

Graft-versus-host disease

Transplantation immunopathology • gastrointestinal epithelial injury

Crypt apoptosis | intestinal injury | clinicopathologic correlation

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Learning objectives

- Explain how graft-derived T cells recognize and injure recipient tissues.
- Identify crypt apoptosis and distinguish it from severe crypt loss.
- Relate intestinal epithelial damage to the clinical diarrhea spectrum.
- Integrate the skin, liver, GI, and immune manifestations into one mechanism.

Hematopoietic transplantation: Clinical setting

- Hematopoietic stem cell transplantation is used for hematologic malignancies.
- Other indications include bone marrow failure and inherited marrow disorders.
- The allogeneic graft introduces a donor-derived immune cell compartment.

Examples of underlying diseases

Hematologic malignancies may require an allogeneic stem cell donor.

Aplastic anemia exemplifies marrow failure.

Sickle cell disease, thalassemia, and selected immunodeficiencies exemplify inherited disorders.

Sources of hematopoietic stem cells

Peripheral blood stem cells
can be mobilized with
growth factors.

Bone marrow is the
historic source of
hematopoietic grafts.

Umbilical cord blood
provides an additional
HSC-rich source.

Conditioning prepares the recipient marrow

Chemotherapy or irradiation depletes host marrow cells before most HSC grafts.



Conditioning opens marrow microenvironmental niches for donor HSC engraftment.



The same process contributes to compromised host immunity.

Direction of injury defines GVHD

GVHD: Donor → host

GVHD: Donor-derived immunocompetent cells attack recipient tissues.

Rejection: Host → graft

Conventional graft rejection: Recipient immune cells attack donor graft tissue.

The direction of recognition, not only the word “graft,” distinguishes them.

Conditions that permit GVHD

The inoculum contains immune-competent cells or precursors.



The recipient is unable to eliminate the transferred alloreactive cells.



Donor cells recognize host alloantigens and produce tissue injury.

Why allogeneic transplantation matters

- Donor and recipient may differ at human leukocyte antigen (HLA) loci.
- Donor T cells can interpret host HLA antigens as foreign.
- Alloreactivity explains why an otherwise therapeutic graft can injure its host.

HLA matching reduces the immunologic mismatch

HSC donor selection uses high-resolution molecular HLA typing.



Matching aims to minimize donor–host antigenic disparity and GVHD.



HLA compatibility modifies risk; It does not redefine the basic donor-to-host mechanism.

Transfusion and solid-organ contexts

- GVHD is most commonly associated with allogeneic HSC transplantation.
- It can rarely follow transplantation of organs rich in lymphoid cells, including liver.
- Transfusion of unirradiated blood can rarely transmit alloreactive cells.

Two principal clinical phenotypes

Acute GVHD

Acute GVHD often develops within days to weeks after allogeneic HSC transplantation.

Chronic GVHD

Chronic GVHD may follow acute disease or emerge insidiously.

They differ in dominant tissue response, not merely the affected organ.

Acute GVHD: Epithelial targeting

Major clinically involved epithelial targets include skin, biliary ducts, and intestine.

Immune-mediated epithelial injury explains rash, cholestatic symptoms, and diarrhea.

Any organ can be involved, but these sites define the classic acute pattern.

The donor T cell is the central effector

Allogeneic HSC preparations contain immunocompetent donor T cells.



Donor T cells recognize recipient alloantigens, including HLA determinants.



Activated donor lymphocytes attack recipient epithelial tissues.

Immune recognition precedes structural injury

Antigen recognition initiates the graft-versus-host reaction.



The effector phase includes direct cellular cytotoxicity.



Sensitized donor T cells also release cytokines that amplify tissue damage.

