



Apoptotic Enterocolitis

Mucosal injury patterns, clinical contexts and biopsy interpretation

An integrated approach to crypt apoptosis, drug injury and GVHD

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Learning objectives

- Identify excess epithelial apoptosis in intestinal biopsies.
- Explain why crypt injury produces epithelial loss and diarrhea.
- Distinguish checkpoint-inhibitor toxicity, mycophenolate injury and gastrointestinal GVHD.
- Use clinical context and ancillary testing to avoid false etiologic attribution.

A reaction pattern—not one etiologic disease

- “Apoptotic enterocolitis” describes increased programmed epithelial cell death in gastrointestinal mucosa.
- Different injuries can converge on a similar microscopic phenotype.
- Histology establishes the pattern; Medication and transplant history often establish the cause.

Interpret apoptosis as a finding requiring etiologic correlation.

Core etiologic contexts

Immune checkpoint inhibitors

Oncologic therapy; Immune-mediated mucosal injury

Mycophenolate mofetil

Immunosuppressive drug-associated epithelial injury

Allogeneic HSCT / GVHD

Donor-derived T-cell injury of recipient crypts

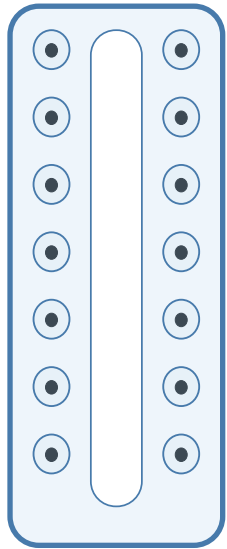
Overlapping morphology ≠ interchangeable diagnoses.

Why the heading matters in practice

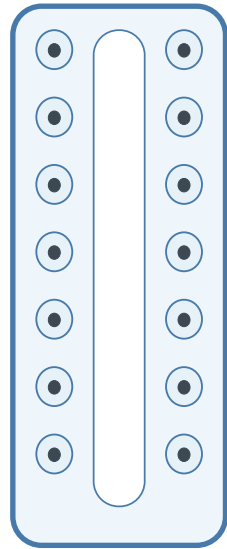
- Diarrhea in cancer or transplant care has multiple potential explanations.
- Mucosal apoptosis can be subtle despite clinically important symptoms.
- An incorrect label may alter oncology or immunosuppression decisions.

Normal intestinal crypt architecture

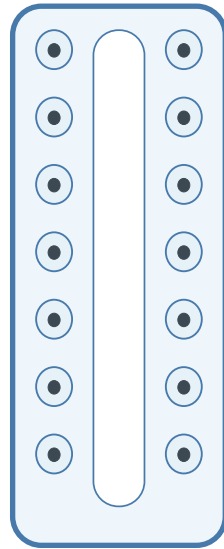
Schematic: Crypt epithelial response



Crypt 1



Crypt 2



Crypt 3

Read the schematic

- Blue epithelium — Surrounds a pale glandular lumen
- Dark small nuclei — Illustrate epithelial cells
- Three crypts — Show the normal repeated architecture

The epithelial renewal compartment is concentrated in the crypts.

Original schematic — not a histologic specimen

Physiologic renewal versus pathologic apoptosis

Physiologic turnover

Epithelial cell production and shedding remain balanced

Architectural integrity is maintained

Pathologic apoptotic injury

Increased epithelial loss overwhelms local replacement

Crypt attenuation, loss and mucosal dysfunction may follow

What an apoptotic body represents

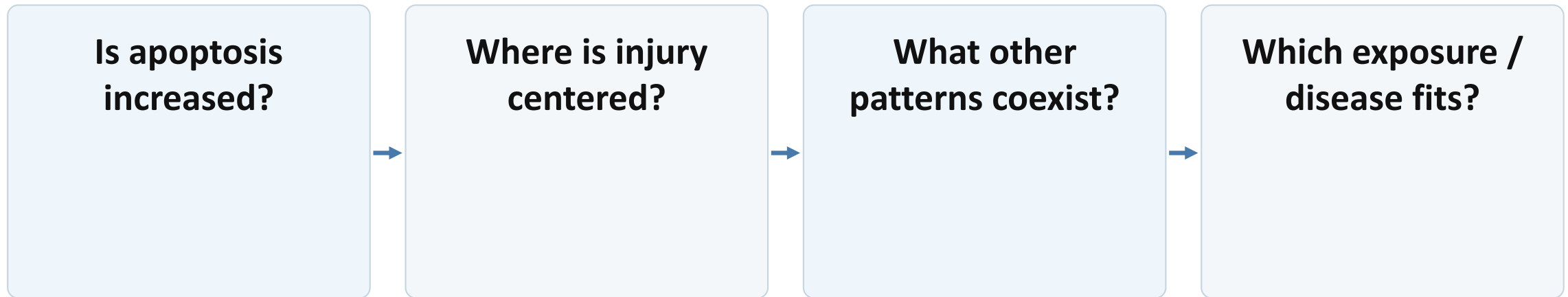
- An epithelial cell undergoing programmed death forms a condensed, fragmented remnant.
- Apoptotic debris may be present within or adjacent to crypt epithelium.
- The distribution and associated injuries are more useful than an isolated body.

