the Evaluation and Management of Enteropathies

Introduction

- **The small intestine it contains the largest part of**
- **the human immune system.**
- **The continuous exposure to the external environment**
- **necessitates the intestinal immune system to differentiate**
- **between innocuous and harmful antigens**
- **leads to tolerance or the mounting of an immune response**

Immune-mediated enteropathies (IME)

- **Excessive reactions of the intestinal immune system**
- **towards non-pathogenic molecules**
- **lead to immune-mediated enteropathies (IME).**
- **Such a response may lead to destruction of mucosal**
- **surface which eventually results in the clinical signs of**
- **a malabsorption syndrome.**

Immune Mediated Enteropathy

- **The spectrum of immune mediated enteropathies**
- **with Chronic or refractory diarrhea**
- **has expanded, over the last decades**
- **Celiac disease (CD) has long been recognized as**
- **the most of both a food intolerance and autoimmune**
- **disorder**

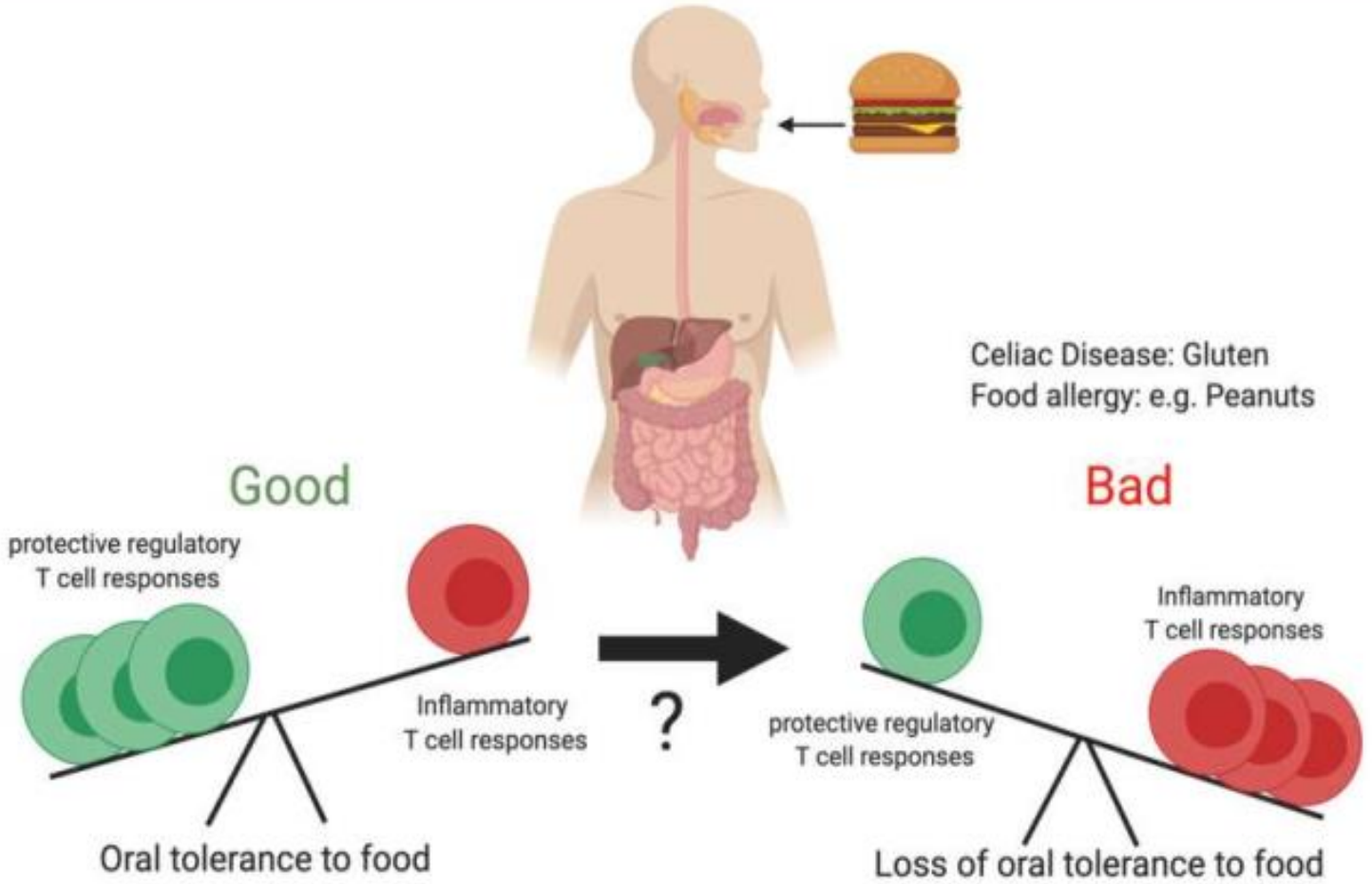
the various enteropathies can be challenging.