Cytotoxic and cytokine-mediated components

CD8+ cytotoxicity

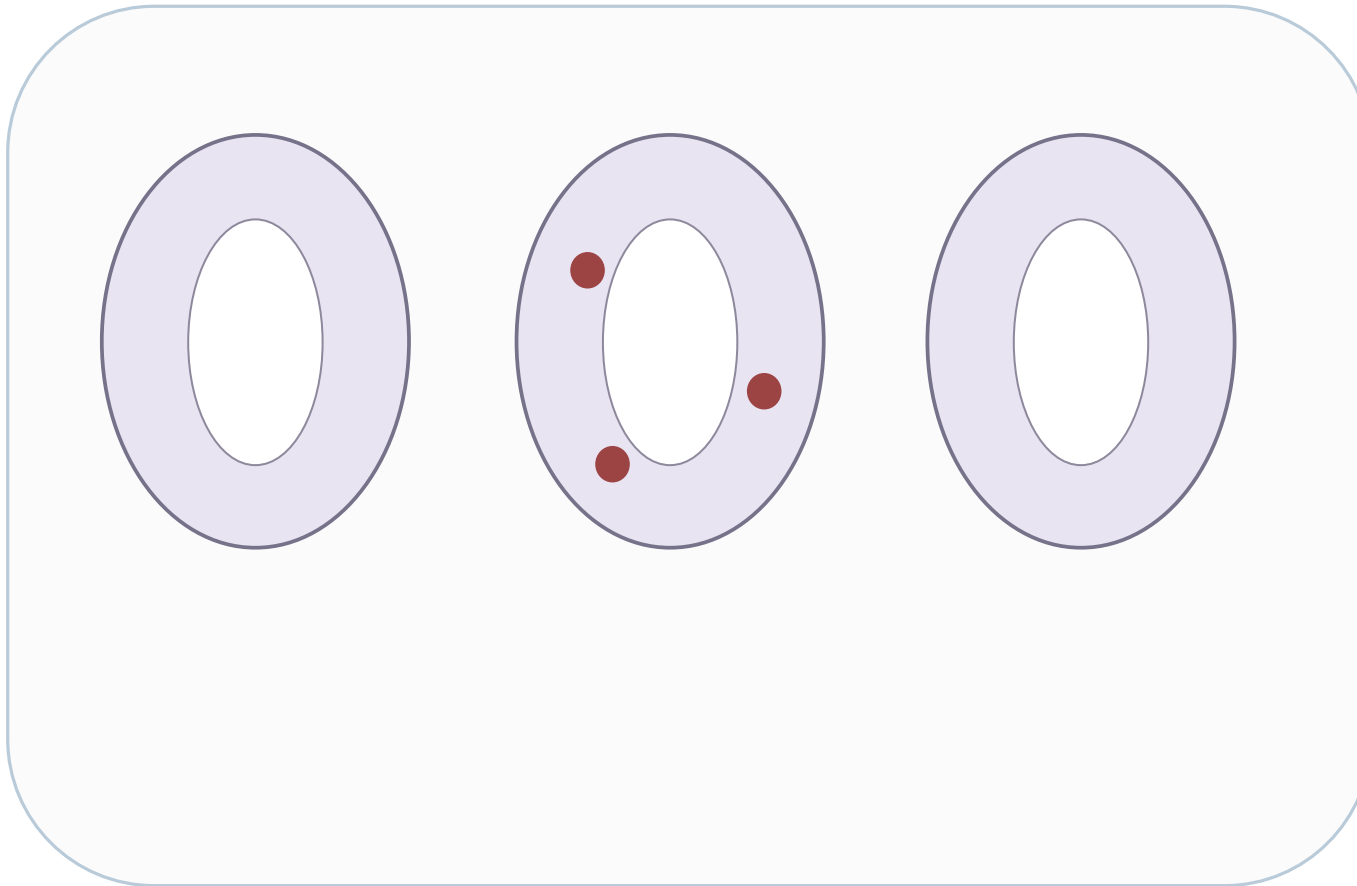
CD8+ T cells may directly injure susceptible host epithelial cells.

T-cell cytokines

T-cell–derived cytokines contribute to injury beyond the cells directly contacted.

Both mechanisms help explain substantial epithelial damage.

