
# Cutaneous Manifestations of Graft vs. Host Disease

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# Disclosures

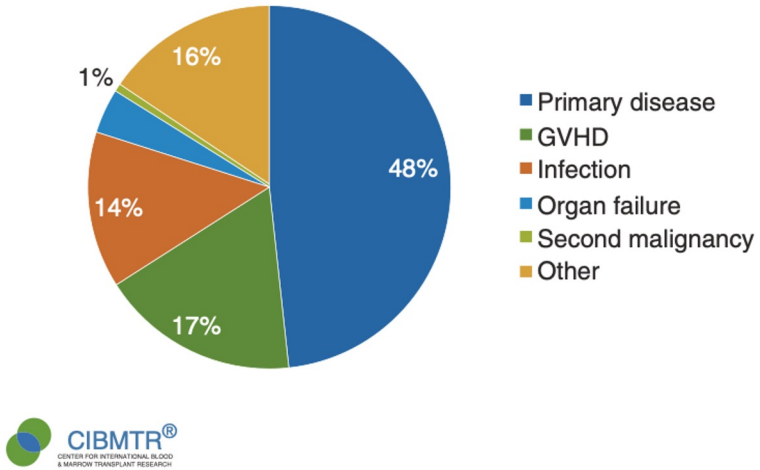
| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| **Gilead** | | | | | x | X | |
| **Merck** | | | | | x | | |

# Agenda

- Overview of acute and chronic Graft versus Host Disease (GvHD)
- Spectrum of GVHD cutaneous manifestations
- Diagnosis and staging of GVHD
- Treatment options

# Trends in HSCT and associated complications

**a** Causes of death after HLA match sibling transplants done in 2012–2013

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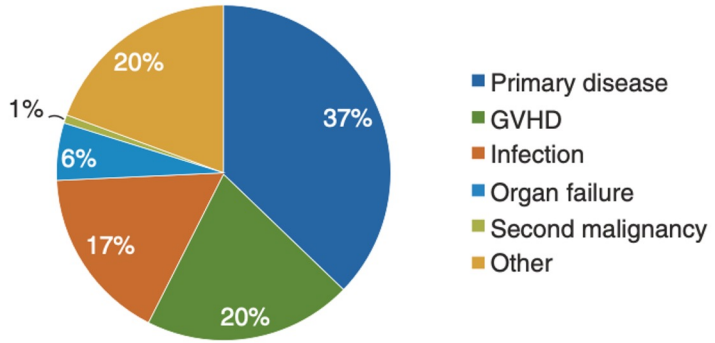
**b** Causes of death after unrelated donor transplants done in 2012–2013

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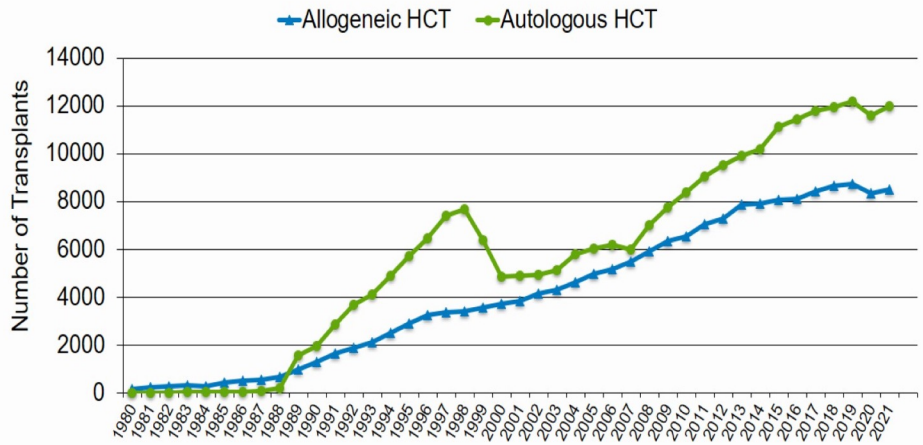
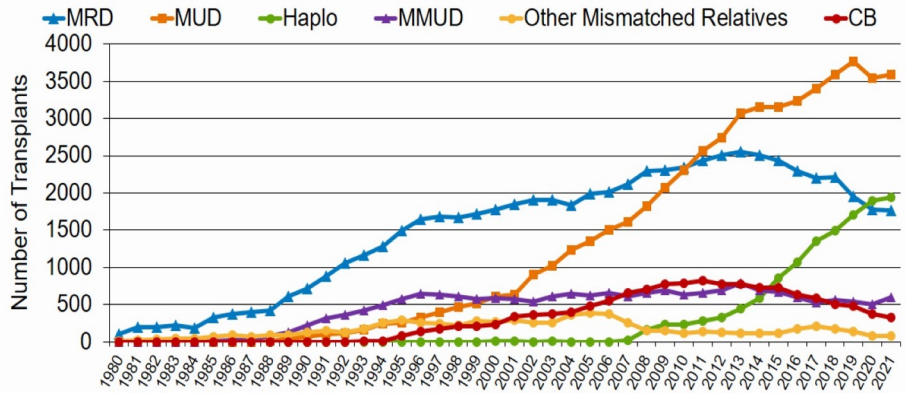
Number of 1st HCTs reported to CIBMTR in the U.S.




Number of Allogeneic HCTs in the U.S. by Donor Type

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Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor; Haplo: ≥2 HLA antigen mismatch; MMUD: Mismatched unrelated donor ≤7/8 HLA allele match; CB: Cord blood

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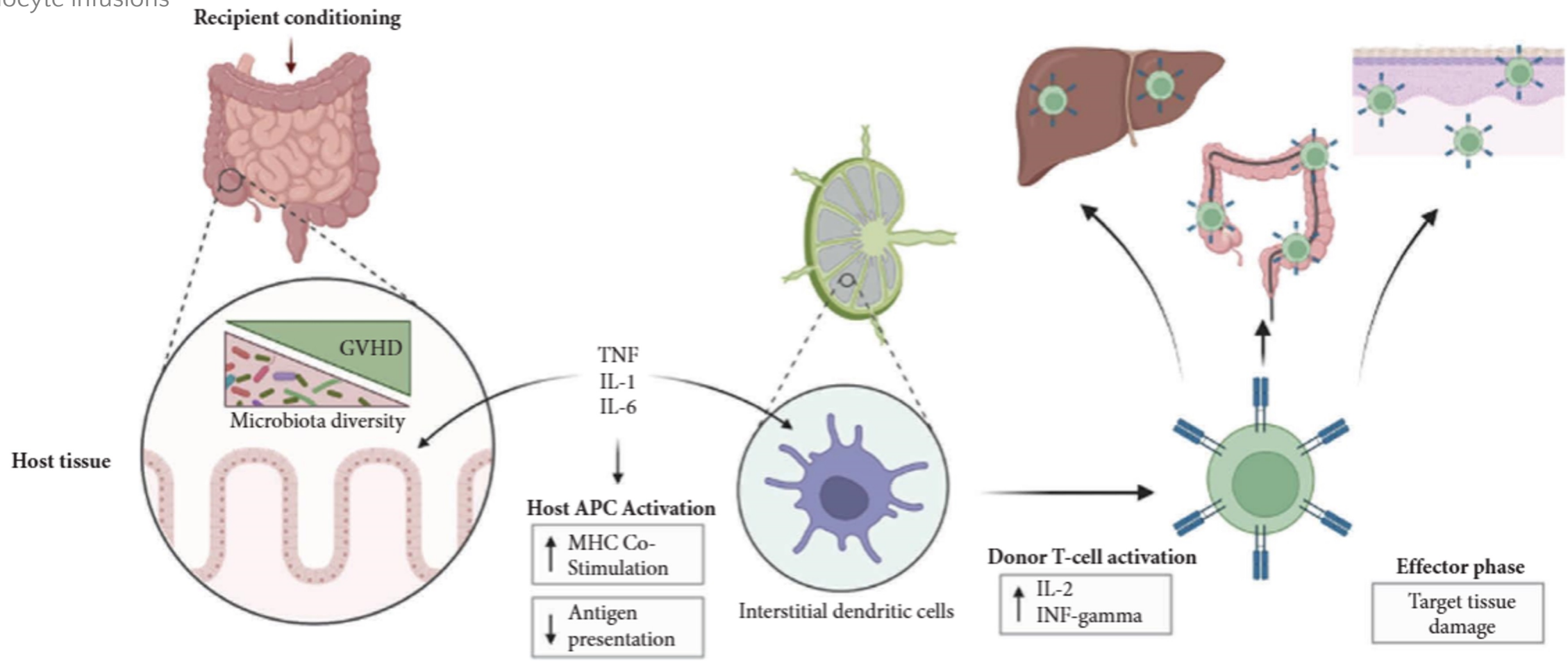
Available at: http://www.cibmtr.org.

# Pathophysiology of acute GVHD

First 100 days post HSCT*

*Can occur after day +100 with reduced intensity condition and donor lymphocyte infusions

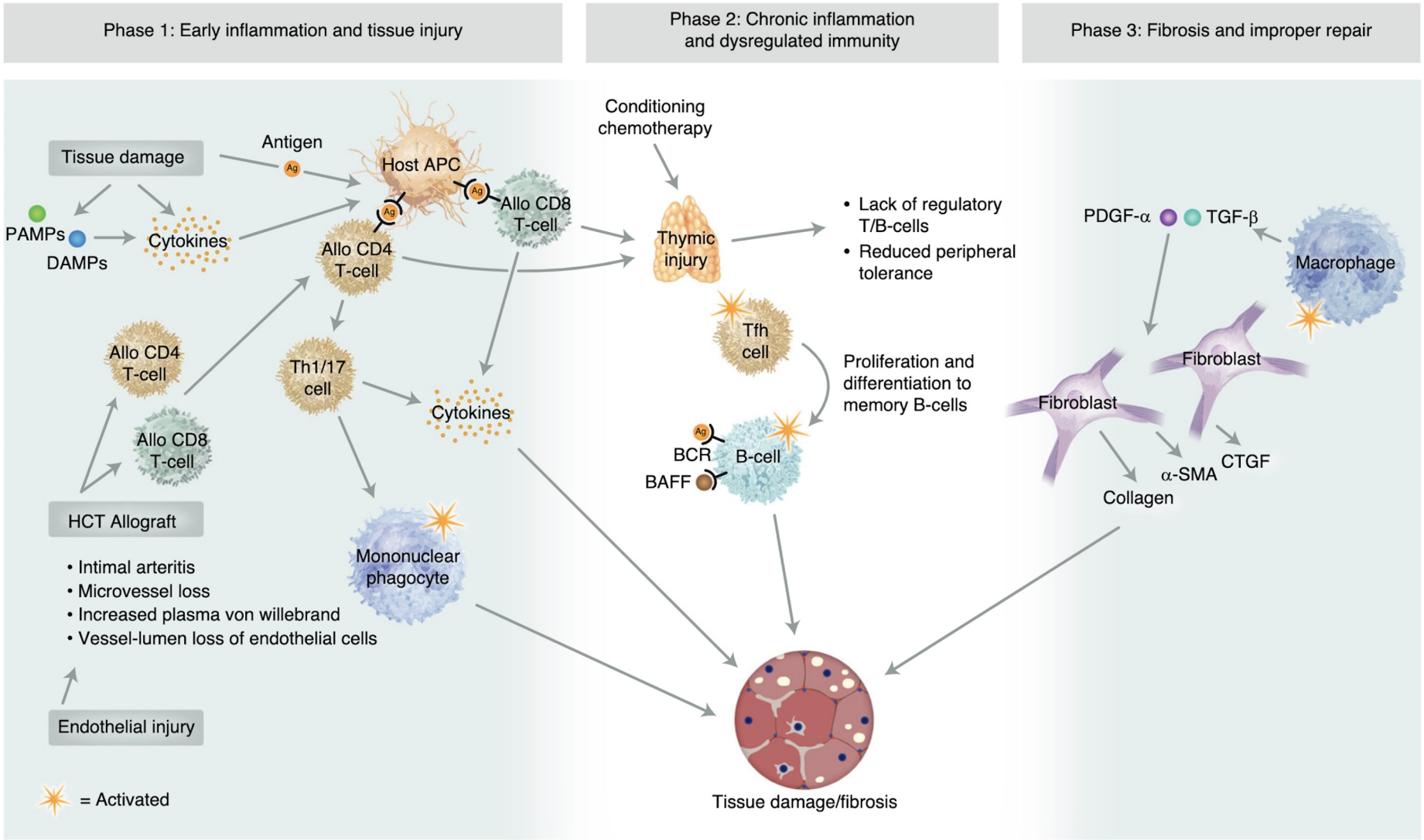
**Affected organs are all exposed to microorganisms through intestinal epithelium, epidermis, and portal circulation**




Kovalenko, I. *et al. Adv. Hematol.* 2023, 1–12 (2023).

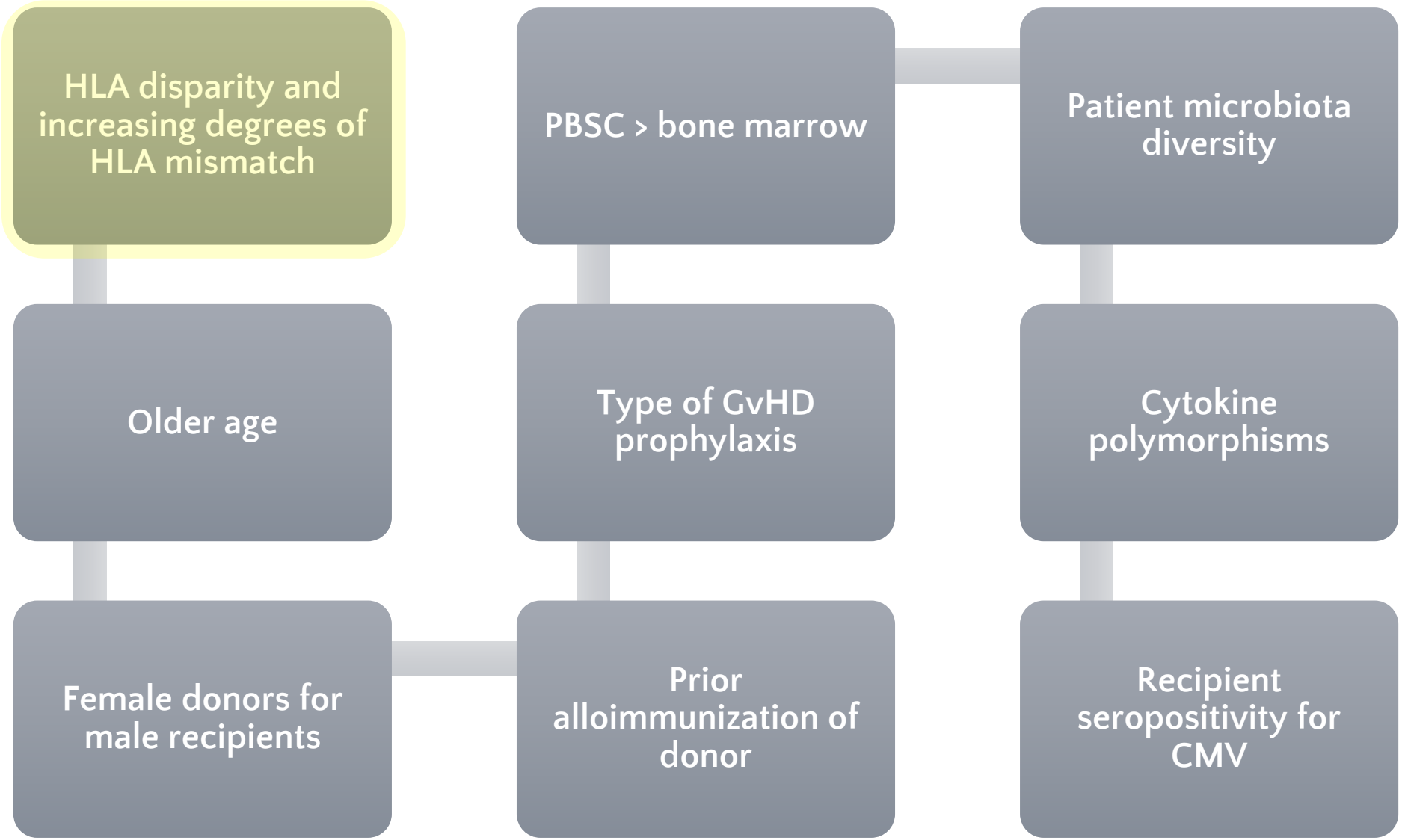
# Pathophysiology of chronic GVHD

After day +100 days post HSCT




Vadakkel, G., Eng, S., Proli, A. & Ponce, D. M. *Bone Marrow Transplant.* 59, 1360–1368 (2024).

# Clinical risk factors for acute and chronic GvHD




Holler, E., Greinix, H. & Zeiser, R. The EBMT Handbook, Hematopoietic Cell Transplantation and Cellular Therapies. 385–393 (2024) doi:10.1007/978-3-031-44080-9_43.

# “Classic” clinical manifestations of aGVHD

| Sites | Clinical manifestation |
|---|---|
| **Skin** | • Erythematous maculopapular rash (initially palms and soles)<br>• May progress to involve the entire body surface<br>• May be pruritic and/or painful<br>• In severe cases, bullae may form leading to desquamation |
| **Liver** | • Cholestasis with or without frank jaundice<br>• Cholestatic enzymes comparatively more deranged than transaminases |
| **Gastrointestinal (GI) tract** | • Upper: anorexia, nausea, and vomiting<br>• Lower: diarrhea, typically green and watery; in severe case diarrhea contains fresh blood and mucosa and is accompanied by abdominal cramps and, on occasion, paralytic ileus |

Holler, E., Greinix, H. & Zeiser, R. The EBMT Handbook, Hematopoietic Cell Transplantation and Cellular Therapies. 385–393 (2024) doi:10.1007/978-3-031-44080-9_43.

