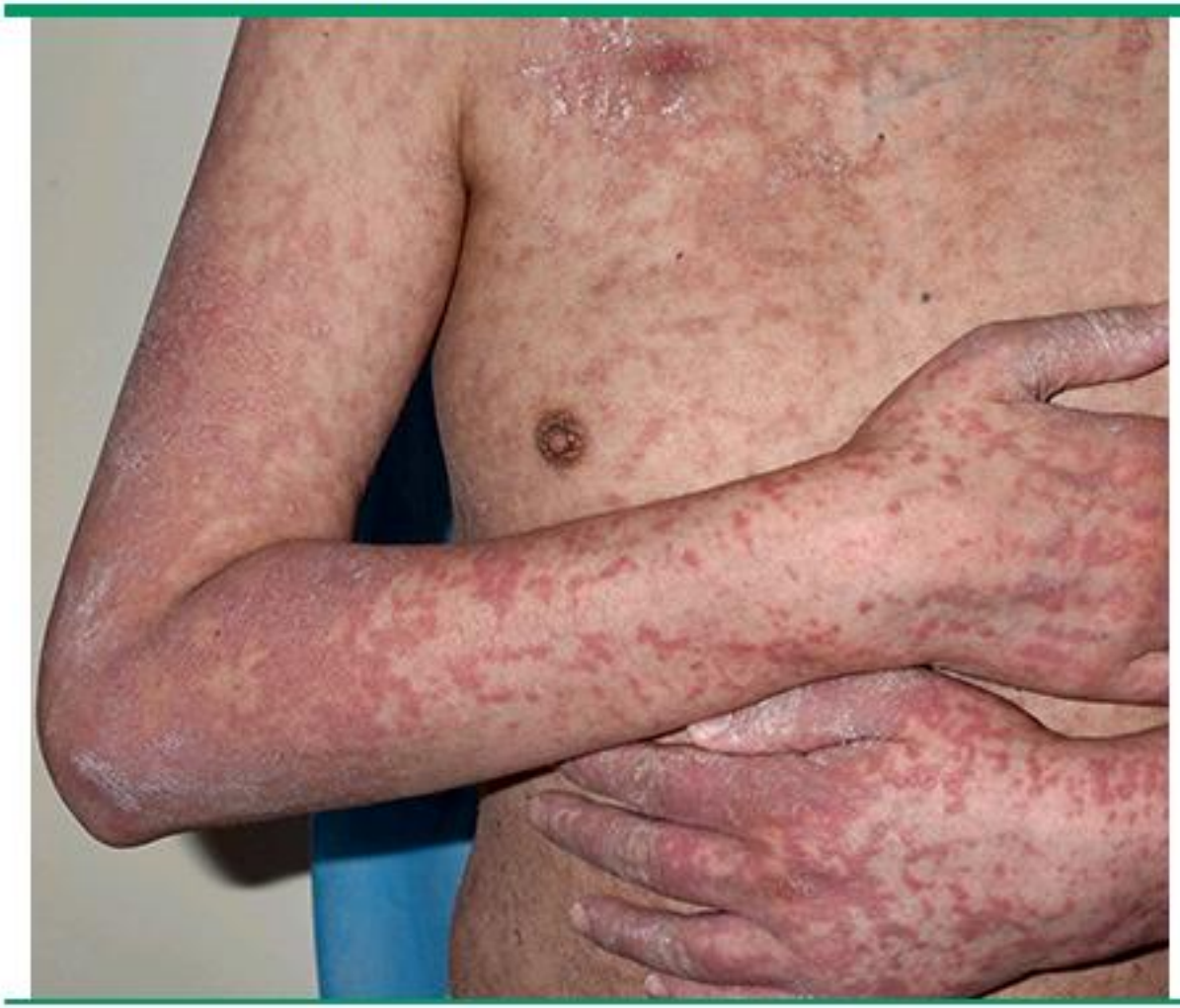
Abbreviations: GVHD, graft-versus-host disease.