Apoptosis is distinct from necrosis

Feature	Apoptosis	Necrosis
Cell response	Single-cell shrinkage / fragmentation	Cell swelling and membrane breakdown
Tissue response	May occur with limited inflammation	Often provokes adjacent inflammation
Biopsy clue	Discrete epithelial apoptotic bodies	Confluent cell / tissue injury

The pathologist asks four separate questions

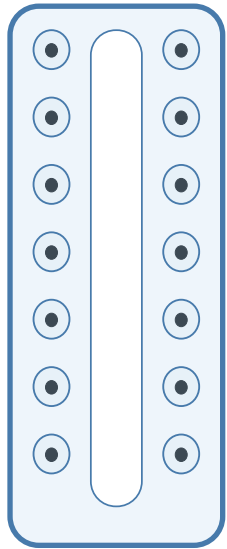
Causal / diagnostic sequence (simplified)



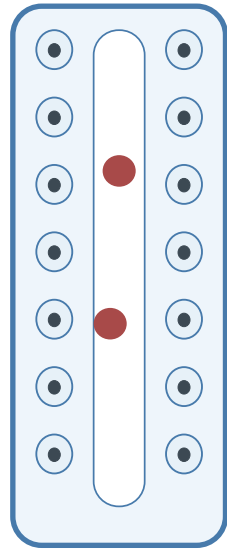
The etiologic diagnosis is the final step, not the first.

Crypt-centered injury can be clinically important

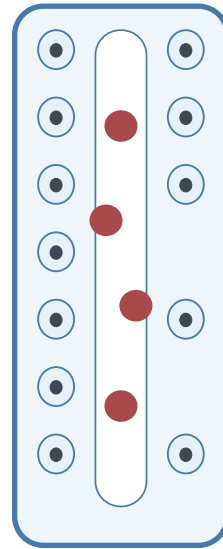
Schematic: Crypt epithelial response



Intact crypt



Crypt apoptosis



More apoptosis

Read the schematic

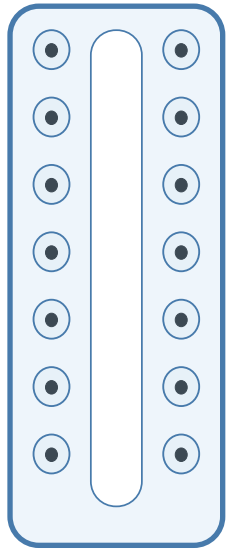
- Blue epithelium — Preserved / altered crypt lining
- Red fragments — Schematic epithelial apoptosis
- Broken gland — Represents severe crypt dropout

Scattered apoptotic cells may signal damage to the crypt renewal compartment.

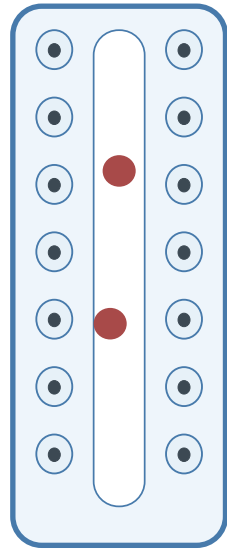
Original schematic — not a histologic specimen

Severe injury progresses to crypt dropout

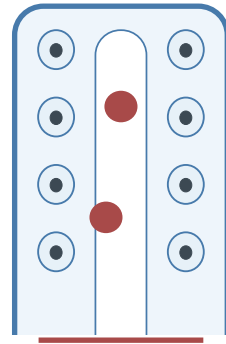
Schematic: Crypt epithelial response



Intact crypt



Apoptotic injury



Crypt dropout

Read the schematic

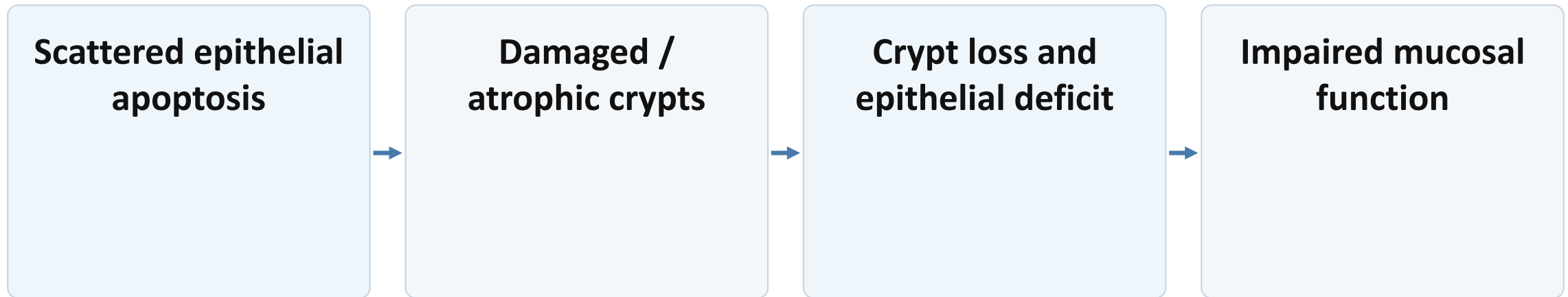
- Blue epithelium — Preserved / altered crypt lining
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- Broken gland — Represents severe crypt dropout

Loss of crypts indicates more extensive epithelial destruction.