Why crypts are central to the diagnosis



Crypt epithelium

Individual apoptotic bodies

Severe injury may destroy crypts

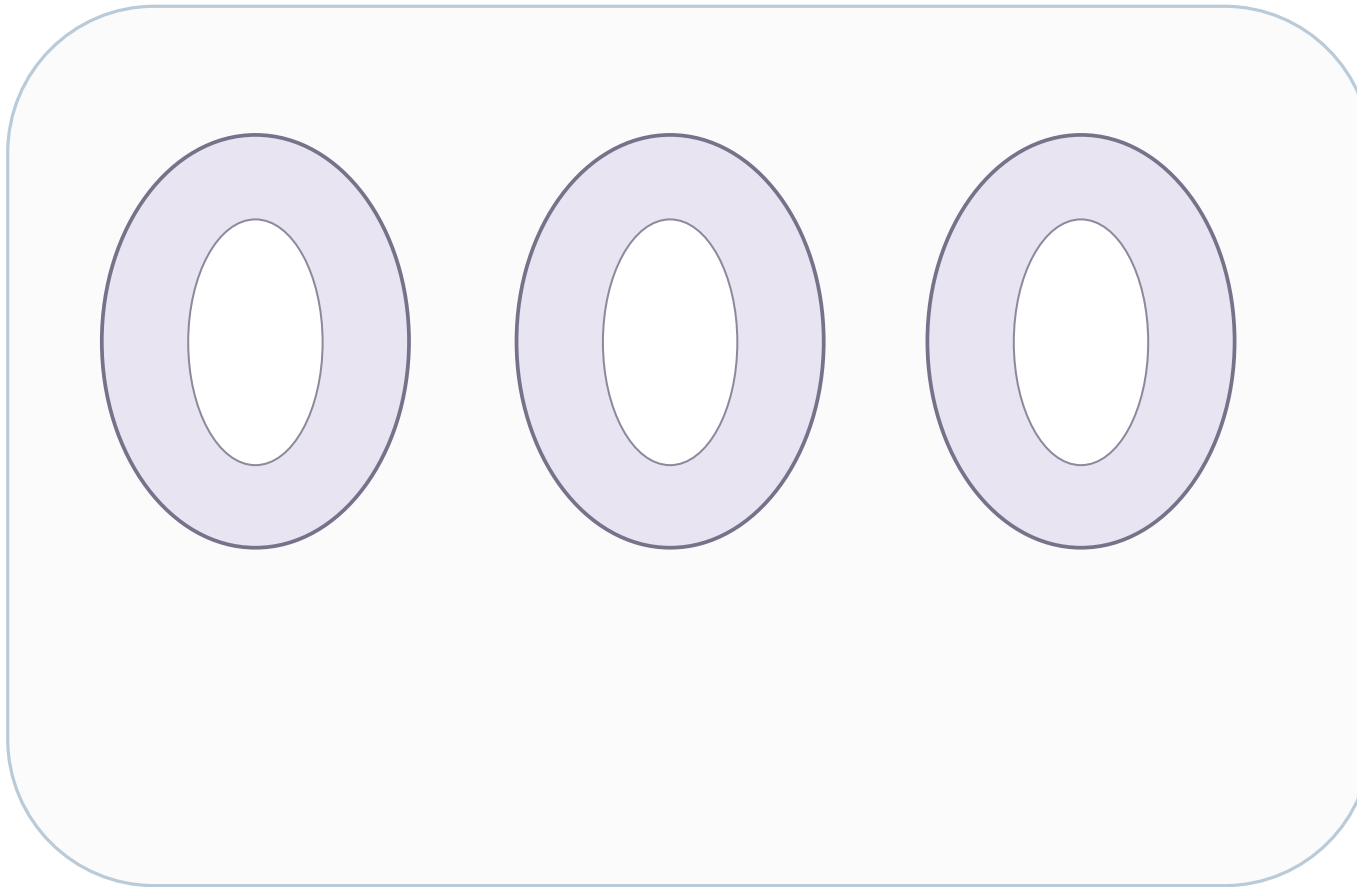
Schematic: Epithelial gland profiles; Not an observed histology image

Two compartments to assess on biopsy

Epithelial crypt compartment → apoptotic cell injury

Lamina propria compartment → often sparse lymphocytes

Normal colonic crypt: Conceptual baseline



Crypt epithelium

Continuous crypt lining

Reference for evaluating
epithelial loss

Schematic: Epithelial gland profiles; Not an observed histology image

Crypt apoptosis: What the term communicates

Viable crypt cell

Intact cellular outline



Apoptotic body

Condensed/fragmented cell



Epithelial cell loss

Crypt may remain recognizable

Apoptosis versus crypt destruction

Individual cell apoptosis

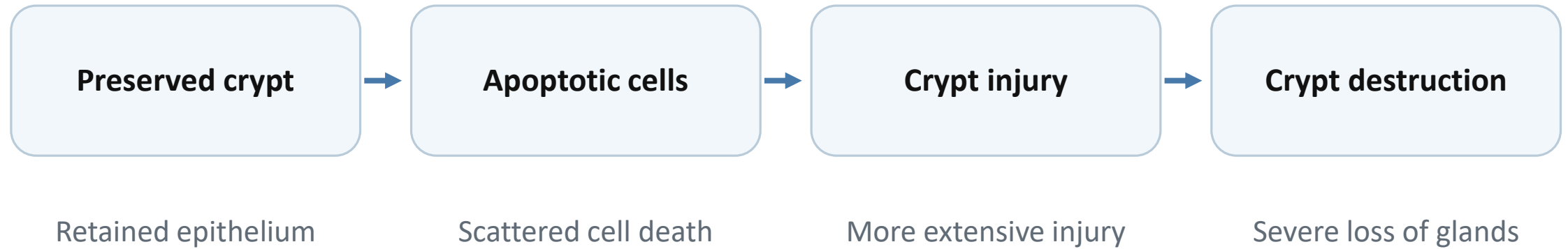
Apoptosis can be present while crypt architecture is still recognizable.