- **In addition to CD, Other condition can mimic the clinical,**
- **pathologic features of enteropathy , such as,**
- **autoimmune enteropathy (AIE),**
- **common variable immunodeficiency disease (CVID)**
- **tropical sprue, Whipple disease,**
- **human immunodeficiency enteropathy,**
- **drug induced enteropathy,**

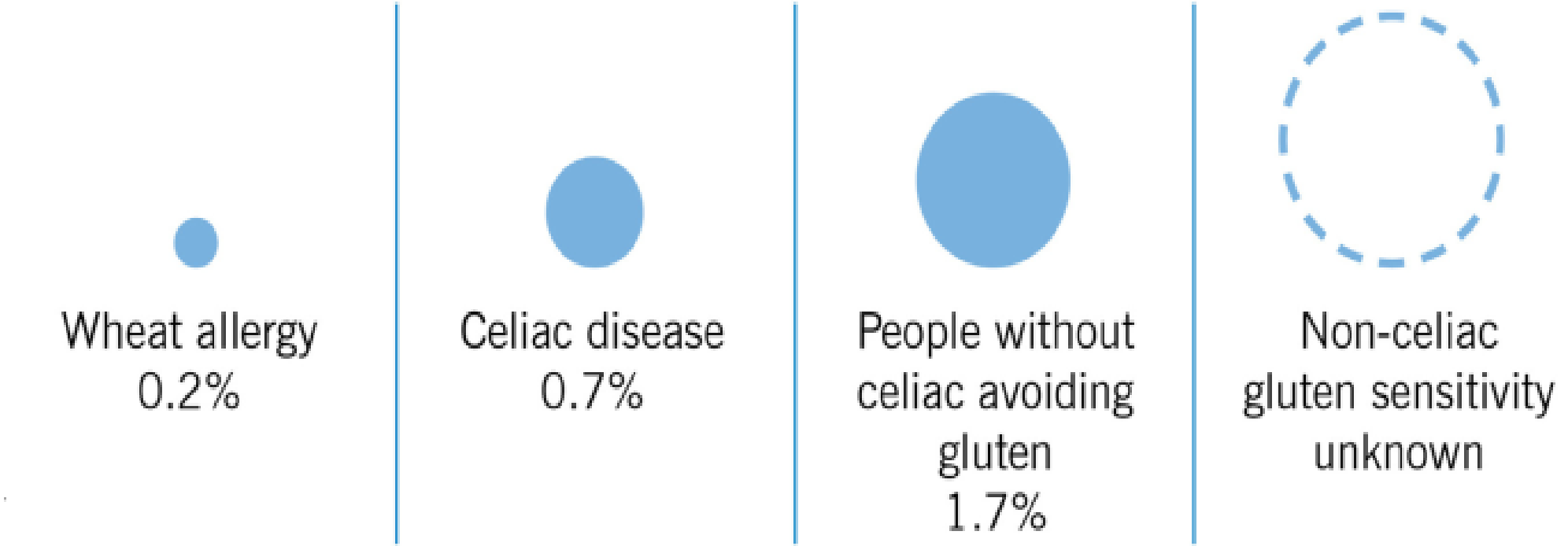
challenging as IME

- **Differentiating between IME can be challenging as**
- **these diseases can partially overlap in clinical,**
- **serological and histological presentation.**
- **Recognition in an early phase is however important to**
- **Adequately initiate appropriate treatment to prevent**
- **further disease, and possibly treatment related complications.**

What causes loss of oral tolerance to dietary antigens?