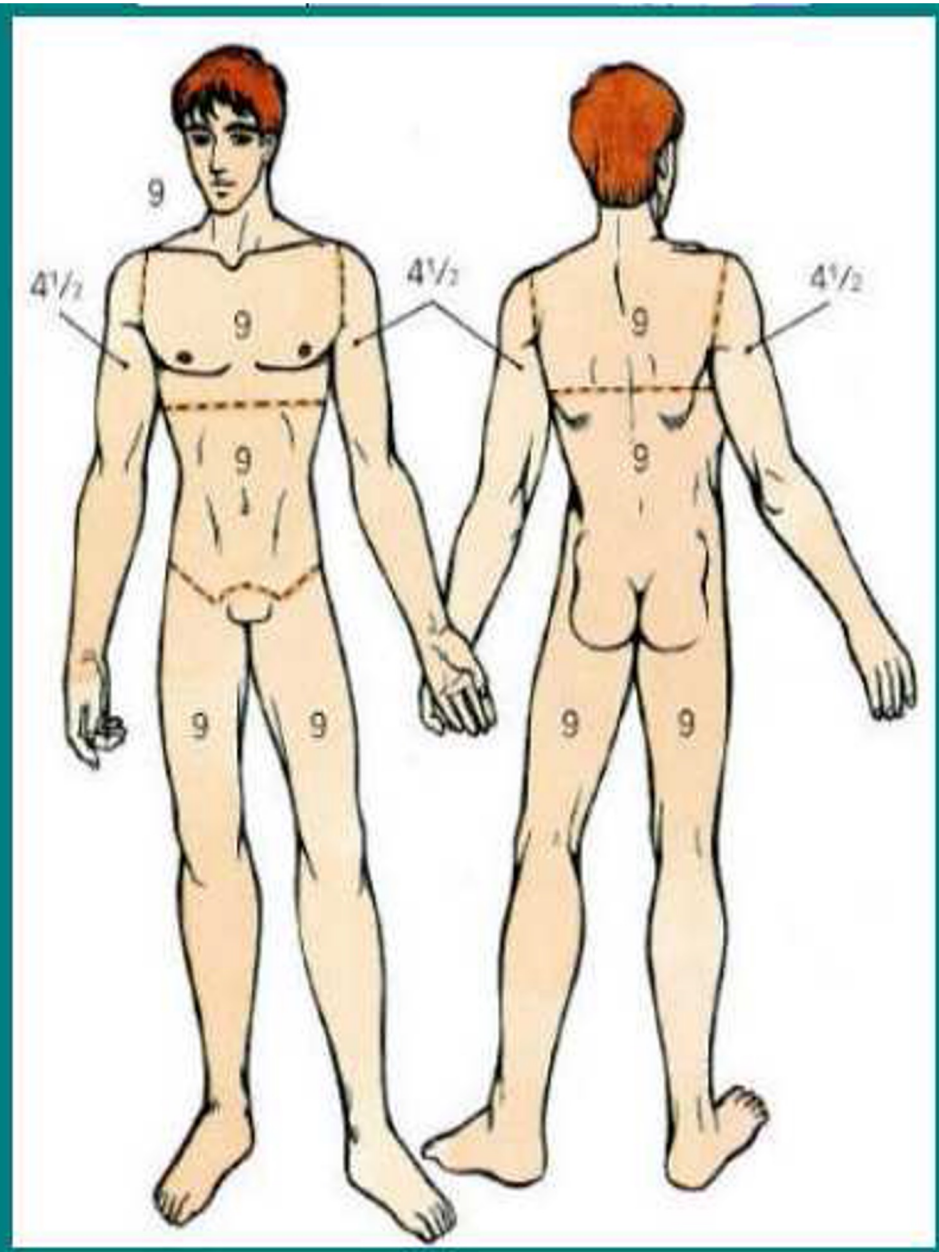
# Grading and prognosis of aGVHD

| Stage | Skin (%BSA) | Liver (bilirubin) | Gastrointestinal | NRM at 100 days |
|---|---|---|---|---|
| **1** | Maculopapular rash < 25% | 2.0–2.9 mg/dL | Diarrhea 0.5–1 L/day or nausea/emesis with positive gut biopsy | 27 % |
| **2** | Maculopapular rash 25–50% | 3.0–5.9 mg/dL | Diarrhea 1–1.5 L/day | 43 % |
| **3** | Maculopapular rash > 50% | 6.0–14.9 mg/dL | Diarrhea > 1.5 L/day | 68 % |
| **4** | Generalized erythema (erythroderma) with desquamation or bullae | > 14.9 mg/dL | Severe abdominal pain with or without ileus | 92 % |

## Subtypes of acute GVHD

| Category | Symptoms after HSCT/DLI | Acute features | Chronic features |
|---|---|---|---|
| **Classic acute** | < 100 days | Yes | No |
| **Persistent, recurrent and late-onset** | > 100 days | Yes | No |
| **Overlap** | > 100 days | Yes | Yes |

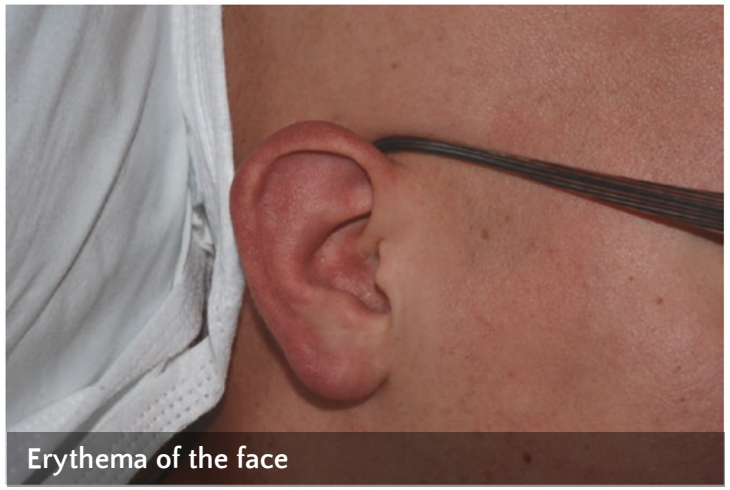
Clinical challenge: differentiating aGVHD from VOD/SOS, chemotherapy toxicity and infection

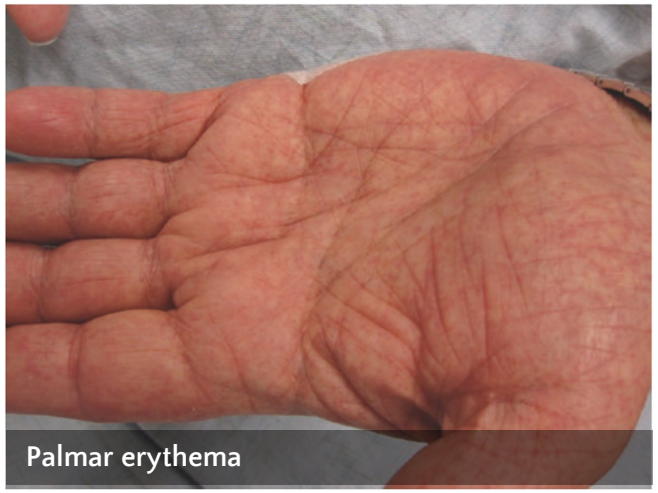


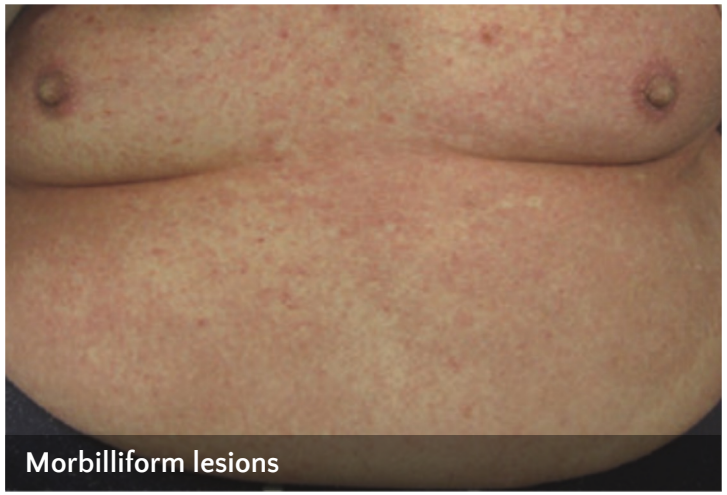

***Regola del nove***
***(calcolo rapido della superficie corporea interessata da un'ustione):***

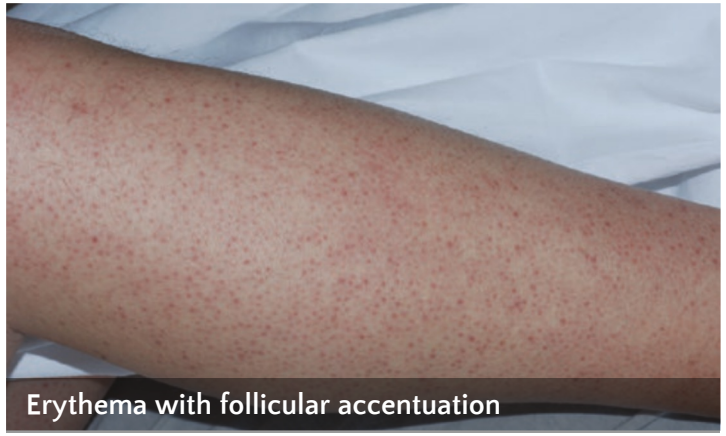
***- capo = 9%***
***- torace = 9%***
***- addome = 9%***
***- dorso (parte superiore) = 9%***
***- dorso (parte inferiore) = 9%***
***- arto superiore (tutto) = 9%***
***- arto inferiore (parte anteriore) = 9%***
***- arto inferiore (parte posteriore) = 9%***
***- scroto = 1%***

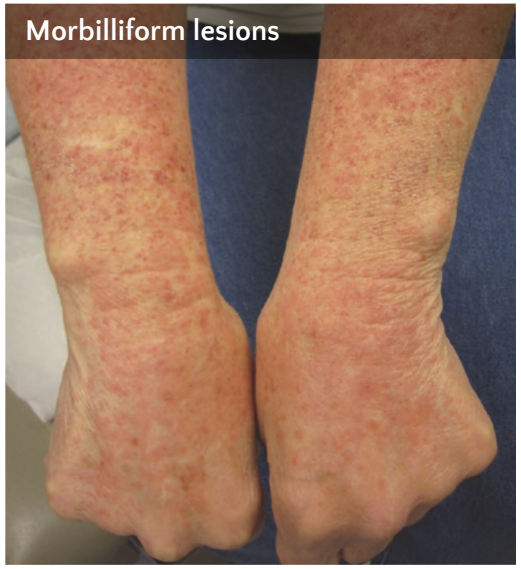
# aGvHD: Spectrum of erythema

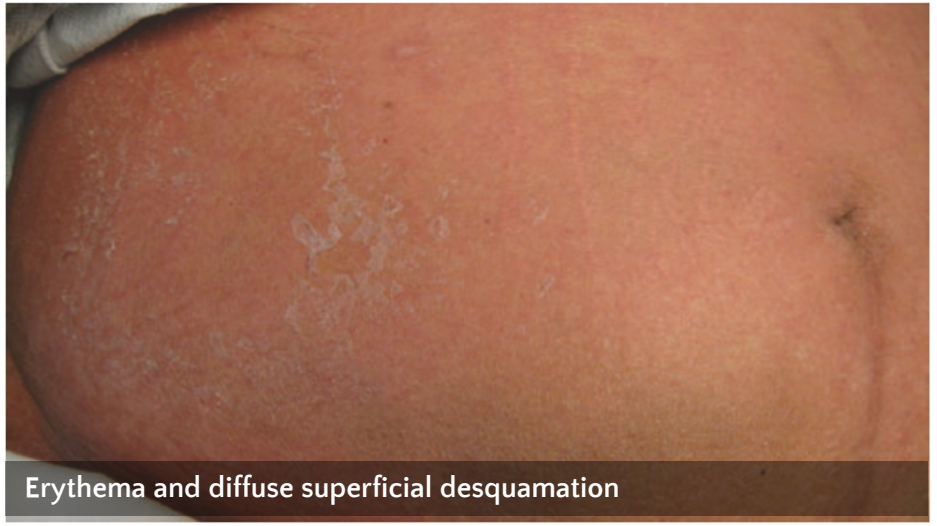

Erythema of the face


Palmar erythema


Morbilliform lesions


Erythema with follicular accentuation

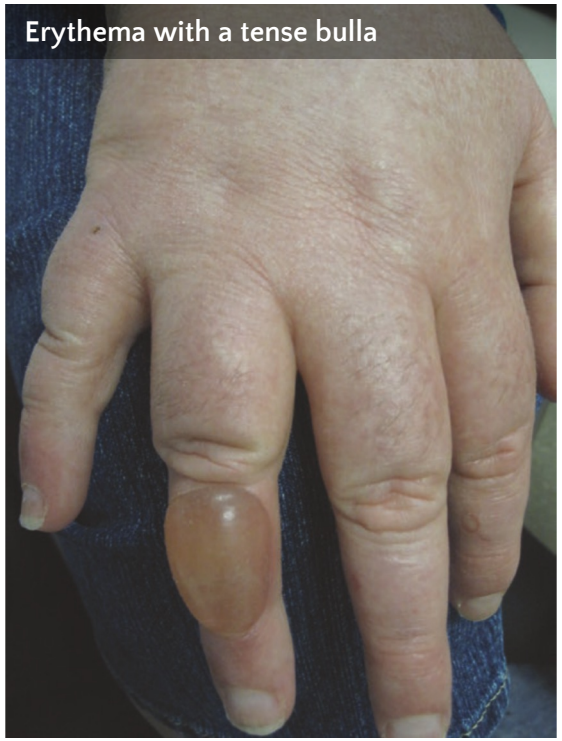

Morbilliform lesions

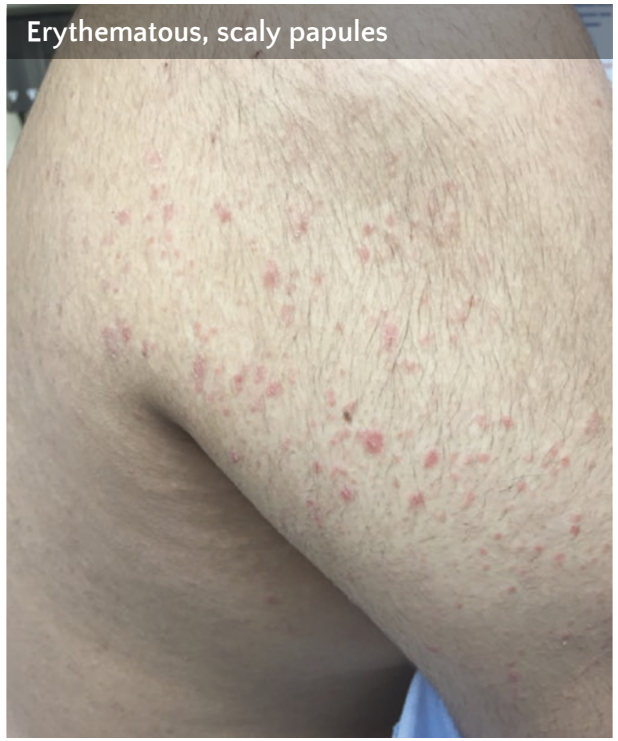

Erythema and diffuse superficial desquamation

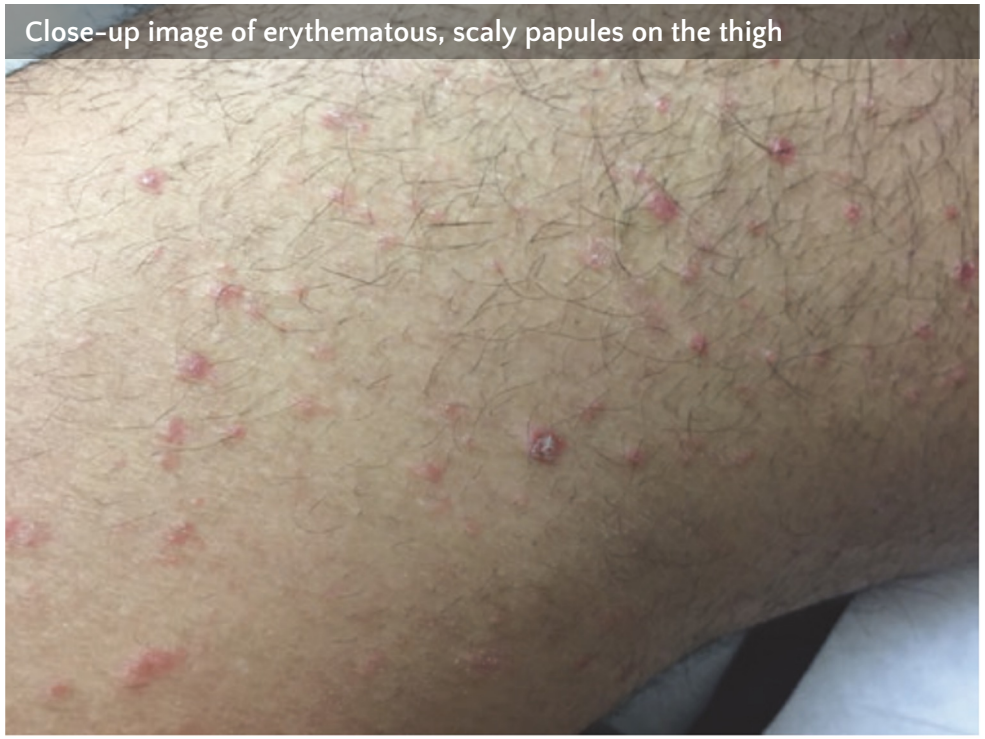
May progress to involve the entire body surface and may be pruritic and/or painful

Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.

# Acute GvHD: Bullae and papules


Erythema with a tense bulla

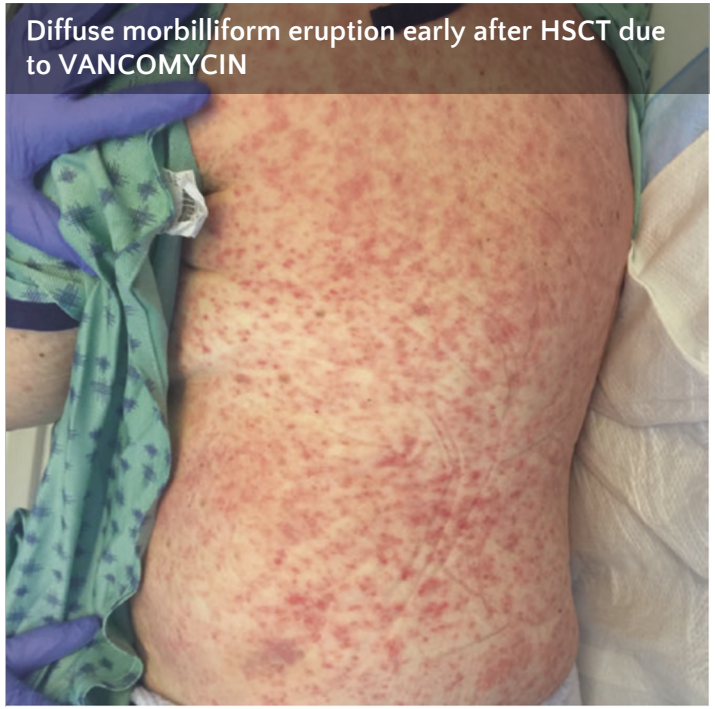

Erythematous, scaly papules


Close-up image of erythematous, scaly papules on the thigh

Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.