Entire crypt destruction

Severe GVHD can destroy entire crypt structures.

The extent of structural loss indicates a different degree of tissue injury.

A morphologic continuum of intestinal injury



How gut injury becomes diarrhea

Immune-mediated mucosal damage compromises intestinal epithelial function.



The common intestinal manifestation is watery diarrhea.



Severe epithelial injury and mucosal ulceration can be accompanied by blood.

Watery diarrhea is the typical GI presentation

- Small bowel and colon involvement commonly produce watery stool output.
- A transplant history makes the symptom clinically significant.
- The symptom alone cannot establish whether the cause is GVHD, a drug, or infection.

Bloody diarrhea signals a severe phenotype

Intestinal GVHD may become bloody in severe cases.



Robbins relates mucosal ulceration in acute GVHD to bloody diarrhea.



Clinical severity must be interpreted alongside tissue damage and context.

Anatomic distribution: Bowel and colon

Small intestine

The small intestine is commonly involved.

Colon

The colon is also commonly involved.

A GI-focused assessment therefore must not treat GVHD as an exclusively colonic disorder.

Histopathologic hallmarks in one view

Epithelial apoptosis—especially within crypts—is the most common histologic feature.

The lamina propria lymphocyte infiltrate is usually sparse.

Entire crypts may disappear with severe epithelial injury.

Integrating the mechanism and biopsy

Donor T-cell recognition
initiates injury to recipient GI
epithelium.



The injury is expressed as
crypt epithelial apoptosis.



Extensive epithelial injury
can progress to crypt
destruction and severe
diarrhea.

Acute GVHD of the skin

Cutaneous lesions show lymphocyte infiltration and keratinocyte apoptosis.



Rash can initially involve neck, ears, palms, and soles.



Rash may become generalized.

Skin and gut share an epithelial target

Skin target

Skin: Apoptotic keratinocytes are the principal named epithelial lesion.

Intestinal target

Gut: Apoptotic intestinal crypt epithelial cells are the key lesion.

The organs differ, but donor T-cell immune injury is the unifying process.

Acute liver involvement

Destruction of small bile ducts is an acute GVHD manifestation.



Bile duct damage is associated with jaundice.



This is epithelial targeting of a biliary compartment rather than crypt epithelium.

Chronic GVHD: A different tissue response

- Chronic GVHD may follow an acute episode.
- It can also begin without an obvious antecedent acute syndrome.
- Fibrosis, chronic epithelial injury, immune dysfunction, and autoimmunity become prominent.

Chronic GVHD of the skin

Destruction of skin appendages is described in chronic disease.



Dermal fibrosis can be extensive.



The resulting skin changes may resemble systemic sclerosis.

Chronic GVHD in the hepatobiliary system

Clinical manifestation

Chronic liver disease can manifest as cholestatic jaundice.

Chronic disease context

The chronic phenotype highlights prolonged hepatobiliary dysfunction.

Correlate this with the acute pattern of small-bile-duct epithelial injury.

Esophageal involvement in GVHD

Esophageal basal epithelial apoptosis can occur.

Mucosal atrophy and submucosal fibrosis are described histologically.

The inflammatory infiltrate need not be prominently acute.

Esophageal stricture links injury to function

Chronic GVHD can involve the GI tract above the small bowel and colon.



Esophageal damage may produce a stricture.



The structural consequence differs from the watery-diarrhea phenotype of intestinal injury.

Immune-organ consequences of chronic GVHD

Chronic GVHD may cause thymic involution.



Lymph-node lymphocyte depletion is also described.



Immune injury contributes to recurrent infection susceptibility.

Autoimmune manifestations in chronic GVHD

Some patients develop autoimmune manifestations.



One proposed mechanism involves donor CD4+ T cells stimulating recipient B cells.



Resulting autoantibody production is a hypothesis, not a universal mechanism.

Comparing acute and chronic GVHD

Acute GVHD

Acute: Injury of skin, biliary, and intestinal epithelium predominates.

Chronic GVHD

Chronic: Skin appendage loss, fibrosis, cholestasis, and immune dysfunction are prominent.

The categories overlap clinically, but their characteristic patterns should be distinguished.

What intestinal apoptosis cannot tell us alone

Apoptosis is not specific to intestinal GVHD.

Robbins also identifies apoptosis with immune checkpoint inhibitor–associated enterocolitis.