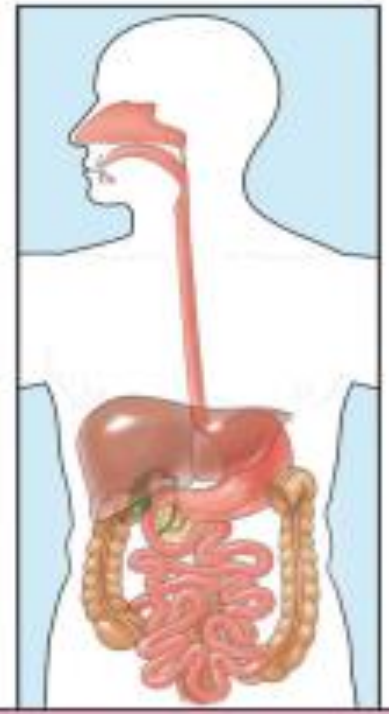


Gluten-related disorders prevalence



Non-celiac gluten sensitivity

- Bloating
- Diarrhea
- Constipation
- Abdominal pain
- Nausea
- Vomiting
- Fatigue
- Abdominal cramping
- Gas
- Altered bowel habits
- Foggy mind
- Mental confusion
- Headache
- Fibromyalgia-like arthralgia or myalgia
- Tingling extremities
- Skin rash
- Depression
- Anxiety
- Arm or leg numbness
- Anemia



Wheat allergy

- Anaphylaxis
- Nasal itching and swelling
- Oropharyngeal itching and swelling
- Wheezing
- Urticaria
- Angioedema
- Asthma
- Allergic rhinitis
- Flushing
- Chest tightness
- Acute exacerbation of atopic dermatitis
- Abdominal pain
- Vomiting
- Headache
- Nausea
- Abdominal cramping
- Diarrhea

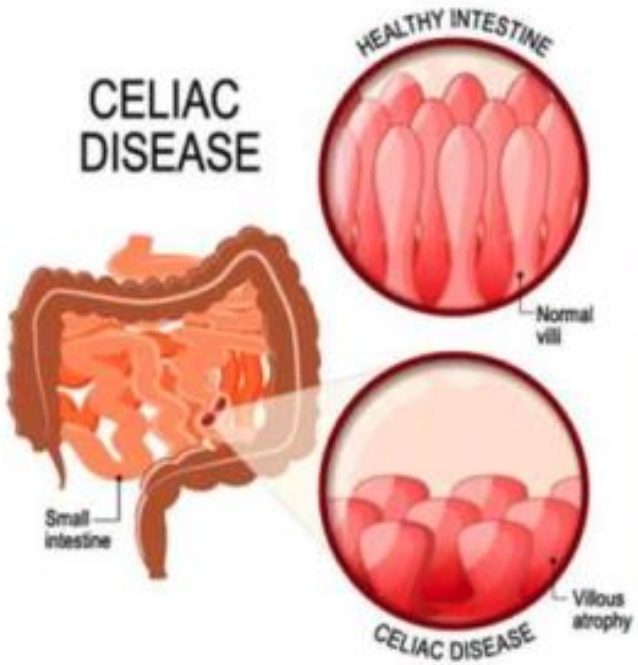
Celiac disease

- Diarrhea
- Steatorrhea
- Weight loss
- Failure to thrive
- Poor growth
- Iron deficiency anemia
- Malabsorption of fat and nutrients
- Vitamin deficiencies
- Dermatitis herpetiformis
- Abnormal liver tests
- Osteoporosis
- Peripheral neuropathy
- Constipation
- Fatigue
- Abdominal cramping
- Arthralgia
- Bone fractures
- Ataxia
- Gas
- Bloating
- Abdominal pain

Figure 1. Symptoms of gluten-related disorders.

