

Microscopic Colitis

Clinicopathologic diagnosis, histologic subtypes, and diagnostic pitfalls

Collagenous colitis • Lymphocytic colitis

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Learning objectives

- Recognize the clinical–endoscopic–histologic diagnostic triad.
- Differentiate collagenous from lymphocytic colitis on colonic biopsy.
- Apply biopsy sampling and ancillary stain principles.
- Avoid common differential-diagnostic and interpretation errors.

Clinical entry point: Normal-looking colon

A 62-year-old woman reports persistent nonbloody, watery diarrhea. Colonoscopy shows no conspicuous mucosal lesion; Random colonic biopsies have been obtained.

Apply the morphology

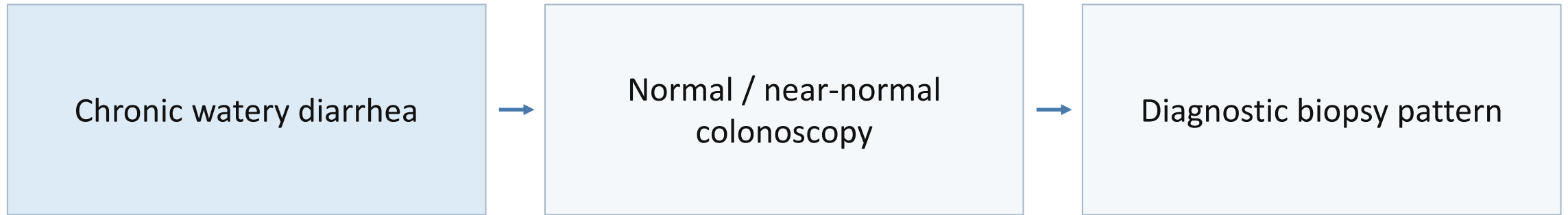
- What mucosal abnormalities may be occult endoscopically?
- Which two tissue features should be examined first?

A histologic diagnosis behind a bland endoscopy

Microscopic colitis is defined by abnormal colonic biopsies, often despite a normal endoscopic appearance.

- Chronic watery, typically nonbloody diarrhea is the clinical setting.
- Histology separates major subtypes that symptoms alone cannot distinguish.

Three-part diagnostic framework



All three contribute; Histologic subtype must be assigned using tissue findings.

Major morphologic entities

Collagenous colitis

- Thickened subepithelial collagen band.
- Surface epithelial injury and mucosal inflammation.

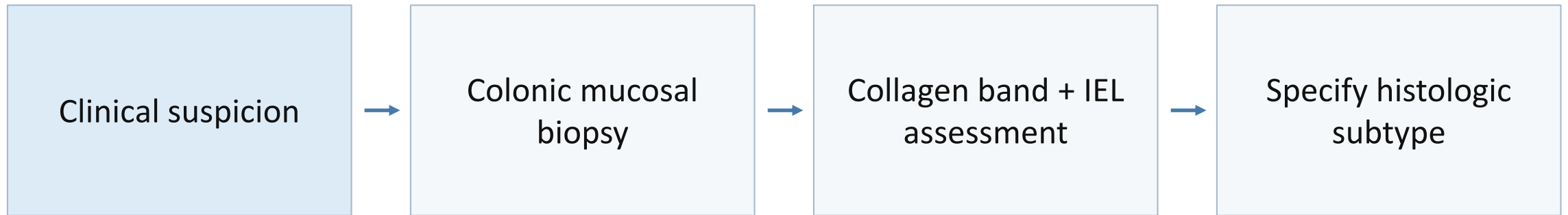
Lymphocytic colitis

- Prominent surface intraepithelial lymphocytes.
- No diagnostic collagen band thickening.

Why two subtypes matter

- Both commonly produce the same watery-diarrhea phenotype.
- Collagen band thickness is the discriminator for collagenous colitis.
- Surface epithelial lymphocyte density is the discriminator for lymphocytic colitis.
- Clinical data and adequate biopsy samples are required for interpretation.

How morphology refines the diagnosis



IEL = intraepithelial lymphocyte; Measurements are interpreted on well-oriented H&E sections.

Clinical presentation: The core syndrome

- Chronic or recurrent watery diarrhea.
- Typically nonbloody stools; Colonoscopy often looks unremarkable.
- Clinical manifestations of collagenous and lymphocytic colitis substantially overlap.
- Do not assign a histologic subtype from symptoms alone.

Why the examination can appear normal

Endoscopic perspective

- No obvious erosions or ulcers may be evident.
- Microscopic epithelial and lamina propria abnormalities can remain invisible.

Pathology perspective

- Surface epithelium and subepithelial compartment are the diagnostic targets.
- Adequate biopsies bridge the endoscopic–histologic gap.

Additional symptoms: Beyond stool consistency

- Urgency, nocturnal stools, and fecal incontinence can occur.
- Abdominal pain and impairment of quality of life can accompany diarrhea.
- A presentation without weight loss; Broader clinical reviews note that some patients lose weight.
- Neither weight loss nor its absence is a histologic discriminator.

