

Celiac Disease

Immune pathogenesis · mucosal morphology · diagnosis

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Learning outcomes

- Explain why dietary gluten triggers T-cell–mediated mucosal injury in susceptible hosts.
- Identify the three major microscopic features and their functional consequences.
- Integrate clinical features, serology, histology, and HLA testing.
- Recognize refractory symptoms and important malignant complications.

Celiac disease: Defining features

Immune-mediated enteropathy caused by dietary gluten in genetically predisposed individuals

- Also called celiac sprue or gluten-sensitive enteropathy.
- Gluten exposure induces a mucosal immune response rather than direct dietary toxicity.
- Small-intestinal mucosal injury is central to malabsorption.

How celiac disease fits into malabsorption

Intraluminal digestion

Conversion of food macromolecules into absorbable units

Terminal digestion

Brush-border hydrolysis of residual peptides and carbohydrates

Transepithelial transport

Absorption and epithelial processing of nutrients and fluid

Lymphatic transport

Movement of absorbed lipids from intestinal mucosa

Celiac disease primarily disrupts the mucosa

Loss of villous surface



Reduced area available for absorption

Immature enterocytes



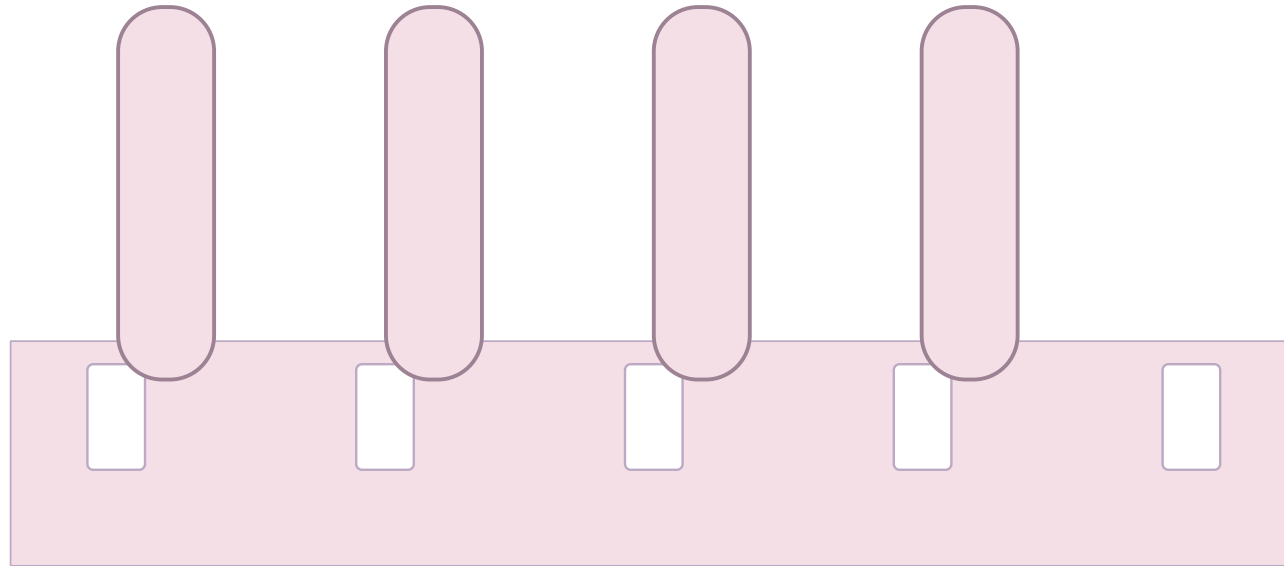
Impaired brush-border terminal digestion

**Damaged mucosal
epithelium**



Inefficient transepithelial nutrient transport

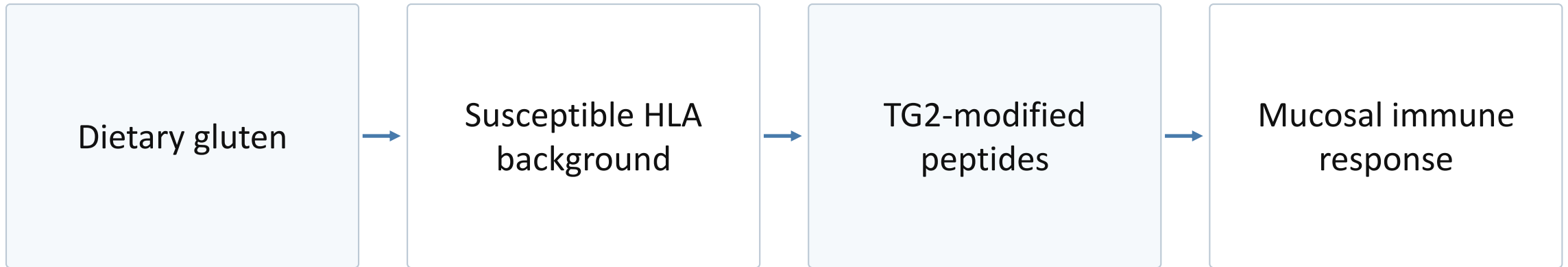
Normal villous architecture



Long absorptive villi with underlying crypts

Schematic—not a histological specimen

The disease requires more than gluten alone



Environment, antigen presentation and mucosal immunity converge.