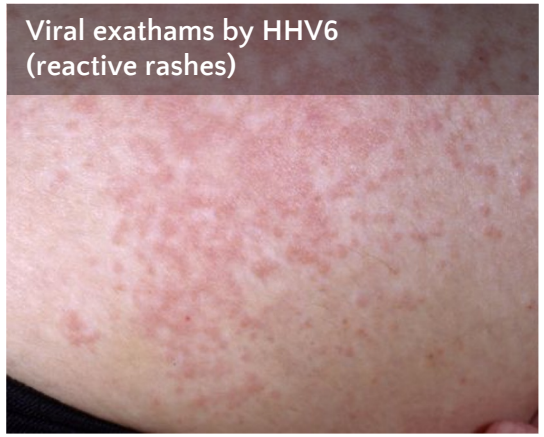
# aGvHD differential diagnosis

Diffuse morbilliform eruption early after HSCT due to VANCOMYCIN

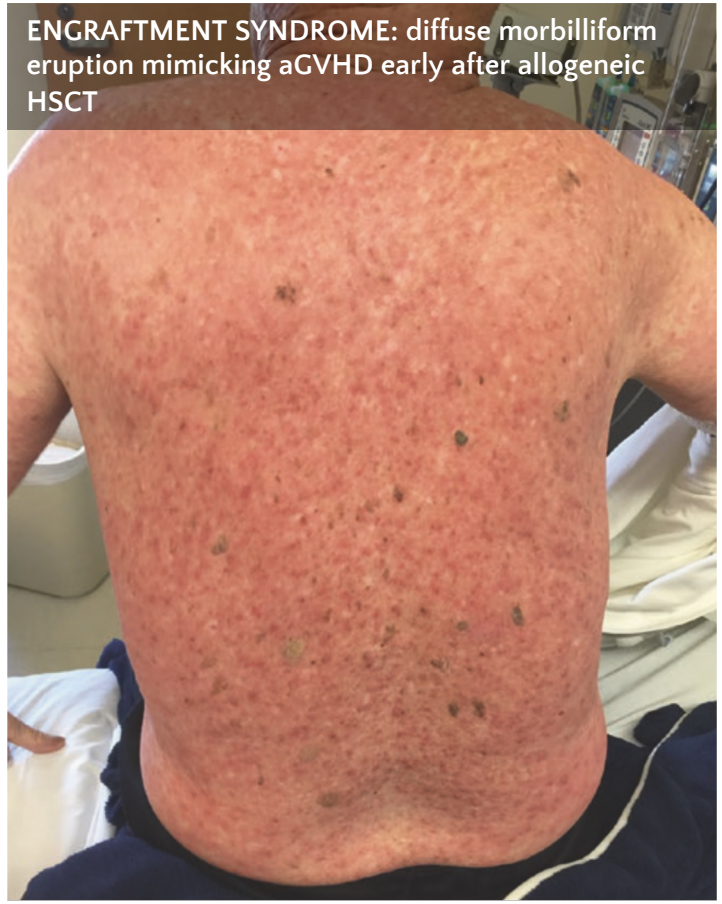


Toxic erythema with CYTARABINE presenting as confluent erythema and edema of the palms

Viral exathams by HHV6 (reactive rashes)



ENGRAFTMENT SYNDROME: diffuse morbilliform eruption mimicking aGVHD early after allogeneic HSCT



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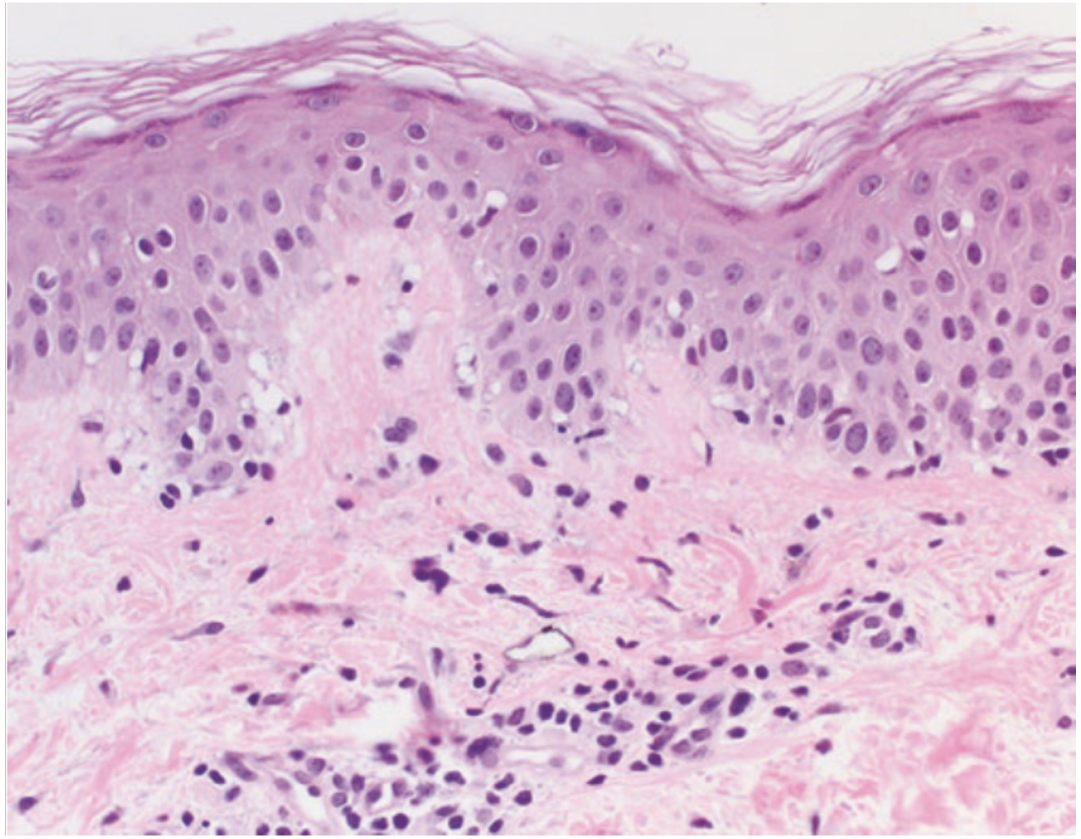
# Histopathology

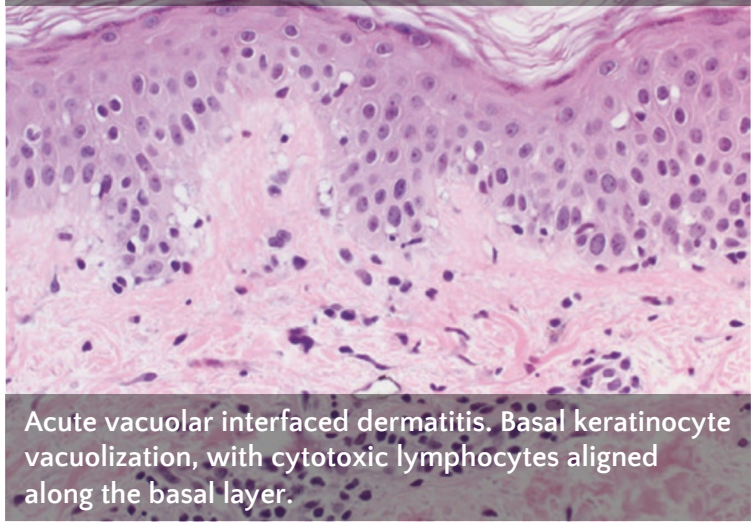


**Histologic grading scheme for acute GVHD**

| GRADE | Lerner grading system | Horn grading system |
|---|---|---|
| **0** | | Normal skin or unrelated cutaneous disease |
| **1** | Vacuolar alteration | Vacuolar alteration |
| **2** | Spongiosis and dyskeratosis (eosinophilic bodies) | Epidermal or follicular dyskeratotic cells, dermal lymphocytic infiltration |
| **3** | Epidermolysis and formation of bulla | Formation of subepidermal clefts and microvesicles |
| **4** | Total epidermal denudation | Epidermal separation from dermis |

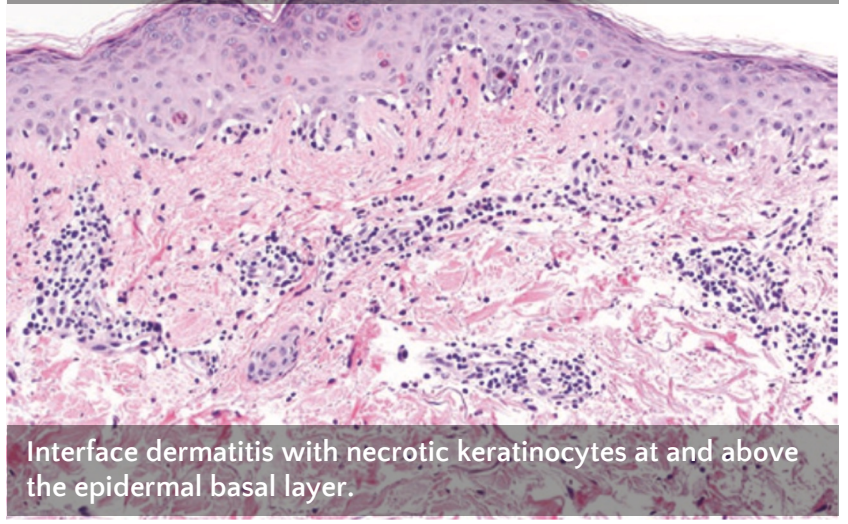
# aGvHD histology

## Histologic grade 1



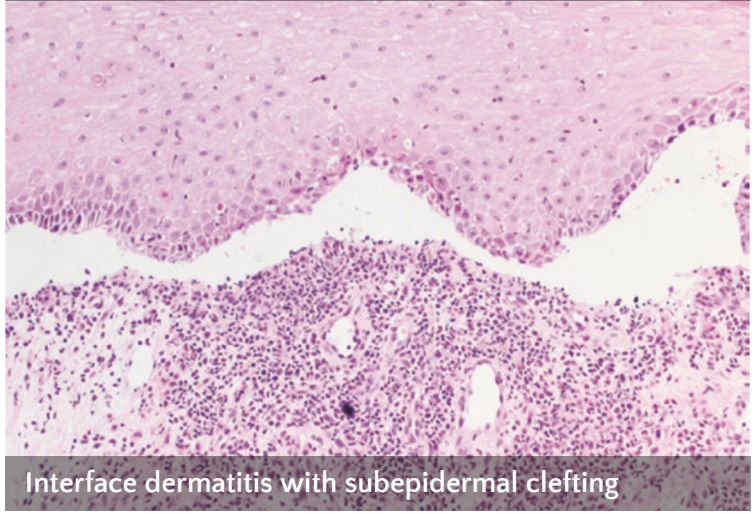
Acute vacuolar interfaced dermatitis. Basal keratinocyte vacuolization, with cytotoxic lymphocytes aligned along the basal layer.

## Histologic grade 2



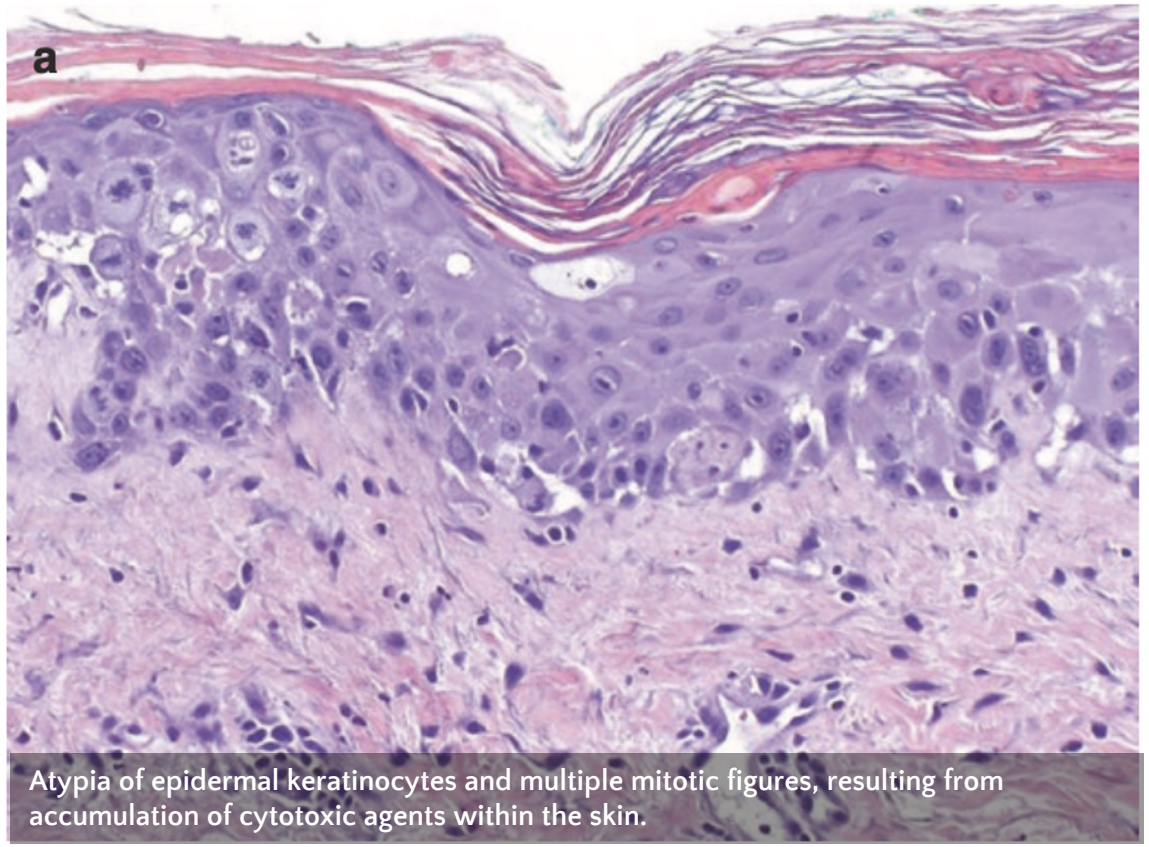
Interface dermatitis with necrotic keratinocytes at and above the epidermal basal layer.

## Histologic grade 3

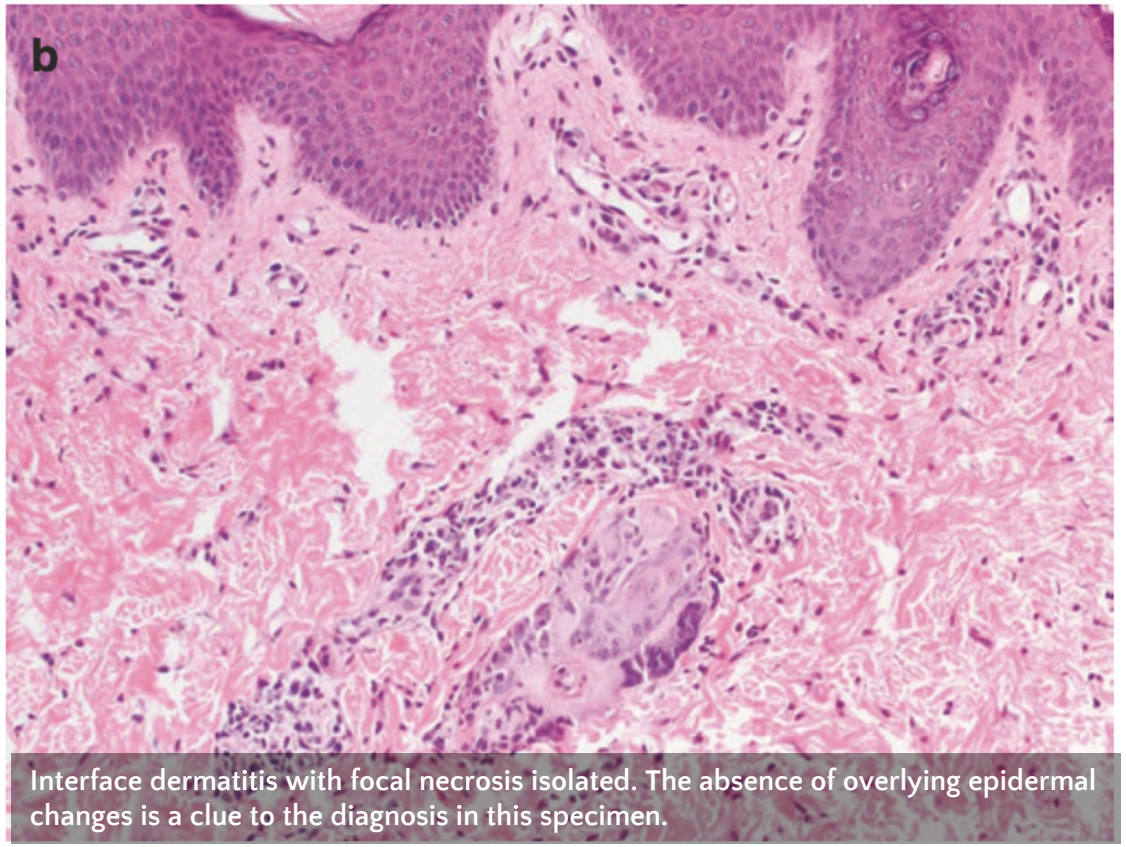


Interface dermatitis with subepidermal clefting

# Toxic erythema of chemotherapy




Atypia of epidermal keratinocytes and multiple mitotic figures, resulting from accumulation of cytotoxic agents within the skin.




Interface dermatitis with focal necrosis isolated. The absence of overlying epidermal changes is a clue to the diagnosis in this specimen.