Original schematic — not a histologic specimen

A useful injury continuum

Causal / diagnostic sequence (simplified)



A schematic continuum—not a mandatory sequence in every patient.

Why diarrhea accompanies epithelial injury

- Intact intestinal epithelium is needed for fluid handling and barrier function.
- Inflammatory injury or epithelial loss can disrupt transport and absorption.
- Diarrhea alone does not establish the mechanism or culprit drug.

Clinical severity and apoptotic-body density need not map one-to-one.

Clinical history is part of the biopsy

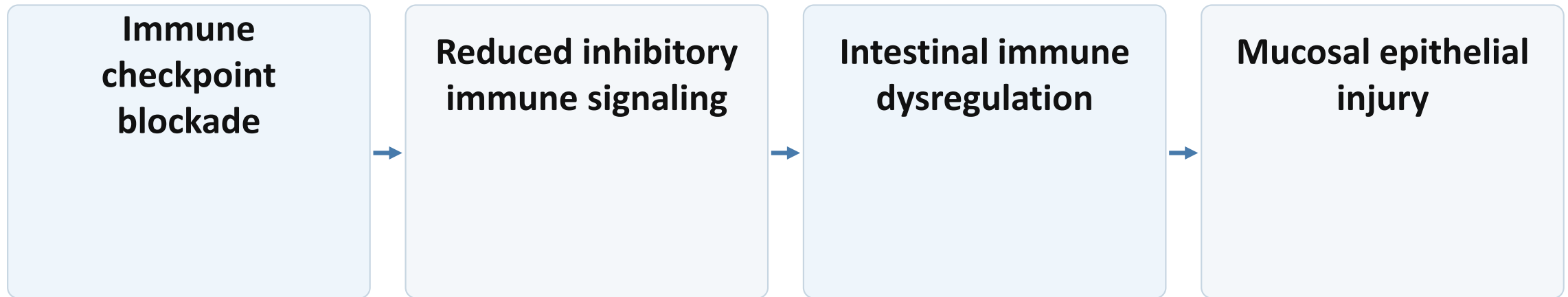
Clinical question	Why it changes interpretation
Checkpoint blockade?	Supports an immune-related treatment injury pattern
Mycophenolate exposure?	Supports a recognized drug-associated apoptotic colonopathy
Allogeneic stem-cell transplant?	Introduces gastrointestinal GVHD into the differential
Infection work-up?	Infections can coexist or mimic mucosal injury

Checkpoint inhibitors: The clinical setting

- Immune checkpoint inhibitors are used in oncology to augment antitumor immune responses.
- Enterocolitis and diarrhea are important treatment-related toxicities.
- Severe toxicity can necessitate discontinuation of treatment.

Checkpoint blockade and off-target intestinal injury

Causal / diagnostic sequence (simplified)



Mechanisms are multifactorial; The source does not specify a single required pathway.

Why checkpoint colitis resembles GVHD

- Both settings can produce apoptosis of intestinal epithelial cells.
- Partial mechanistic overlap as plausible but incompletely established.
- Shared morphology does not imply the same initiating immune event.

Mechanistic analogy is not proof of mechanistic identity.

Checkpoint colitis has more than one histologic pattern

Active colitis

Cryptitis, crypt abscesses ± apoptosis

Apoptosis / crypt injury

Apoptotic bodies with attenuation or dropout

Other inflammatory patterns

Chronic-active and microscopic-colitis-like changes

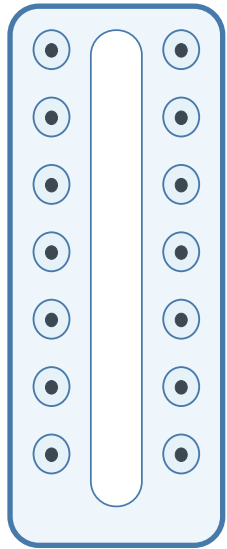
The full biopsy may not look purely “GVHD-like”.

Active colitis pattern under checkpoint therapy

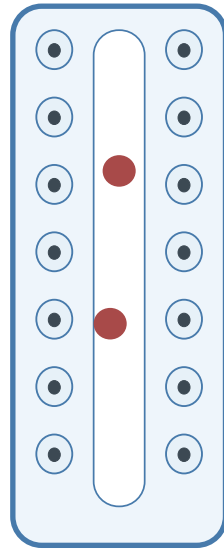
- Neutrophils may invade crypt epithelium (cryptitis).
- Crypt lumina can contain neutrophils (crypt abscesses).
- Prominent epithelial apoptosis may coexist and suggest drug-related injury.

An apoptosis-predominant checkpoint biopsy

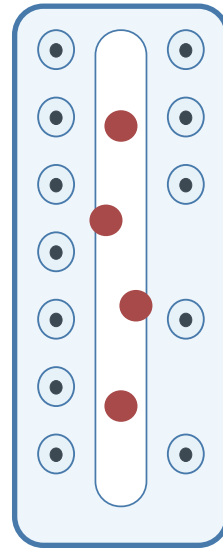
Schematic: Crypt epithelial response



Intact crypt



Crypt apoptosis



More apoptosis

Read the schematic

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Predominant apoptosis may occur without conspicuous architectural chronicity.