Dietary exposure: The initiating trigger

- Wheat, rye and barley contain the relevant gluten-related proteins.
- Luminal and brush-border enzymes generate smaller gluten-derived peptides.
- Some peptides retain sequences rich in proline and glutamine.
- Susceptible individuals develop immune recognition of these peptides.

Why gluten-derived peptides are immunogenic

Proline- and glutamine-rich peptides



Products of partial digestion of gluten proteins

TG2 enzymatic modification



Glutamine residues can be deamidated

Modified peptide presentation



HLA-DQ2/DQ8 binding drives antigen-specific CD4 activation

Tissue transglutaminase 2 is a central mediator

TG2 converts selected glutamine residues in gluten peptides to glutamic acid

- The reaction is deamidation.
- Negatively charged peptide residues facilitate HLA-DQ2/DQ8 presentation.
- TG2 also becomes the target of disease-associated autoantibodies.

Genetic predisposition: HLA-DQ2 and HLA-DQ8

HLA-DQ2

- Present in most patients.
- Presents appropriately modified gluten peptides to CD4 T cells.

HLA-DQ8

- Accounts for much of the remaining HLA-associated disease.
- Performs a related peptide-presentation function.

HLA susceptibility does not establish disease

- HLA-DQ2/DQ8 alleles are susceptibility factors, not a stand-alone diagnosis.
- Environmental exposure and immune responses remain necessary.
- Disease-concordance patterns in twins support additional genetic and nongenetic contributions.
- Absence of both alleles can help exclude celiac disease.

Additional genetic and autoimmune associations

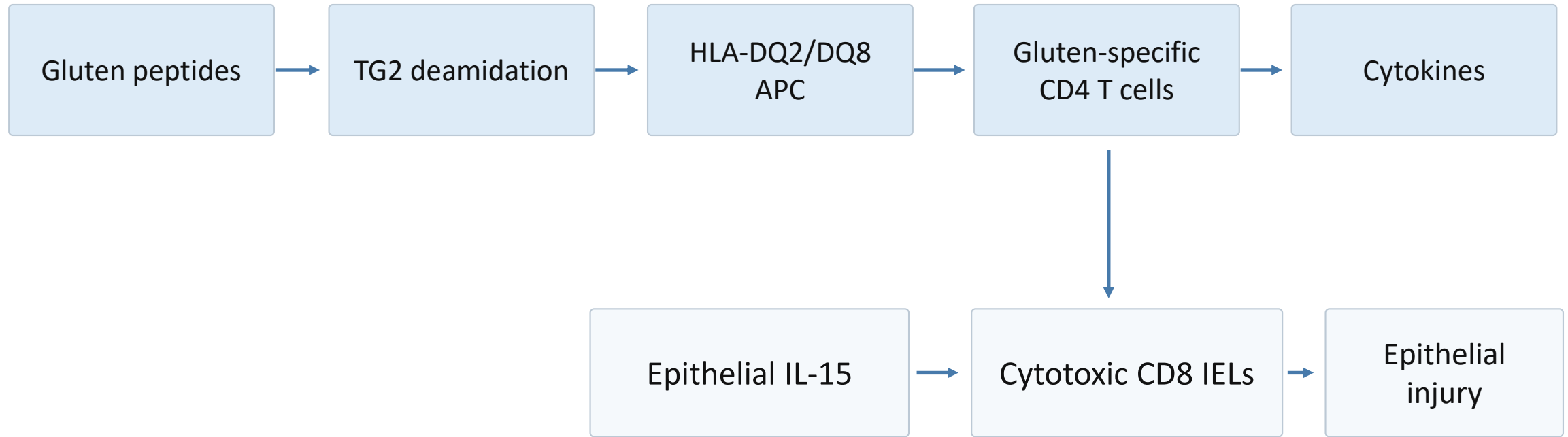
Beyond the main HLA alleles

- Other HLA and non-HLA loci contribute to risk.
- Polymorphisms affect inflammatory and immunoregulatory pathways.