# Histological differential diagnosis

| | | aGVHD | Engraftment syndrome | Toxic Erythema of Chemotherapy | Stevens-Johnson Toxic Epidermal Necrolysis |
|---|---|---|---|---|---|
| **EPIDERMIDIS** | Keratinocytes<br>- Necrotic<br>- Atypical | <br>+<br>- | <br>+<br>- | <br>+<br>+ | <br>+<br>- |
| | Lymphocytic exocytosis | + | - | - | + |
| | Basal vacuolization | + | + | + | + |
| **DERMIS** | Perivascular lymphocytes | + | + | - | ± |
| | Eosinophils | ± | - | - | + |
| | Neutrophils | - | - | ± | - |
| | Edema | - | - | + | + |
| **ADNEXAE** | Vacuolar alteration | + | - | + | + |
| | Necrotic keratinocytes | + | - | - | + |
| | Peri-eccrine neutrophils | - | - | + | - |
| | Squamous syringometaplasia | - | - | + | - |

# Chronic GVHD Classification

| SKIN†<br><br>SCORE %BSA | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| *GVHD features to be scored by BSA:*<br>**Check all that applies:**<br>☐ Maculopapular rash/erythema<br>☐ Lichen planus-like features<br>☐ Sclerotic features<br>☐ Papulosquamous lesions or ichthyosis<br>☐ Keratosis pilaris-like GVHD | ☐ No BSA involved | ☐ 1-18% BSA | ☐ 19-50% BSA | ☐ >50% BSA |
| **SKIN FEATURES SCORE:** | ☐ No sclerotic features | | ☐ **S**uperficial sclerotic features "not hidebound" (able to pinch) | **Check all that applies:**<br>☐ Deep sclerotic features<br>☐ "Hidebound" (unable to pinch)<br>☐ Impaired mobility<br>☐ Ulceration |
| *Other skin GVHD features (NOT scored by BSA)*<br>**Check all that applies:**<br>☐ Hyperpigmentation<br>☐ Hypopigmentation<br>☐ Poikiloderma<br>☐ Severe or generalized pruritus<br>☐ Hair involvement<br>☐ Nail involvement | | | | |
| ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*<br>_____ | | | | |

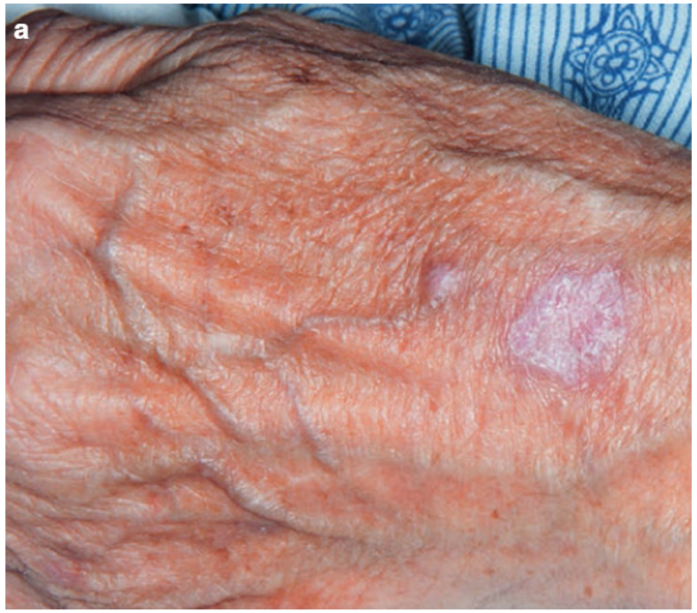
# NIH–defined classic cGVHD risk score

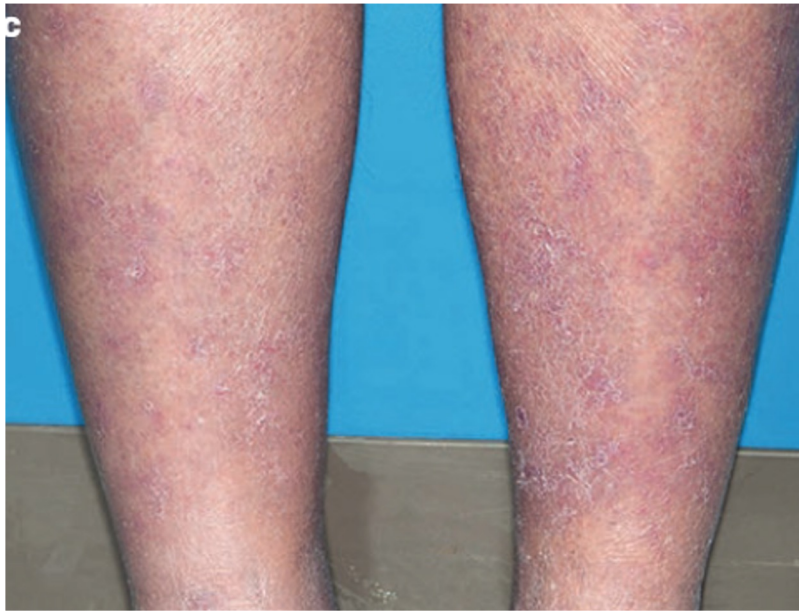
| OVERALL SEVERITY | MILD | MODERATE | SEVERE |
|---|---|---|---|
| *No. of involved organs* | 1–2 | ≥3 | ≥3 |
| *Severity of involved organs* | Mild (excluding lung) | Mild–moderate (lung only mild) | Severe (lung moderate/severe) |

| | | | | |
|---|---|---|---|---|
| **Overall GVHD Severity** *(Opinion of the evaluator)* | ❑ **No GVHD** | ❑ **Mild** | ❑ **Moderate** | ❑ **Severe** |

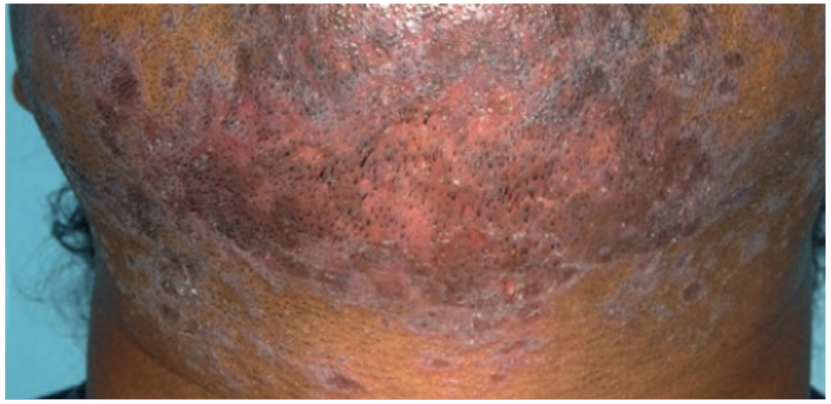
# cGVHD “classic” cutaneous manifestations

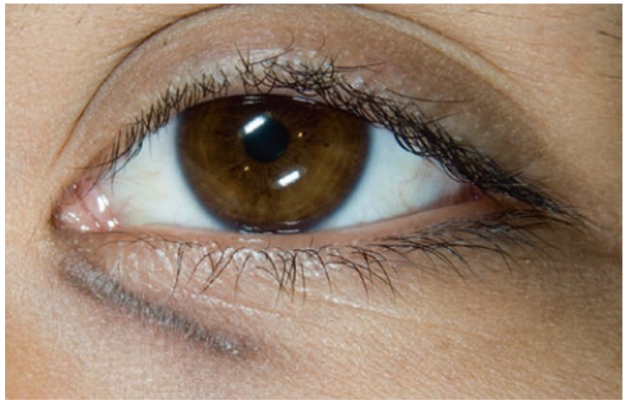
## lichen planus–like lesions




The purple, polygonal lichen planus–like papules and plaques may be solitary or confluent

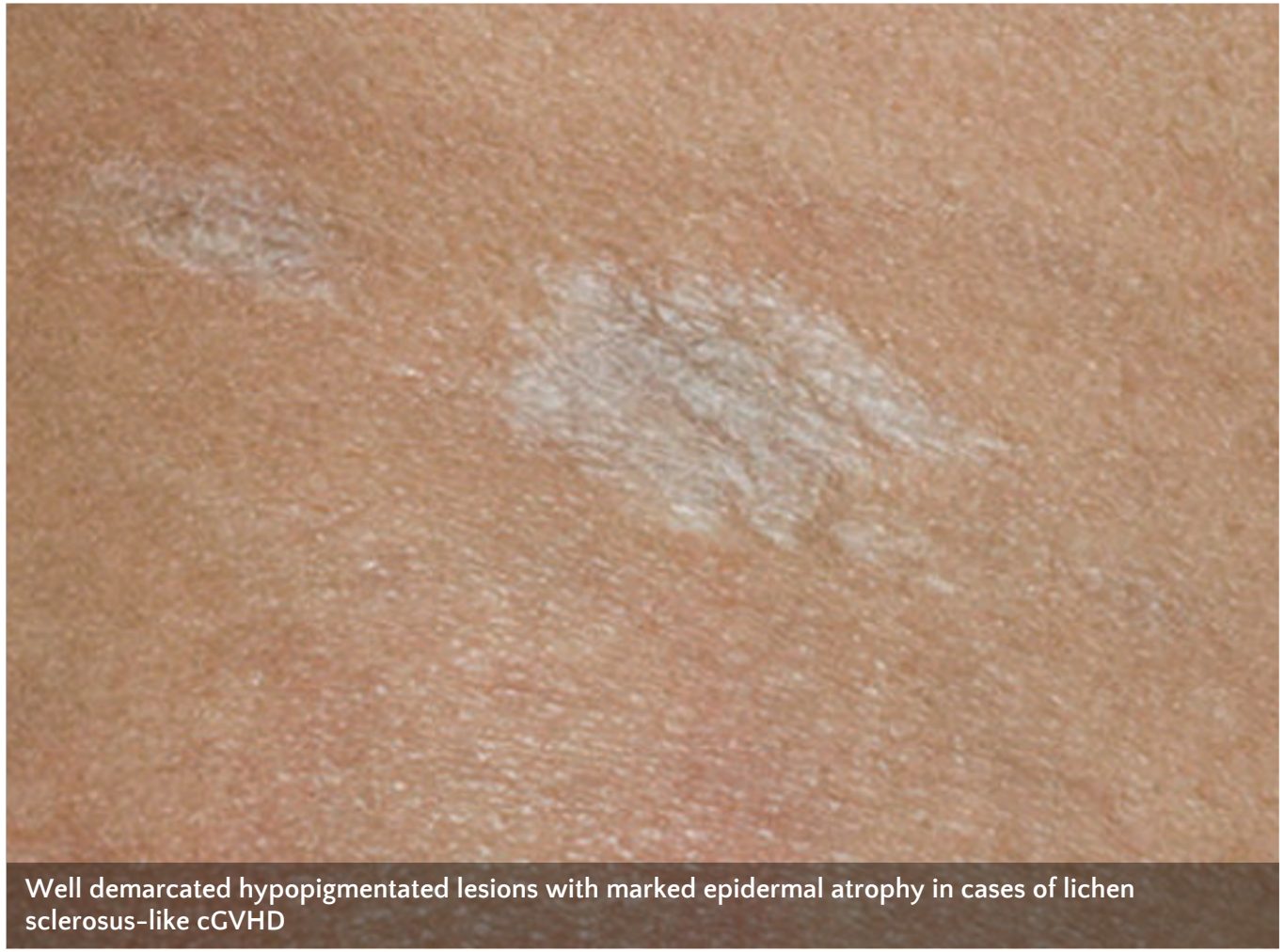




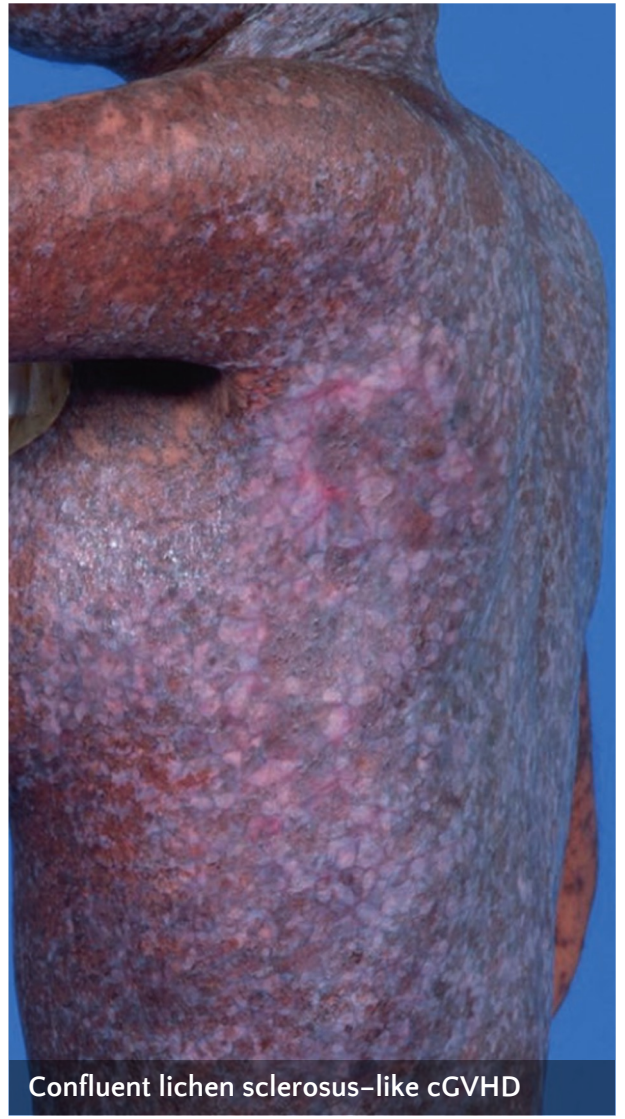
Inflammation may lead to significant postinflammatory pigment changes, including the hypopigmentation and hyperpigmentation at areas of previous tissue damage or scarring

Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.

# Lichen sclerosus–like cGVHD



Well demarcated hypopigmentated lesions with marked epidermal atrophy in cases of lichen sclerosus-like cGVHD



Confluent lichen sclerosus–like cGVHD

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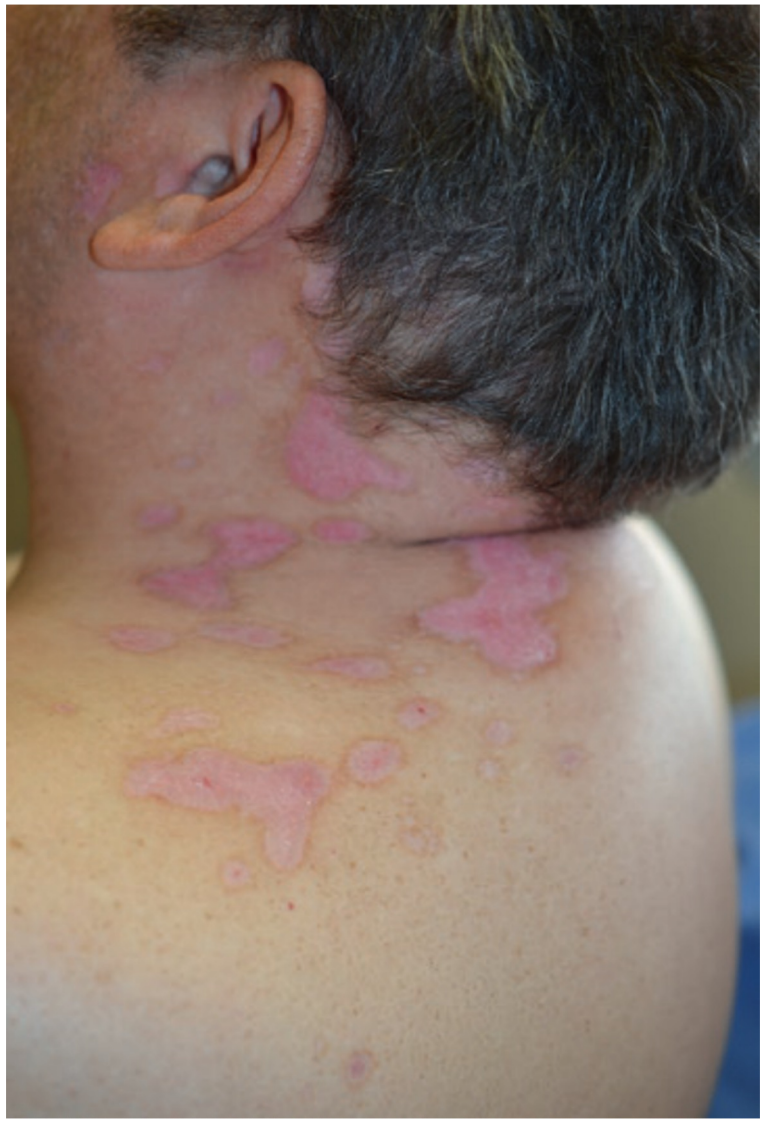
# Infiltrated hypopigmented plaques developing at the site of VZV



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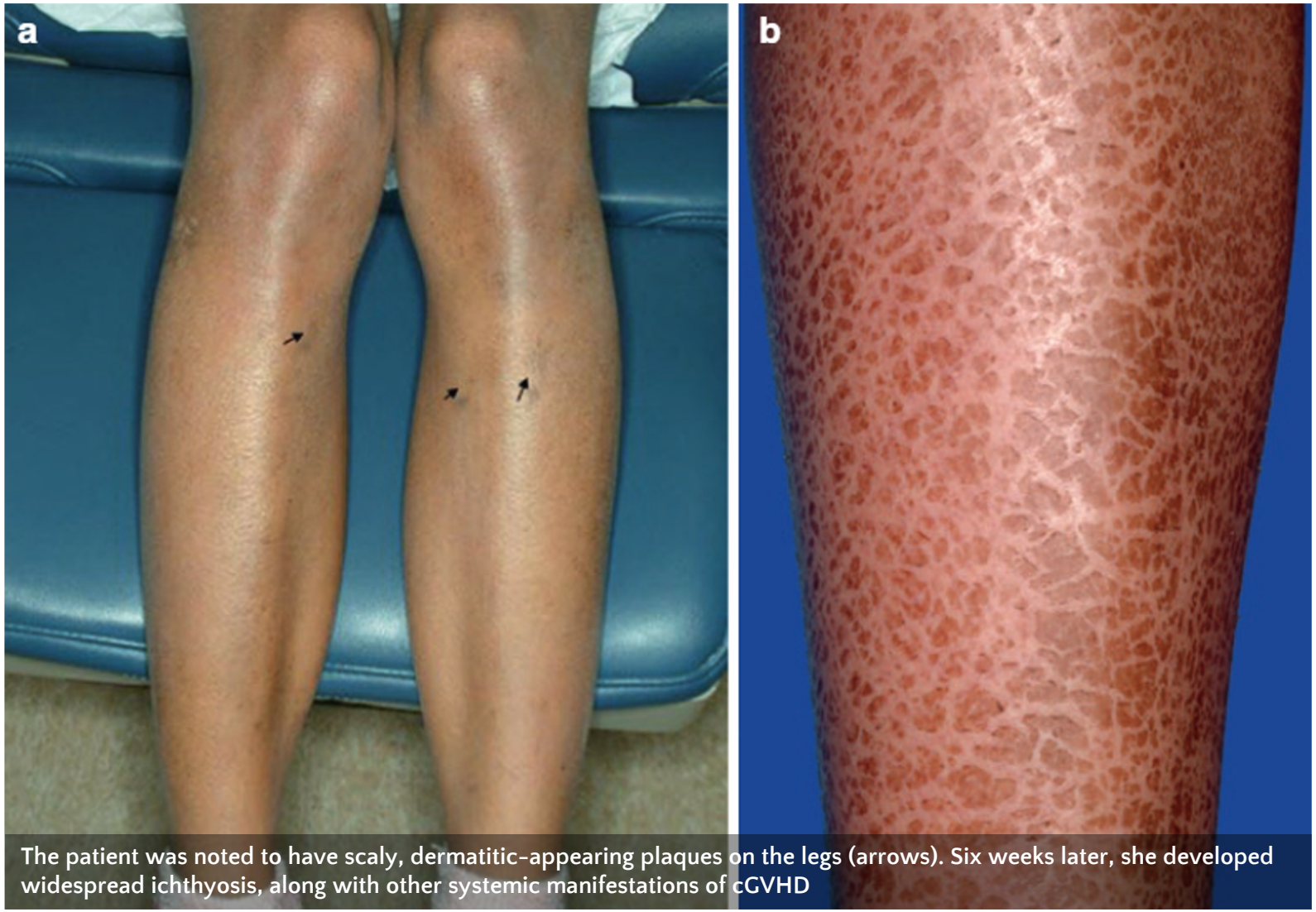
# Ichthyosis