Mycophenolate mofetil is another associated cause of apoptotic enteritis/colitis.

Checkpoint inhibitor–associated enterocolitis

Checkpoint therapy

The most common morphology noted is epithelial apoptosis.

Allogeneic GVHD

The mechanism may partially overlap with GVHD, but remains incompletely defined.

The therapeutic context is cancer immunotherapy rather than an allogeneic graft.

Mycophenolate-associated epithelial injury

- Mycophenolate mofetil is associated with apoptotic enteritis and colitis.
- Its pharmacologic immunosuppressive role does not exclude GI toxicity.
- Medication review is essential before assigning apoptosis to GVHD.

Infection is a major competing concern

- HSC recipients often have profound immunodeficiency.
- Viral infections can complicate the post-transplant course.
- Watery diarrhea in a graft recipient cannot be attributed to GVHD without considering infection.

Cytomegalovirus after transplantation

CMV is an important opportunistic infection in HSC recipients.



Reactivation of latent CMV is a recognized mechanism.



Coexisting immune injury and infection complicate clinical interpretation.

Norovirus as a cause of prolonged diarrhea

- Chronic norovirus infection in immunosuppressed transplant patients.
- Some cannot clear infection and experience sustained diarrhea.
- Symptom persistence by itself does not discriminate GVHD from infection.

An etiologic comparison for apoptotic enterocolitis

GVHD: Donor T-cell response against host tissue after allogeneic transplantation.

Checkpoint colitis:
Treatment-associated immune toxicity with overlapping epithelial apoptosis.

Mycophenolate:
Medication-associated apoptotic injury; Viral infection remains a separate differential.

Why donor T-cell depletion is a dilemma

Reducing donor T cells
markedly reduces GVHD.



But elimination of these cells
increases graft failure and
leukemia relapse risks.



Control of Epstein–Barr
virus–infected B-cell clones is
also weakened.

T cells also support engraftment

Donor T cells as important
for HSC engraftment.



Cytokine-mediated support
of stem cells is a proposed
explanation.



Complete T-cell depletion
trades lower GVHD risk for
potential engraftment
difficulty.

EBV-related lymphoproliferative risk

Donor T-cell immune surveillance constrains EBV-infected B-cell clones.



Marked donor T-cell depletion can increase EBV-related B-cell lymphoma.



This is distinct from direct GVHD tissue injury.

The central prevention trade-off

Lower GVHD risk

Fewer donor T cells: Less graft-versus-host epithelial attack.

Reduced immune protection

Fewer donor T cells: Less graft-versus-leukemia and antiviral surveillance.

Optimal transplantation seeks immune protection without uncontrolled host injury.

Case: Watery diarrhea after HSC transplant

- Scenario: Recipient of allogeneic HSCs develops watery diarrhea.
- A biopsy demonstrates crypt epithelial apoptosis with scant stromal lymphocytes.
- Interpretation: A GVHD-compatible pattern in an appropriate setting; Review treatment and infectious causes.

Case: Extensive intestinal epithelial loss

- Scenario: Post-transplant diarrhea becomes bloody and severe.
- Sampling shows complete destruction of multiple crypt profiles.
- Interpretation: Severe epithelial injury can explain the clinical escalation.

Case: Same biopsy pattern, different therapy

- Scenario: A patient treated with immune checkpoint blockade develops enterocolitis.
- Crypt-associated epithelial apoptosis resembles the GVHD lesion.
- Interpretation: The clinicotherapeutic context prevents a false GVHD attribution.

Case: Rash, jaundice, and diarrhea

- Scenario: Within weeks of allogeneic transplantation, a patient develops all three findings.
- Skin, bile duct, and intestinal epithelium are the classic acute targets.
- Interpretation: A multi-organ pattern supports an acute GVHD syndrome.

Diagnostic reasoning: Concordant evidence

Start with the graft history and potential exposure to alloreactive donor cells.



Assess pattern and severity of GI epithelial apoptosis and crypt injury.



Integrate extraintestinal signs while considering drug injury and opportunistic infections.

Core clinicopathologic synthesis

- The immune effectors originate in donor hematopoietic cells.
- Crypt epithelial apoptosis is the dominant intestinal microscopic clue.
- Severity can extend from watery diarrhea to crypt destruction and bloody stool.
- Sparse mucosal lymphocytes do not rule out meaningful GVHD-related injury.

Selected references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed. Graft-Versus-Host Disease section.
- Same volume. Transplantation of Hematopoietic Stem Cells section.
- Same volume. Apoptotic Enterocolitis, esophageal GVHD, and immunocompromised-host norovirus discussions.