

Transplantation of Hematopoietic Stem Cells

Mechanisms, graft-versus-host disease, and immune complications

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Learning objectives

- Explain why hematopoietic stem cells can restore hematopoiesis after conditioning.
- Trace donor T-cell recognition to acute and chronic graft-versus-host disease.
- Relate characteristic organ pathology to clinical manifestations and infection risk.

Emphasis: Mechanism → morphology → clinicopathologic interpretation.

Why hematopoietic stem cell transplantation matters

- Transplanted hematopoietic stem cells (HSCs) can establish new marrow hematopoiesis.
- Use in hematologic malignancy, marrow failure and inherited disorders.
- Success requires engraftment, while immune complications may limit recovery.

The therapeutic graft is a living hematopoietic and immune-cell system.

Major indications

Indication group	Examples from the source	Transplantation goal
Hematologic malignancy	Hematologic cancers	Reconstitute hematopoiesis in a treated host
Marrow failure	Aplastic anemia	Restore hematopoietic cell production
Inherited marrow disease	Sickle cell anemia; thalassemia	Provide a new hematopoietic system
Inherited immune defect	Immunodeficiency states	Restore defective immune-cell production

Examples are the textbook's; The list is not an eligibility guideline.

Malignancy: The marrow is both target and substrate

- HSC transplantation is used to treat hematologic malignancies.
- Pretransplant treatment can deplete host cells and create marrow space.
- Transferred cells must engraft and regenerate blood-forming cells.

Graft-versus-leukemia control is relevant when considering donor T-cell depletion.

Marrow failure: Replacing deficient hematopoiesis

- Aplastic anemia is an explicit example of a marrow failure indication.
- The transplanted HSC population must populate recipient marrow niches.
- Engraftment offers a route toward sustained hematopoietic output.

Core distinction: Correcting a deficient blood-forming compartment.

Inherited erythroid disorders

- Sickle cell anemia and thalassemia are listed as inherited marrow-disorder indications.
- The therapeutic target is the hematopoietic lineage that produces circulating blood cells.
- Successful graft function depends on stem-cell survival and proliferation.

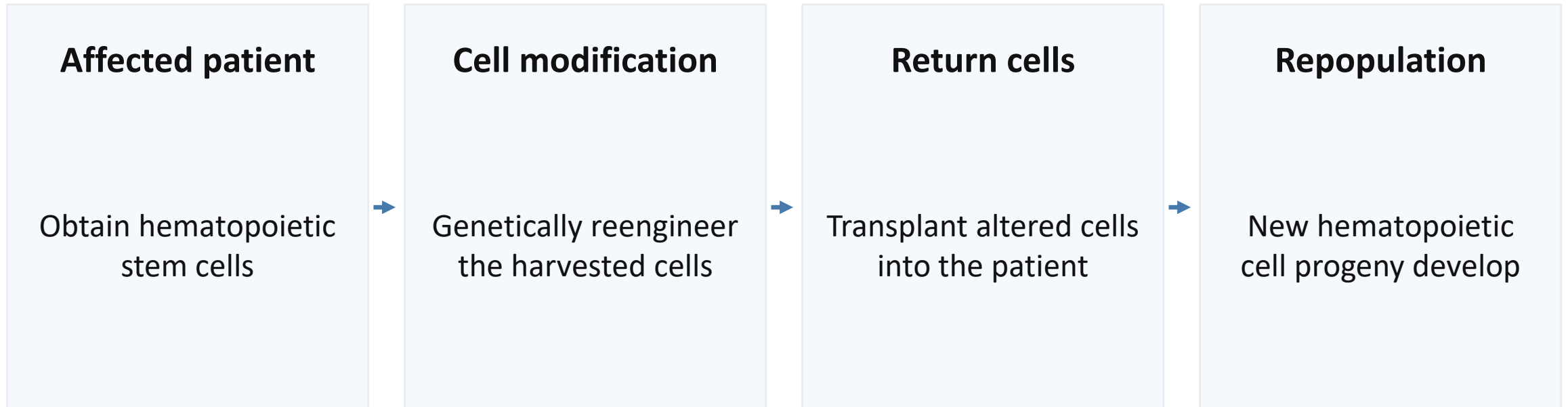
Indications; It does not prescribe patient selection criteria.

Inherited immunodeficiency states

- Some inherited immunodeficiencies can be approached by HSC transplantation.
- Corrected hematopoietic progenitors can contribute to immune-cell reconstitution.
- Immune reconstitution itself may be delayed after the transplant.

Restoration of immunity is both a treatment goal and a post-transplant vulnerability.

Genetically reengineered HSC transplantation



This approach is used in selected immunodeficiencies and inherited marrow disorders; No specific vector or gene is specified.

HSC procurement: Historical and current sources

Historical source

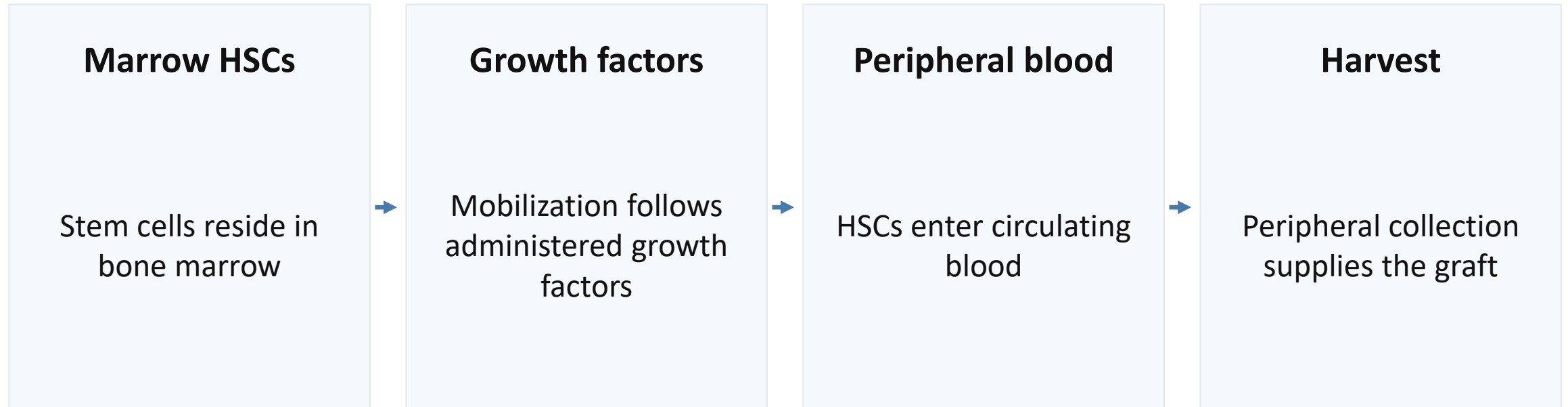
- Bone marrow was the conventional HSC collection site.
- It remains a source of transplantable hematopoietic cells.

Other sources emphasized

- Mobilized peripheral blood is now commonly used.
- Newborn umbilical cord blood is rich in HSCs.

The source distinguishes procurement methods, not comparative clinical outcomes.

Mobilizing HSCs into peripheral blood



Mobilization is a procurement step, not equivalent to engraftment.

Umbilical cord blood as an HSC source

- Umbilical cord blood from newborn infants contains many HSCs.
- It provides an alternative to harvest from bone marrow or mobilized blood.
- The choice of source precedes the distinct process of recipient conditioning.

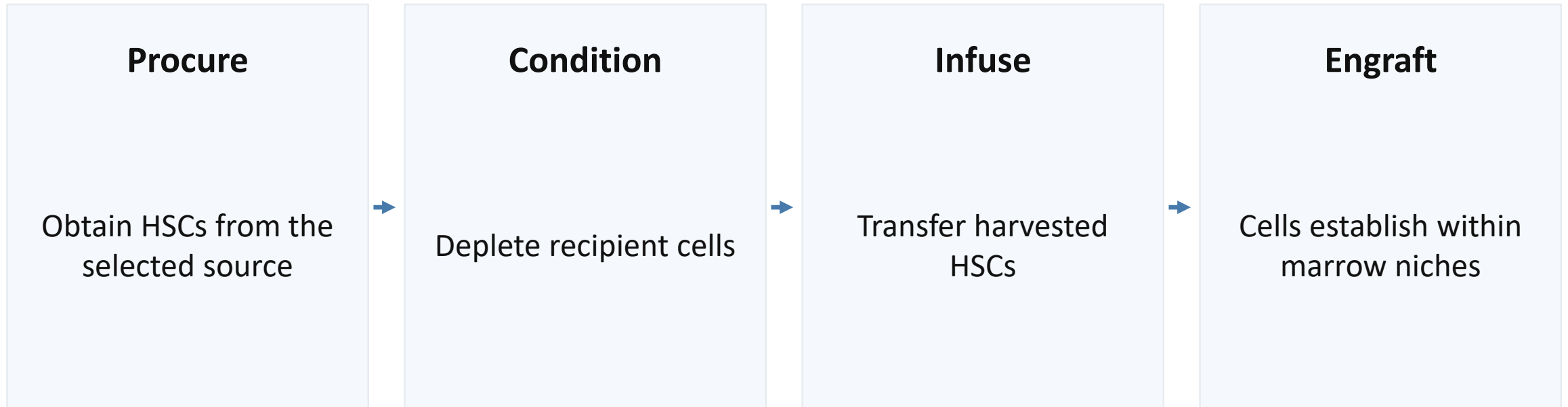
The supplied excerpt does not quantify cell doses, success rates or collection trade-offs.