Celiac disease: gluten-induced autoimmunity and intestinal destruction





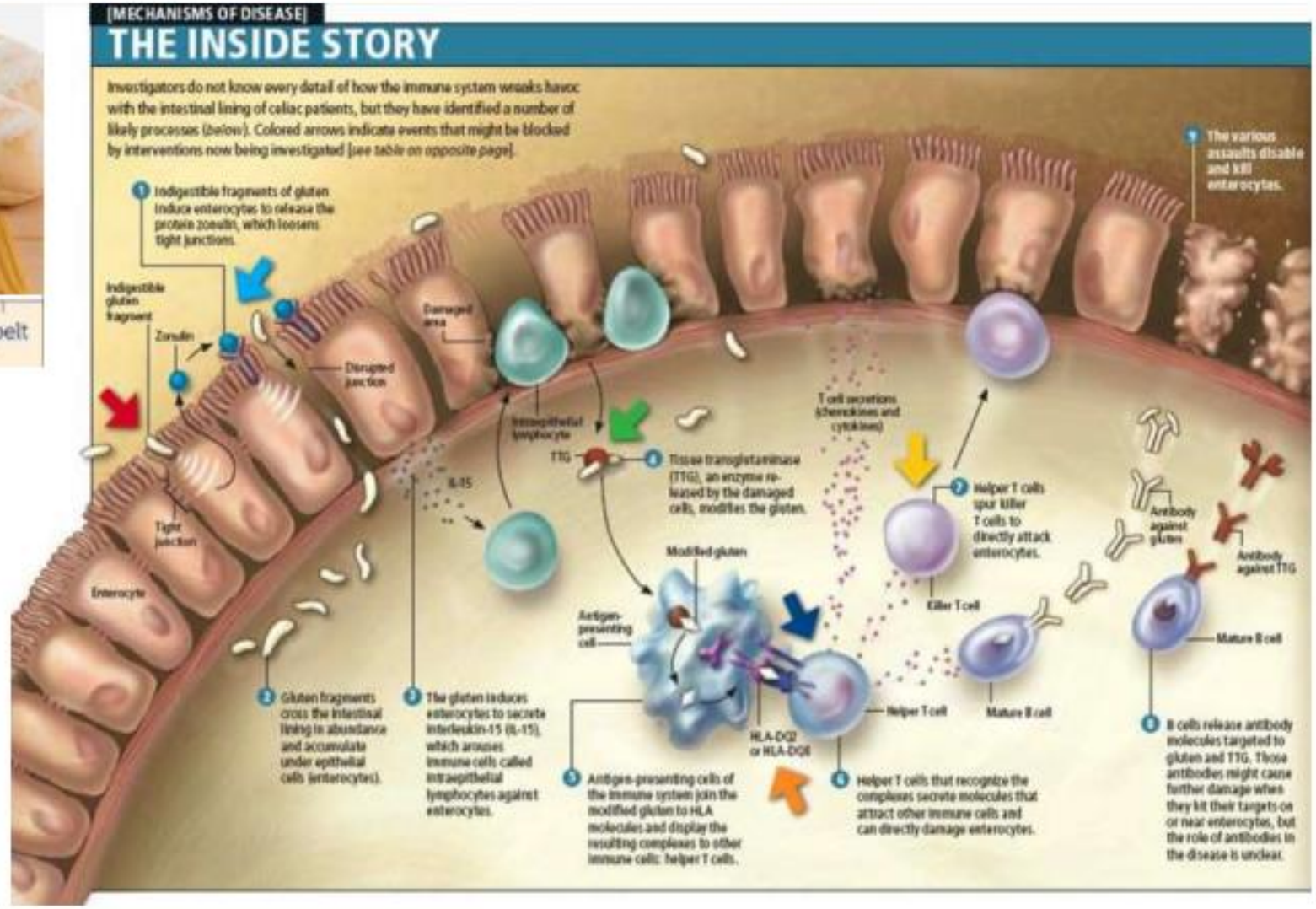
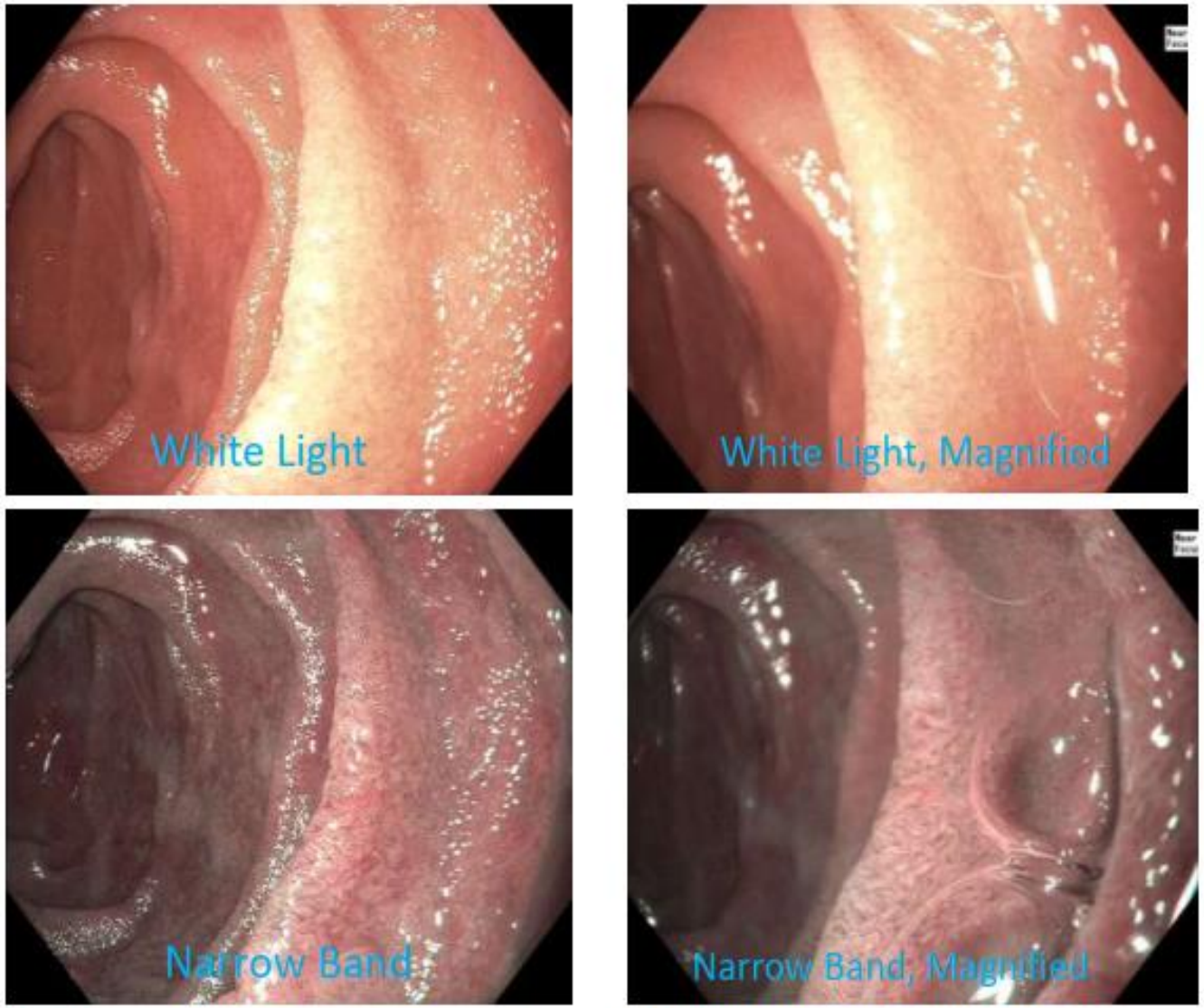