Clinical sex and age association

Collagenous colitis occurs particularly in middle-aged and older women.

- The demographic pattern raises suspicion but is not diagnostic.
- Lymphocytic colitis also occurs in adults beyond this group.

Associations and triggers

Immune-associated conditions

- Celiac disease.
- Graves disease and rheumatoid arthritis.
- Autoimmune or lymphocytic gastritis.

Medications

- NSAID-associated histologic changes are recognized.
- A possible association with proton pump inhibitors is noted by Robbins.
- Medication review is essential; Association does not establish causality.

Celiac disease deserves active consideration

An association with celiac disease is particularly prominent in lymphocytic colitis.

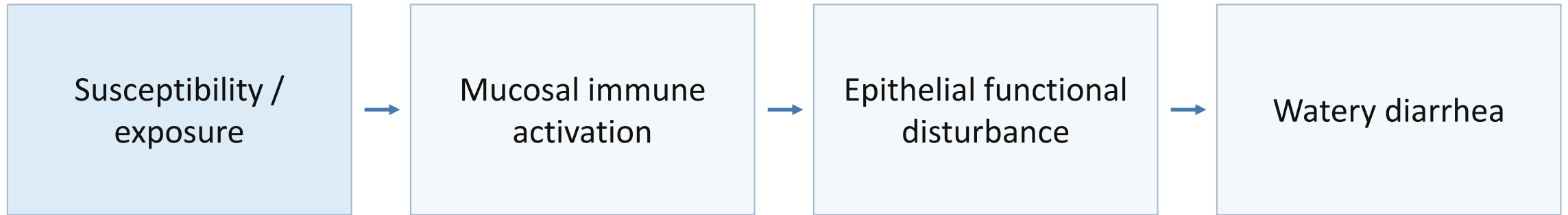
- Assess clinical context and perform appropriate celiac screening when indicated.
- Coexistence is possible; These diagnoses are not mutually exclusive.

The medication-association caveat

Exposure is a clue; It is not proof that a drug caused the colitis.

- Review the timeline of use, symptom onset, and alternatives.
- Avoid interpreting an epidemiologic association as a pathognomonic biopsy pattern.

Conceptual pathophysiology, not a single proven pathway



Schematic synthesis: The exact initiating mechanism is incompletely established; This is not a definitive molecular pathway.