Three graft sources: What the textbook states

Source	Source description	Specific text-supported feature
Bone marrow	Direct marrow collection	Historically used for HSC transplantation
Peripheral blood	Collection after mobilization	Growth factors mobilize HSCs from marrow
Umbilical cord blood	Blood of newborn infants	Rich source of HSCs

No comparative engraftment kinetics or GVHD rates are provided in the source.

Transplantation as a sequential process



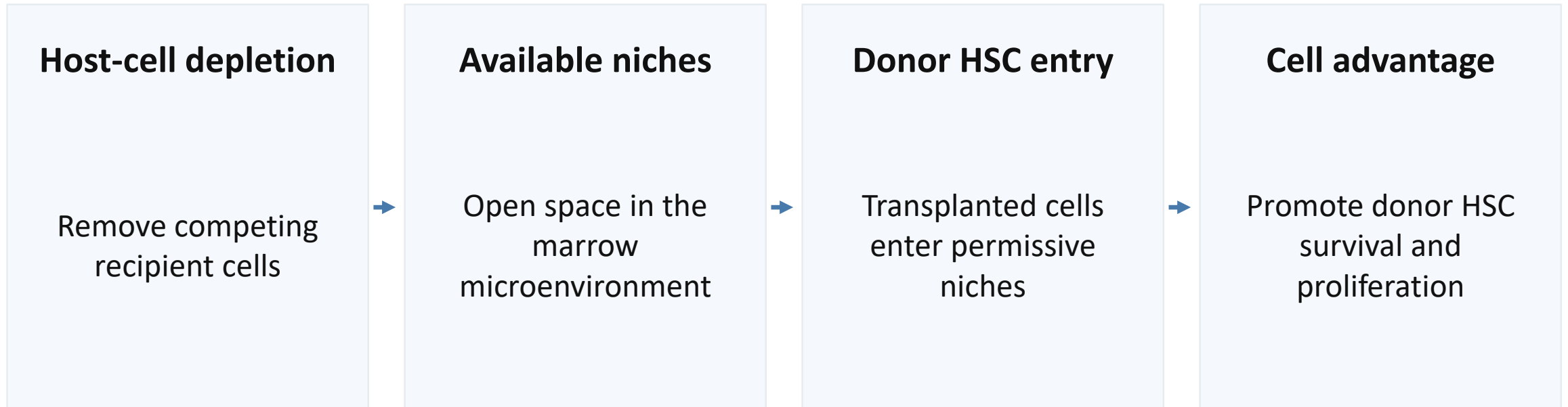
An explanatory sequence distilled from the source; Not a detailed clinical protocol.

Recipient conditioning

- Irradiation or chemotherapy is used in most indications described.
- Treatment depletes host cells before HSC transplantation.
- This also contributes to the immunodeficiency that follows transplantation.

Conditioning has a desired marrow effect and an important immune cost.

Why conditioning improves engraftment



The marrow niche is part of the mechanism; Transplant success is not merely cell infusion.

Conditioning: Intended effect versus cost

Intended effect

- Makes niches available for transplanted HSCs.
- Favors survival and proliferation of the graft.

Immunologic cost

- Myeloablation depletes recipient leukocytes.
- Lymphodepletion contributes to infection susceptibility.

The same intervention permits engraftment and creates vulnerability.

Engraftment is a microenvironmental event

- HSCs require marrow niches that support stem-cell persistence.
- Depleting host cells reduces competition within these niches.
- Donor cells then have an opportunity for survival and proliferation.

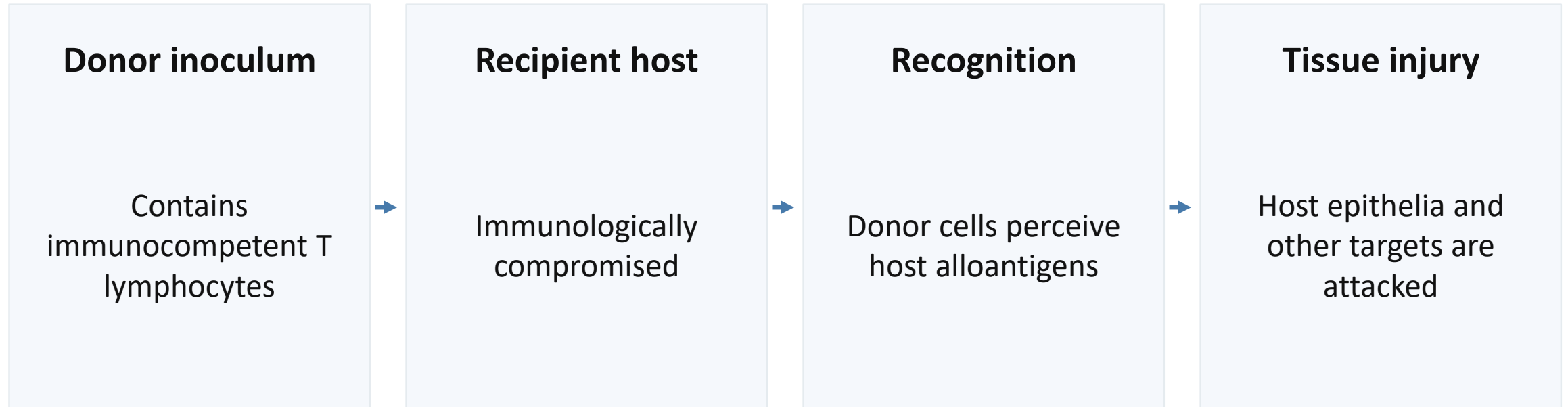
A successful graft must establish a continuing source of hematopoiesis.

The two signature complications

- Graft-versus-host disease (GVHD): Donor-derived immune cells attack host tissues.
- Immunodeficiency: Host defense is impaired during and after transplantation.
- Both are linked to the immune biology of the HSC graft and its recipient.

These two complications receive special emphasis in the Robbins section.

GVHD: Immunologic direction of attack



Unlike host-mediated graft rejection, GVHD proceeds from graft immune cells toward the host.

Necessary setting for GVHD

- The transferred graft contains competent immune cells or their precursors.
- The host cannot adequately eliminate the transferred immune cells.
- The graft's immune cells recognize host antigens and react.

The transplant contains the effector system causing tissue injury.

Directionality: Rejection versus GVHD

Solid-organ graft rejection

- Host immune responses recognize graft alloantigens.
- The transplanted organ is the primary target.

Graft-versus-host disease

- Donor-derived T lymphocytes recognize host alloantigens.
- Recipient organs become targets of donor-cell attack.

Same principle—alloantigen recognition; Opposite direction of injury.

GVHD outside conventional HSC transplantation

- GVHD is seen most commonly following HSC transplantation.
- Robbins also describes rare GVHD after lymphoid-cell-rich solid organs, such as liver.
- Transfusion of unirradiated blood is another rare setting.

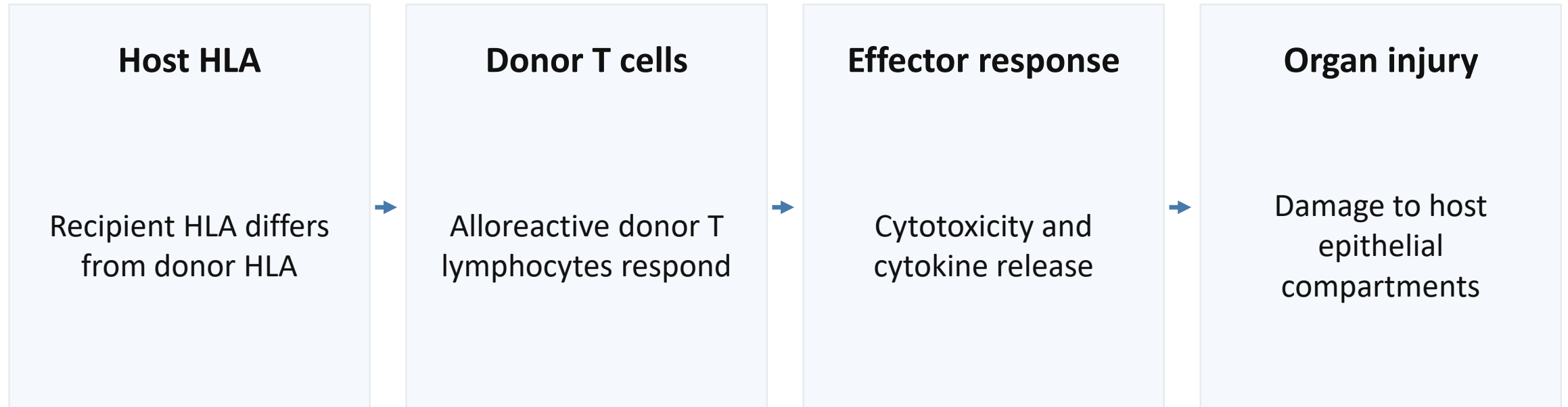
The critical transferable component is immunologically active donor lymphocytes.