Crypt atrophy and dropout in checkpoint colitis

- Atrophic crypts show attenuated epithelial lining.
- Lumina may contain apoptotic debris mixed with inflammatory cells.
- Crypt loss reflects more severe mucosal epithelial injury.

Checkpoint injury may imitate chronic colitis

- Architectural change and chronic inflammatory patterns can occur.
- Persistent or prominent chronicity requires consideration of pre-existing or unmasked IBD.
- Morphologic attribution depends on the chronology and earlier biopsies if available.

Microscopic-colitis-like patterns also occur

Lymphocytic-like

Intraepithelial lymphocytes and superficial epithelial injury

Consider symptoms and checkpoint exposure

Collagenous-like

Thickened subepithelial collagen with inflammation

Do not force all ICI injury into an apoptotic-only pattern

Endoscopic appearance does not define the histology

- Checkpoint-associated colitis may show erythema, erosions, ulceration or a less striking surface appearance.
- A biopsy evaluates mucosal inflammation, apoptosis and microscopic-pattern injury.
- Normal-appearing mucosa does not always exclude pathologic microscopic findings.

Diarrhea after checkpoint therapy: Differential

Possibility	Evidence to seek
Immune-mediated drug toxicity	Temporal association, compatible biopsy, exclusion of mimics
Infection	Appropriate stool / tissue studies and immune status
Inflammatory bowel disease	Prior history or sustained features of chronicity
Other drugs / treatment effects	Full medication and treatment timeline

The clinical cost of attribution error

Causal / diagnostic sequence (simplified)



Biopsy interpretation should explicitly address credible mimics.

Reporting checkpoint-associated mucosal injury

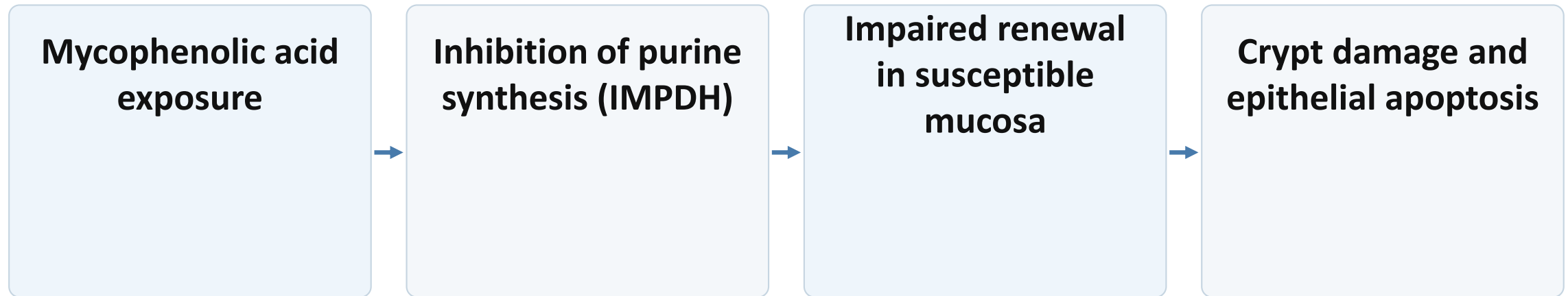
- Describe the predominant pattern rather than asserting a unique microscopic hallmark.
- Mention elevated crypt apoptosis, active colitis, dropout or chronicity when present.
- Use qualified language: Findings can be compatible with checkpoint-related injury in context.

Mycophenolate: A second major cause

- Mycophenolate mofetil is an immunosuppressive therapy with recognized gastrointestinal adverse effects.
- Robbins explicitly associates it with apoptotic enteritis and colitis.
- The pattern can occur in patients already at risk of transplant-related infection.

Mycophenolate and epithelial renewal

Causal / diagnostic sequence (simplified)



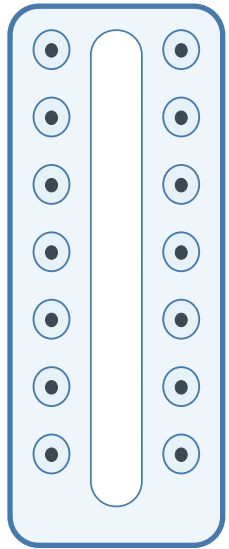
Mechanistic context from external literature; The association, not this biochemical sequence.

A mixed-pattern injury is typical of mycophenolate

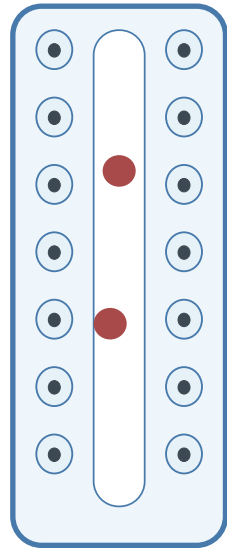
- Crypt apoptosis may coexist with distortion, focal active inflammation or isolated crypt damage.
- An IBD-like or a GVHD-like morphology can dominate different biopsies.
- The mixed pattern is a useful clue, but is not diagnostic in isolation.