Why watery diarrhea develops

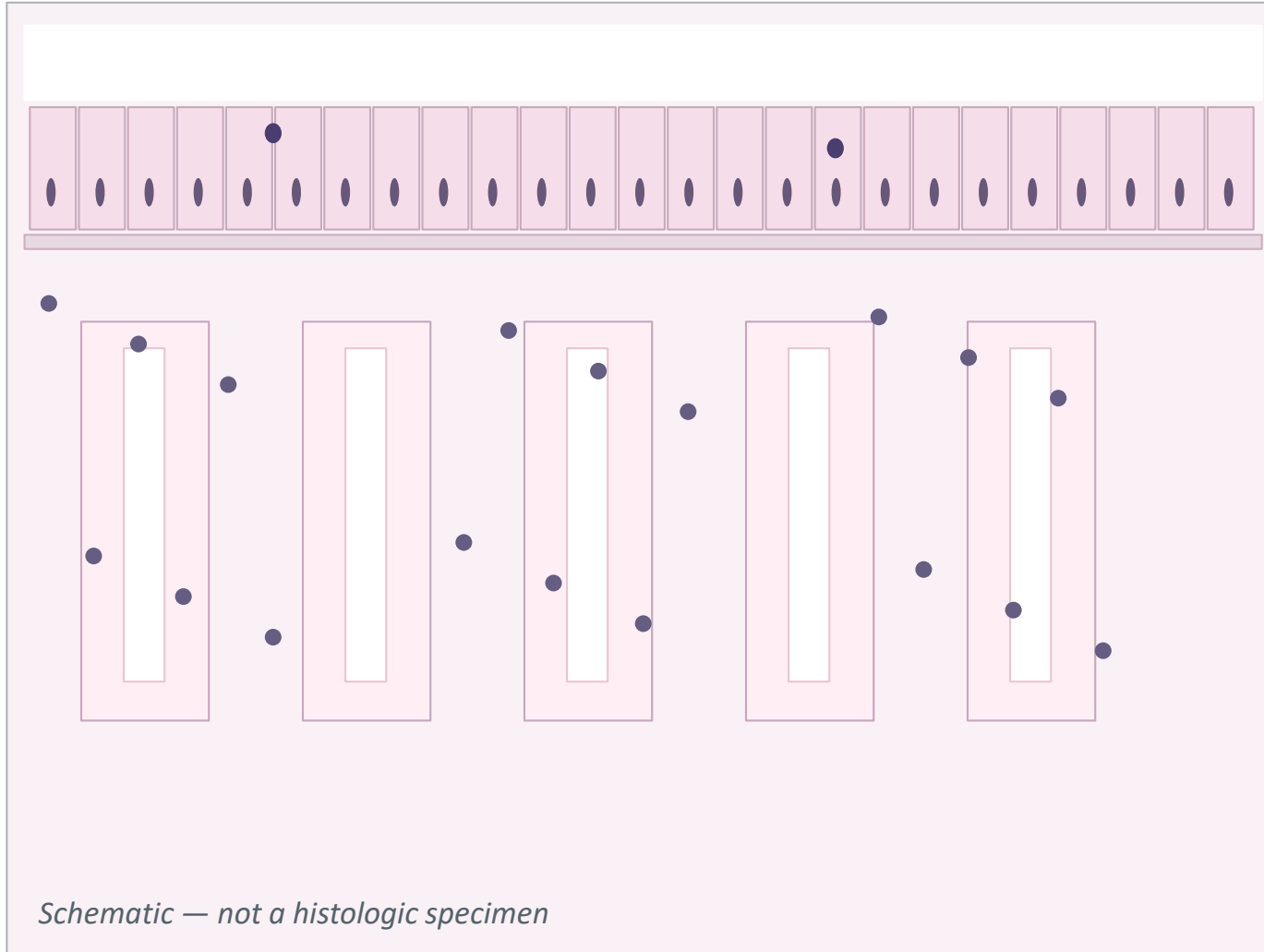
Observed tissue pattern

- Surface epithelial alterations.
- Lamina propria inflammatory infiltrate.
- Intraepithelial immune cells.

Functional interpretation

- These abnormalities plausibly disrupt mucosal fluid handling.
- Do not derive a quantitative secretory mechanism from morphology alone.

Normal reference: Surface, lamina propria, and crypts



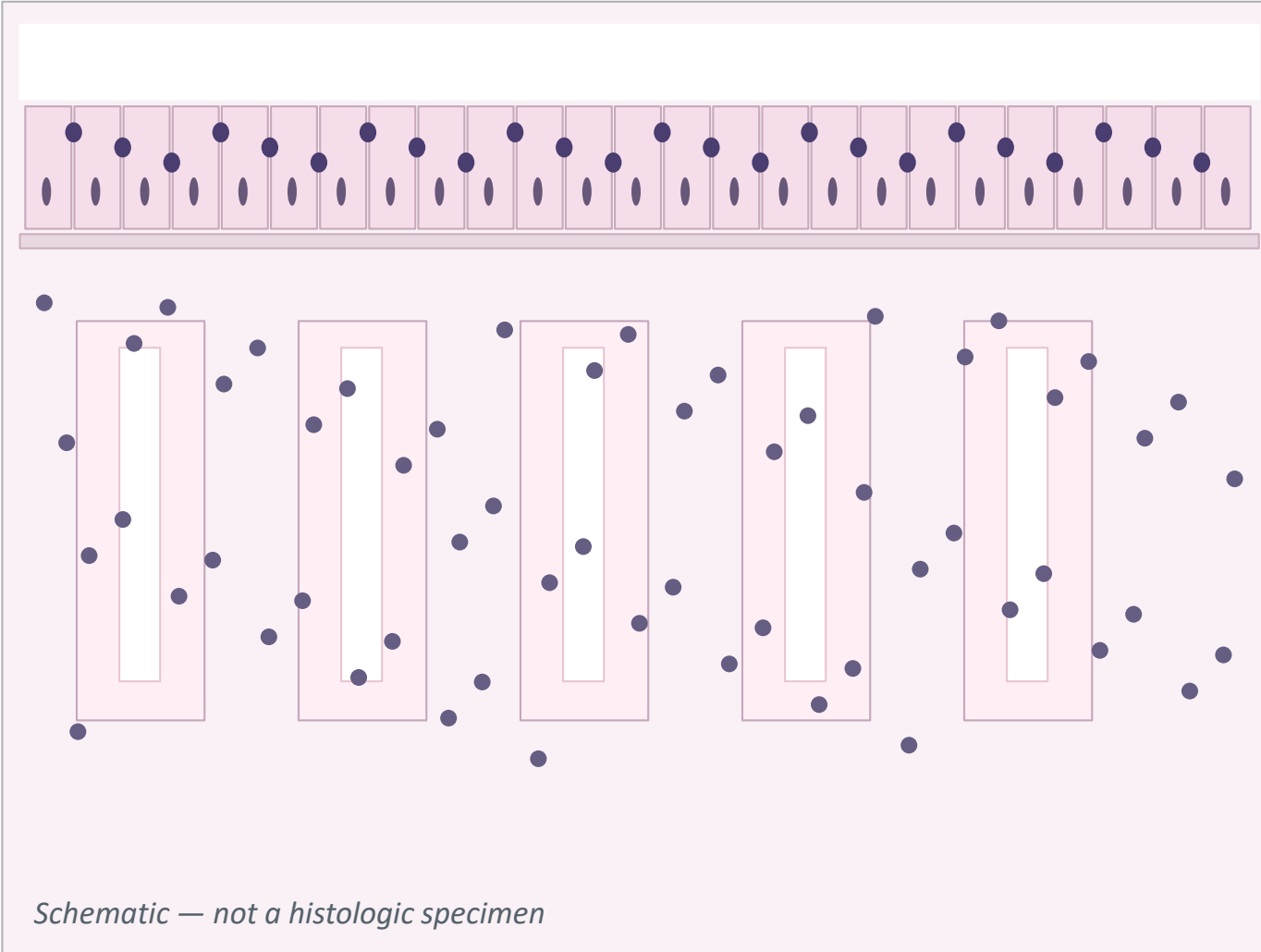
Reference architecture

- Surface columnar epithelium covers the mucosa.
- Crypts descend into the lamina propria.
- Only limited normal IELs are expected.