Allogeneic grafts carry immunocompetent donor cells

- Allogeneic HSC preparations may include donor T lymphocytes.
- Donor T cells can recognize recipient HLA molecules as foreign.
- This alloimmune response initiates injury of recipient tissues.

Donor T cells are central effectors, not incidental graft contamination.

From donor HLA recognition to organ damage



Flow is conceptual: Direct cytotoxicity and cytokine-mediated tissue injury.

HLA matching mitigates the alloimmune problem

- Donor and recipient HLA alleles are matched as closely as practicable.
- Robbins specifies DNA sequencing–based molecular typing of HLA alleles.
- The purpose is to minimize donor T-cell recognition of the recipient.

High-resolution typing addresses the immunologic source of alloreactivity.

Classification of GVHD in the Robbins section

Form	Textbook temporal framing	Main characteristic injury
Acute GVHD	Days to weeks after allogeneic HSC transplant	Skin, small bile ducts and intestinal epithelia
Chronic GVHD	May follow acute disease or arise insidiously	Fibrosing skin injury, cholestatic liver injury, GI and immune damage

Do not substitute a rigid numerical acute/chronic cutoff; None is given in this excerpt.

Acute GVHD: Early donor-cell–mediated injury

- Acute GVHD develops within days to weeks after allogeneic transplantation.
- Targeted injury is especially prominent in epithelial tissues.
- Severity of tissue damage does not require a dense lymphocytic infiltrate.

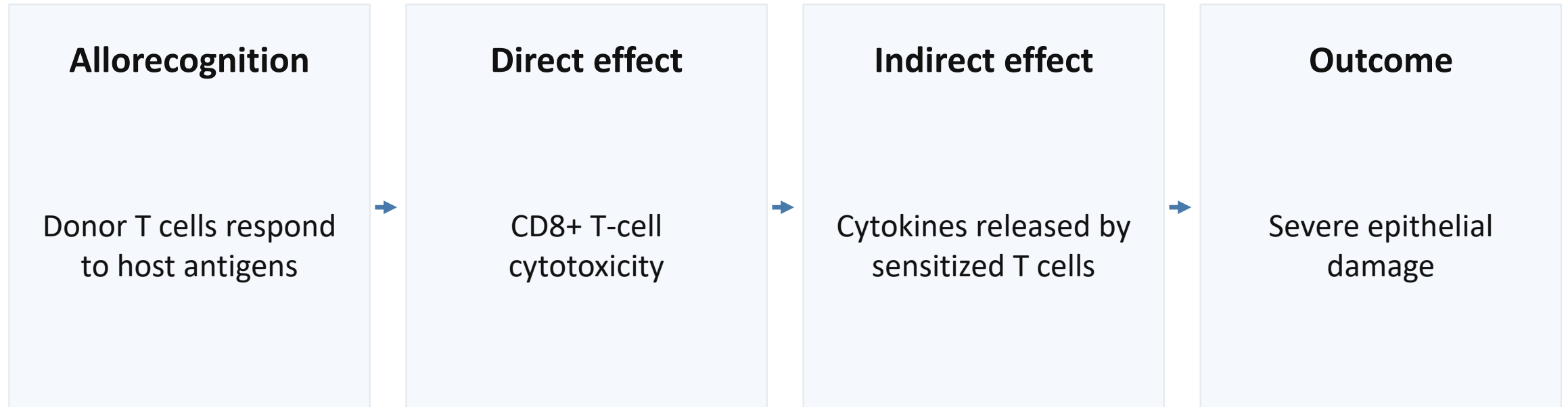
Early presentation plus epithelial injury links mechanism to morphology.

Acute GVHD: The major organ pattern

Target	Pathologic process	Clinical expression
Skin	Lymphocytic infiltration; keratinocyte apoptosis	Rash beginning at characteristic sites
Small bile ducts	Immune-mediated epithelial destruction	Jaundice
Intestinal mucosa	Mucosal injury and ulceration	Bloody diarrhea

The three manifestations represent injury to different epithelial compartments.

Two complementary mechanisms of acute injury



The source attributes considerable damage to cytokines in addition to direct killing.

Why severe damage can coexist with sparse infiltrates

- Acute GVHD lesions are often not densely infiltrated by lymphocytes.
- Effector T cells can injure targets directly through cytotoxicity.
- Released cytokines can amplify tissue damage beyond visible cellular numbers.

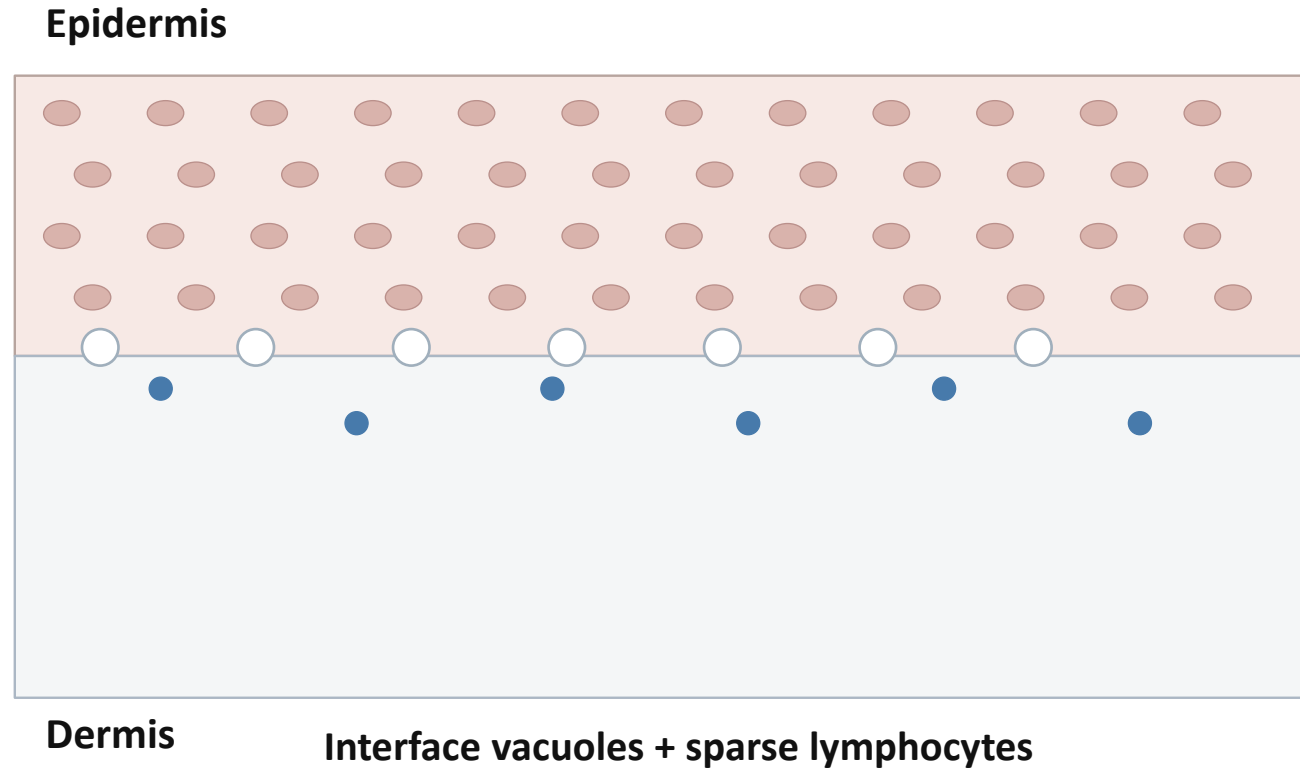
Do not exclude acute GVHD simply because biopsy inflammation appears sparse.

Acute cutaneous GVHD: Rash distribution

- Rash may first appear on neck and ears.
- Palms and soles are also characteristic early sites in the source.
- The eruption can subsequently become generalized.

A distinct early distribution can precede more widespread skin involvement.