Associated immune disorders

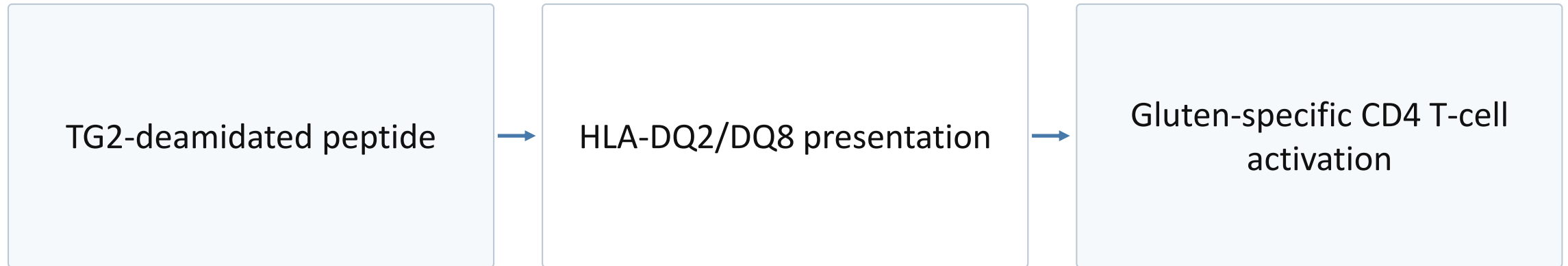
- Type 1 diabetes mellitus
- Autoimmune thyroiditis
- Sjögren syndrome and IgA nephropathy

The initiating antigen-presentation cascade



Parallel epithelial IL-15 and CD4 T-cell help drive the IEL injury arm

Antigen-presenting cells activate CD4 T cells



Recognition of the peptide–MHC complex initiates the adaptive mucosal response.

Cytokines amplify the inflammatory response

- Gluten-responsive CD4 T cells release inflammatory mediators.
- The source highlights IFN- γ , IL-21 and IL-2.
- Cytokine signaling supports mucosal inflammation and lymphocyte responses.
- This immune activation links antigen presentation to tissue injury.

Epithelial IL-15 promotes intraepithelial immunity

IL-15 from intestinal epithelial cells helps expand and activate cytotoxic intraepithelial lymphocytes

- IL-15 operates alongside CD4 T-cell–driven responses.
- The epithelium becomes an active participant in inflammation.
- Expansion of cytotoxic lymphocytes increases epithelial injury.

Intraepithelial CD8 T cells are effectors

- Activated intraepithelial CD8 T cells accumulate among enterocytes.
- These cells can produce IFN- γ and granzyme B.
- They contribute directly to epithelial cell damage.
- Their increase is a key microscopic clue to celiac disease.

Cytotoxic recognition involves innate-like receptors

Effector receptors



NKG2D and NKG2C on activated cytotoxic cells

Epithelial ligands



MICA and HLA-E on intestinal epithelial cells

Functional outcome



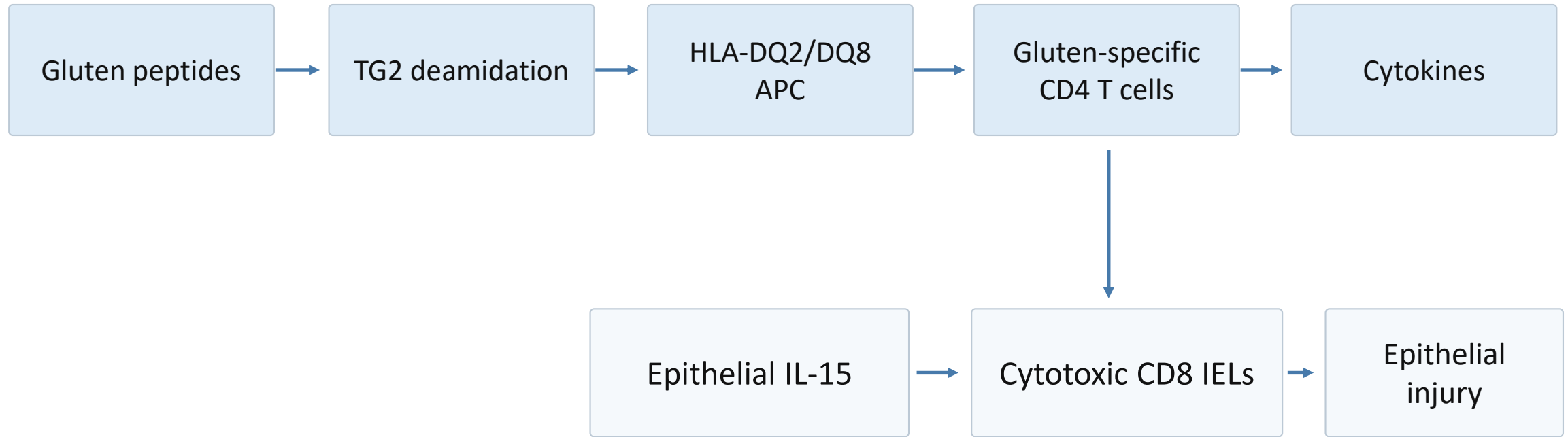
Enhanced recognition and epithelial cytotoxicity