Start with the colonic biopsy at low power

- Determine whether the mucosa is well oriented.
- Review surface epithelial integrity and crypt architecture.
- Identify lamina propria inflammatory expansion.
- Evaluate collagen deposition beneath surface epithelium.

Surface epithelium is the diagnostic compartment



Lymphocytic pattern

- IELs sit within the surface epithelial layer.
- Do not count lamina propria lymphocytes as epithelial lymphocytes.
- A surface-oriented assessment is essential.

Intraepithelial lymphocytes are T cells

Small, dark lymphocyte nuclei within surface epithelium are diagnostically informative.

- The cells as intraepithelial T lymphocytes.
- CD3 staining may assist in equivocal cases; H&E remains the primary diagnostic platform.

Count surface IELs consistently



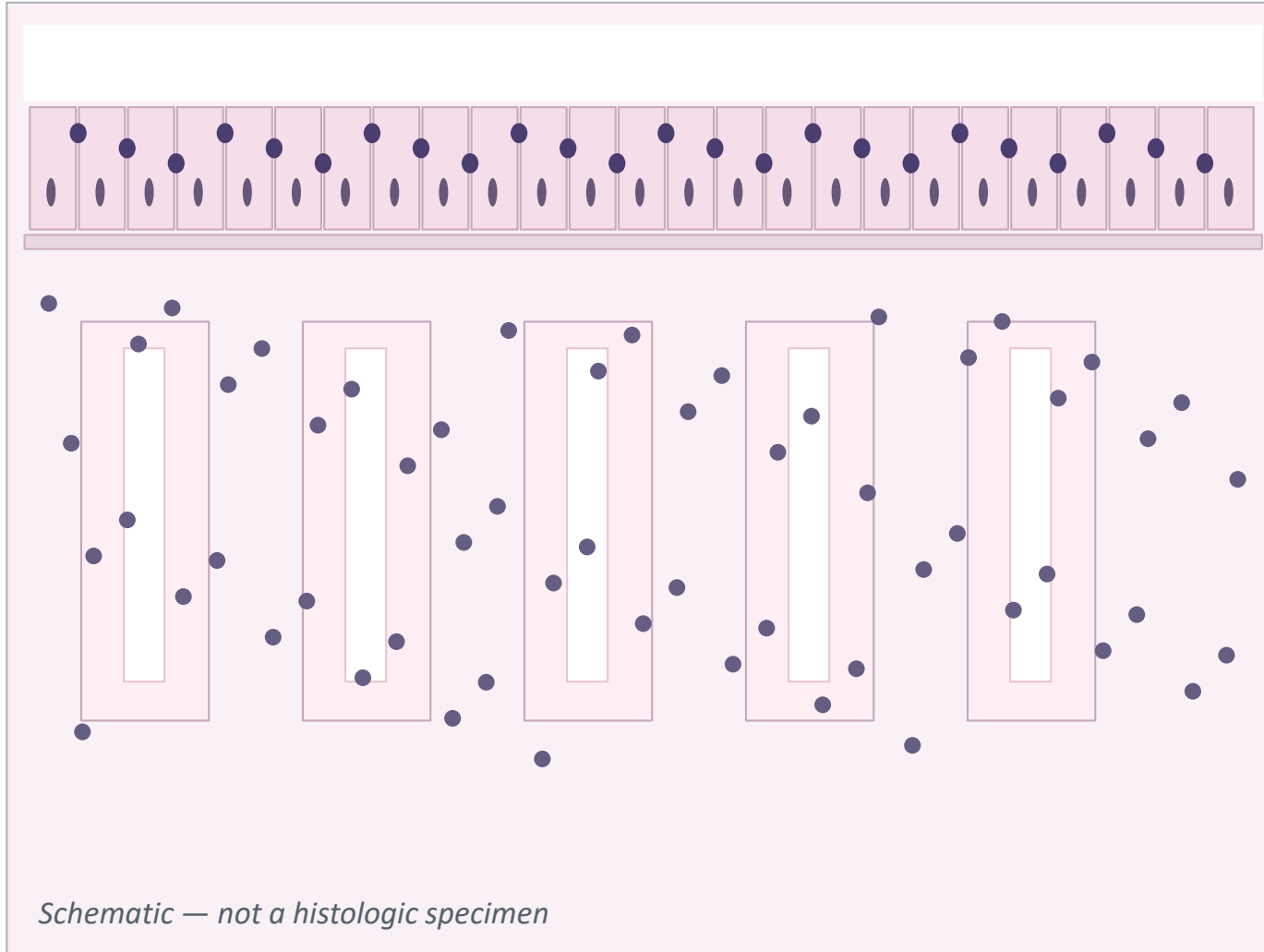
Apply validated histologic criteria to H&E-stained tissue; Avoid tangential or denuded epithelium.