Acute skin GVHD: Epithelial interface injury

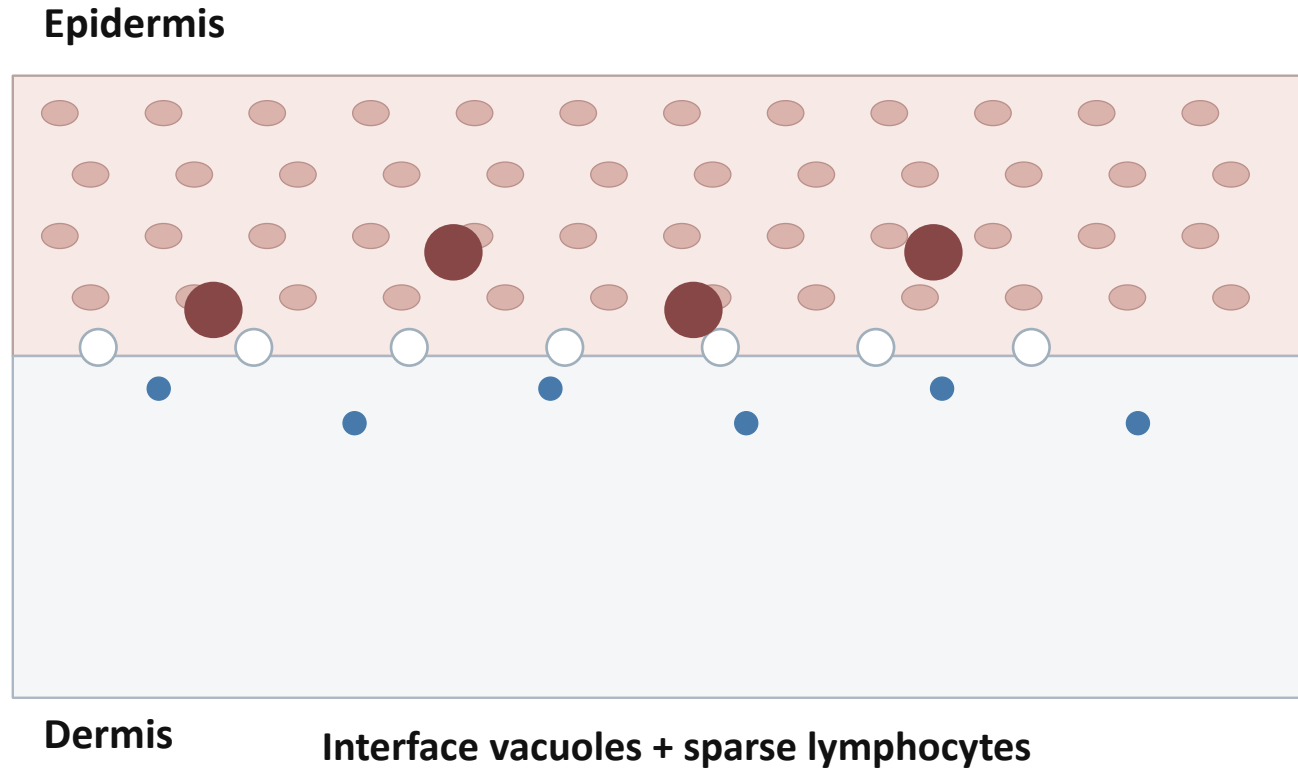


SCHEMATIC (not a histologic specimen)

- Sparse lymphocytes are present near the dermoepidermal junction.
- Small spaces or vacuoles develop at the dermoepidermal interface.

Original schematic based on the supplied description of Fig. 6.36A–B.

Acute skin GVHD: Keratinocyte apoptosis



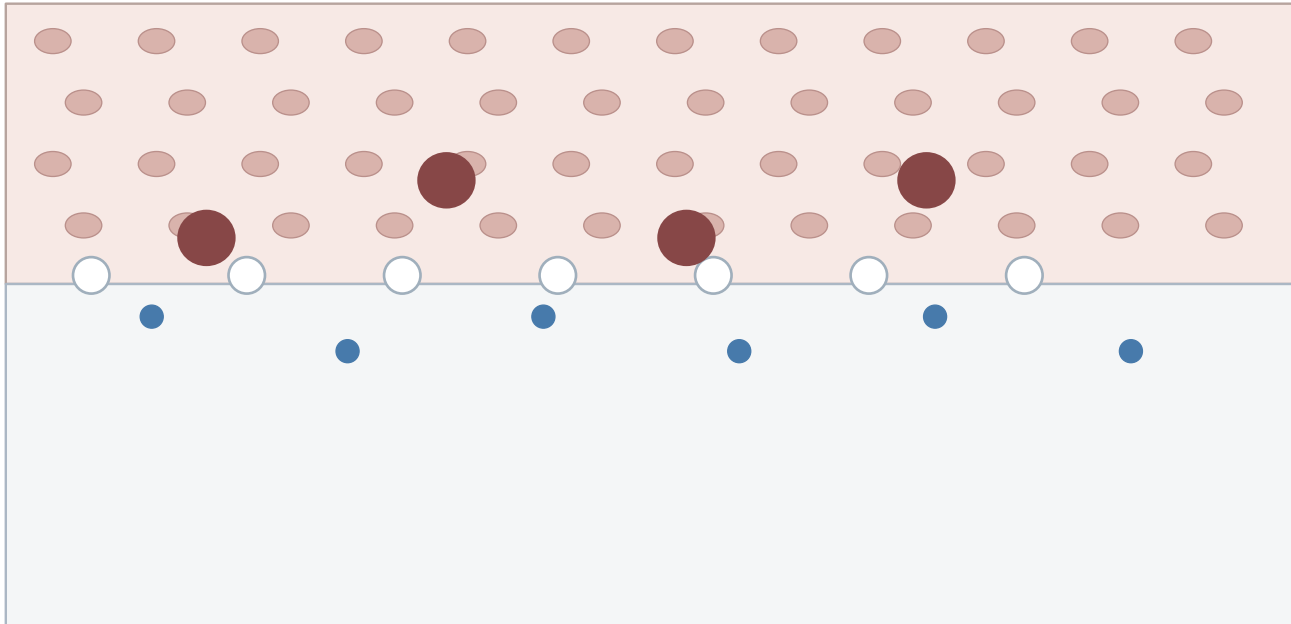
- Apoptotic keratinocytes are an important biopsy feature.
- Damaged cells may display abnormal keratin staining (dyskeratosis).

SCHEMATIC (not a histologic specimen)

Original schematic—not an H&E specimen or a reproduction of the Robbins image.

Acute skin GVHD: Altered epidermal maturation

Epidermis



Dermis

Interface vacuoles + sparse lymphocytes

SCHEMATIC (not a histologic specimen)

- Disorganization of keratinocyte maturation.
- The pattern accompanies interface damage and cell death.

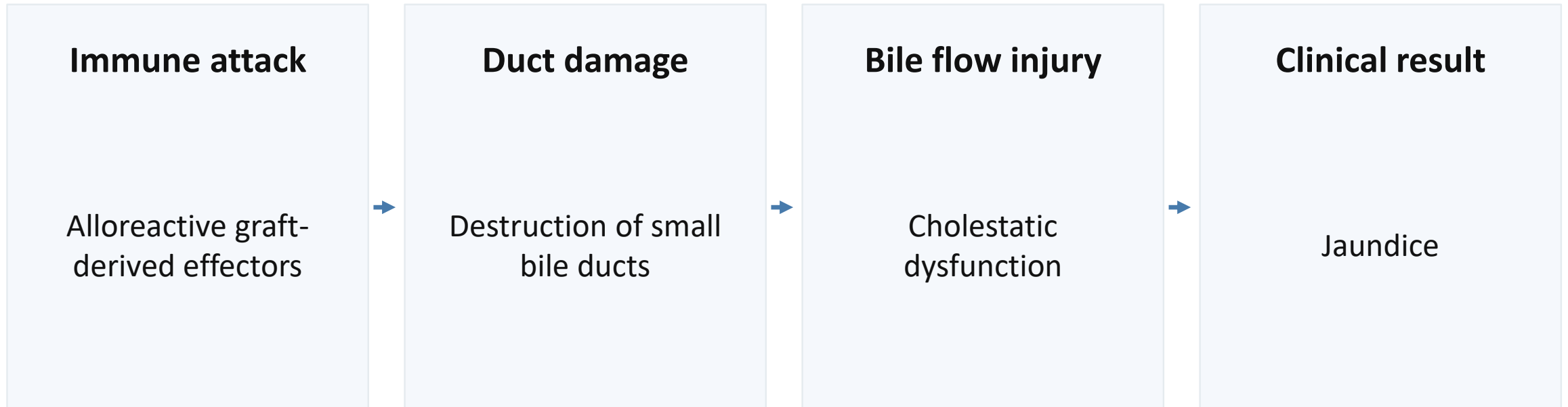
A morphologic combination is more informative than any single finding.

Acute skin GVHD: Integrating clinical and biopsy clues

- A characteristic rash establishes the clinical context.
- Biopsy may show sparse junctional lymphocytes, basal vacuoles and apoptotic cells.
- Clinical and pathologic findings must be interpreted together.