B-cell responses generate anti-TG2 antibodies



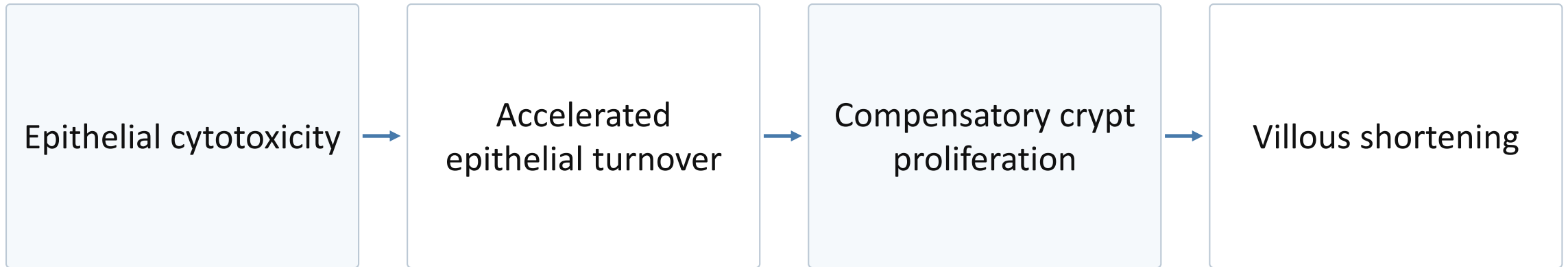
Anti-TG2 antibodies are diagnostically useful markers of the mucosal immune response.

Celiac pathogenesis: Integrated mechanism



Parallel epithelial IL-15 and CD4 T-cell help drive the IEL injury arm

Epithelial injury changes intestinal architecture



Repeated injury and regeneration produce the characteristic mucosal pattern.

Histologic evaluation targets proximal small bowel

- Diagnostic tissue is generally obtained from the second part of the duodenum or proximal jejunum.
- These segments receive high concentrations of dietary gluten.
- Assess villi, crypts, epithelium and lamina propria together.
- Morphologic findings are interpreted with clinical and serologic context.

The classic histopathologic triad

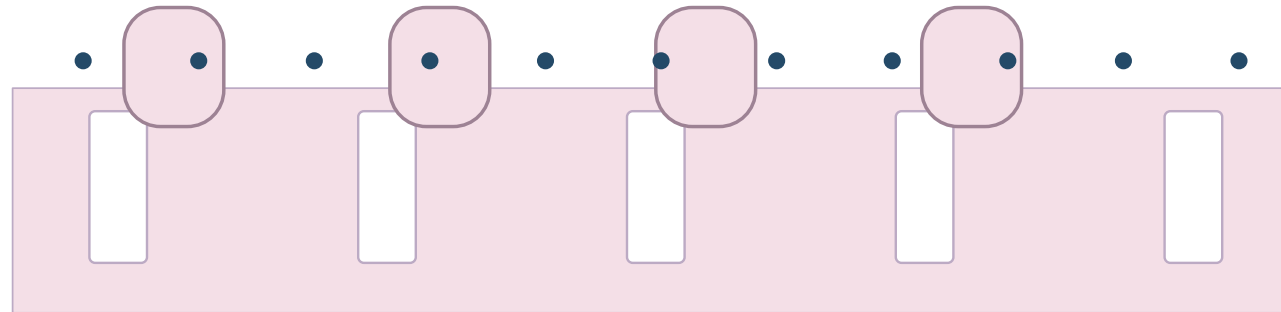
Villous atrophy

Crypt hyperplasia

**Intraepithelial
lymphocytosis**

Increased lamina propria inflammatory cells commonly accompany fully developed disease.

Villous atrophy: Lost absorptive architecture



Shortened absorptive projections; Increased proliferative crypt compartment

Schematic—not a histological specimen

Why villous loss produces malabsorption

Villous shortening



Less mucosal surface in contact with nutrients

Loss of brush border



Reduced terminal digestive capacity

Less mature epithelium



Lower capacity for epithelial transport

Crypt hyperplasia is compensatory

- Injury increases epithelial turnover.
- Crypts become enlarged and proliferative.
- Increased crypt mitotic activity accompanies mucosal regeneration.
- Rapid cell production can limit terminal enterocyte maturation.

Intraepithelial lymphocytosis marks immune injury

- Small CD8 T lymphocytes increase within surface epithelium.
- Lymphocytes lie among larger epithelial cells.
- This finding may appear before marked villous atrophy.
- It reflects activated mucosal immunity but is not specific on its own.