Lymphocytic colitis: Key threshold

≥20 intraepithelial lymphocytes per 100 surface epithelial cells

- The lamina propria also shows increased inflammation.
- The subepithelial collagen band is not significantly thickened.

Lymphocytic colitis: Simplified tissue map



Lymphocytic pattern

- Numerous dark IEL profiles lie in surface epithelium.
- A mixed inflammatory infiltrate expands lamina propria.
- The collagen band remains thin.

Lamina propria inflammation in lymphocytic colitis

- Lymphocytes and plasma cells commonly predominate.
- Other inflammatory cells may be present.
- This increase supports the diagnosis but is not specific in isolation.
- Surface IEL density remains the defining feature.

Surface injury accompanying lymphocytic colitis

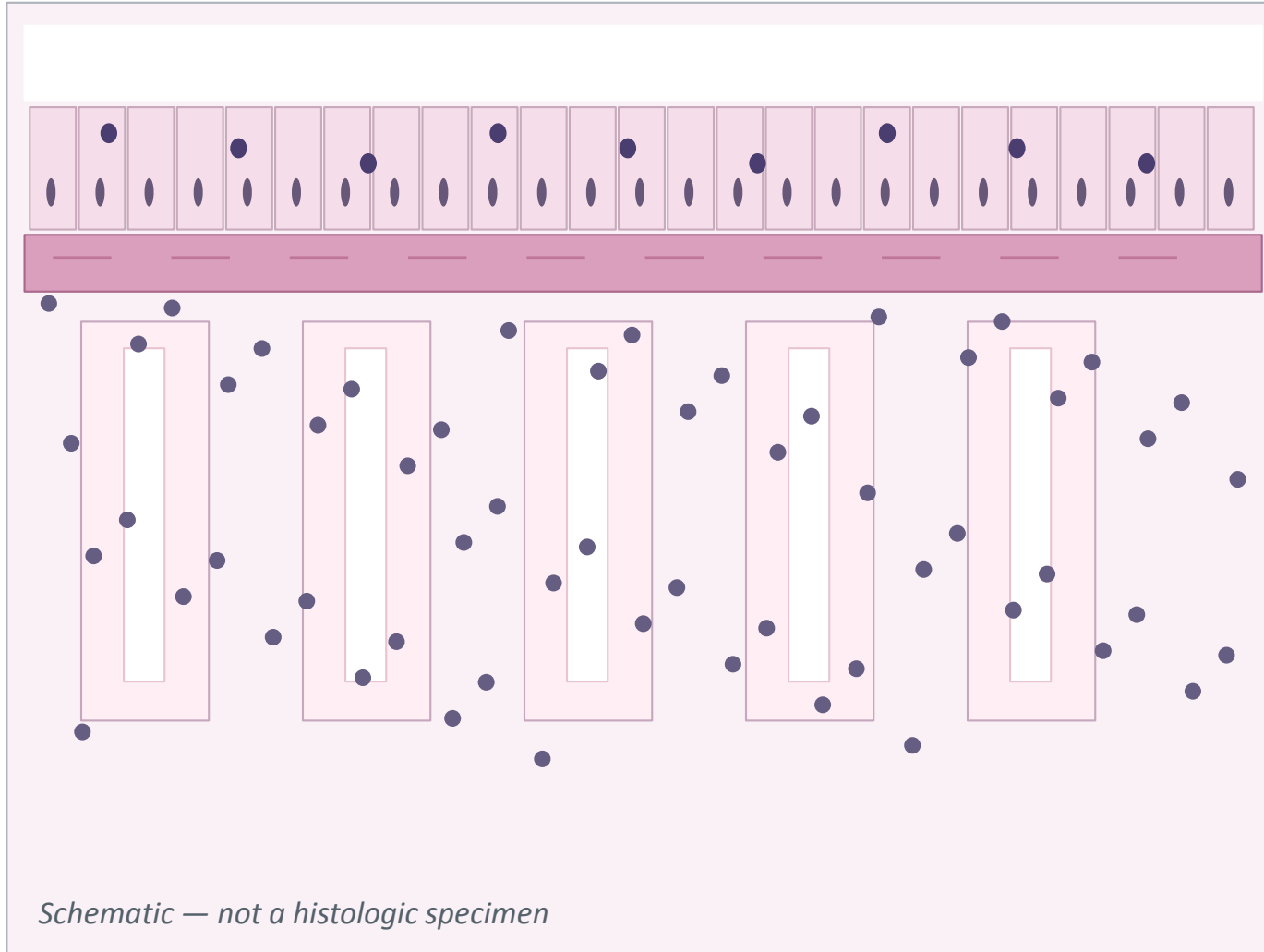
- Surface epithelial flattening or mucin depletion may occur.
- Inflammatory change can coexist with relatively preserved crypt architecture.
- Epithelial injury supports the pattern but does not replace IEL assessment.