Chronic graft-versus-host disease



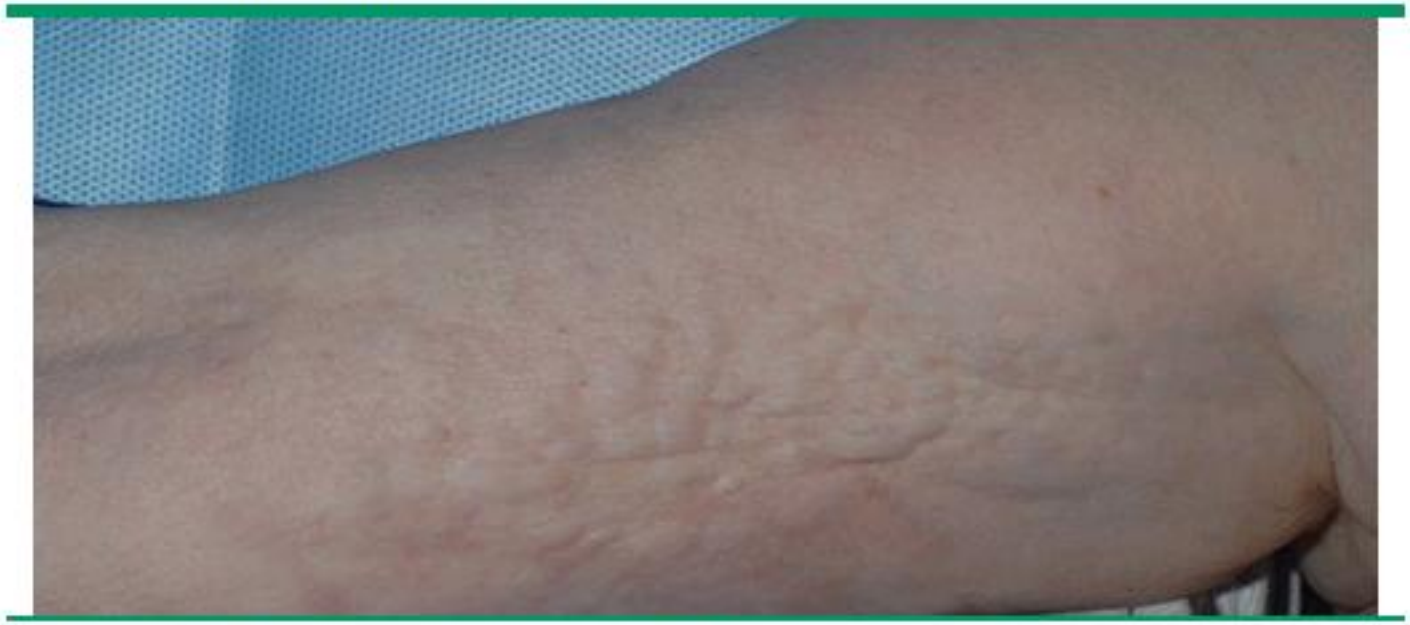
Poikilodermatous changes in chronic graft-versus-host disease. Mottled pigmentation and erythema are present on the extremity.

Chronic graft-versus-host disease



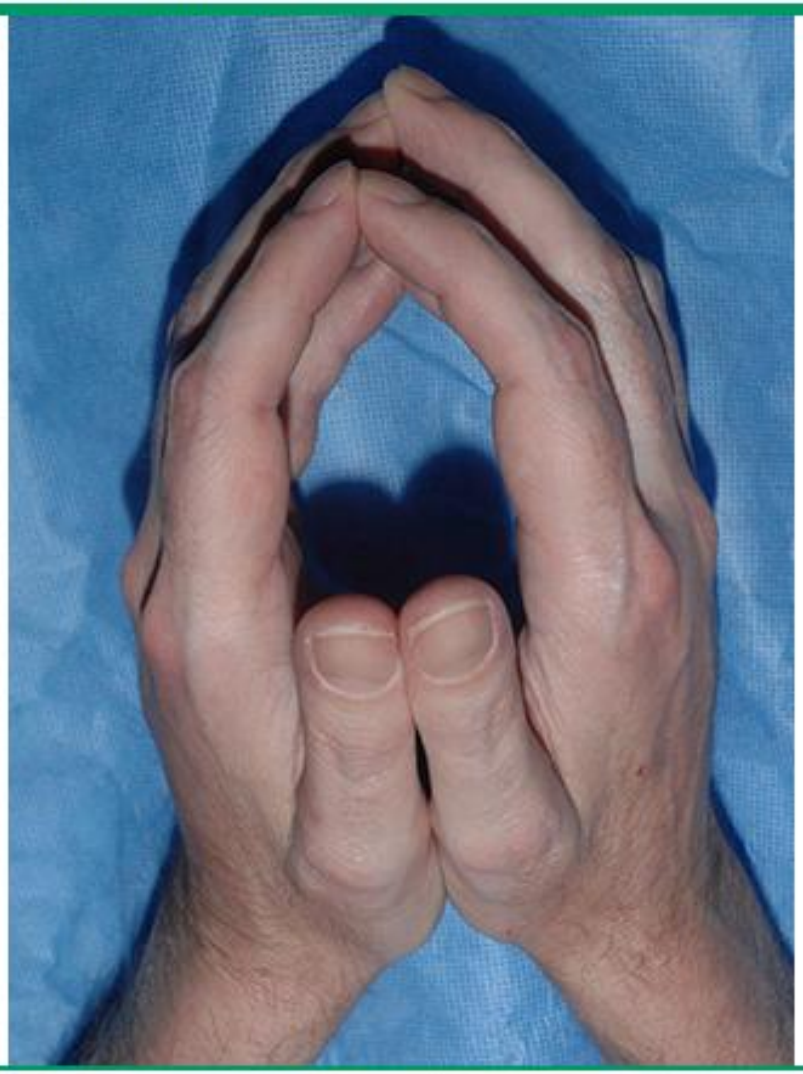
Violaceous papules and plaques, many with a reticulated appearance, are present on the trunk and extremities.