Lamina propria inflammatory expansion

- Plasma cells become prominent in established disease.
- Mast cells and eosinophils may also increase.
- Changes are particularly conspicuous in upper lamina propria.
- These findings support inflammation but do not define celiac disease alone.

Early disease may lack complete villous atrophy

Earlier or subtle injury

- Increased intraepithelial lymphocytes
- Preserved or less severely shortened villi

Fully developed injury

- Marked villous flattening
- Crypt hyperplasia and prominent IELs
- Lamina propria cellular infiltrate

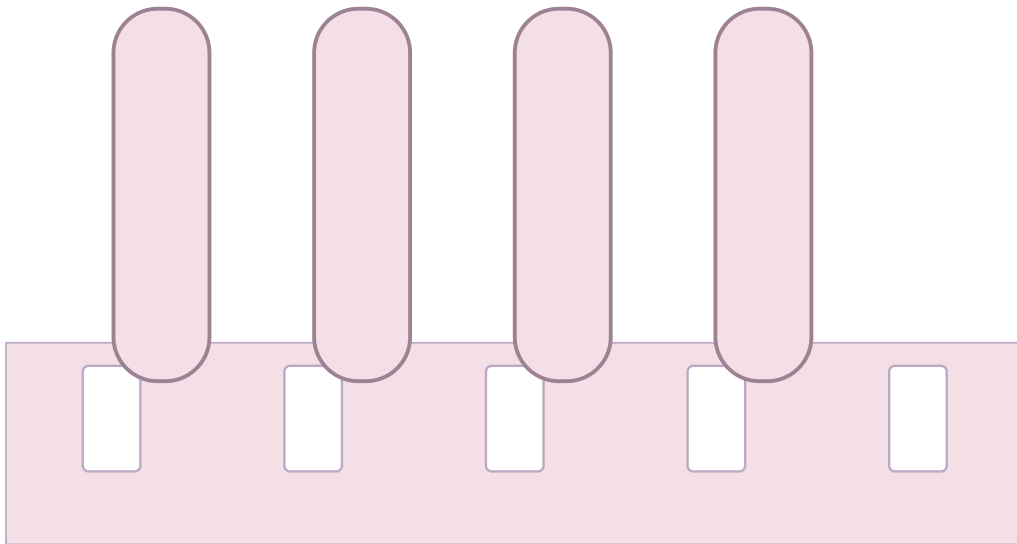
The triad is not pathognomonic

Neither intraepithelial lymphocytosis nor villous atrophy is specific to celiac disease

- Other enteritides, including viral enteritis, may overlap histologically.
- A biopsy alone can be misleading without supporting information.
- Correlate tissue findings with disease-specific serology.

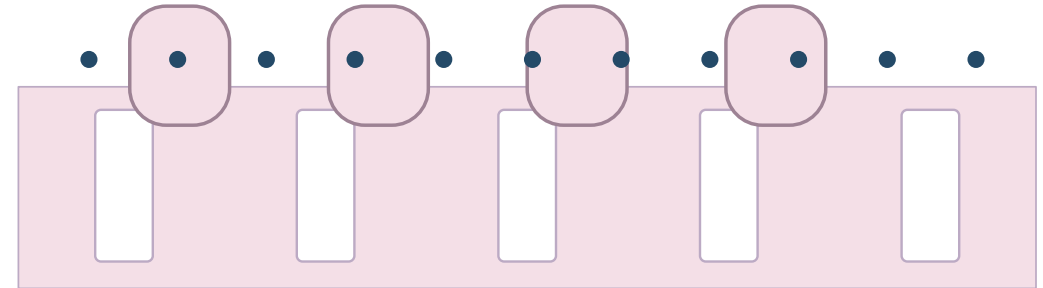
Compare normal and celiac mucosa

Normal mucosal architecture



Tall villi + shorter crypts

Celiac mucosal injury



Shortened villi + crypt hyperplasia + IELs

Schematic—not a histological specimen

Morphology predicts physiologic impairment

Villi become shorter



Absorptive area decreases

Crypts turn over faster



Mature brush-border function decreases

**Epithelial inflammation
persists**



Nutrient transport becomes inefficient

Terminal digestion suffers from epithelial immaturity

Newly generated enterocytes may not develop full brush-border digestive function

- Increased crypt mitoses reflect accelerated turnover.
- Terminal carbohydrate and peptide digestion can be impaired.
- Mucosal structural damage and functional deficits reinforce malabsorption.

Transepithelial transport is compromised

- Intestinal absorptive epithelium is the site of nutrient uptake.
- Villous atrophy decreases functioning epithelial surface.
- Inflammation and rapid turnover impair mature transport capacity.
- Combined defects account for the varied nutritional consequences.