Collagenous colitis: Defining thickness

Subepithelial collagen band $\geq 10\text{ }\mu\text{m}$ on appropriately oriented tissue

- A dense band greater than $10\text{ }\mu\text{m}$.
- European consensus uses $\geq 10\text{ }\mu\text{m}$ with accompanying lamina propria inflammation.

Collagenous colitis: Simplified tissue map



Collagenous pattern

- A conspicuous band lies immediately beneath surface epithelium.
- IELs may also be increased.
- Lamina propria shows mixed inflammatory cells.

Read the band beneath the surface epithelium

- The diagnostically relevant deposit is subepithelial.
- Band thickness can be irregular and variable between fragments.
- Entrapped small vessels or inflammatory cells may be visible.
- A correctly oriented surface segment supports measurement.

Collagenous colitis: Linked tissue abnormalities

Subepithelial band

- Dense collagen accumulation immediately below surface.
- An irregular deep interface may be evident.

Surface and lamina propria

- Epithelium may be flattened, damaged, or focally detached.
- Mixed inflammatory cells occupy lamina propria.

The collagen band is not an isolated finding

A thick band should be interpreted alongside mucosal inflammation and epithelial change.

- A focal apparent band can be misleading in poorly oriented tissue.
- Context reduces the risk of reporting a nonspecific artifact as disease.

Direct comparison: Dominant histologic findings

Feature	Collagenous colitis	Lymphocytic colitis
Subepithelial band	≥10 µm	Not significantly thickened
Surface IELs	Often increased	≥20 per 100 cells
Lamina propria	Mixed inflammatory infiltrate	Mixed inflammatory infiltrate
Crypt architecture	Usually largely preserved	Usually largely preserved

The histologic spectrum includes incomplete forms

Borderline biopsy abnormalities may fall short of full collagenous or lymphocytic criteria.

- The European 2021 guideline defines incomplete forms.
- Robbins' short section describes the two major entities, not the incomplete subcategories.

Incomplete forms: Consensus definitions

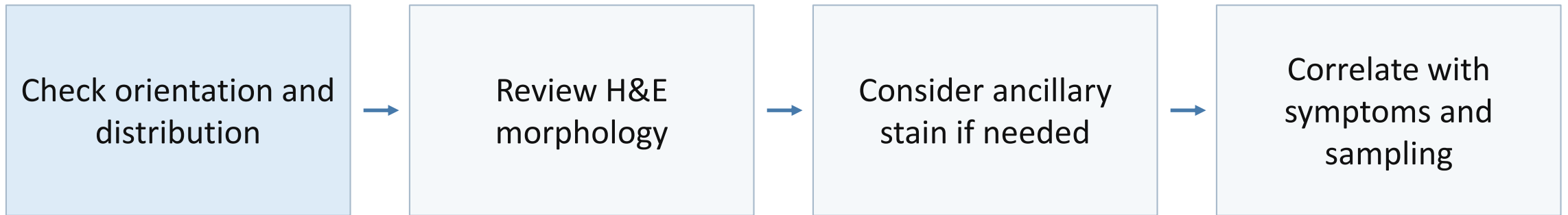
Incomplete collagenous colitis

- Subepithelial collagen band $>5\text{ }\mu\text{m}$ but $<10\text{ }\mu\text{m}$.
- Inflammatory infiltrate must be considered.

Incomplete lymphocytic colitis

- >10 but <20 IELs per 100 surface cells.
- Normal collagen band with mild lamina propria inflammation.

Interpreting a borderline pattern



Do not automatically classify borderline abnormalities as a fully developed major subtype.

Ancillary stains: Distinct purposes

Trichrome / collagen stains

- May delineate a thickened subepithelial collagen band.
- Aids borderline or subtle collagen deposition.

CD3 immunohistochemistry

- Highlights intraepithelial T cells.
- May aid recognition/counting of IELs in difficult specimens.

CD3 immunostaining requires interpretive restraint

Counts obtained by CD3 may exceed counts appreciated on H&E.

- European guidance identifies potential overdiagnosis if H&E cutoffs are transferred uncritically to immunostains.
- A confirmed phenotype and routine morphology remain central.

Collagen band artifact: How it arises

Tangential sectioning

- Oblique passage through surface tissue can exaggerate apparent thickness.
- A poorly oriented fragment cannot support a reliable thickness measurement.

Mitigation

- Seek vertically oriented, intact mucosal surfaces.
- Review deeper levels or supplementary stain when genuinely needed.

Pitfall: Damaged surface epithelium

- Denudation can remove the very compartment needed for IEL assessment.
- Crush, tangential sectioning, and fragmentation limit confidence.
- Do not infer a normal IEL count from a biopsy lacking evaluable surface.
- State specimen limitations in the report when consequential.