## Sudden onset is an important signal of cGVHD




The patient was noted to have scaly, dermatitic-appearing plaques on the legs (arrows). Six weeks later, she developed widespread ichthyosis, along with other systemic manifestations of cGVHD

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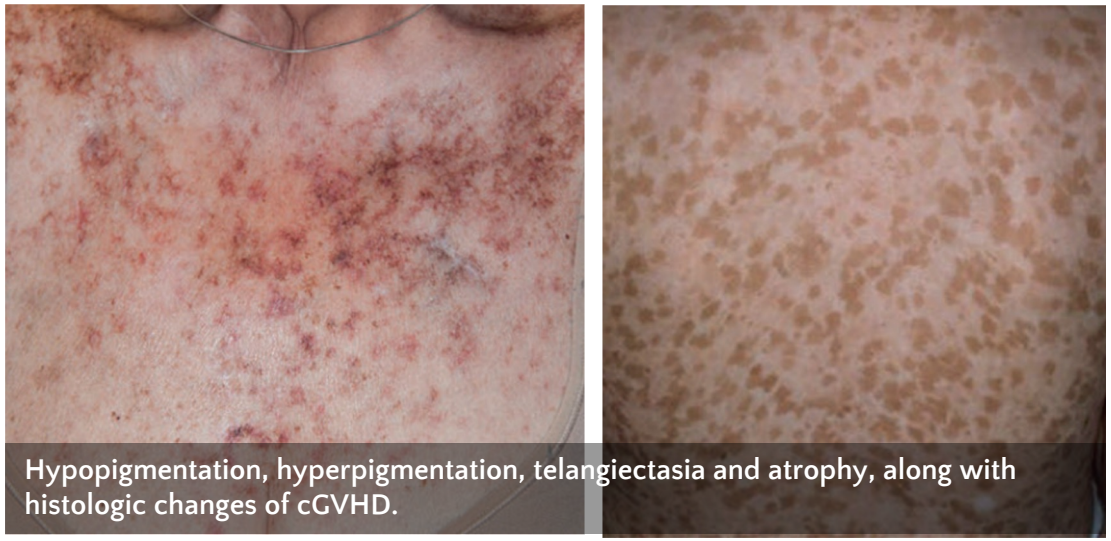
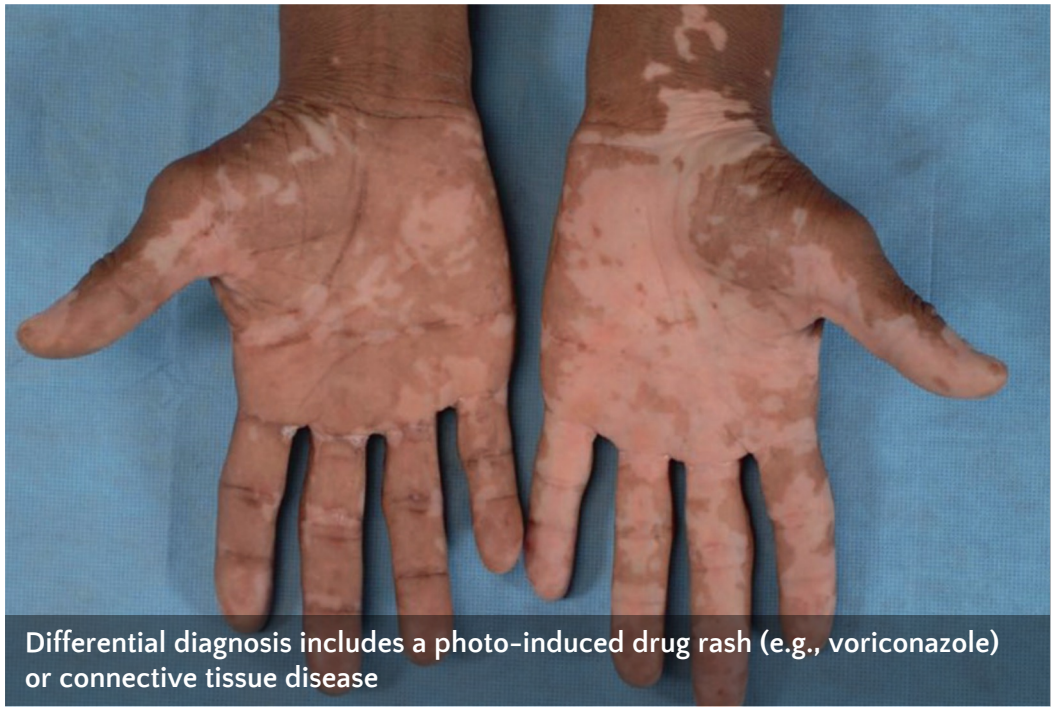
# Poikiloderma



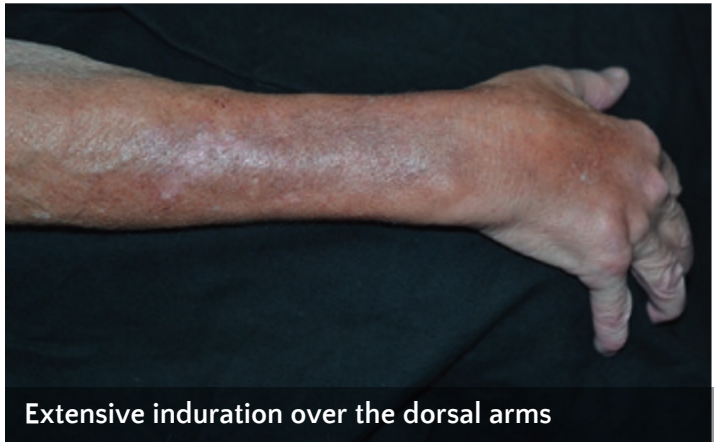
Hypopigmentation, hyperpigmentation, telangiectasia and atrophy, along with histologic changes of cGVHD.



Differential diagnosis includes a photo-induced drug rash (e.g., voriconazole) or connective tissue disease

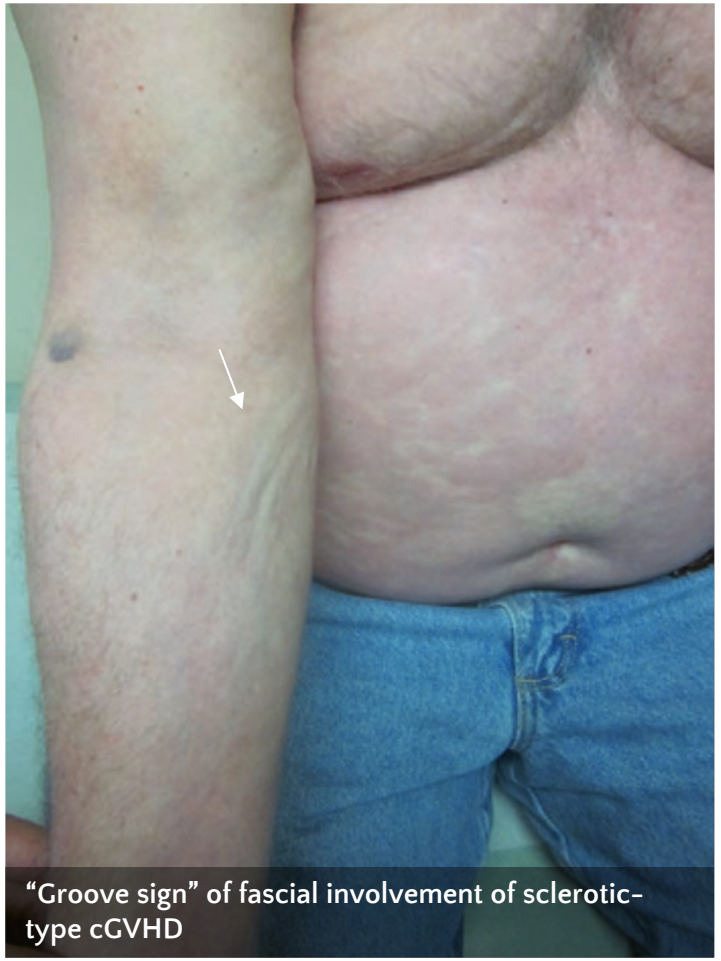
Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.

# Dermal and Subcutaneous cGvHD

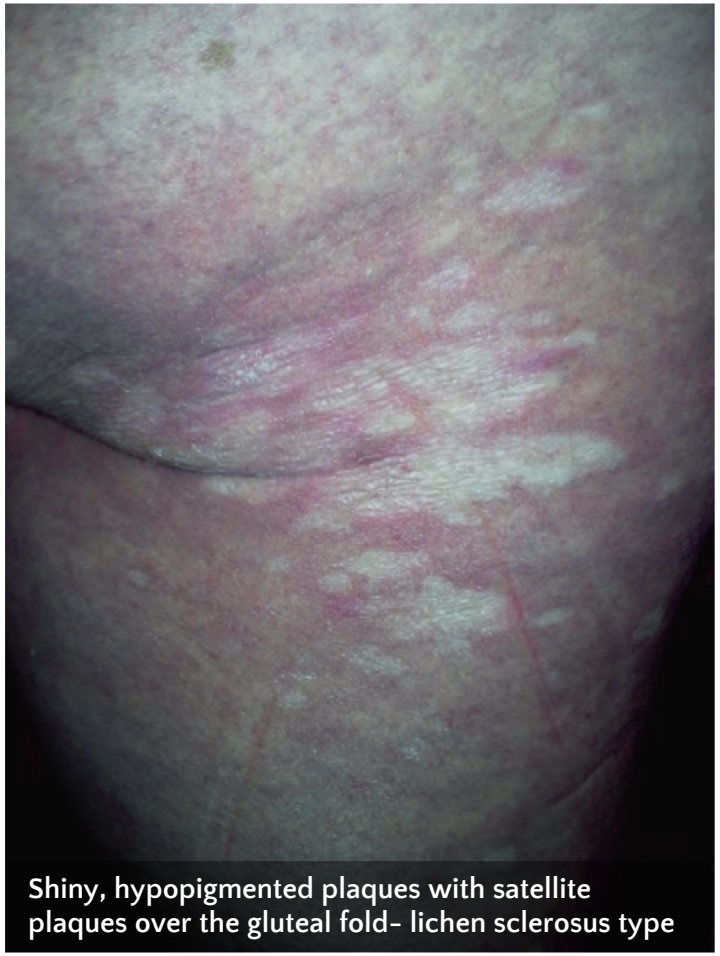


Extensive induration over the dorsal arms

Praying-hands sign indicating fascial disease of her forearms



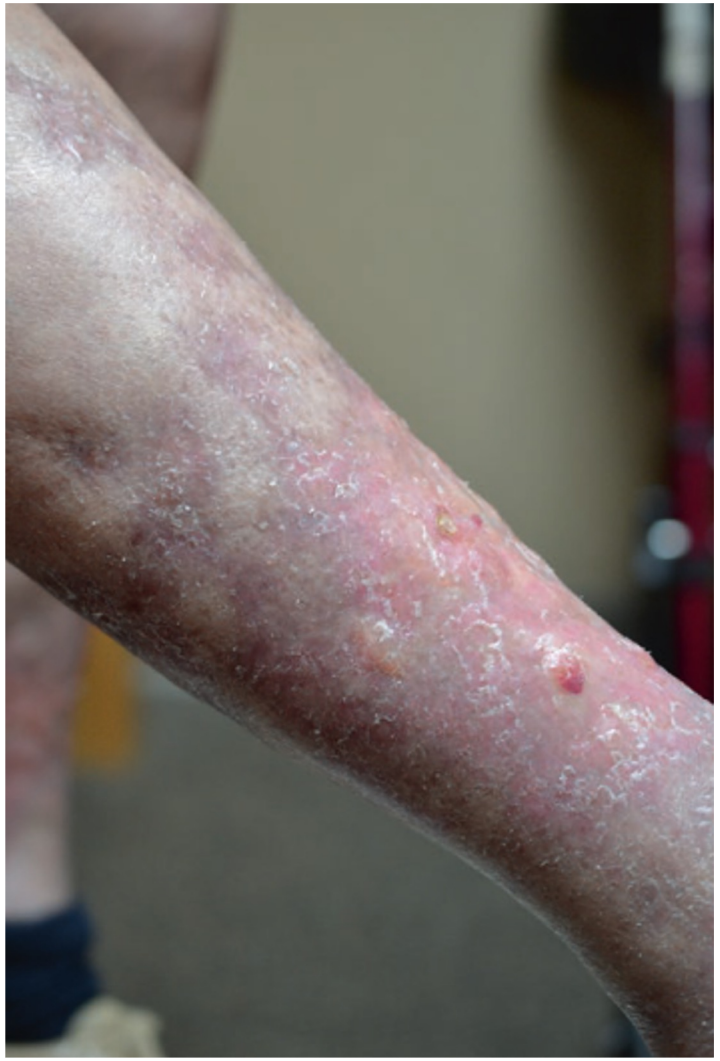
“Groove sign” of fascial involvement of sclerotic-type cGVHD

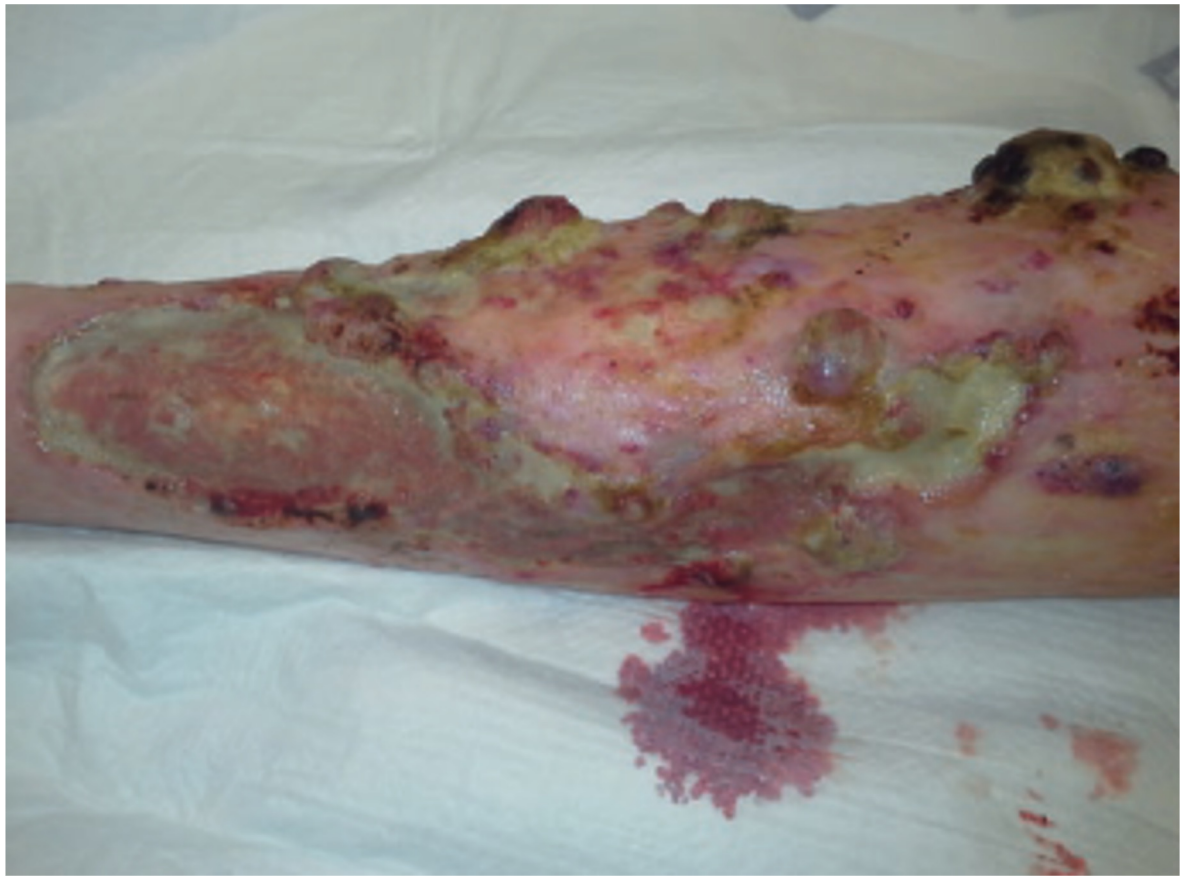


Shiny, hypopigmented plaques with satellite plaques over the gluteal fold- lichen sclerosus type

Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.