Malabsorption explains gastrointestinal symptoms

**Inadequate nutrient
absorption**



Chronic diarrhea and steatorrhea may occur

**Retained intestinal
contents**



Bloating, distention and flatus

**Persistent negative
nutrient balance**



Weight loss and muscle wasting

Micronutrient deficiency has systemic effects

Deficiency / mechanism	Potential clinical expression
Impaired iron or vitamin absorption	Anemia; fatigue
Calcium and vitamin D deficits	Osteopenia / osteoporosis
Additional nutrient insufficiency	Growth failure; other systemic symptoms
Prolonged intestinal injury	Broader malnutrition phenotype

Adult disease can remain unrecognized

- The source describes common adult recognition between 30 and 60 years of age.
- Presentation ranges from chronic gastrointestinal symptoms to subtle complaints.
- Atypical or asymptomatic disease can escape attention for years.
- Iron-deficiency anemia may be a presenting clue.

The adult symptom spectrum is broad

Gastrointestinal presentation

- Chronic diarrhea
- Bloating
- Weight loss or abdominal discomfort

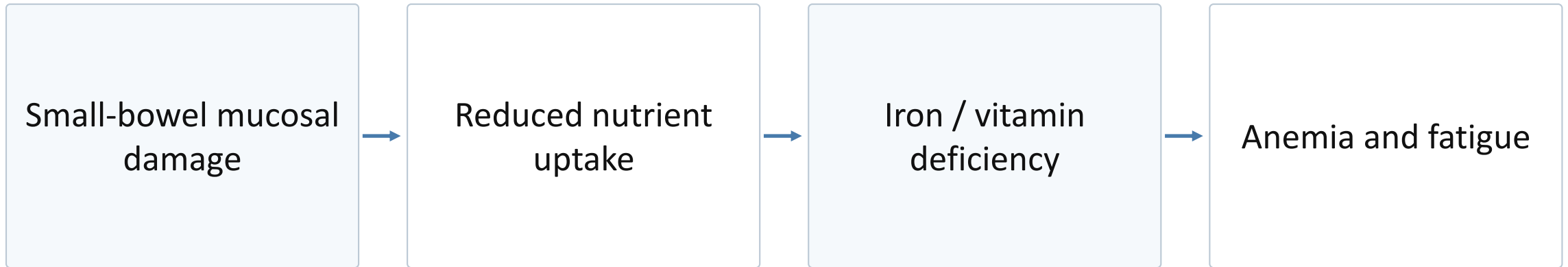
Less obvious presentation

- Fatigue
- Anemia
- Incidental positive disease serology
- No overt symptoms

Silent and latent disease are distinct

Term in Robbins	Serology	Villous atrophy	Symptoms
Silent disease	Positive	Present	Absent
Latent disease	Positive	Absent	May be absent / variable

Anemia may be the first recognized manifestation



Clinical recognition may begin outside gastroenterology.

Dermatitis herpetiformis links skin and gut

- A characteristic itchy, blistering eruption may accompany celiac disease.
- The disease is an extraintestinal manifestation of gluten-related immunity.
- The gastrointestinal phenotype can be clinically subtle.
- The source refers to the dermatology chapter for skin-specific morphology.

Pediatric disease may follow gluten introduction

- Classic pediatric presentation may begin after gluten enters the diet.
- Typical onset between 6 and 24 months in classic cases.
- Young children may develop abdominal distention, irritability and chronic diarrhea.
- Failure to thrive and muscle wasting reflect significant malabsorption.

Nonclassical childhood symptoms delay recognition

Older-child complaints

- Recurrent abdominal pain
- Nausea or vomiting
- Bloating or constipation

Consequences to recognize

- Iron-deficiency anemia
- Short stature
- Delayed puberty
- Arthralgia or aphthous stomatitis