Pitfall: Site-related physiologic variation

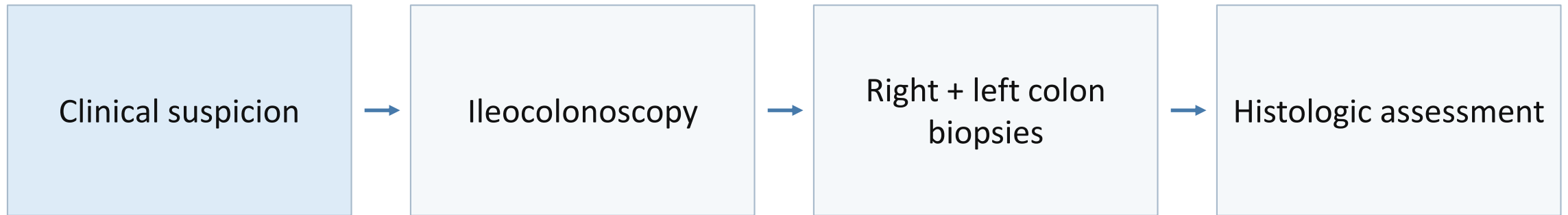
- Right- and left-colon samples may differ in baseline cellularity.
- Knowledge of biopsy site helps interpret subtle/borderline changes.
- Separately labeled containers may reduce ambiguity.
- Morphology is evaluated in clinical and anatomic context.

Biopsy sampling must be anatomically adequate

Guidance recommends biopsies from at least the right and left colon.

- A normal-appearing colon still requires tissue sampling when MC is suspected.
- Rectal-only sampling is not sufficient for dependable exclusion.

Practical biopsy workflow



If location-specific questions matter, submit right and left samples in separate labeled containers.

Why sampling strategy matters

Patchiness / distribution

- Diagnostic features can vary by colonic segment.
- Limited distal sampling risks missed disease.

Report-level context

- Anatomic site informs normal variation.
- A well-sampled negative study is more informative than rectal-only sampling.

An organized pathology report

- State whether the findings support collagenous, lymphocytic, or incomplete microscopic colitis.
- Document the relevant collagen-band and/or surface IEL findings.
- Comment on orientation or sampling limitations when material.
- Correlate with the clinical history and medication exposure.

Normal colonoscopy does not exclude microscopic colitis

The biopsy, not the gross examination, establishes the microscopic diagnosis.

- Macroscopic disease may be absent or nonspecific.
- Visible subtle changes do not reliably separate the two subtypes.

Fecal calprotectin is not an exclusion test

A low or normal fecal calprotectin value does not reliably rule out microscopic colitis.

- European recommendations do not support calprotectin for exclusion or routine monitoring.
- Persistent clinical suspicion should guide biopsy rather than this marker alone.

Microscopic colitis versus IBS-D

Possible clinical overlap

- Chronic loose or watery stools can resemble a functional bowel disorder.
- A visually normal colonoscopy does not resolve the distinction.

Decisive discriminator

- Microscopic colitis shows a characteristic mucosal biopsy pattern.
- IBS-D does not require the defining collagen/IEL abnormalities.

Microscopic colitis versus active classic IBD

Pattern	Microscopic colitis	Classic active IBD
Endoscopic appearance	Often near normal	May show visible active mucosal injury
Histologic focus	IELs and/or collagen band	Activity and chronic crypt abnormalities
Crypt architecture	Often largely preserved	Chronic distortion may occur
Clinical correlation	Watery, nonbloody diarrhea	Phenotype and activity variable

Alternative causes of watery diarrhea

Competing processes

- Celiac disease or bile acid diarrhea can coexist or mimic symptoms.
- Medication exposure may contribute.

Pathologic discipline

- Do not force a diagnosis when changes are nondiagnostic.
- Consider additional workup when biopsy findings fail to explain symptoms.

Drug-related microscopic-colitis-like changes

NSAIDs, and possibly PPIs, can be associated with a similar histologic pattern.

- A compatible tissue pattern does not independently prove drug causation.
- Clinical medication review remains essential.

Differentiating other colitides in context

Diversion colitis

- Occurs in a defunctionalized bowel segment.
- Prominent mucosal lymphoid follicles favor the diversion context.

Graft-versus-host injury

- Follows allogeneic transplantation.
- Epithelial/crypt apoptosis is a key morphologic clue.

A second adjacent mimic: Apoptotic colitis

Checkpoint inhibitor-related enterocolitis

- May show prominent epithelial apoptosis.
- Oncology exposure and severity inform interpretation.

Mycophenolate-associated injury

- Apoptotic enterocolitis can follow immunosuppression.
- Drug history and injury pattern matter.

Clinical care focuses on symptoms, not histologic surveillance

Routine follow-up biopsies are not recommended solely to document microscopic response.

- Symptom burden guides clinical assessment.
- Therapeutic response does not substitute for establishing the initial diagnosis.

Evidence-based induction: Oral budesonide

- European and AGA guidance recommend budesonide for symptomatic disease.
- Recommendation applies to both collagenous and lymphocytic colitis.
- Treatment is a clinical decision after diagnostic evaluation.
- The histologic subtype is informative but treatment responses overlap.

Relapse can occur after initial improvement

Recurrence after induction may require maintenance-directed clinical management.