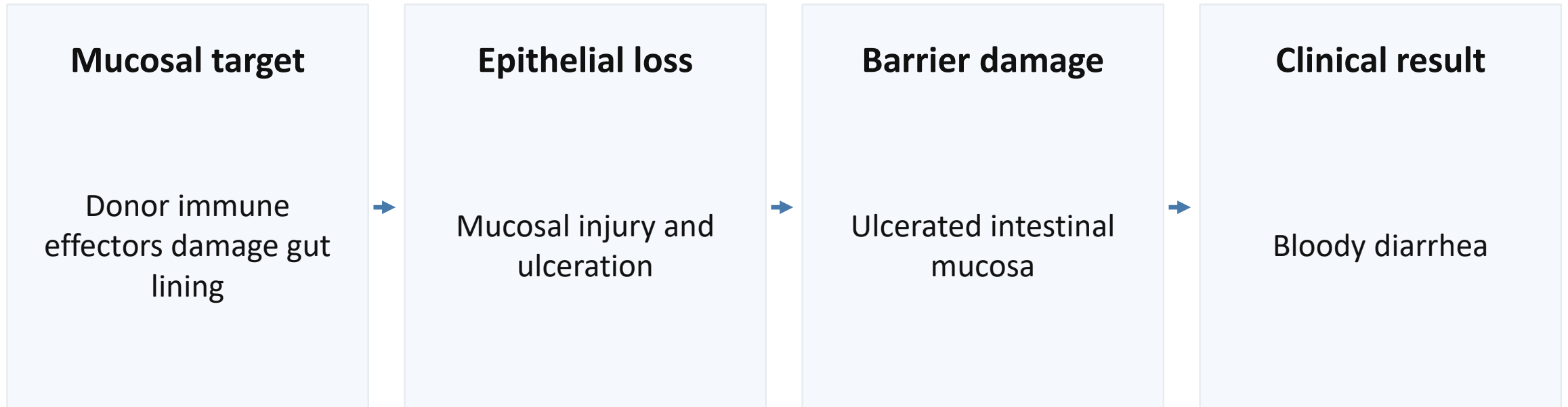
The supplied figure caption is descriptive; No validated diagnostic threshold is given.

Acute liver GVHD: Biliary epithelial injury



The source describes bile duct destruction as the substrate for jaundice.

Acute intestinal GVHD: Explaining diarrhea



The lesion-to-symptom chain is intestinal mucosal ulceration → bloody diarrhea.

Acute GVHD: Morphology–manifestation coupling

Organ	Histologic / structural target	Expected clinical clue
Skin	Epidermal keratinocytes	Spreading rash
Liver	Small intrahepatic bile ducts	Jaundice
Intestine	Mucosal epithelium	Bloody diarrhea

Three organs can be explained by one donor T-cell–mediated pathogenic model.

Application: Early multisystem syndrome

ILLUSTRATIVE TEACHING SCENARIO

An immunocompromised recipient develops a rash affecting the palms, jaundice and bloody diarrhea in the weeks following an allogeneic HSC transplant.

Clinicopathologic reasoning

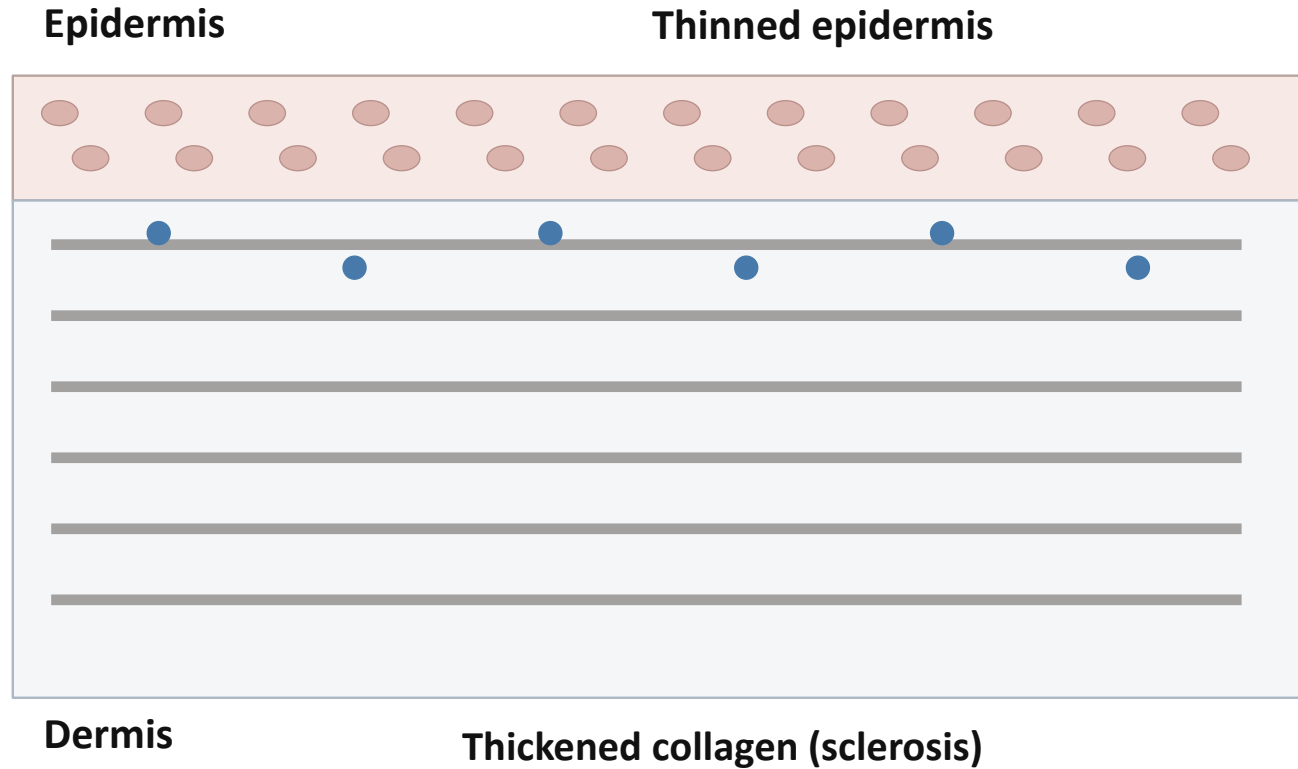
- The temporal setting and triad are compatible with acute GVHD.
- Skin keratinocytes, small bile ducts and intestinal mucosa are the target structures.
- This is an illustrative teaching scenario, not a real patient.

Chronic GVHD: Not simply persistent acute rash

- Chronic GVHD may follow an acute episode or begin insidiously.
- A hallmark is extensive cutaneous injury with fibrosis and appendage loss.
- The liver, gastrointestinal tract and immune system may also be injured.

Tissue sclerosis and multisystem dysfunction become dominant teaching features.