Chronic graft-versus-host disease



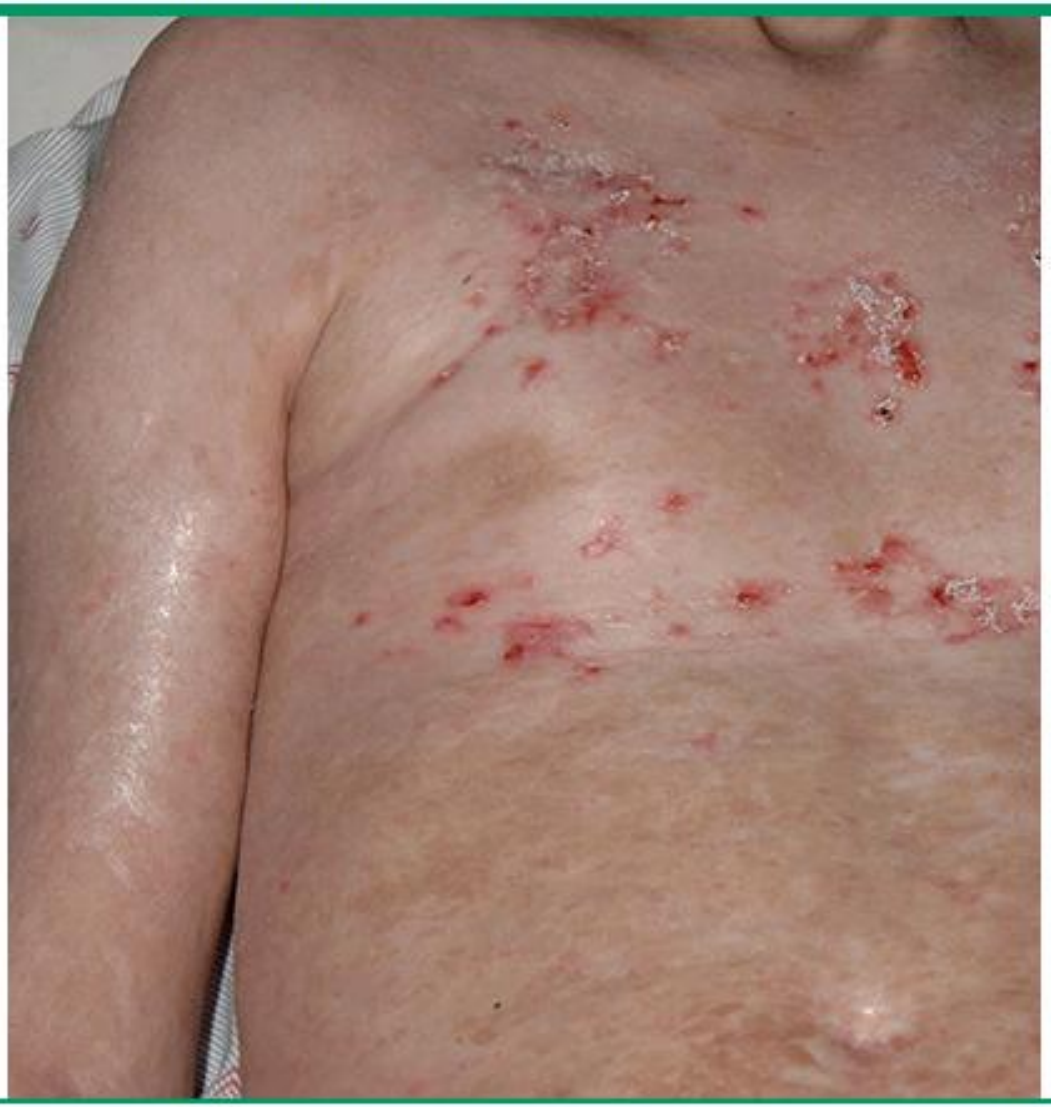
A cellulite-like plaque is present on the upper arm in this patient with subcutaneous fibrosis secondary to chronic graft-versus-host disease.