# Advanced dermal and subcutaneous cGvHD

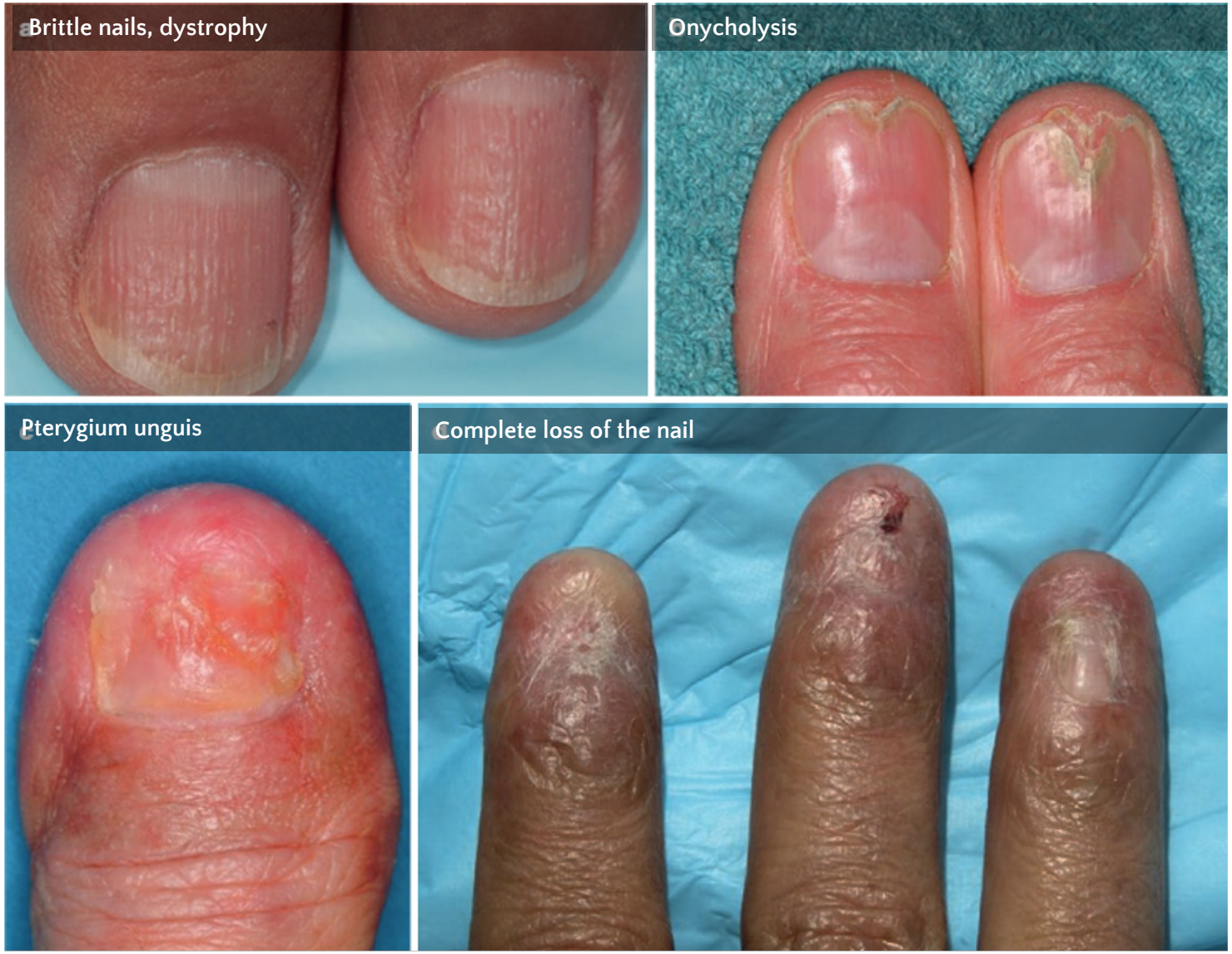




Extensive vascular plaques with large ulcerations at the site of previous plaques, occurring within long-standing sclerotic-type cGVHD and representing the GVHD-angiomatosis phenomenon

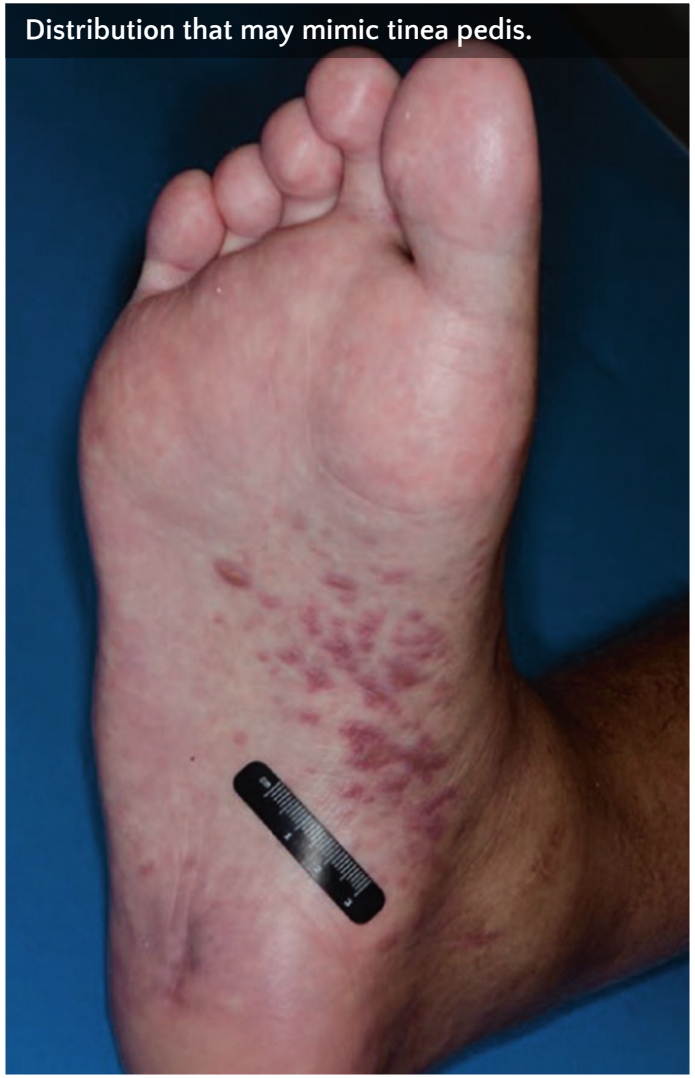
Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-

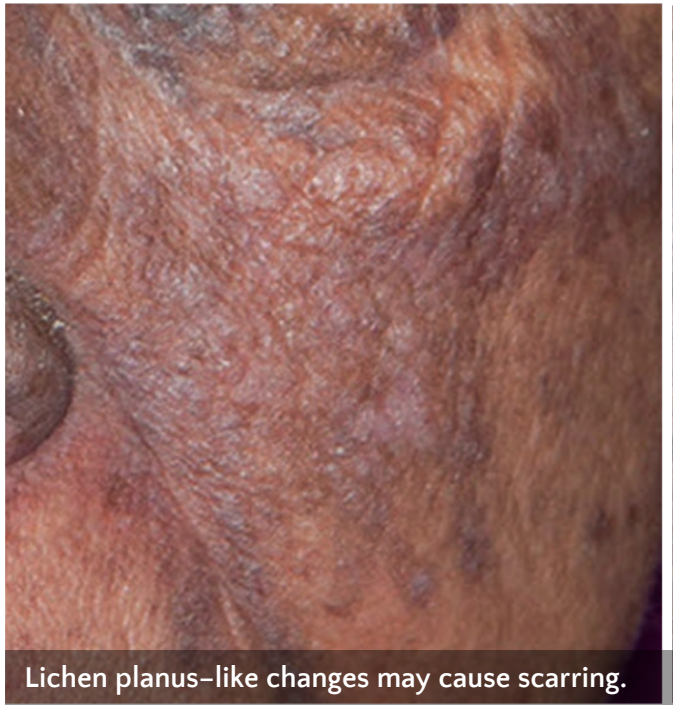
# Nail changes

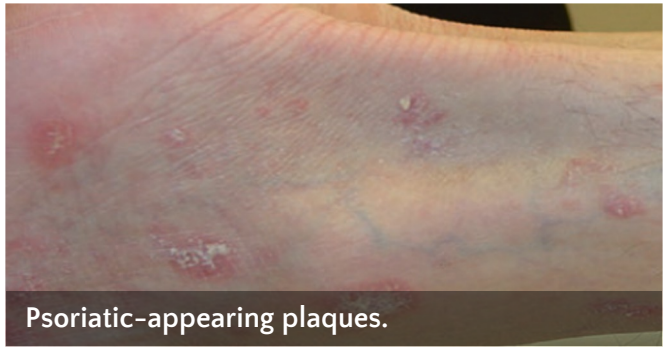


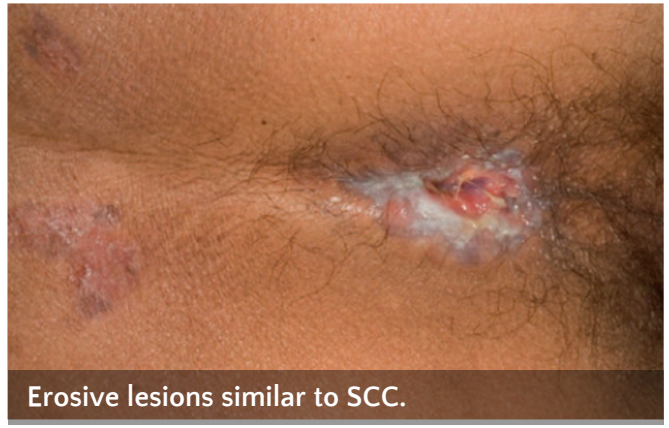

Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.

# Less common presentations of cGvHD


Distribution that may mimic tinea pedis.

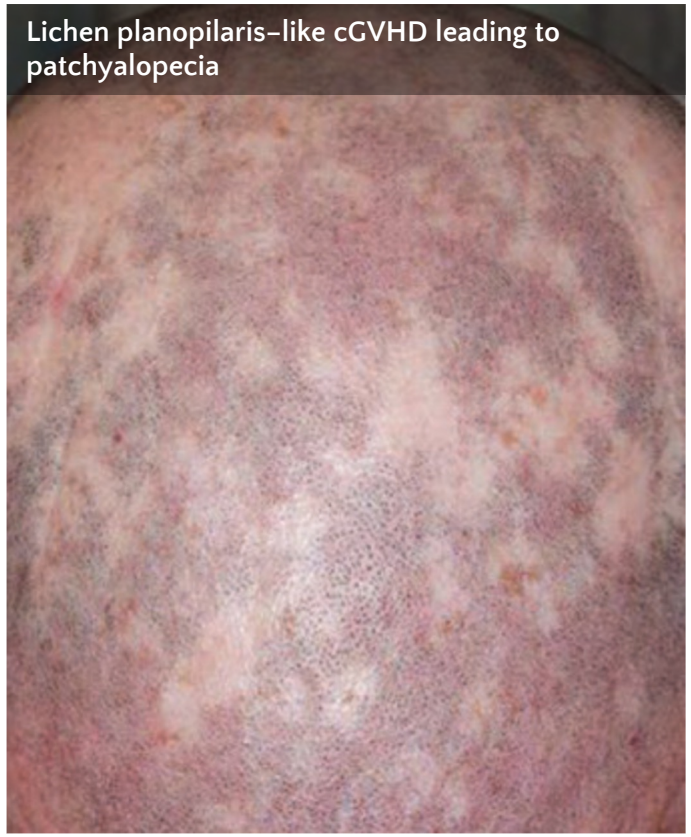

Lichen planus–like changes may cause scarring.


Psoriatic-appearing plaques.

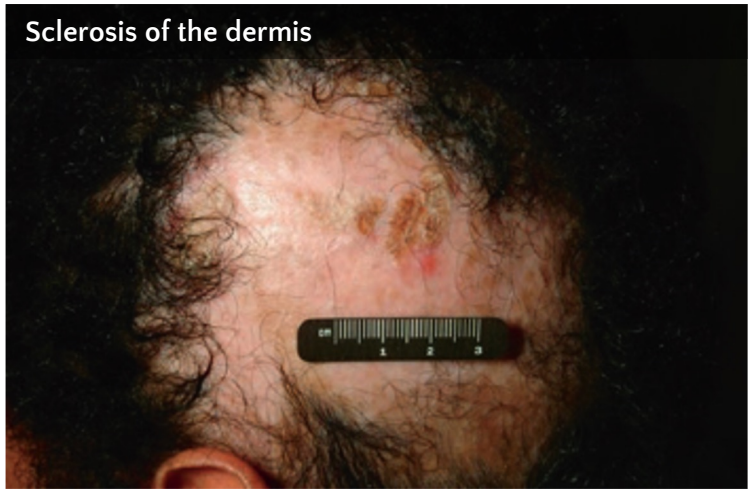

Erosive lesions similar to SCC.

Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.

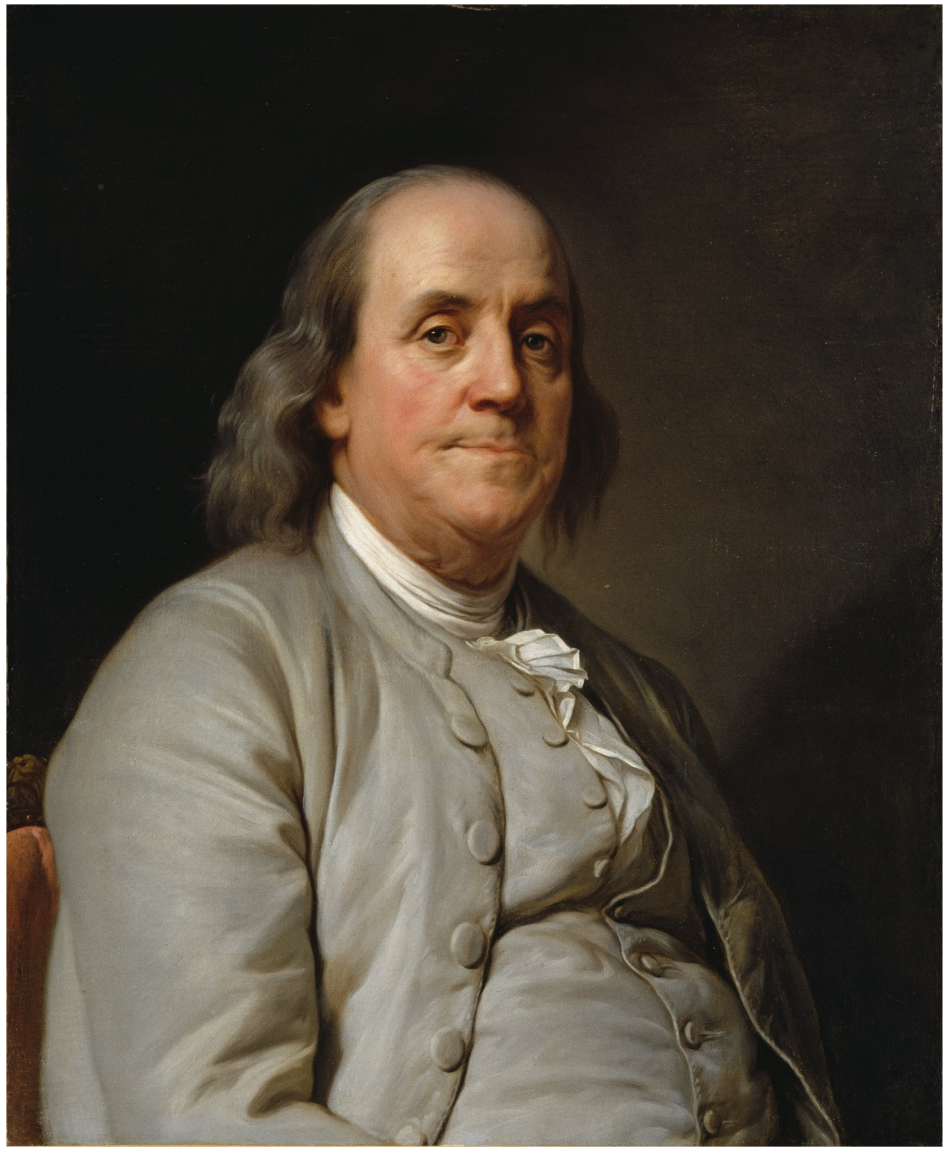
# Alopecia


Lichen planopilaris–like cGVHD leading to patchyalopecia


De novo alopecia areata


Sclerosis of the dermis

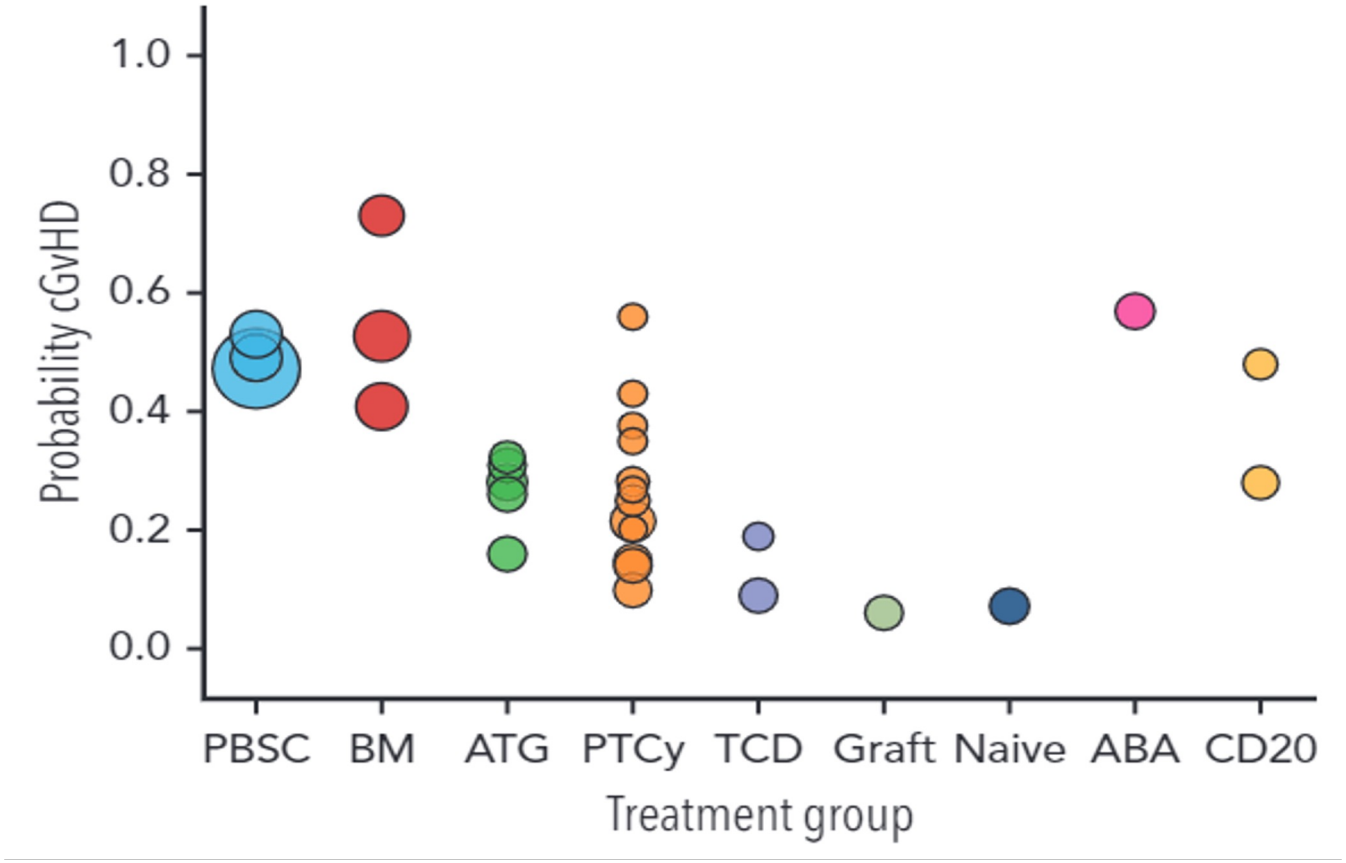
Cotliar, J. A. Atlas of Graft-versus-Host Disease. 21–28 (2016) doi:10.1007/978-3-319-46952-2_3.