Chronic skin GVHD: Dermal sclerosis

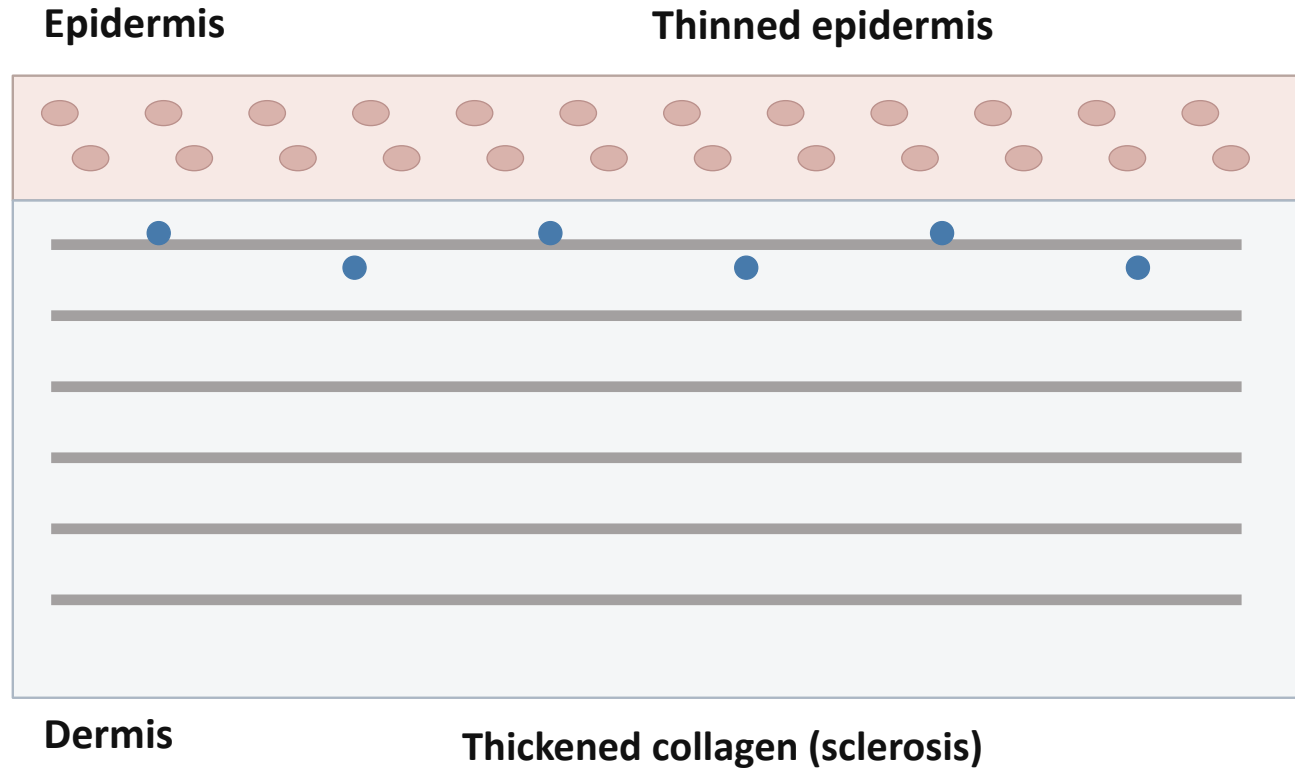


SCHEMATIC (not a histologic specimen)

- The dermis develops thickened collagen bundles.
- This fibrotic pattern can resemble systemic sclerosis.

Original native PowerPoint schematic; Not genuine histopathology.

Chronic skin GVHD: Epidermal atrophy



- The epidermis becomes thinned because of atrophy.
- Sparse interface inflammation and occasional injured keratinocytes may remain.

SCHEMATIC (not a histologic specimen)

Based on the textbook description of Fig. 6.36C.

Loss of cutaneous appendages in chronic GVHD

- Destruction of skin appendages during chronic injury.
- Appendage loss accompanies prominent dermal fibrosis.
- These alterations reflect structural damage rather than a simple exanthem.

Observe the deep structural consequences of ongoing tissue injury.

Acute versus chronic skin GVHD

Acute skin pattern

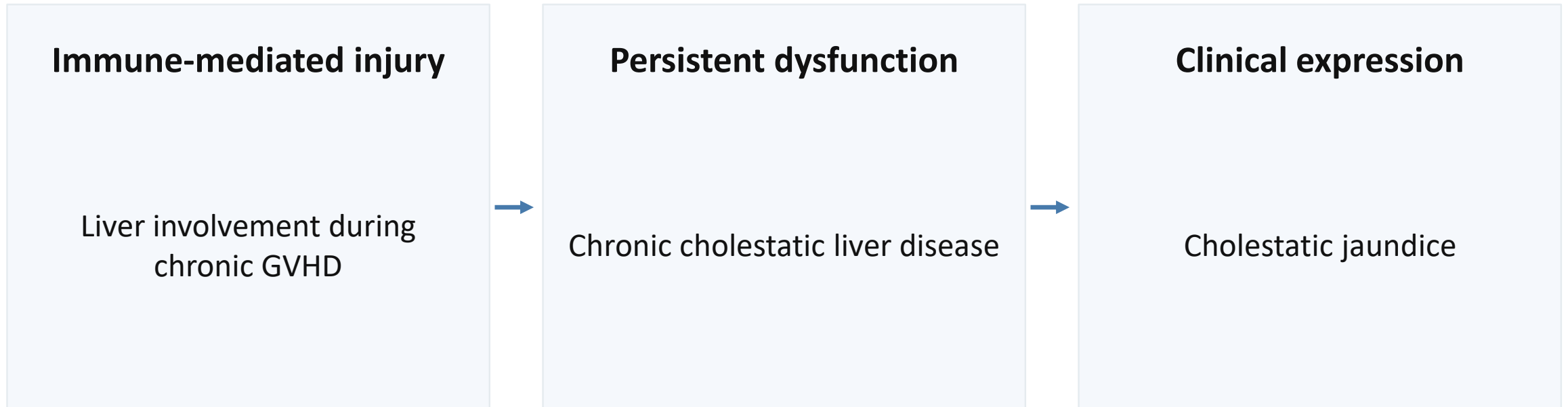
- Interface inflammation and basal vacuolization.
- Apoptotic or dyskeratotic keratinocytes.
- Clinically prominent rash.

Chronic skin pattern

- Thin, atrophic epidermis.
- Thick dermal collagen with sclerosis.
- Destruction of skin appendages.

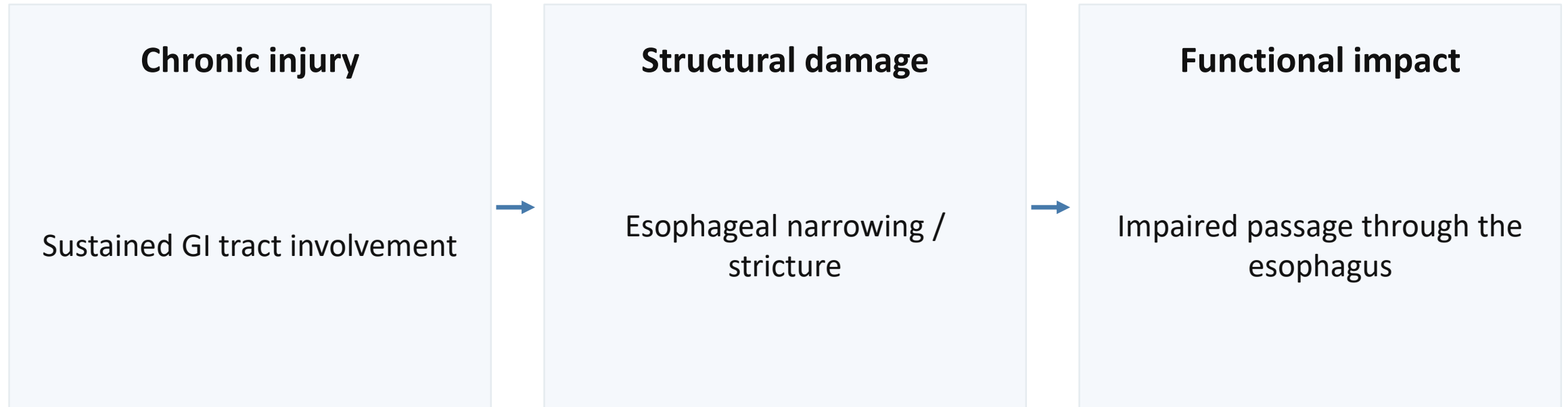
Both may show sparse lymphocytes; The structural pattern differentiates them.

Chronic hepatic GVHD: Cholestatic disease



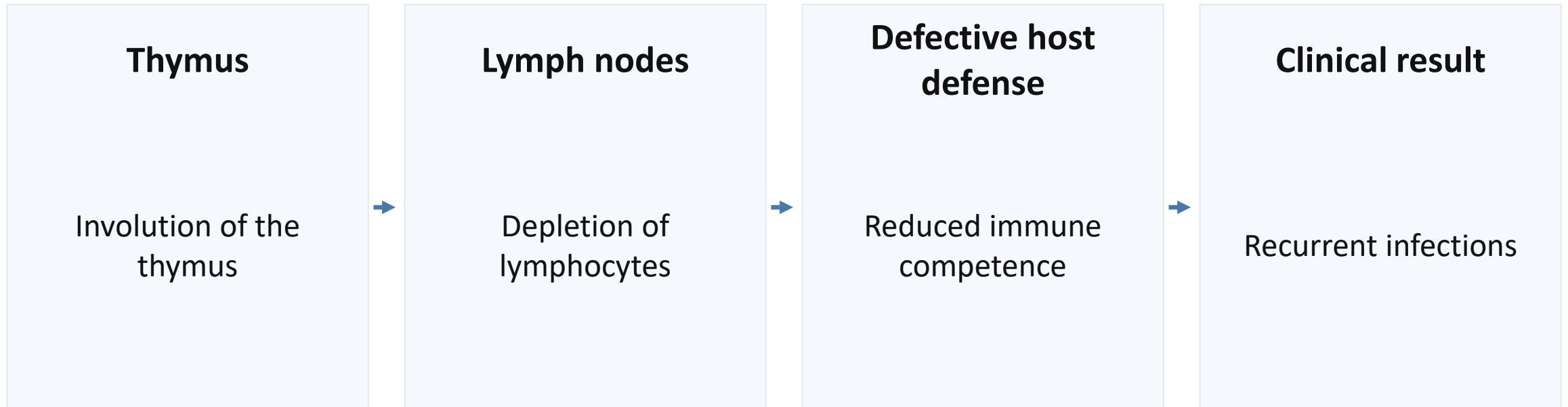
The source does not supply a biochemical cutoff or a histologic grading system.