Chronic graft-versus-host disease



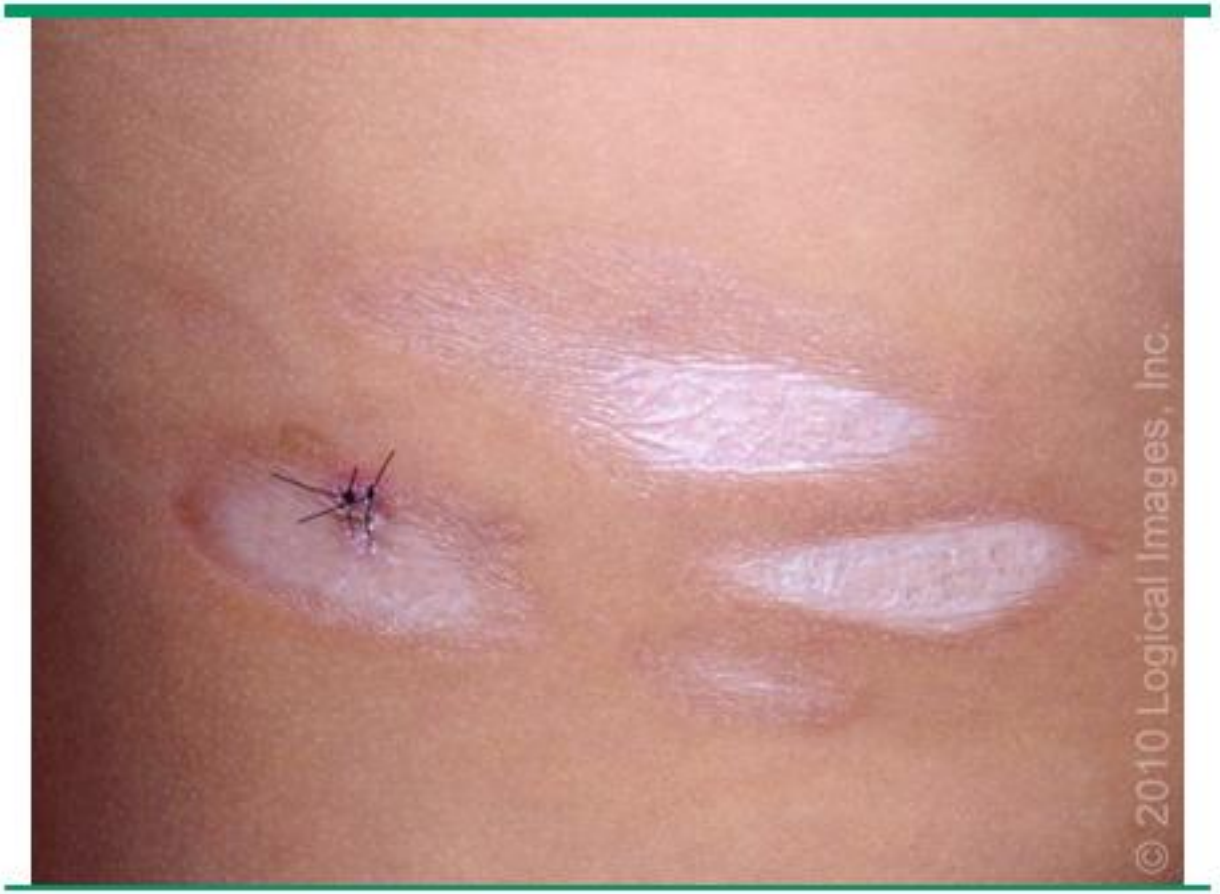
Deep sclerosis leading to joint contractures limited the ability to extend the fingers in this patient with chronic GVHD ("prayer sign"). The overlying skin appears normal.

Chronic graft-versus-host disease



Multiple firm, sclerotic plaques are present with areas of shallow ulceration. Dyspigmentation is also present.

Lichen sclerosus



Oval porcelain-white plaques are present on the trunk of this patient with extragenital lichen sclerosus.