**“An ounce of prevention is worth a pound of cure.”**

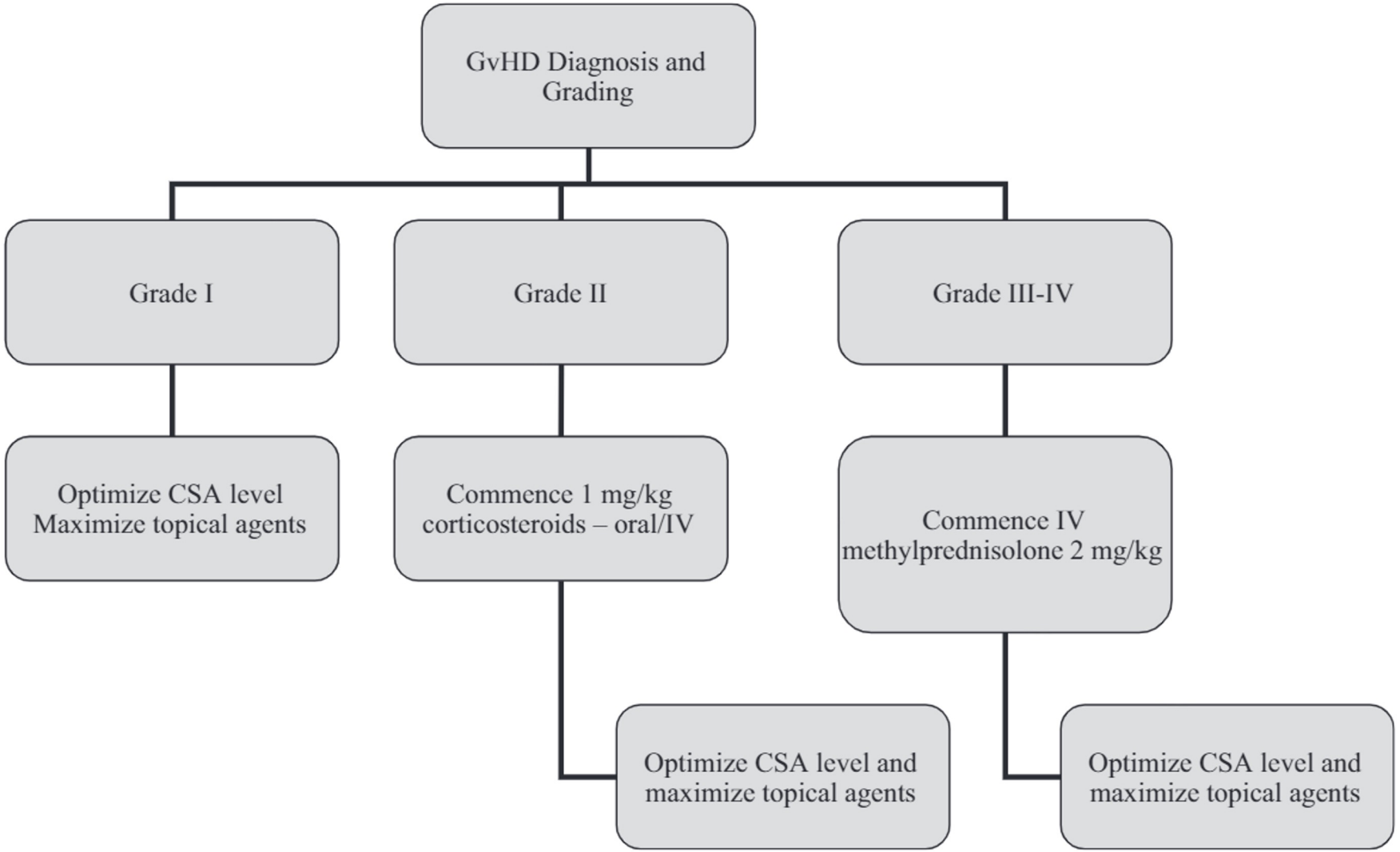
Benjamin Franklin

# Prevention is the cornerstone for management of GVHD




Pidala et al. *Blood* 144, 1363–1373 (2024).

# Treatment algorithm summarizing initial treatment of aGvHD




Dignan, F. L. *et al.*. *Br. J. Haematol.* 158, 30–45 (2012).

# Treatments for aGVHD

## BCSH, BSBMT and ASBMT recommendations for Grade 2 aGVHD or greater

| Therapeutic options (aGVHD grade II or greater) | |
|---|---|
| **Systemic corticosteroids**<br><br>**Failure (Corticosteroid-Resistant):**<br>• progression within 3–5 days of starting treatment or<br>• an incomplete response by 7–14 days) or<br>• recurrence after initial dose reduction (steroid dependence)<br>6-month OS: 50%<br>long-term OS: 5-30% | Dose of **1 - 2 mg/kg** (prednisolone equivalent).<br>**50% of patients do not respond**<br>**30% of patients do not have a sustained response**<br>Budesonide capsules for patients with GI involvement |
| **Extracorporeal photopheresis (ECP)** | CR 52–82 % in steroid-refractory aGVHD; ORR 75–86 % in steroid-refractory cutaneous aGVHD |
| **Sirolimus** | ORR 57–76 % in steroid-refractory aGVHD; CR 50–72 % in steroid-refractory aGVHD |
| **Anti-thymocyte globulin (ATG)** | Low dose rabbit-ATG showed 90 % response for skin and gut aGVHD and an overall 1-year survival of 55 % |
| **Mycophenolate mofetil** | ORR 47–65 % in prospective trials of steroid-refractory aGVHD ; ORR 60 % in a retrospective study of steroid-refractory aGVHD ; CR 26–60 % CR in steroid-refractory aGVHD |
| **Methotrexate** | ORR 58–95 % in steroid-refractory aGVHD using 5 or 10 mg/m2 IV every 3–10 days; CR 42 % in steroid-refractory aGVHD using weekly 5 mg/m2 infusion |

Dignan, F. L. *et al. Br. J. Haematol.* 158, 30–45 (2012)
Patel, D. A., et al. *Drugs* 83, 893–907 (2023).

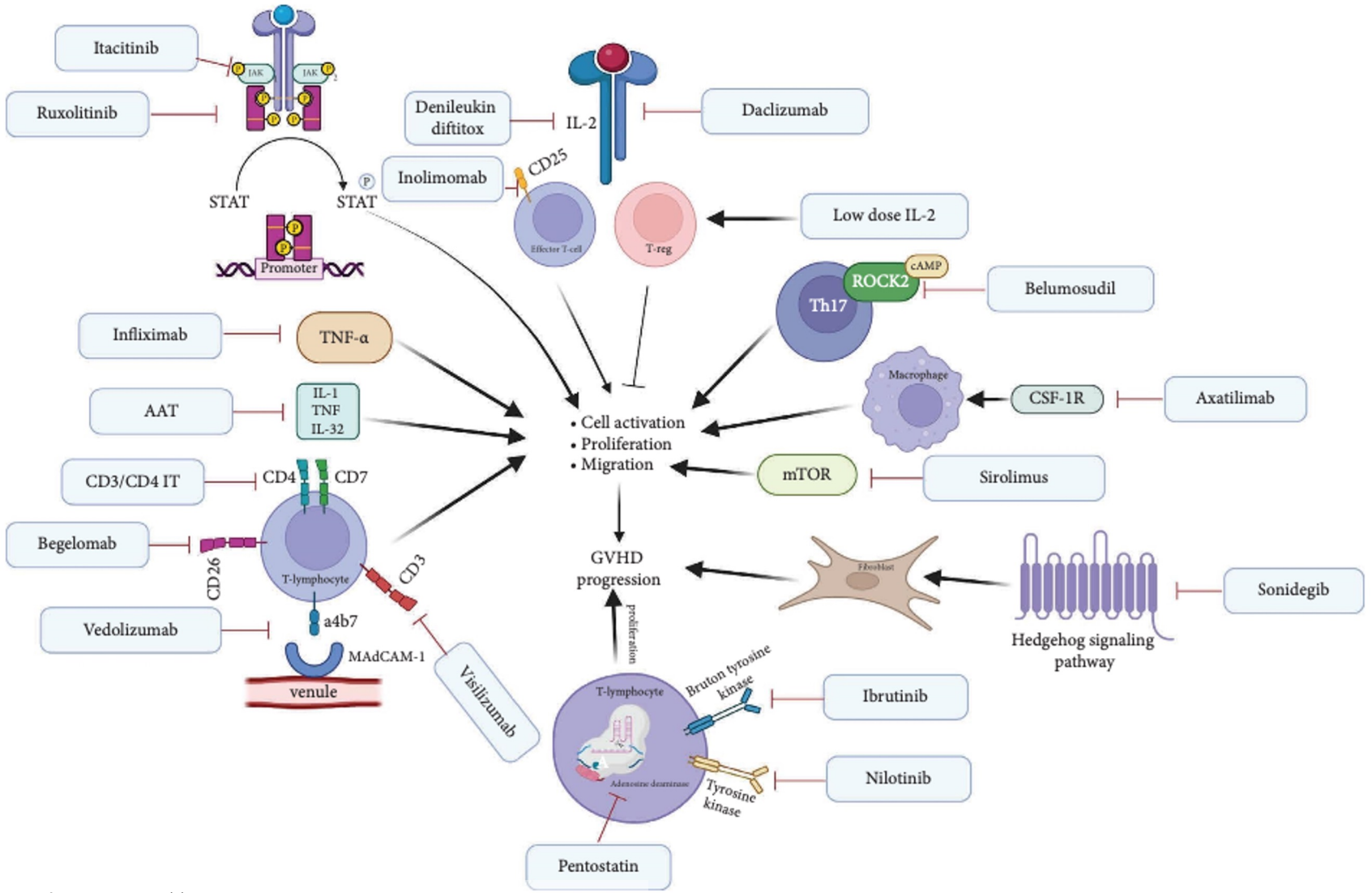
# Recommended therapies for steroid-refractory aGVHD

- **Ruxolitinib was superior to "standard of care" for grade 2–4 SR aGVHD (REACH-2)**
  - **ORR at day 28** 62% versus 39% (BAT); odds ratio 2.64
  - **Durable Response at day 56** 40% versus 22% (BAT); odds ratio 2.38
  - **Loss of Response at 6 months** 10% versus 39% (BAT); odds ratio 4
  - **Thrombocytopenia occurrence** 33% versus 18%
- **No consensus treatment for SR-aGVHD beyond ruxolitinib**

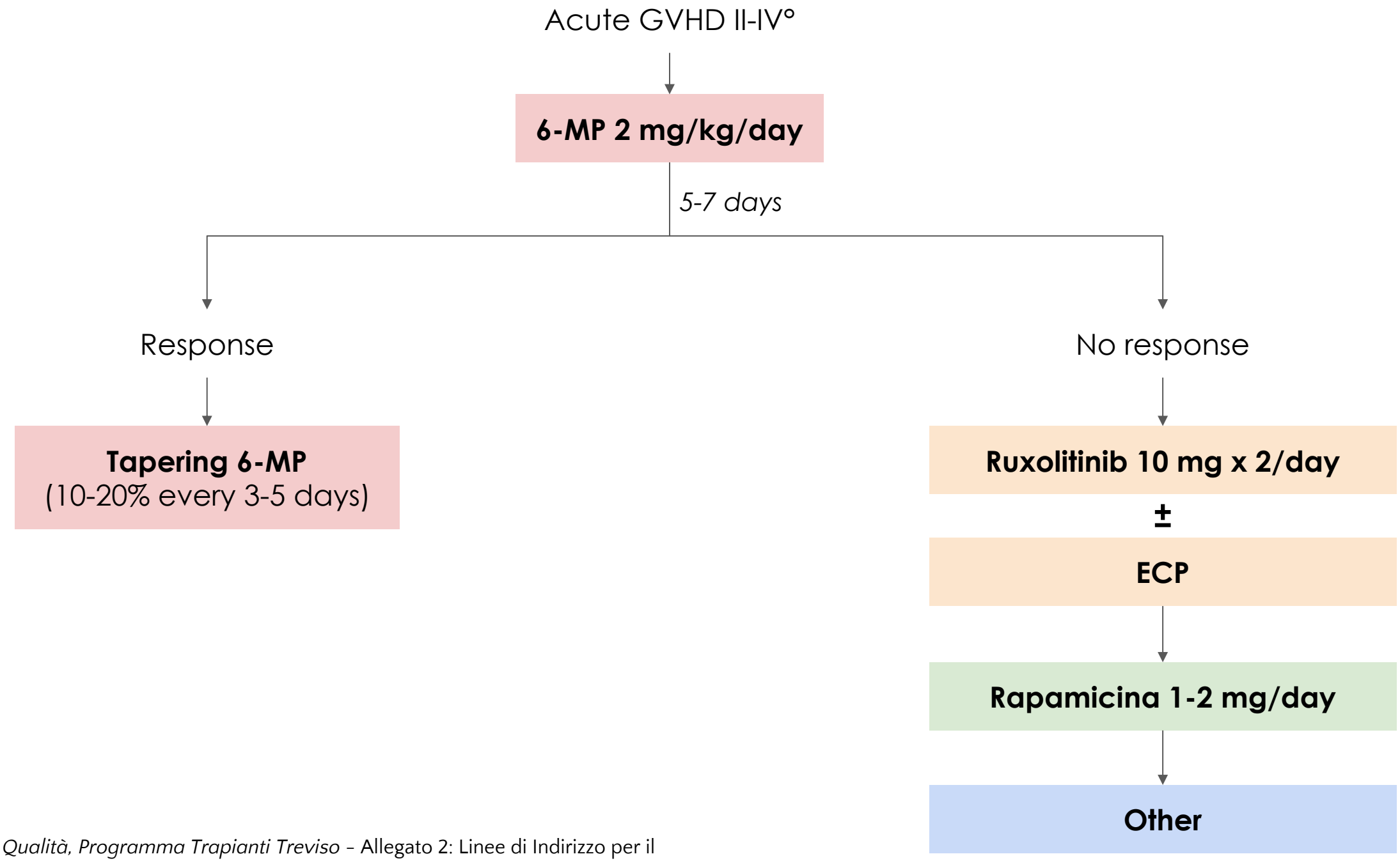
Zeiser R et al. N Engl J Med. 2020;382(19):1800–10.
Watkins, B. *et al. J. Clin. Oncol.* 39, 1865–1877 (2021).
Moreland, L., Bate, G. & Kirkpatrick, *Nat. Rev. Drug Discov.* 5, 185–186 (2006).

# Treatment of steroid-refractory GVHD treatment

multiple drugs, multiple targets …

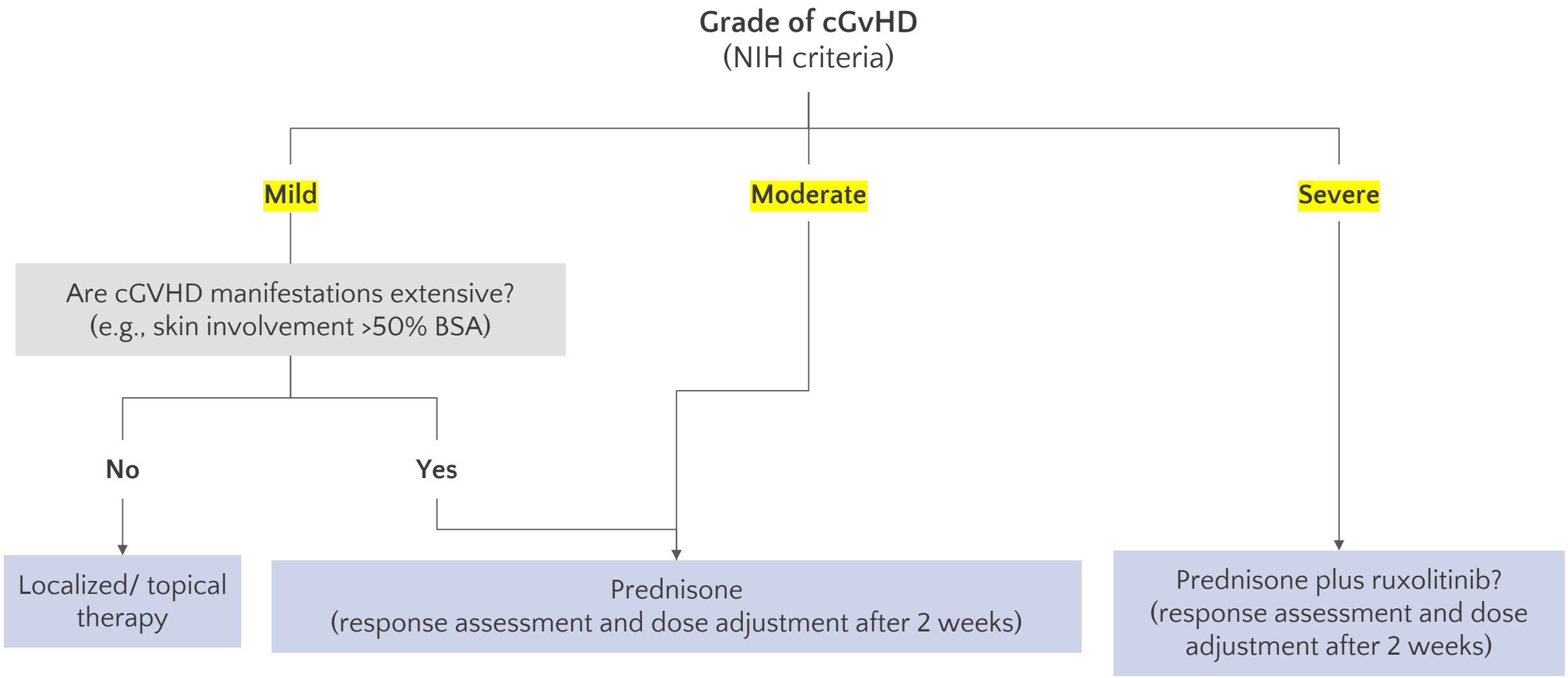



Kovalenko et al. *Advances in Hematology*, *2023*(1), 1-12.