Morphology: Apoptosis plus crypt disarray

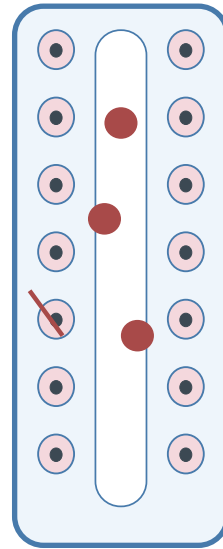
Schematic: Crypt epithelial response



Intact crypt



Apoptotic injury



Mixed injury

Read the schematic

- Blue epithelium — Preserved / altered crypt lining
- Red fragments — Schematic epithelial apoptosis
- Broken gland — Represents severe crypt dropout

Concurrent apoptotic bodies and altered crypt architecture suggest a drug-injury pattern.

Original schematic — not a histologic specimen

Mycophenolate injury can mimic IBD

- Crypt distortion and inflammatory activity may resemble inflammatory bowel disease.
- Increased crypt epithelial apoptosis favors a drug-associated process in the proper setting.
- IBD should not be diagnosed solely from architecture without assessing drug history.

Mycophenolate injury can mimic GVHD

- Both may show prominent epithelial apoptosis and crypt damage.
- The clinical transplant type and concurrent medicines are critical.
- After allogeneic HSCT, dual exposures can make a single-cause interpretation unreliable.

Histologic details worth actively seeking

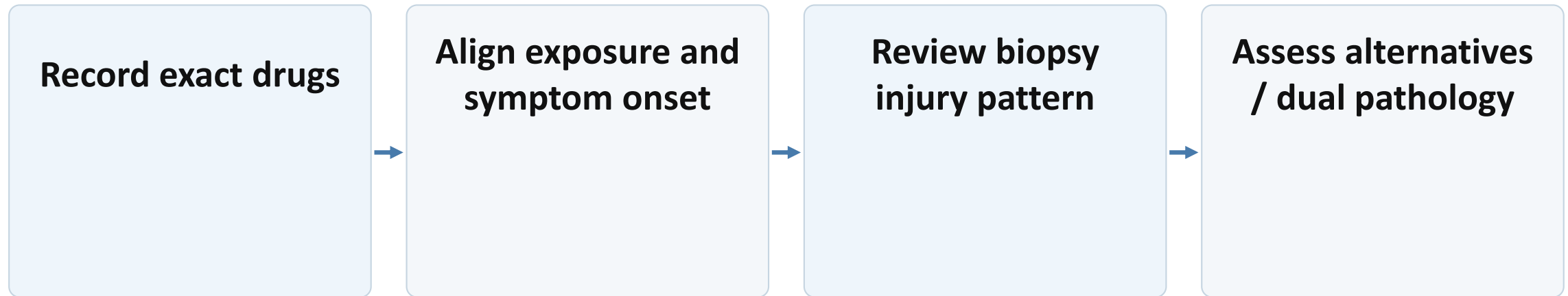
Feature	Interpretive relevance
Damaged / dilated crypts	Supports focal epithelial drug injury when other causes are excluded
Architectural distortion	Can mimic chronic IBD; not specific
Increased crypt apoptosis	Central injury feature, shared by GVHD and checkpoint colitis
Eosinophils / reactive changes	May coexist; no single ancillary clue is definitive

Endoscopy in mycophenolate injury

- The mucosa can be erythematous, eroded, ulcerated or deceptively unremarkable.
- Changes may be patchy and are not inherently specific for a drug.
- Multiple biopsy sites can document the distribution and coexistent lesions.

A drug list can outweigh an isolated microfeature

Causal / diagnostic sequence (simplified)



“Drug-induced” is a clinicopathologic conclusion.

Mycophenolate injury versus idiopathic IBD

Observation	Mycophenolate-associated	Idiopathic IBD
Crypt apoptosis	Often conspicuous	May occur, usually less defining
Crypt distortion	May be present	May be prominent in established disease
Clinical support	Exposure and exclusion of mimics	Compatible longitudinal history
Conclusion	Neither column alone is diagnostic	Integrate clinical course

A key pitfall: Dual pathology

- A patient taking mycophenolate can simultaneously acquire infectious colitis.
- In transplant populations, immune injury, infection and drug toxicity may overlap.
- Do not stop the search after recognizing apoptosis.

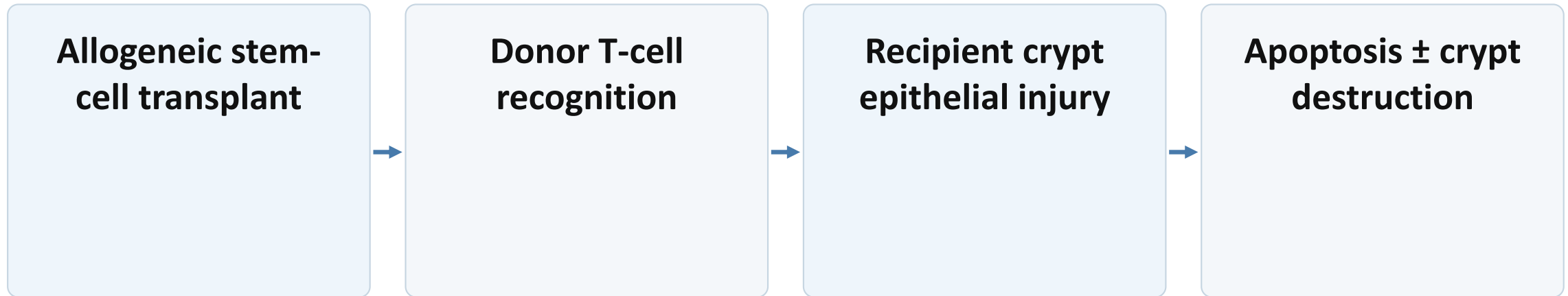
One biopsy can contain more than one pathologic process.