Growth failure is a clinical expression of malabsorption

Reduced nutrient uptake



Insufficient material for growth

**Chronic mucosal
inflammation**



Persisting intestinal dysfunction

**Childhood disease
burden**

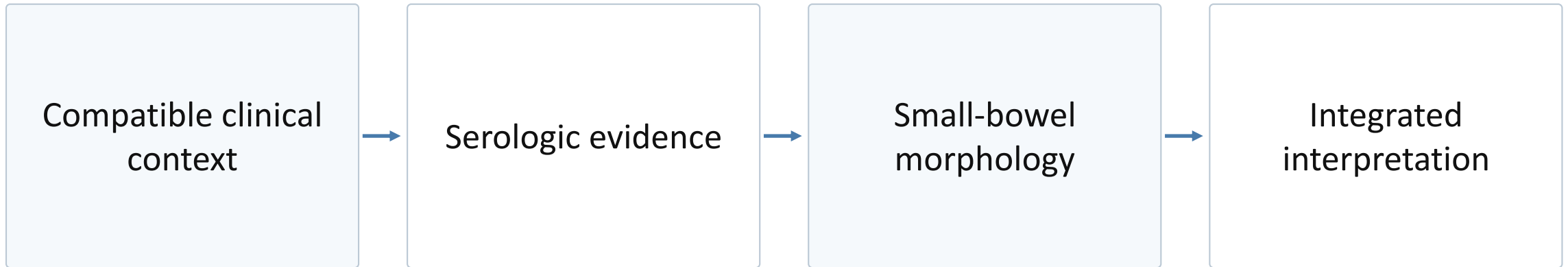


Poor weight gain or short stature

Adult and pediatric patterns are not identical

Dimension	Adults	Children
Clinical recognition	Often atypical or silent	Classic and nonclassical forms
Typical prominent clues	Anemia, bloating, fatigue	Distention, growth impairment, pain
Important extraintestinal clues	Dermatitis herpetiformis, anemia	Short stature, delayed puberty, anemia

Diagnostic reasoning requires concordant evidence



No single morphologic alteration is sufficient in isolation.

Anti-TG2 IgA is the main serologic test

- Noninvasive serology is generally performed before biopsy.
- IgA antibodies to tissue transglutaminase 2 as the most sensitive serologic test.
- An antibody result requires interpretation in its clinical setting.
- Serologic response can also track the effect of dietary gluten exclusion.

Antiendomysial IgA provides additional evidence

- IgA antiendomysial antibodies may be present.
- This is an additional disease-associated serologic marker.
- The result supports the immune-mediated diagnosis alongside other data.
- Serologic markers complement rather than replace careful histopathologic interpretation.

IgA deficiency changes test selection

Suspected celiac disease



Consider the reliability of IgA-based serology

If IgA deficient



IgG anti-tissue transglutaminase may be detected

Interpretation



Integrate with biopsy and clinical features

HLA typing is most useful for exclusion

Both DQ2 and DQ8 absent

- Strongly argues against celiac disease.
- Useful negative predictive information.

DQ2 and/or DQ8 present

- Indicates susceptibility, not certainty.
- Does not independently confirm celiac disease.

Integrating serology with biopsy

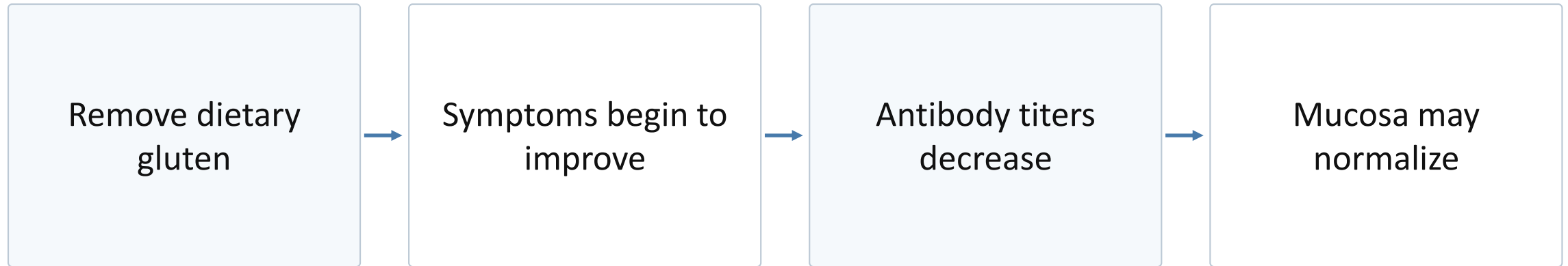
Serologic finding	Biopsy finding	Interpretive caution
Celiac-associated antibodies	Compatible mucosal triad	Joint evidence supports diagnosis
Antibodies without atrophy	May represent latent disease	Avoid equating positive serology with atrophy
IEL increase without specific antibodies	Nonspecific mucosal pattern	Investigate other causes of enteritis

Gluten-free diet removes the driving exposure

Strict dietary exclusion of gluten is the principal treatment

- Withdrawal removes the antigenic trigger.
- Clinical manifestations and anti-TG2 antibody titers typically improve.
- Mucosal structure can recover with time.

Clinical and mucosal recovery are not instantaneous



Normal or near-normal mucosal histology within approximately 6–24 months.

A gluten-free diet may reduce long-term sequelae

- Improvement in nutrient absorption may correct anemia.
- Long-term skeletal complications may become less likely.
- The source identifies potential benefits for female infertility.
- Dietary treatment may also reduce certain malignancy risks.

Refractory sprue changes the clinical question

- Refractory sprue refers to loss of response despite a strict gluten-free diet.
- Persistent or recurrent symptoms demand reassessment.
- Refractory disease can be a precursor to enteropathy-associated T-cell lymphoma.
- Do not assume every recurrence represents inadvertent gluten exposure.