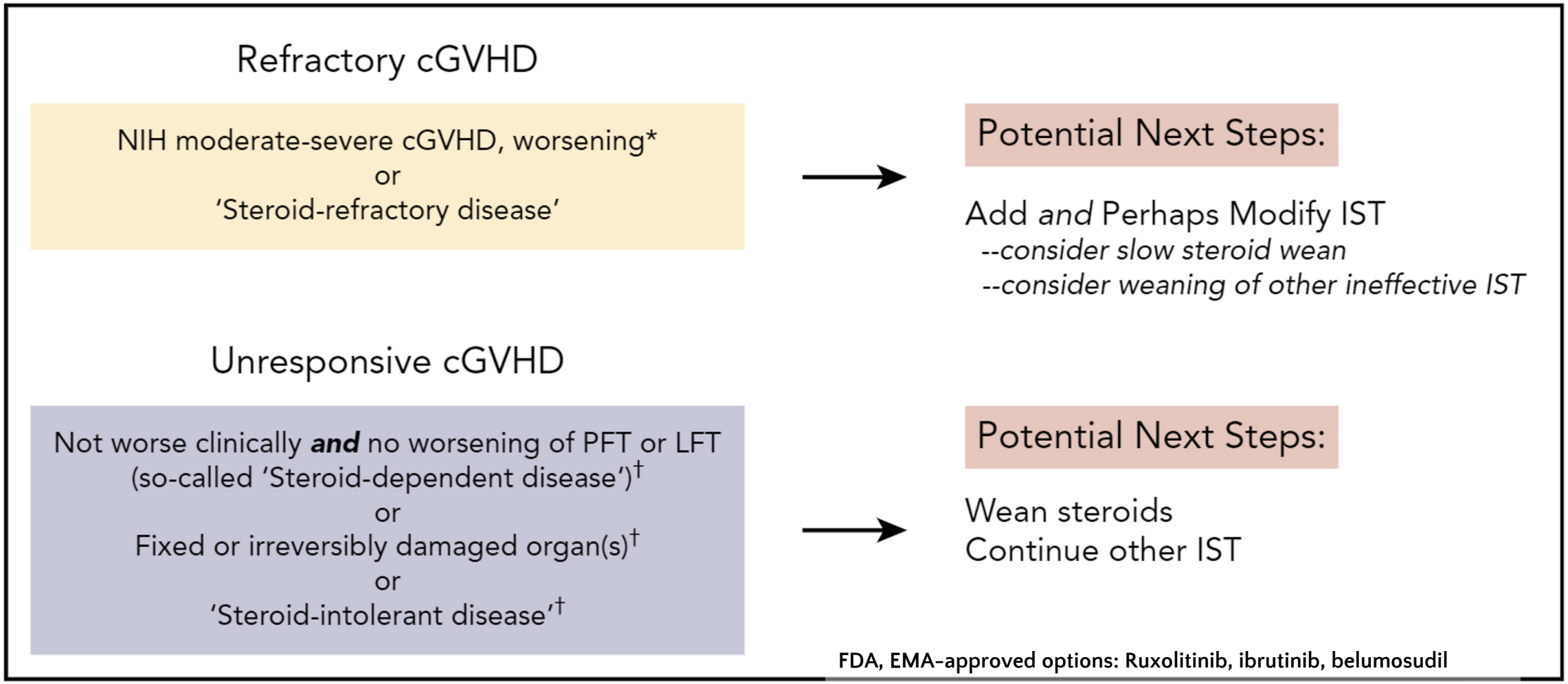



*Manuale della Qualità, Programma Trapianti Treviso* – Allegato 2: Linee di Indirizzo per il Trapianto Allogenico di Cellule Staminali Ematopoietiche, pag 49.

# Initial management of Chronic GVHD



# Rationale approaches in not responding patients?




* Progressive disease despite prednisone 1 mg/kg/day for two weeks
Stable disease after four to six weeks of prednisone ≥0.5 mg/kg/day
Inability to taper prednisone to <0.5 mg/kg/day

Sarantopoulos S et al. *Blood*. 2019;133 (11):1191–1200.

# Identifying optimal treatment for steroid-refractory cGVHD

## Balancing possible benefits vs. definite risks

**Table 1. Adverse reactions of commonly used therapies in refractory chronic GVHD[14]**

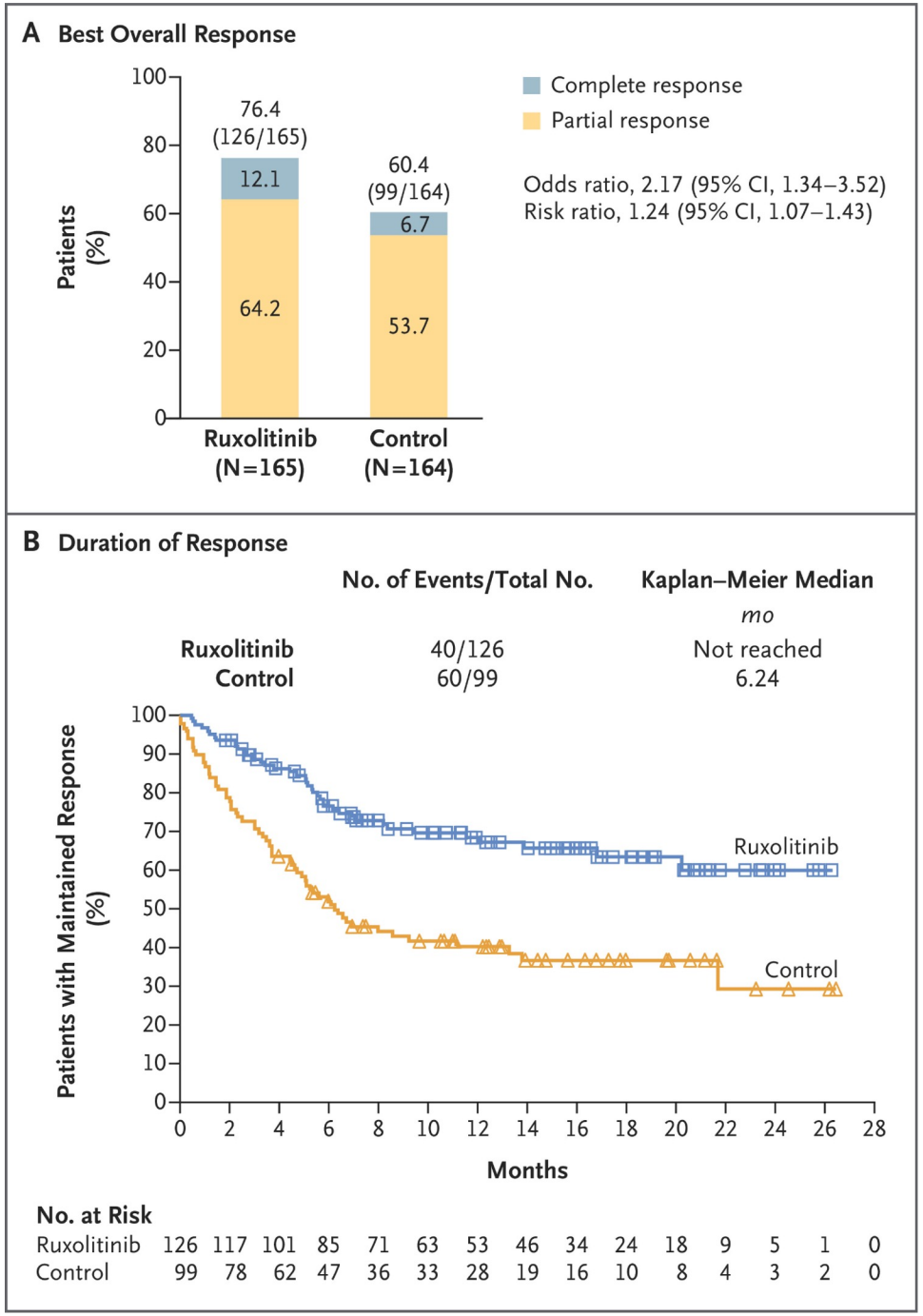
| Agent | Potential major adverse effects (with major study citations) | Common (>10%) generally less severe adverse effects |
|---|---|---|
| Bortezomib | Peripheral neuropathy, thrombocytopenia, malignancy relapse[106] | Herpes virus reactivation |
| ECP | Vascular access complications[107] | Thrombocytopenia |
| FAM | New FDA MedWatch warning; warning only applies to azithromycin use in prophylactic (not treatment) setting[108,109] | |
| Ibrutinib (Imbruvica R) | Pneumonia,[29] impaired platelet function | Fatigue, muscle pain, peripheral edema |
| Imatinib | | Peripheral edema |
| Interleukin-2 | Injection site induration, infections[36] | Constitutional flu-like symptoms |
| MMF (Cellcept) | Viral reactivation, hypertension, pneumonia, posttransplantation lymphoproliferative disease[110] | GI toxicity, neutropenia, leukopenia |
| Pamolidomide | Tremor, muscle cramps, peripheral neuropathy[111] | Skin rash |
| Rituximab (Rituxan R) | Infection, late neutropenia[38,39,112] | B lymphopenia |
| Ruxolitinib (Jakafi R) | Viral reactivation/infection, bacterial infections[35] | Cytopenias |
| Sirolimus (Rapamune) | TAM when used in combination with calcineurin inhibitors, renal insufficiency,[113] proteinuria | Peripheral edema, hyperlipidemia, cytopenias |

This list of agents represents a fraction of agents being actively evaluated. Preferred use of any agent still requires validation via larger clinical trials.

ECP, extracorporeal photopheresis; FAM, fluticasone, azithromycin, and montelukast; FDA, US Food and Drug Administration; GI, gastrointestinal; MMF, mycophenolate mofetil; TAM, transplantation-associated microangiopathy.

Sarantopoulos S et al. *Blood*. 2019;133 (11):1191-1200.

# Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease (REACH-3)




**Overall response at week 24** 49.7% versus 25.6% (BAT); OR 2.99

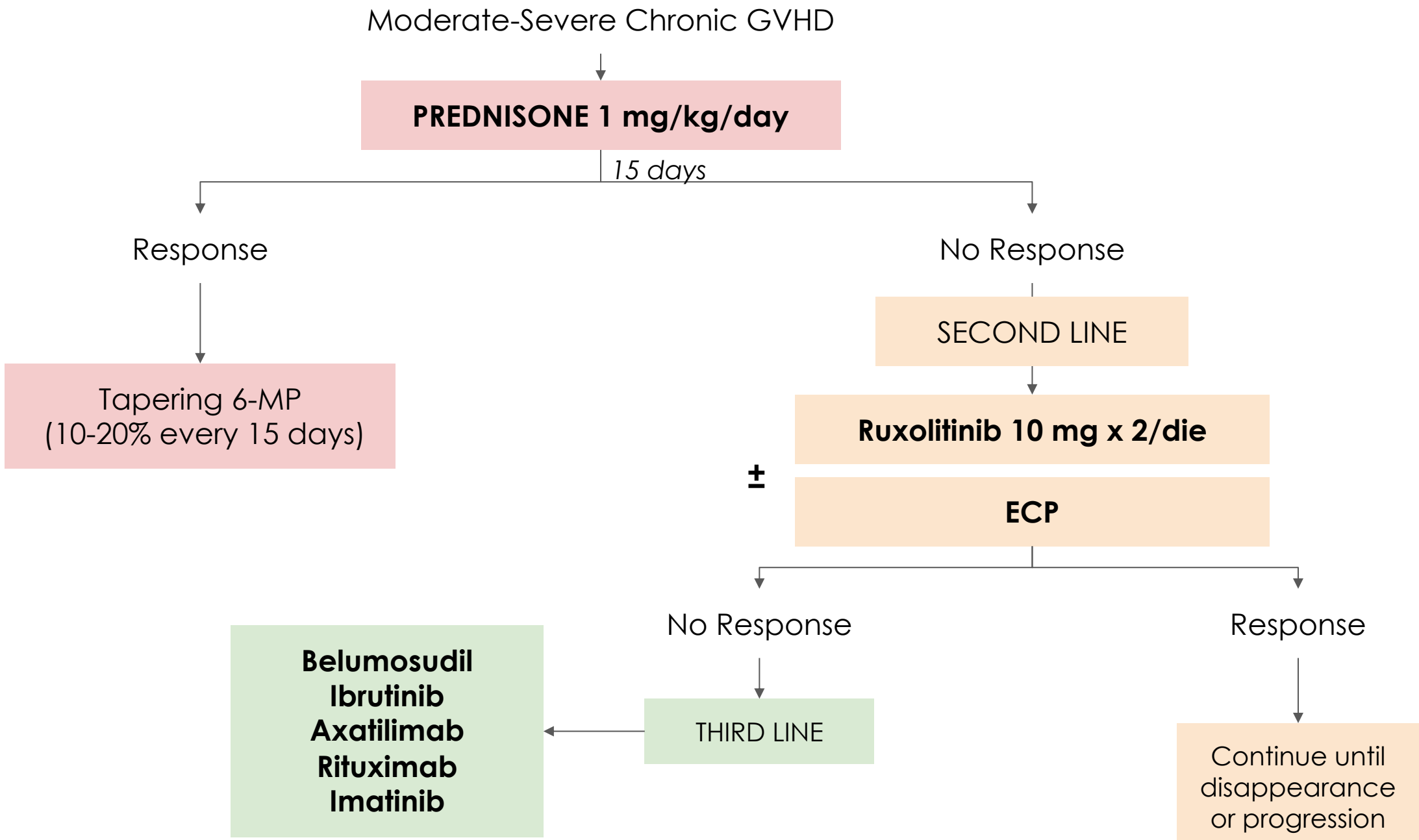
**Best overall response at week 24** 76.4% versus 60.4% (BAT); OR 2.17

**Failure-free survival at 6 months** 74.9% versus 44.5% months (BAT)

**Thrombocytopenia occurrence** 15.2% versus 10.1%

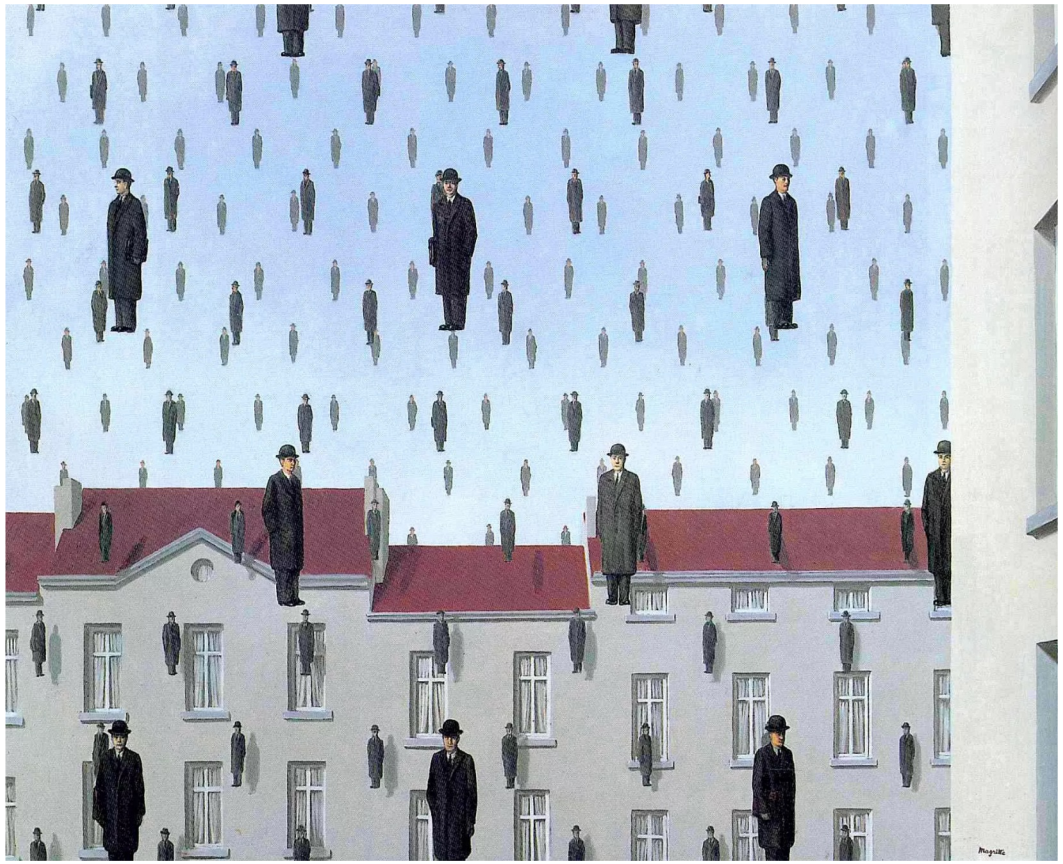
**Anemia occurrence** 12.7% versus 7.6%

Zeiser R et al. *NRJM*. 2021;385 (3):228-238.




*Manuale della Qualità, Programma Trapianti Treviso* – Allegato 2: Linee di Indirizzo per il Trapianto Allogenico di Cellule Staminali Ematopoietiche, pag 56.

# Steroid-refractory GVHD: need for personalized approach



Renè Magreitte, 1953 *Golcande*
Menile Collection, Houston, Texas, USA

Piete Bruegel the Elder, 1553
*The Fight Between Carnival and Lent*
Kunsthistorisches Museum, Vienna, Austria

# Unmet needs

Better understanding of the pathobiology of GVHD and SR-GVHD to target biochemical pathways with steroid-sparing drugs that have novel mechanism of action.

At onset of GVHD-most patients are treated similarly with HD corticosteroids, leading to a number of both under-treated and over-treated patients

Some biomarkers and risk scores have shown promise- but still have unproven clinical utility for predicting risk of severe GVHD and SR-GVHD

Future for machine learning and AI-guided therapies?

**Problem for trials**: Mortality correlated with maximum clinical severity, but this can only be assigned *retrospectively after response to treatment is known*

“Life can only be understood backwards; but it must be lived forwards.”