Gastrointestinal GVHD: The reference comparator

- Occurs after allogeneic hematopoietic stem-cell transplantation.
- Donor T cells target recipient gastrointestinal epithelium.
- Small intestine and colon are frequently involved.

GVHD has a distinct initiating mechanism

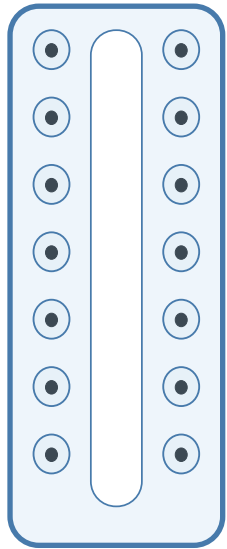
Causal / diagnostic sequence (simplified)



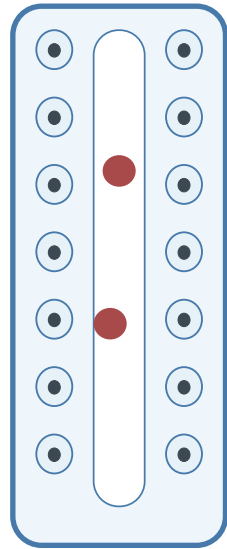
This initiating context differs from checkpoint drug blockade.

Crypt apoptosis is central in gastrointestinal GVHD

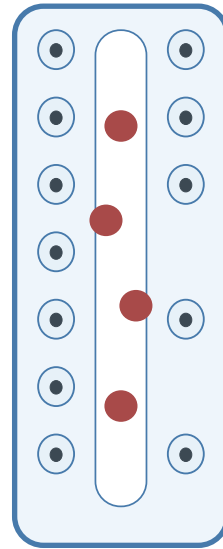
Schematic: Crypt epithelial response



Intact crypt



Crypt apoptosis



More apoptosis

Read the schematic

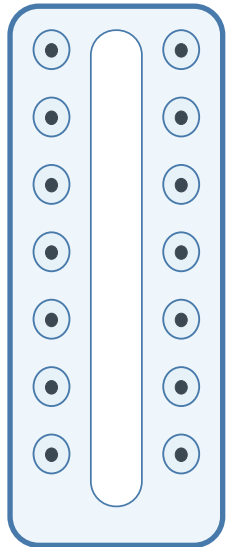
- Blue epithelium — Preserved / altered crypt lining
- Red fragments — Schematic epithelial apoptosis
- Broken gland — Represents severe crypt dropout

Epithelial apoptosis, particularly of crypt cells, is the commonest histologic finding in the Robbins section.

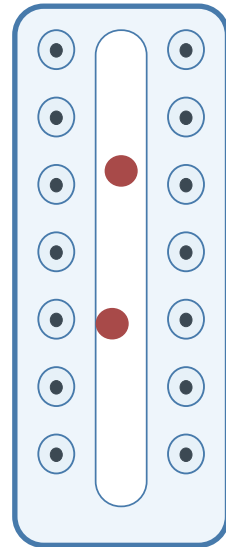
Original schematic — not a histologic specimen

Severe GVHD can eliminate crypts

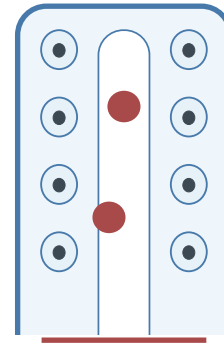
Schematic: Crypt epithelial response



Intact crypt



Apoptotic injury



Crypt dropout

Read the schematic

- Blue epithelium — Preserved / altered crypt lining
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- Broken gland — Represents severe crypt dropout

Complete crypt destruction is possible in severe intestinal GVHD.

Original schematic — not a histologic specimen

Sparse inflammation does not exclude immune injury

- That the lamina propria lymphocytic infiltrate is often sparse.
- Prominent crypt epithelial damage can therefore outweigh the inflammatory-cell density.
- Interpret the epithelial compartment independently from the stroma.

A low-cellularity lamina propria can accompany substantial crypt injury.

The GVHD clinical phenotype

- Intestinal GVHD often causes watery diarrhea.
- With severe damage, diarrhea may become bloody.
- Clinical transplant timing, medications and infections remain essential to interpretation.