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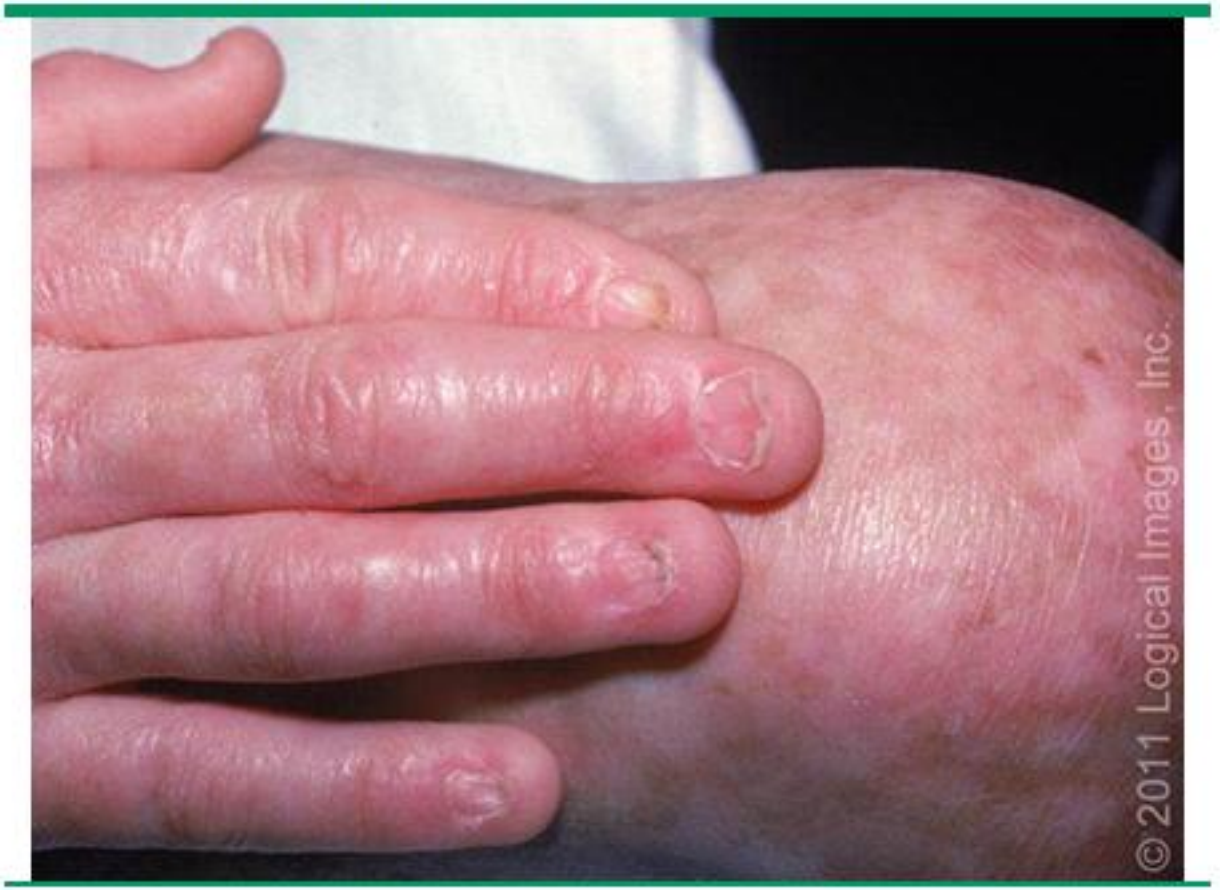
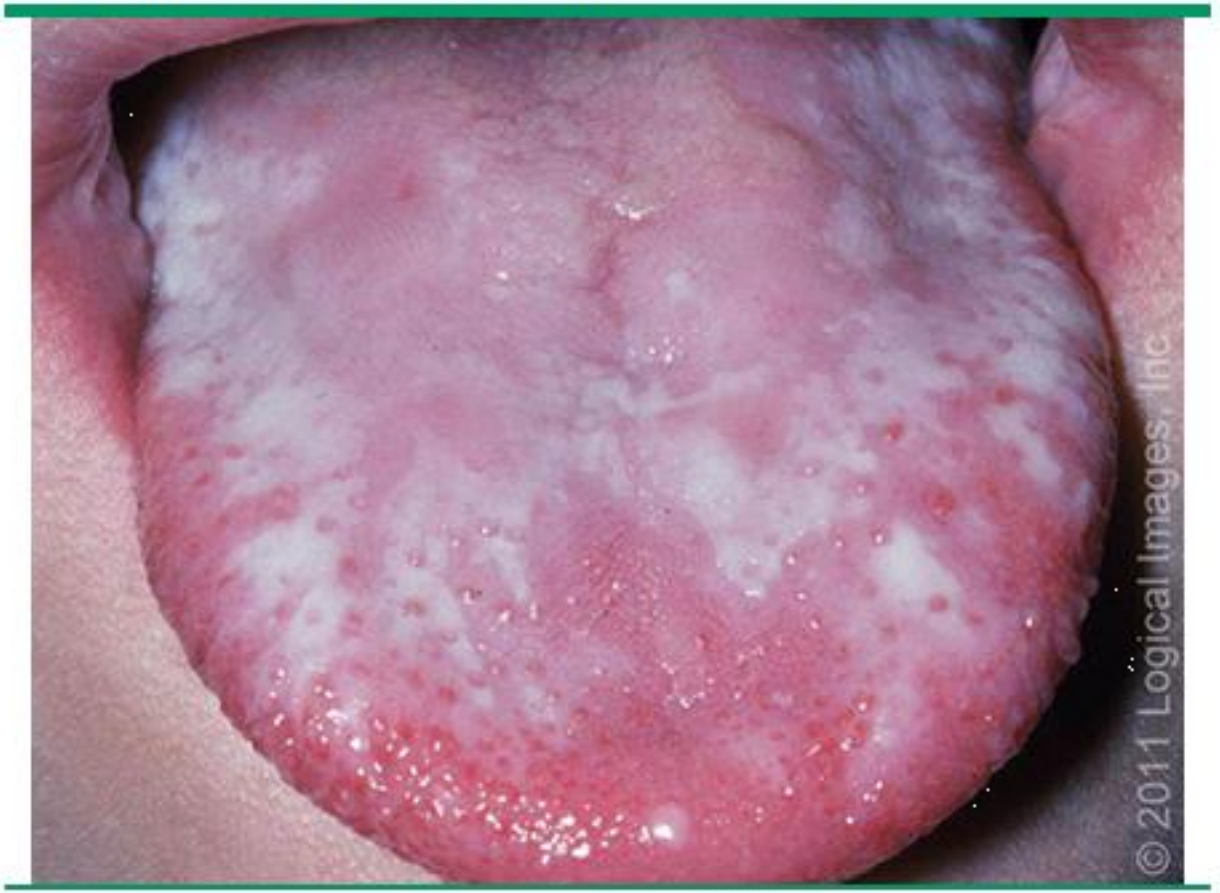
Chronic graft-versus-host disease



Dystrophic nails are present in this patient with chronic graft-versus-host disease.

Oral chronic graft-versus-host disease



Multiple white plaques are present on the tongue.