- AGA guidance supports budesonide maintenance after recurrent symptoms.
- European guidance recognizes maintenance benefit, strongest evidence in collagenous colitis.

Nonresponse: Reconsider causes of ongoing diarrhea

Diagnostic review

- Reassess tissue adequacy and original histologic findings when indicated.
- Review medication contributors and alternative diagnoses.

Clinical reassessment

- Celiac disease merits screening in MC.
- Bile acid diarrhea may be considered when budesonide fails.

Case 1: A subepithelial band

A 59-year-old woman has watery, nonbloody diarrhea. Her colonic biopsy shows a broad subepithelial collagen layer, flattened surface cells, and increased lamina propria mononuclear cells.

Apply the morphology

- Which finding establishes the likely subtype?
- What sectioning artifact must be excluded?

Case 1: Interpretation

Collagenous colitis—provided the band is genuinely thickened in well-oriented surface mucosa.

- The relevant threshold in European guidance is $\geq 10\text{ }\mu\text{m}$.
- Confirm the inflammatory context and avoid a tangential-section false positive.

Case 2: Prominent surface lymphocytes

A 48-year-old patient with celiac disease develops persistent watery diarrhea. The colon looks normal, but biopsy shows conspicuous surface epithelial lymphocytes and no thickened collagen band.

Apply the morphology

- Which cell population should be counted?
- What threshold supports lymphocytic colitis?

Case 2: Interpretation

Lymphocytic colitis if surface IELs meet the accepted criterion (≥ 20 per 100 surface epithelial cells).

- Inflammatory cells in lamina propria are supportive, not the IEL denominator.
- Celiac disease may coexist with lymphocytic colitis.

Case 3: Borderline numbers

A patient has watery diarrhea. Biopsy shows a collagen band of 7 μm on well-oriented H&E and a mild inflammatory infiltrate, without the full lymphocytic-colitis pattern.

Apply the morphology

- Does the specimen meet major collagenous-colitis criteria?
- Which consensus category may be appropriate?

Case 3: Interpretation

The findings may fit incomplete collagenous colitis—not definitive classic collagenous colitis.

- European incomplete collagenous criteria: $>5\text{ }\mu\text{m}$ and $<10\text{ }\mu\text{m}$ with inflammation.
- Sampling, orientation, and clinical correlation still matter.

Case 4: A tempting false negative

An older adult has persistent watery diarrhea. Only a small rectal biopsy was taken and shows no diagnostic collagen band or surface intraepithelial lymphocytosis.

Apply the morphology

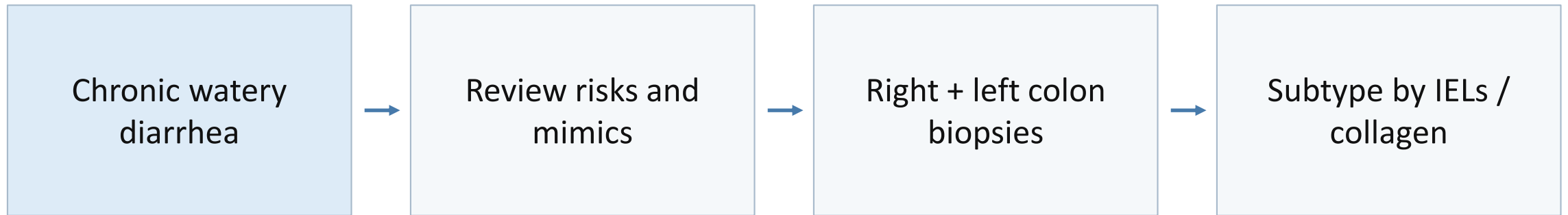
- Can microscopic colitis be excluded confidently?
- What sampling strategy should follow if suspicion persists?

Case 4: Interpretation

Rectal-only negative tissue is insufficient to confidently exclude microscopic colitis.

- Obtain sampling from right and left colon when clinically appropriate.
- Do not overstate the negative predictive value of a limited specimen.

Integrated diagnostic pathway



The pathologist and endoscopist contribute complementary evidence; Neither a normal scope nor symptoms alone can subtype the disease.

High-yield morphologic discriminators

Question	Answer
What is dominant in CC?	Subepithelial collagen band $\geq 10\text{ }\mu\text{m}$
What is dominant in LC?	Surface IELs ≥ 20 per 100 cells
Are crypts usually destroyed?	No; architecture often largely preserved
Can endoscopy be normal?	Yes; obtain appropriate biopsies
What undermines measurement?	Tangential surface section or denudation

Five diagnostic errors to avoid

- Reassuring a patient solely because colonoscopy appears normal.
- Measuring a tangentially cut collagen layer as true thickening.
- Counting lamina propria lymphocytes as surface IELs.
- Excluding disease from rectal-only or poorly preserved tissue.
- Attributing microscopic colitis to a drug without clinical corroboration.

Core references

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- Nielsen OH, et al. Microscopic colitis: etiopathology, diagnosis, and rational management. eLife. 2022;11:e79397.
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