Chronic gastrointestinal GVHD: Stricture



Esophageal strictures among chronic manifestations.

Chronic GVHD damages immune architecture



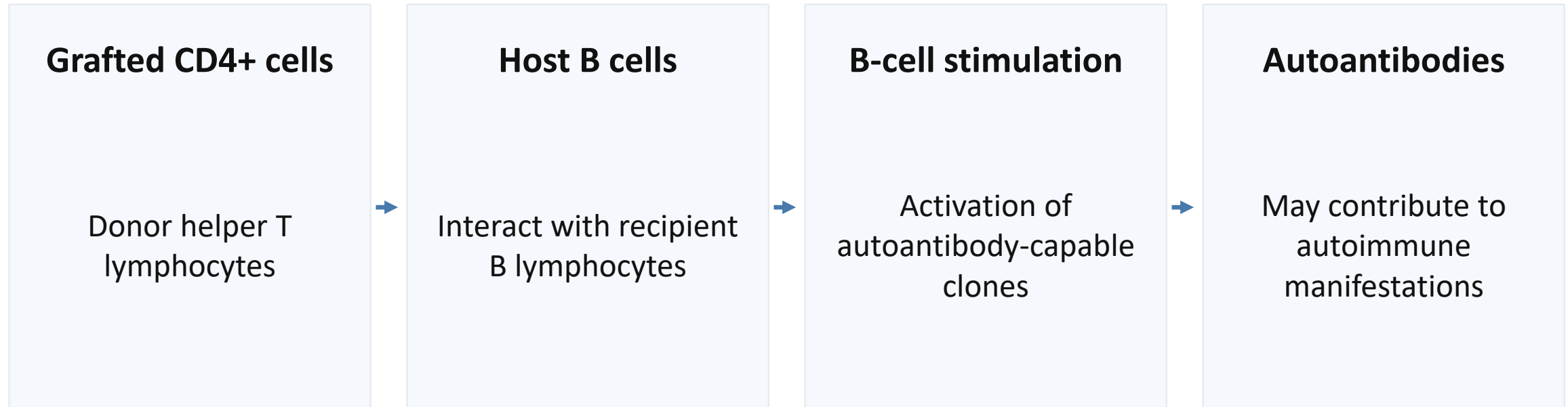
Immune-organ damage connects chronic GVHD to late susceptibility to infection.

Recurrent infection in chronic GVHD

- The thymus may involute, compromising the immune organ framework.
- Lymphocyte depletion occurs in lymph nodes.
- These abnormalities are associated with recurrent infections.

Immune deficiency may be a feature of GVHD as well as transplantation itself.

Autoimmunity in chronic GVHD: Proposed mechanism



This is presented by Robbins as a postulated mechanism, not an established universal pathway.

Chronic GVHD can resemble autoimmune disease

- Cutaneous sclerosis may resemble systemic sclerosis.
- Other recipients develop manifestations interpreted as autoimmunity.
- The source proposes donor CD4+ T-cell stimulation of host B cells as one explanation.

Clinical resemblance is not evidence of identical pathogenesis.

Acute and chronic GVHD: Full clinicopathologic comparison

Domain	Acute form	Chronic form
Onset	Days to weeks	After acute disease or insidious
Skin	Rash; keratinocyte apoptosis	Atrophy; sclerosis; appendage loss
Liver	Small bile duct destruction; jaundice	Chronic cholestatic liver disease
GI tract	Mucosal ulceration; bloody diarrhea	Esophageal stricture
Immune effects	Donor-cell epithelial injury	Immune-organ depletion; autoimmunity

Categories here follow the Robbins 11th-edition source, not contemporary staging criteria.

Application: Sclerosing skin disease

ILLUSTRATIVE TEACHING SCENARIO

After hematopoietic stem cell transplantation, a recipient develops tight skin. An illustrative skin section shows epidermal atrophy and thick dermal collagen bundles.

Clinicopathologic reasoning

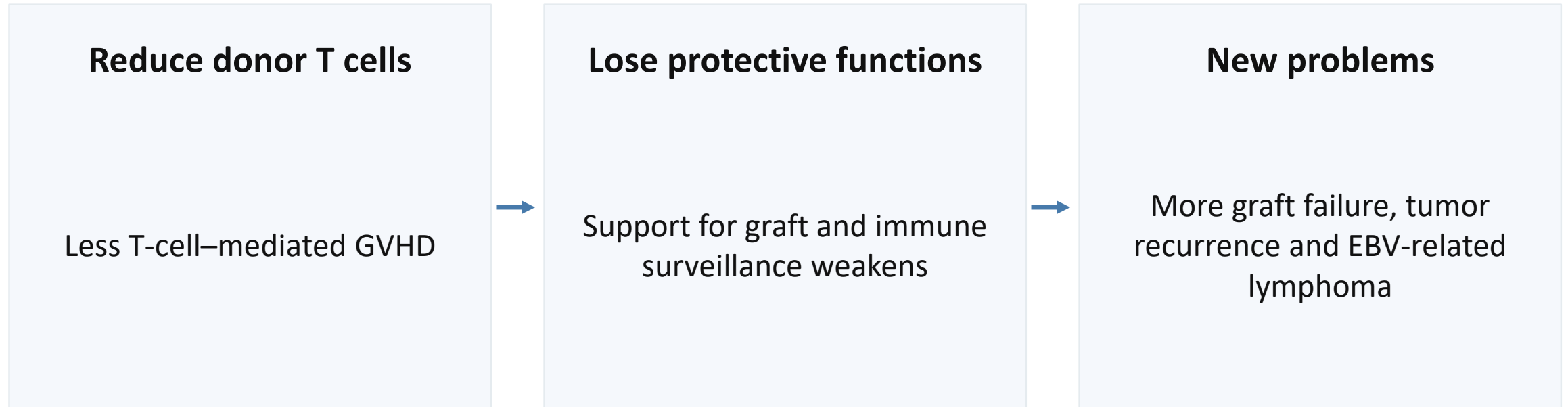
- The source pattern supports chronic cutaneous GVHD.
- Epidermal thinning and dermal sclerosis contrast with acute keratinocyte apoptosis.
- This scenario is constructed from textbook-described findings.

Donor T-cell depletion: Direct protective effect

- T lymphocytes in the donor graft are the key mediators of GVHD.
- Removing donor T cells before infusion markedly reduces GVHD.
- The approach as virtually eliminating this complication.

A mechanistically targeted intervention has consequences beyond preventing GVHD.

The cost of donor T-cell depletion



The excerpt emphasizes this as a therapeutic trade-off rather than a simple win.

Why donor T cells also support the graft

- The textbook associates donor T lymphocytes with successful engraftment.
- A proposed contribution is production of colony-stimulating factors (CSFs).
- T-cell depletion may therefore raise the incidence of graft failure.

CSF production is suggested, not demonstrated as the only mechanism.

The graft-versus-leukemia contribution

- Donor immune cells can participate in control of recipient leukemia cells.
- Removing these donor T cells increases leukemic tumor recurrence in the source.
- GVHD reduction must be weighed against loss of antitumor immune control.

The same donor-cell alloreactivity can cause harm and confer antileukemic benefit.

Control of EBV-infected B-cell clones

- Donor T cells help suppress Epstein–Barr virus–infected B-cell clones.
- Extensive T-cell depletion can undermine this immune surveillance.
- An increased incidence of EBV-related B-cell lymphoma is described.

Post-transplant lymphoid cancer risk depends in part on immune control.

Donor T cells: Harmful and protective roles

Immune function	Benefit or harm	Effect of depletion described
Alloreactivity to host	GVHD tissue injury	Less GVHD
Support of HSC engraftment	Graft persistence	More graft failure
Leukemia-cell control	Antitumor effect	More recurrence
EBV-infected B-cell control	Immune surveillance	More EBV-related B-cell lymphoma

These are associations; No event rates are specified.

Application: The T-cell depletion dilemma

ILLUSTRATIVE TEACHING SCENARIO

A transplant team considers depleting donor T lymphocytes to lessen GVHD after allogeneic HSC transplantation.