Table 5. Physical Supportive Nursing Care for Children With Chronic Graft-Versus-Host Disease

Organ System	Nursing Support Care
Dermal	Educate children and parents to prevent further skin injury; develop strategies to manage symptoms, including itching and dry skin
Ocular	Discuss ways to manage relief of dry eyes and sensitivity to light, such as warm compress and protective eyewear and use of moisturizing eyedrops
Oral	Encourage frequent water sipping; maintain good oral/dental hygiene; salivary stimulants (sugar free gum, sugar free candy)
Gastrointestinal	Recommend diet modification as appropriate: for example, soft and moist food when patients are sensitive to foods that have rough and dry textures; maintain appropriate weight of children
Musculoskeletal	Teach stretching exercises and deep muscle massage to improve range of motion
Immunological	Educate about ways to prevent opportunistic infections; stress importance of contacting the physician if children have symptoms of infection, for example, fever more than 38°C and chills

NIH consensus criteria for organ scoring of chronic GVHD

	Score 0	Score 1	Score 2	Score 3
Performance score: ☐ KPS ECOG LPS	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100 percent)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80 to 90 percent)	☐ Symptomatic, ambulatory, capable of self-care, >50 percent of waking hours out of bed (ECOG 2, KPS or LPS 60 to 70 percent)	☐ Symptomatic, limited self-care, >50 percent of waking hours in bed (ECOG 3 to 4, KPS or LPS <60 percent)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement Percent BSA involved: ☐	☐ No symptoms	☐ <18 percent BSA with disease signs but **NO** sclerotic features	☐ 18 to 50 percent BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50 percent BSA OR deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops >3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5 percent)	☐ Symptoms associated with mild to moderate weight loss (5 to 15 percent)	☐ Symptoms associated with significant weight loss >15 percent, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dL or bilirubin, enzymes 2 to 5 x ULN	☐ Bilirubin or enzymes >5 x ULN
LUNGS• FEV1 ☐ DLCO ☐	☐ No symptoms ☐ FEV1 >80 percent **OR** LFS = 2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60 to 79 percent **OR** LFS 3 to 5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40 to 59 percent **OR** LFS 6 to 9	☐ Severe symptoms (shortness of breath at rest; requiring oxygen) ☐ FEV1 ≤39 percent **OR** LFS 10 to 12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
GENTIAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations, or complications related to chronic GVHD
Check all that apply and assign a score to its severity (0 to 3) based on its functional impact where applicable (none = 0, mild = 1, moderate = 2, severe = 3)

Esophageal stricture or web_____
Ascites (serositis)_____
Myasthenia gravis_____
Polymyositis_____
Platelets <100,000/microL _____
Pericardial effusion_____
Nephrotic syndrome_____
Cardiomyopathy_____
Cardiac conduction defects_____
Progressive onset_____
Pleural effusion(s)_____
Peripheral neuropathy_____
Eosinophilia >500 microL_____
Coronary artery involvement_____

Others (specify): _____

GVHD: graft-versus-host disease; KPS: Karnofsky Performance Status; ECOG: Eastern Cooperative Oncology Group; LPS: Lansky Performance Status; BSA: body surface area; ADL: activities of daily living; LFTs: liver function tests; AP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
* AP may be elevated in growing children, and not reflective of liver dysfunction.
• Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO is not available, grading using FEV1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80 percent = 1; 70 to 79 percent = 2; 60 to 69 percent = 3; 50 to 59 percent = 4; 40 to 49 percent = 5; <40 percent = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2 to 12.

Risk Factors

- HLA mismatch
- Gender mismatch
- Older age
- Multipara
- Peripheral stem cell>bone marrow>cord

Prevention and Treatment

- Pharmacologically
- A choice among regimens must take into consideration the underlying disease, the degree of HLA disparity, the conditioning regimen, and patient characteristics. Common regimens include:
  - Methotrexate **plus** cyclosporine – A short course of intravenous methotrexate (eg, given on days +1, +3, +6, and +11
  - Methotrexate **plus** tacrolimus
  - Mycophenolate **(MMF) plus a calcineurin inhibitor (**cyclosporine **or** tacrolimus**)**
- **T cell depletion**

(Chao, 2015, uptodate)

Efficacy of drug prophylaxis for acute graft-versus-host disease

Drug(s)	GVHD, percent
None	52-100
Methotrexate	56-70
Cyclosporine	33-54
ATG-methotrexate-prednisone	21
Cyclosporine-methotrexate	15-33
Cyclosporine-prednisone	12-21
Cyclosporine-methotrexate-prednisone	9-32

None of these regimens improve disease-free survival.

Consensus recommendations for the prophylaxis and treatment of GVHD in allogeneic transplantation

Prevention of GVHD

GVHD prophylaxis: myeloablative conditioning

- The standard prophylaxis is cyclosporine plus a short course of methotrexate. Tacrolimus plus methotrexate is regarded as equivalent, but experience in Europe is too limited to support recommendations. Institutions using tacrolimus plus methotrexate should establish institutional guidelines* and follow them.
- Antithymocyte globulin has been shown to reduce chronic GVHD and improve the quality of life in transplantations from an unrelated donor. Therefore, antithymocyte globulin can be included in the prophylaxis regimen for unrelated donor transplantations. Institutions using antithymocyte globulin should follow the EBMT/ELN recommendations or establish institutional guidelines and follow them.