GVHD versus checkpoint injury

Feature	Gastrointestinal GVHD	Checkpoint-related enterocolitis
Typical context	Allogeneic HSCT	Cancer immunotherapy
Initiating context	Donor T-cell response	Immune checkpoint blockade
Common overlap	Crypt apoptosis / dropout	Crypt apoptosis / dropout
Additional patterns	Variable injury / mimics	Active or microscopic-colitis-like changes

GVHD versus mycophenolate injury

Feature	GVHD	Mycophenolate-associated
Clinical clue	Allogeneic HSCT	Current or prior mycophenolate exposure
Microscopic overlap	Apoptosis and crypt loss	Apoptosis and crypt damage
Other clues	Often sparse lamina propria cells	May show mixed IBD-like morphology
Diagnostic principle	Exclude treatment / infection mimics	Drug attribution needs clinical support

A three-way etiologic comparison

Question	Checkpoint toxicity	Mycophenolate	GVHD
Usual exposure	ICI therapy	Mycophenolate	Allogeneic HSCT
Shared signal	Epithelial apoptosis	Epithelial apoptosis	Crypt apoptosis
Common companion	Active colitis	Mixed / IBD-like changes	Crypt attenuation / dropout
Major constraint	Exclude infection	Exclude other injury	Exclude drug / infection mimics

Infection belongs in every differential

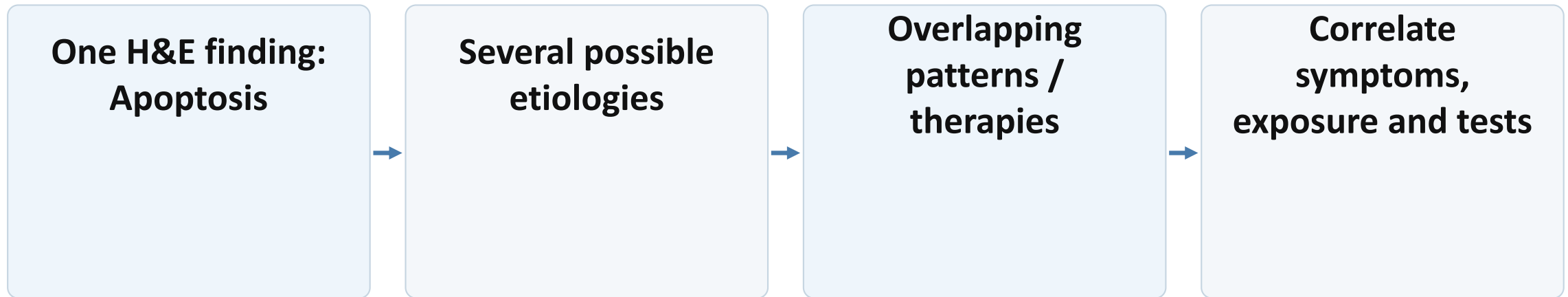
- Immunosuppressed patients can develop opportunistic gastrointestinal infection.
- Infectious injury and apoptosis-associated processes can coexist.
- Histology and appropriately directed ancillary studies complement clinical microbiology.

CMV and other mimics: When to investigate

- Consider viral infection particularly in transplant or immunosuppressed patients.
- Evaluate suspicious cytopathic change and the clinical laboratory picture.
- CMV immunohistochemistry is an ancillary test when warranted, not a replacement for tissue review.

Why histology alone is insufficient

Causal / diagnostic sequence (simplified)



Reject the shortcut “apoptosis = GVHD”.

Low-power biopsy assessment

- Assess specimen adequacy and site before interpreting focal crypt abnormalities.
- Scan overall crypt density, architecture and inflammation.
- Look for erosions or ulceration that could alter the biopsy context.

Intermediate-power crypt assessment

- Identify crypt attenuation, dilatation, damage and dropout.
- Note whether abnormalities are diffuse or patchy across the sample.
- Compare crypt injury with the density and distribution of inflammation.

High-power assessment of epithelial apoptosis

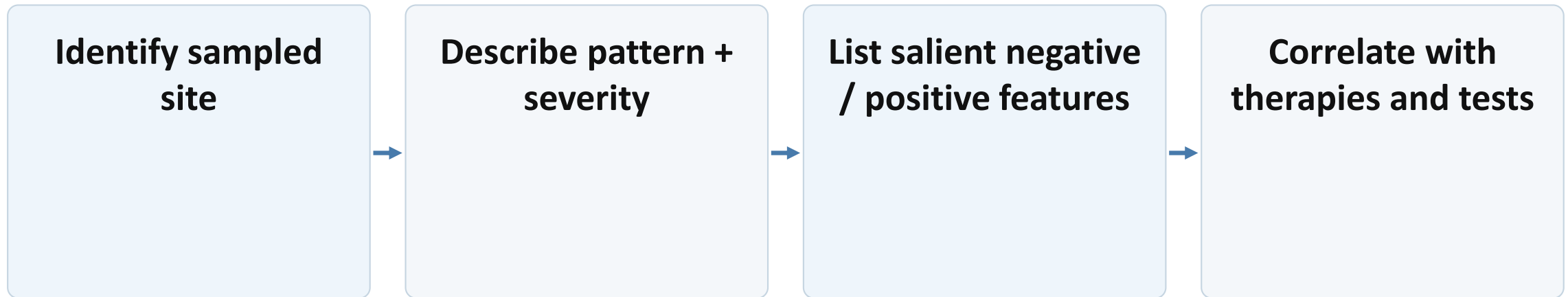
- Locate apoptotic bodies within the epithelium rather than luminal detritus alone.
- Assess their frequency across multiple well-oriented crypts.
- Avoid asserting a universal numerical cutoff: Thresholds vary by setting and publication.