Clinicopathologic reasoning

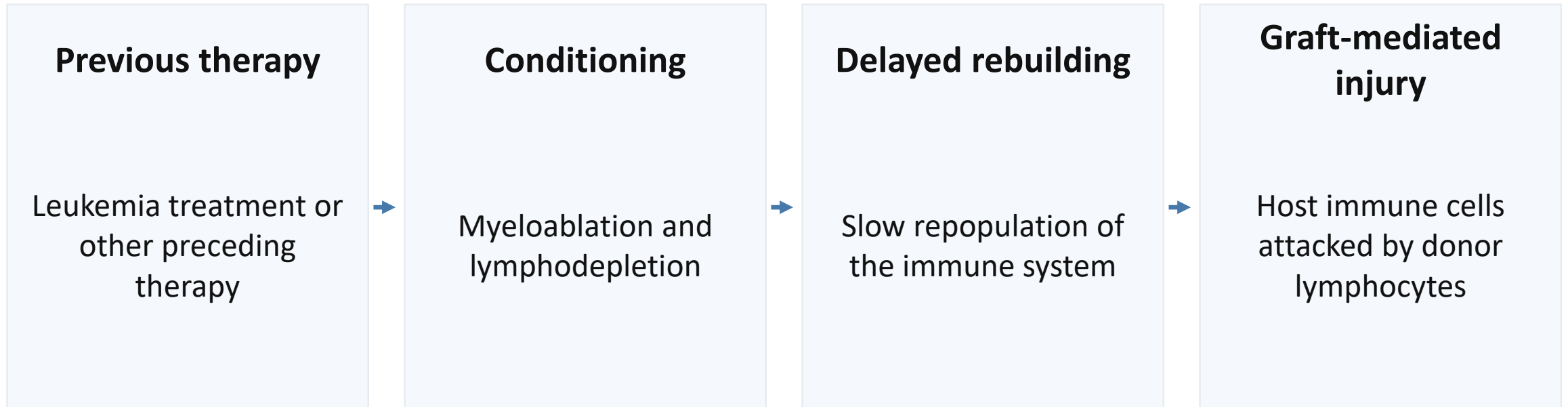
- Expected benefit: Marked reduction in GVHD.
- Recognized costs: Graft failure, leukemia recurrence and EBV-related B-cell lymphoma.
- The teaching issue is balancing tissue injury against immune protection.

Immunodeficiency after HSC transplantation

- Profound immune suppression is a frequent post-transplant complication.
- It reflects accumulated effects of past treatment, conditioning and delayed immune recovery.
- Transferred lymphocytes may also attack host immune cells.

Infection risk has multiple causal routes, not a single mechanism.

Four contributors to post-transplant immune deficiency



This causal map reproduces the four factors enumerated in the supplied text.

Prior therapy and pretransplant immune injury

- Underlying-disease treatment may already compromise host immunity.
- Myeloablation and lymphodepletion add further cell loss.
- Thus immune deficits can predate successful donor-cell engraftment.

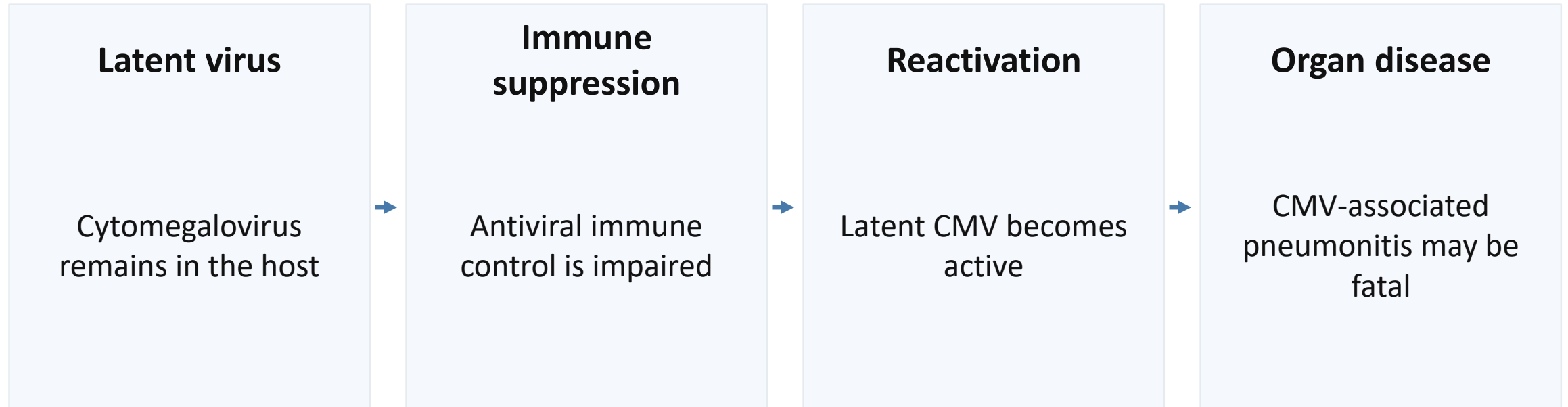
The timeline of immune suppression starts before the graft is infused.

Immune reconstitution is not immediate

- Following transplantation, immune-system repopulation takes time.
- Delayed replacement leaves a period of profound immunodeficiency.
- This vulnerability can persist despite establishment of transplanted cells.

Do not equate engraftment with immediate fully effective host defense.

CMV infection: A major post-HSC-transplant threat



Reactivation of latent CMV as a particularly important infection.

CMV pneumonitis: Clinicopathologic importance

- CMV reactivation is emphasized among infections after HSC transplantation.
- Pneumonitis is a potentially fatal complication.
- This complication illustrates the clinical cost of impaired antiviral immunity.

The supplied section provides no incidence, diagnostic assay or treatment regimen.

Two immune complications, two different mechanisms

GVHD

- Donor immune effectors attack host tissues.
- Produces skin, hepatic, intestinal and chronic systemic injury.

Immunodeficiency

- Host defenses fail to protect against microorganisms.
- Predisposes to opportunistic infection and viral reactivation.

The processes are related and may coexist, but should not be conflated.

Application: Serious pulmonary infection

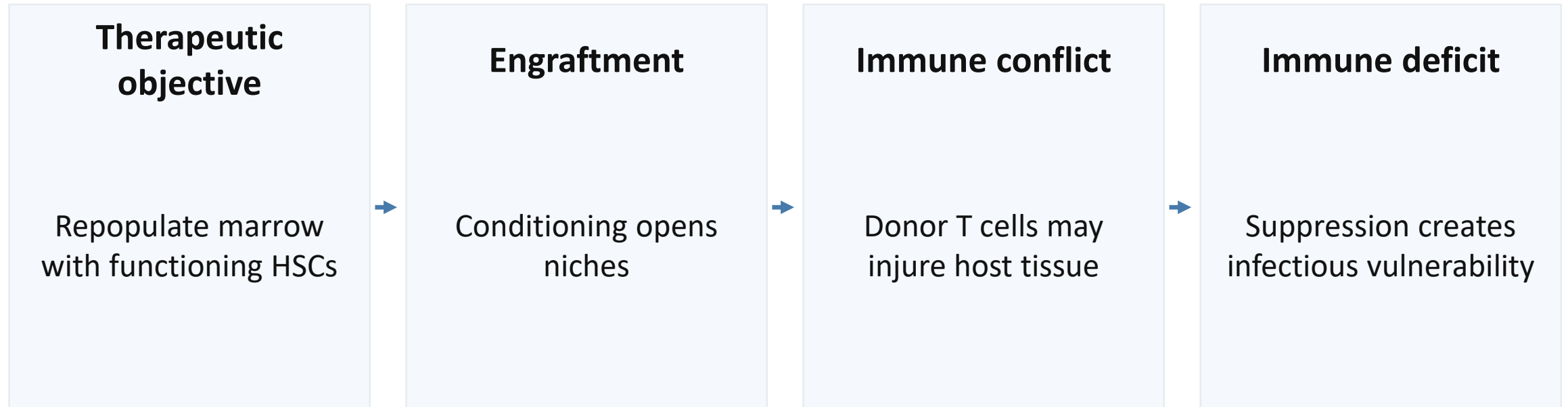
ILLUSTRATIVE TEACHING SCENARIO

An HSC-transplant recipient remains markedly immunocompromised and develops pneumonitis. The clinical discussion identifies activation of latent cytomegalovirus.

Clinicopathologic reasoning

- CMV reactivation is an important post-transplant mechanism.
- Myeloablation, slow immune reconstitution and other factors impair antiviral defense.
- The source warns that CMV pneumonitis can be fatal.

Integrated view: Benefit, alloreactivity and vulnerability



Understanding transplantation requires both hematopoietic recovery and immune biology.

Rapid recognition: Complication → mechanism

Finding	Likely process	Textbook explanation
Early rash + bloody diarrhea	Acute GVHD	Epithelial injury in skin and gut
Sclerosis + epidermal atrophy	Chronic GVHD	Fibrosing injury of skin
Recurrent infections + lymphoid depletion	Chronic GVHD immune effects	Thymic and nodal injury
CMV pneumonitis	Post-transplant immunodeficiency	Loss of control over latent infection

A pattern-recognition table, not a validated diagnostic algorithm.

Essential conclusions

- Conditioning creates marrow niches for donor HSC engraftment but depletes host immune cells.
- Donor T-cell recognition of host HLA drives GVHD; epithelial apoptosis and later sclerosis explain manifestations.
- T-cell depletion suppresses GVHD but can impair engraftment, leukemia control and EBV surveillance.
- Delayed immune reconstitution contributes to infection risk, notably CMV reactivation.

Connect each complication to the cells and tissue structures that produce it.