Cyclosporine

- The initial dose is 3 mg/kg/day.
- The administration is initiated on the day preceding the infusion of the graft (day −1). In case of two or more graft products given on more than one day, the day of the first product is counted as day 0.
- The drug is given as short intravenous (IV) bolus infusion in two daily doses.
- The administration is changed to oral route when oral intake is possible.
- The first oral dose is twice the IV dose, administered in two daily doses.
- The dose is adapted according to whole blood cyclosporine concentration or toxicity (renal insufficiency, microangiopathy, neurological problems) necessitating change of dosage.
- The cyclosporine target concentration is 200 to 300 micrograms/L during the first three to four weeks, then 100 to 200 micrograms/L until three months after transplantation if there is no GVHD or toxicity.
- Cyclosporine concentrations are measured from whole blood at 12 hours after a dose (trough level before the next infusion/dose).
- The duration of cyclosporine prophylaxis is six months in the absence of GVHD.
- The dose is tapered from three months onwards if no GVHD is present. The dose is not tapered as long as there are signs of acute GVHD or signs of chronic GVHD exceeding mild skin disease.

Methotrexate

- The initial dose is 15 mg/m^2 given on day +1.
- Three additional doses of 10 mg/m^2 are given, on days +3, +6 and +11. The day +11 dose is omitted in case of any toxicity of WHO grade II or higher.
- The drug is given as bolus IV injection.
- No dose adaptation is made except for possible omission of day +11 dose (see above).
- Leucovorin rescue is given to all patients.
- Leucovorin administration is started 24 hours after each methotrexate dose. The dosage is 15 mg x 3 given every six hours after methotrexate administration on day +1, the same dose x 4 given every six hours after methotrexate doses on days +3, +6 and +11.
- Leucovorin is administered orally, in case of severe mucositis IV route is used.

Antithymocyte globulin (rabbit)

- The brand of antithymocyte globulin is ATG-Fresenius (ATG-F) or Thymoglobulin.
- The dose of ATG-F is 10 mg/kg on three days (total 30 mg/kg) and that of Thymoglobulin is 2.5 mg/kg on three days (total 7.5 mg/kg).
- Antithymocyte globulin is administered on days −3, −2 and −1.

GVHD prophylaxis: reduced intensity conditioning

GVHD prophylaxis: reduced intensity conditioning

- The standard prophylaxis is cyclosporine plus mycophenolate mofetil.
- Antithymocyte globulin has been shown to reduce chronic GVHD and improve the quality of life in transplantations from an unrelated donor. Therefore, antithymocyte globulin can be included in the regimen for unrelated donor transplantations. Institutions using antithymocyte globulin should follow the EBMT/ELN recommendations or establish institutional guidelines and follow them.

Cyclosporine

- Depending on the intensity of conditioning, the prophylaxis can be given either IV or PO. If the IV route is used, the recommendation for the initial dosing of cyclosporine is the same as for transplantations with myeloablative conditioning.
- If the oral route is used, the initial dose is 12 mg/kg/day.
- The administration is started on day -1.
- The daily dose is given in two doses with a 12-hour interval.
- The doses are adapted according to whole blood cyclosporine concentrations, toxicity (renal insufficiency, microangiopathy, neurological problems) necessitating change of dosage or decreasing chimerism.
- The target concentrations are 200 to 300 micrograms/L during the first three to four weeks, then 100 to 200 micrograms/L until three months (if no GVHD, toxicity or decrease in chimerism).
- The cyclosporine concentrations are measured from whole blood at 12 hours after a cyclosporine dose (trough levels before next infusion/dose).
- The duration of prevention is six months, if there are no signs of GVHD. In case of persistent disease or relapse (sub-population chimerism or other sensitive method) prevention should be reduced earlier.
- The dose is tapered from three months onwards if there are no signs of GVHD. The dose is not tapered as long as there are signs of acute GVHD or signs of chronic GVHD exceeding mild skin disease.

Mycophenolate mofetil

- The dose is 30 mg/kg/day, given orally in two doses.
- The administration is started on day +1.
- The dose is adapted according to toxicity.
- The duration of mycophenolate mofetil prophylaxis is one month in sibling transplantations, three months in transplantations from unrelated or mismatched donor.
- In case of persistent disease or relapse (sub-population chimerism or other sensitive method) prevention should be reduced earlier.

Antithymocyte globulin (rabbit)

- The brand is ATG-F or Thymoglobulin.
- The dose of ATG-F is 10 mg/kg on three days (total 30 mg/kg) and that of Thymoglobulin is 2.5 mg/kg on three days (total 7.5 mg/kg).
- Antithymocyte globulin is administered on days -3, -2 and -1.

Prophylaxis in cord blood transplantation

- The recommended prophylaxis is cyclosporine plus mycophenolate mofetil, with dosing and duration of administration as described above for transplantations with reduced intensity conditioning.