Enteropathy-associated T-cell lymphoma

An aggressive lymphoma arising from intestinal intraepithelial T lymphocytes

- Celiac disease increases its risk.
- The relevant cellular lineage is the cytotoxic intraepithelial T-cell compartment.
- Refractory symptoms warrant attention to this complication.

Small-intestinal adenocarcinoma risk also increases

- Celiac disease is associated with an elevated risk of small-intestinal adenocarcinoma.
- Cancer may present with new or recurrent gastrointestinal complaints.
- Loss of a previously good response to diet requires evaluation.
- The source does not provide a specific individual risk prediction.

Alarm features on a strict gluten-free diet

**Recurrent abdominal
pain**



Consider refractory disease or another process

Persistent diarrhea



Re-evaluate malabsorption and mucosal pathology

Unexplained weight loss



Investigate refractory sprue and malignancy

Villous atrophy has alternative etiologies

Celiac-related pattern

- Villous loss
- Crypt hyperplasia
- Increased intraepithelial lymphocytes

Overlapping conditions

- Viral enteritis may show overlap.
- Other nonceliac enteropathies may alter villi.
- Specific serology and clinical context discriminate.

Compare celiac disease with autoimmune enteropathy

Feature	Celiac disease	Autoimmune enteropathy (neighbor topic)
Main mechanism	Gluten + HLA-associated mucosal immunity	Immune-regulatory defects may predominate
Clinical setting	Adults or children	Often severe childhood diarrhea
Tissue caution	IEL increase; villous atrophy	Overlapping enteropathy; neutrophils may occur

Case 1: Anemia without prominent diarrhea

Hypothetical teaching vignette

An adult with persistent fatigue has anemia. Gastrointestinal symptoms are modest. Celiac-associated serology is positive, and duodenal sampling shows villous shortening with increased intraepithelial lymphocytes.

Which mechanism best connects the biopsy to the anemia?

Case 1: The injury impairs absorption

Mucosal surface loss and immature enterocytes impair nutrient uptake.

- Villous atrophy reduces the functioning absorptive area.
- Crypt hyperplasia accompanies accelerated turnover of immature epithelium.
- The combination can cause nutrient deficiency even without florid diarrhea.

Case 2: Symptoms despite dietary treatment

Hypothetical teaching vignette

A patient with established celiac disease previously improved on a strict gluten-free diet but now develops recurrent abdominal pain, persistent diarrhea and weight loss despite continued adherence.

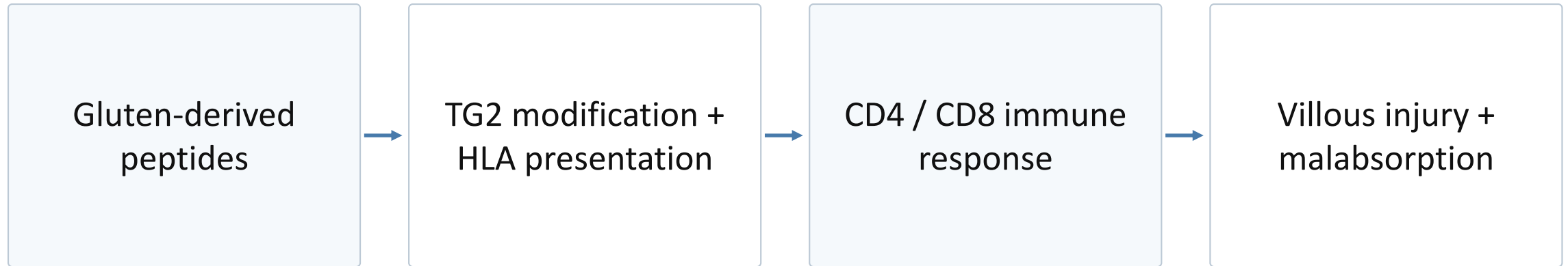
What important complications must be considered?

Case 2: Reassess for refractory disease or cancer

Refractory sprue and malignancy are important considerations.

- Refractory sprue represents a loss of clinical response to gluten exclusion.
- Enteropathy-associated T-cell lymphoma is an aggressive associated malignancy.
- Small-intestinal adenocarcinoma is another recognized cancer risk.

The causal chain in one view



Understanding the immune mechanism explains both biopsy changes and clinical phenotype.

Morphology and diagnosis: Final synthesis

Villous atrophy

Crypt hyperplasia

**Intraepithelial
lymphocytosis**

Increased lamina propria inflammatory cells commonly accompany fully developed disease.

Source and visual attribution

- Primary text: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th edition (2026).
- The malabsorption framework and autoimmune-enteropathy comparison use adjacent textbook sections.
- Original native PowerPoint schematics depict conceptual mechanisms and mucosal architecture—not clinical specimens.
- No textbook figures or clinical micrographs were reproduced.