Assess companion findings separately

Companion finding	Question raised
Neutrophilic cryptitis / abscess	Is there an active inflammatory component?
Basal inflammation / distortion	Is there substantial chronic mucosal injury?
Crypt dropout / attenuation	How extensive is epithelial injury?
Viral cytopathy / ulceration	Is a second injury process present?

A structured pathology sign-out

Causal / diagnostic sequence (simplified)



Report the observed morphology before the favored etiology.

Suggested descriptive biopsy wording

- “Colonic mucosa with increased crypt epithelial apoptosis and focal crypt injury.”
- Add observed associated active colitis, architecture change or dropout as appropriate.
- “Findings are compatible with treatment-related injury in the correct clinical setting; Clinical correlation is required.”

The most common interpretation traps

One finding, one disease

Do not equate crypt apoptosis
with GVHD alone

Morphology without timeline

Different therapies may yield
overlapping injury

Missing co-pathology

Infection and drug injury can
coexist

Case 1: Diarrhea during cancer immunotherapy

- Illustrative scenario: An oncology patient develops watery diarrhea while receiving checkpoint blockade.
- Biopsy shows active cryptitis plus increased epithelial apoptosis.
- Question: Which alternative diagnoses must be considered before attributing all injury to the drug?

Teaching answer (shown for discussion): Infection, pre-existing or unmasked IBD, and other treatment or drug effects; Integrate stool studies, medications and biopsy.

Case 2: Diarrhea in a solid-organ recipient

- Illustrative scenario: A renal-transplant patient takes mycophenolate and develops persistent diarrhea.
- Biopsy shows crypt apoptosis, focal distortion and isolated damaged crypts.
- Question: Why is a primary IBD label premature?

Teaching answer (shown for discussion): Mycophenolate can produce an IBD-like injury pattern; Exposure, infections and clinical evolution must be assessed.

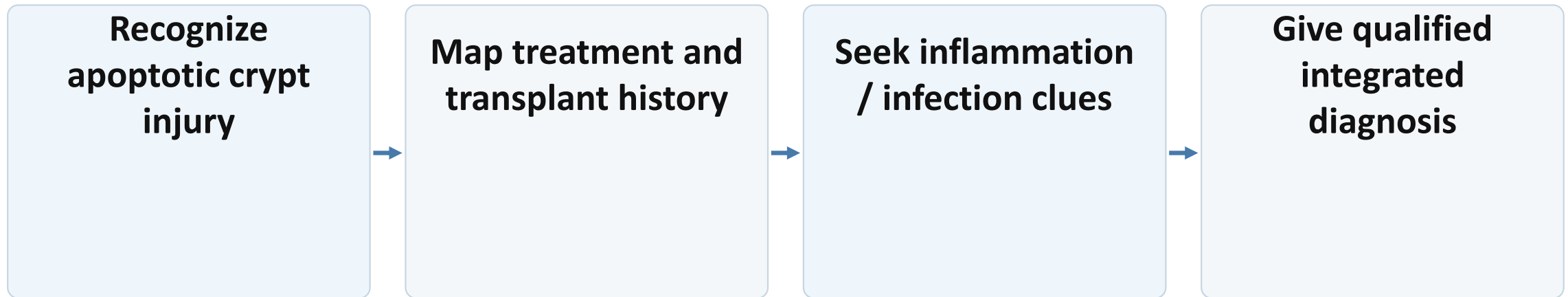
Case 3: Diarrhea after allogeneic HSCT

- Illustrative scenario: A stem-cell recipient develops profuse watery diarrhea.
- Biopsy shows crypt cell apoptosis and some crypt loss, with sparse lamina propria lymphocytes.
- Question: What is favored and what confounders remain?

Teaching answer (shown for discussion): GI GVHD is a key consideration; Concurrent drugs, infections and timing can complicate attribution.

Integrated work-up: From biopsy pattern to cause

Causal / diagnostic sequence (simplified)



No etiologic decision is made from apoptotic bodies alone.

What each major clue can—and cannot—tell you

Clue	Supports	Does NOT prove
Increased apoptosis	Apoptotic-type injury	A specific etiologic category
Checkpoint exposure	Possible immune-related colitis	Exclusion of infectious colitis
Mycophenolate exposure	Possible drug toxicity	Absence of GVHD / infection
Allogeneic transplant	GVHD risk	Every crypt lesion is GVHD

Five principles to retain

- Apoptotic enterocolitis is a convergent epithelial injury pattern.
- Checkpoint therapy, mycophenolate and GVHD are core clinical settings.
- Crypt apoptosis can coexist with active inflammation, architectural distortion or dropout.
- The clinical timeline and infection assessment are indispensable.
- Biopsy reports should describe what is seen and qualify causal attribution.

Selected references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026; Chapter 17, p. 734.

Sun et al. Immune checkpoint inhibitor–related colitis. Am J Clin Pathol. 2024. PMID: 38377034.

Liapis et al. Histological spectrum of mycophenolate mofetil–related colitis. Histopathology. 2013. doi:10.1111/his.12222.

Zhang & Hagen. GI biopsies post-stem cell transplant: approach to diagnosis. Surg Pathol Clin. 2023. PMID: 37863563.

ECCO Topical Review on the clinicopathological spectrum and differential diagnosis of IBD. J Crohns Colitis. 2022.

Apoptotic colonopathy under immunosuppression: mycophenolate-related effects and beyond. PMID: 24013803.