Treatment of GVHD

Treatment of GVHD
Treatment of acute GVHD
First-line treatment
• The first-line treatment of acute GVHD is methylprednisolone.
• Treatment is initiated for acute GVHD of grade II or higher.
• The initial methylprednisolone dose is 2 mg/kg/day.
• Methylprednisolone is given in two divided doses per day.
• The initial dose is continued for seven days. Treatment can be changed in case of clear progression after five days, but there is no evidence that change in treatment will affect the outcome.
• No reduction of the dose is done during the first seven days.
• Tapering of the dose is done slowly and depending on the response. No marked dose reductions are done in the early phase. Methylprednisolone is not discontinued before all signs of GVHD have disappeared.
• Failure of treatment (corticosteroid resistance) is defined as no response after seven days of treatment or clear progression after five days.
• Non-absorbable oral steroid (budesonide) is given, along with systemic corticosteroid, for GI GVHD in the dose of 9 mg/kg/day in one daily dose orally.
• Topical steroids are used for skin GVHD according to center policy.
• The decision to initiate treatment is based on clinical signs. Skin biopsy before initiation of treatment is recommended, but the decision to treat should not depend on the biopsy result. The same recommendation applies to upper GI or sigmoid biopsy if GI manifestation is suspected.
Second-line treatment
• The indication for second-line treatment is failure of methylprednisolone treatment as defined above.
• There is no standard second-line treatment for acute GVHD. Widely used components are mycophenolate mofetil, anti-TNF-antibodies, other monoclonal antibodies, antithymocyte globulin, extracorporeal photopheresis, methotrexate and mesenchymal stem cells. Continuation of calcineurin inhibitors and corticosteroids with optimal supportive care is considered a valid option. Centers should have and follow their institutional guidelines, and the patients should be treated in trials as far as possible.
Treatment of chronic GVHD
• Indication for starting treatment of chronic GVHD depends on the type and severity of symptoms and the speed of symptom progression in the context of other relevant variables, such as disease risk, chimerism, and minimal residual disease results.
• Evaluation of chronic GVHD according to the NIH consensus guidelines is recommended.
• The first-line treatment of newly diagnosed chronic GVHD in patients not on any immunosuppressive drug, or receiving cyclosporine (or tacrolimus) only, is corticosteroid.
• If the patient is already on corticosteroid treatment (for example, following treatment of acute GVHD), cyclosporine is added to the treatment and the dose of corticosteroid is increased.
• If the patient is already receiving corticosteroid and cyclosporine at the time of the onset of chronic GVHD, no standard treatment is available.
• Continuation of corticosteroid and cyclosporine with optimal supportive measures is a valid option. Alternatively, the patient should be treated in a clinical trial if possible.
• The time needed to preliminarily assess the efficacy of the first-line treatment of chronic GVHD is at least one month.
• There is no standard second-line treatment for chronic GVHD. The most widely used components of second-line treatment, in addition to corticosteroids, are extracorporeal photopheresis, mycophenolate mofetil, rituximab, calcineurin inhibitors and mTOR inhibitors. Centers should have and follow their institutional guidelines, and the patients should be treated in trials as far as possible.

Consensus recommendations for standard practice in the prophylaxis and treatment of GVHD in allogeneic transplantation for standard risk malignant diseases in adult patients using matched sibling or unrelated donor.
GVHD: graft-versus-host disease; EBMT: European Group for Blood and Marrow Transplantation; ELN: European LeukemiaNet; GI: gastrointestinal; mTOR: mammalian target of rapamycin; WHO: World Health Organization.
* The expression "institutional guidelines" is used here in a strict sense, according to the principles of the JACIE/FACT criteria. Institutional guidelines should include a written document (standard operating procedure) with as specified details as those in the EBMT-ELN recommendations and specify in a "change control2" document on how the institutional guidelines will be validated compared with the standardized approach.

Treatment

- "A retrospective EBMT study has determined that grade I acute GVHD is the optimal level for patients with malignant disease, at least in adult patients.[2] Accordingly, treatment for acute GVHD is commenced when patients reach grade I or II. First-line therapy consists of **corticosteroids,** usually prednisolone or methyl prednisolone in doses of 1–2 (–5) mg/kg body weight/day, depending on the severity.
- Immunosuppression as mentioned above should be at least maintained, if not increased. One or a few doses of ATG are also often added at this stage, but at the cost of an increased risk of relapse".

BMT JOURNAL, 200 *Bone Marrow Transplantation* (2005) **35**, S65–S67..Novel approaches in GVHD therapy. J Svennilson[1] on behalf of the Paediatric Diseases Working Party of (EBMT)

References

- BMT JOURNAL, 200 *Bone Marrow Transplantation* (2005) **35**, S65–S67. doi:10.1038/sj.bmt.1704850:Novel approaches in GVHD therapy.J Svennilson[1] on behalf of the Paediatric Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT)5
- LiuY. & Hockenberry M. Review of Chronic GVHD in Children After Allogenic SCT: Nursing Perspective. (2011). Journal of Pediatric Oncology Nursing. 28(1) 6-15.
- Chao N. Clinical Manifestation, Diagnosis, and Grading of GVHD. (2015) Up To Date.