Table 1. Etiologies of Seronegative Villous Atrophy

Etiology
Immune-mediated
Serongative CeD
Common variable immune deficiency
Autoimmune enteropathy
Intestinal lymphoma
Sarcoidosis
Infectious
Parasitic infections (*Giardia lamblia*)
Tropical sprue/environmental enteropathy
Whipple disease
Small intestinal bacterial overgrowth
Tuberculosis
HIV enteropathy
Iatrogenic
Medications
Olmesartan
Azathioprine
Mefenic acid
Methotrexate
Mycophenolate mofetil
Chemotherapy
Graft vs host disease
Radiation enteritis
Transplanted small intestine
Inflammatory
Crohn's disease
Collagenous sprue
Eosinophilic enteritis

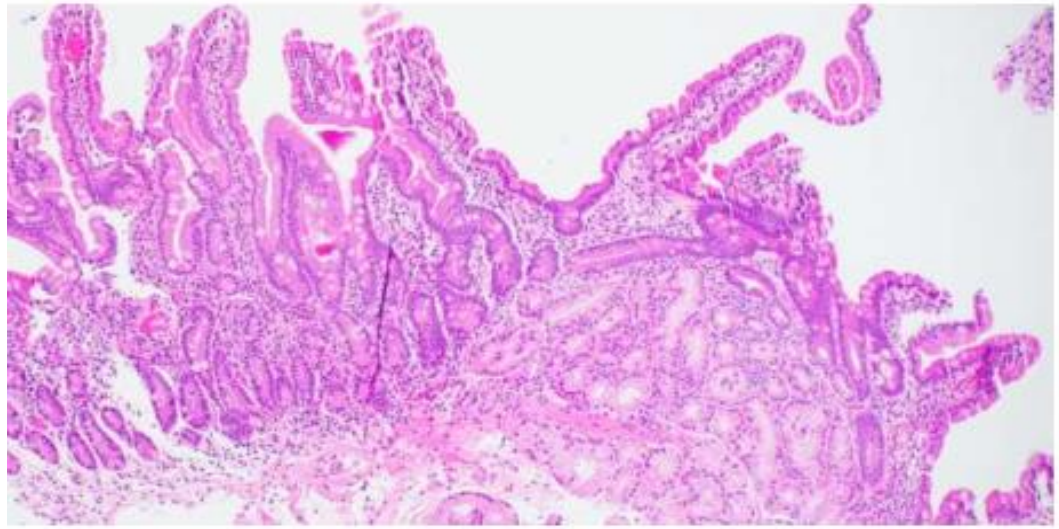
Endoscopy of the 2nd Part of the Duodenum (normal)

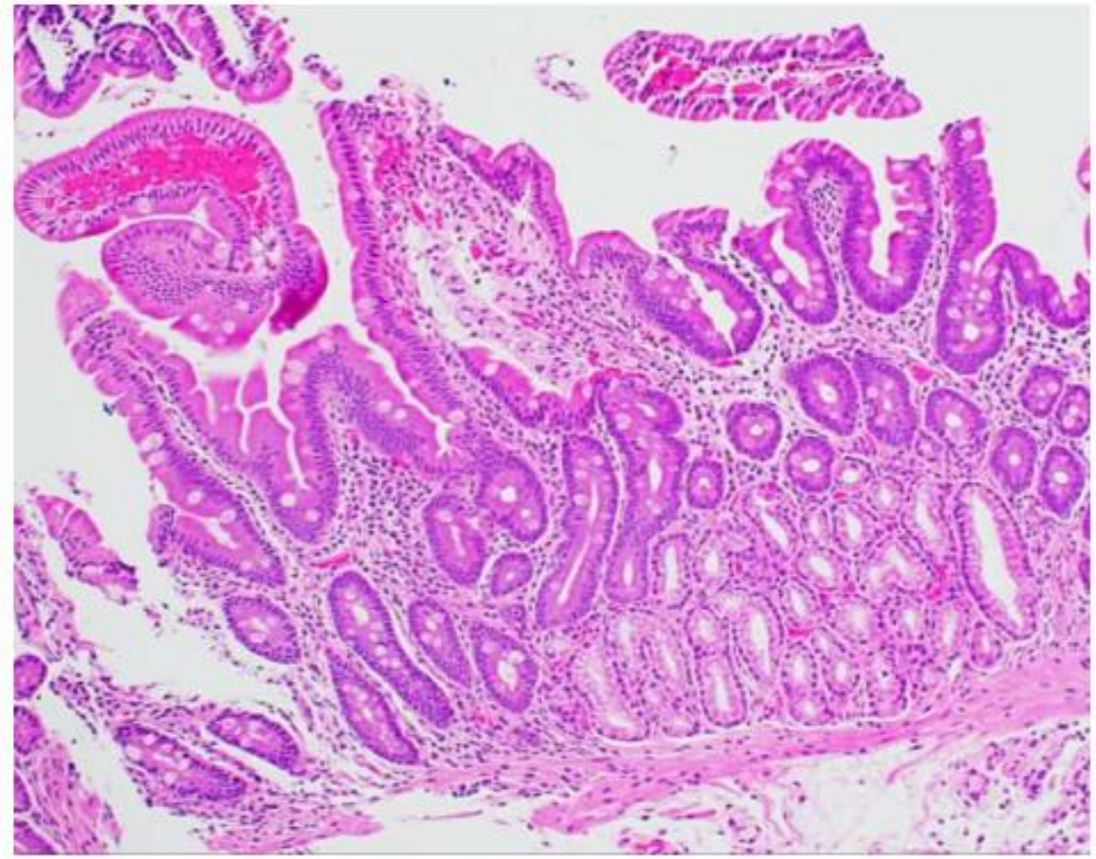


NewYork-Presbyterian
Columbia University Medical Center

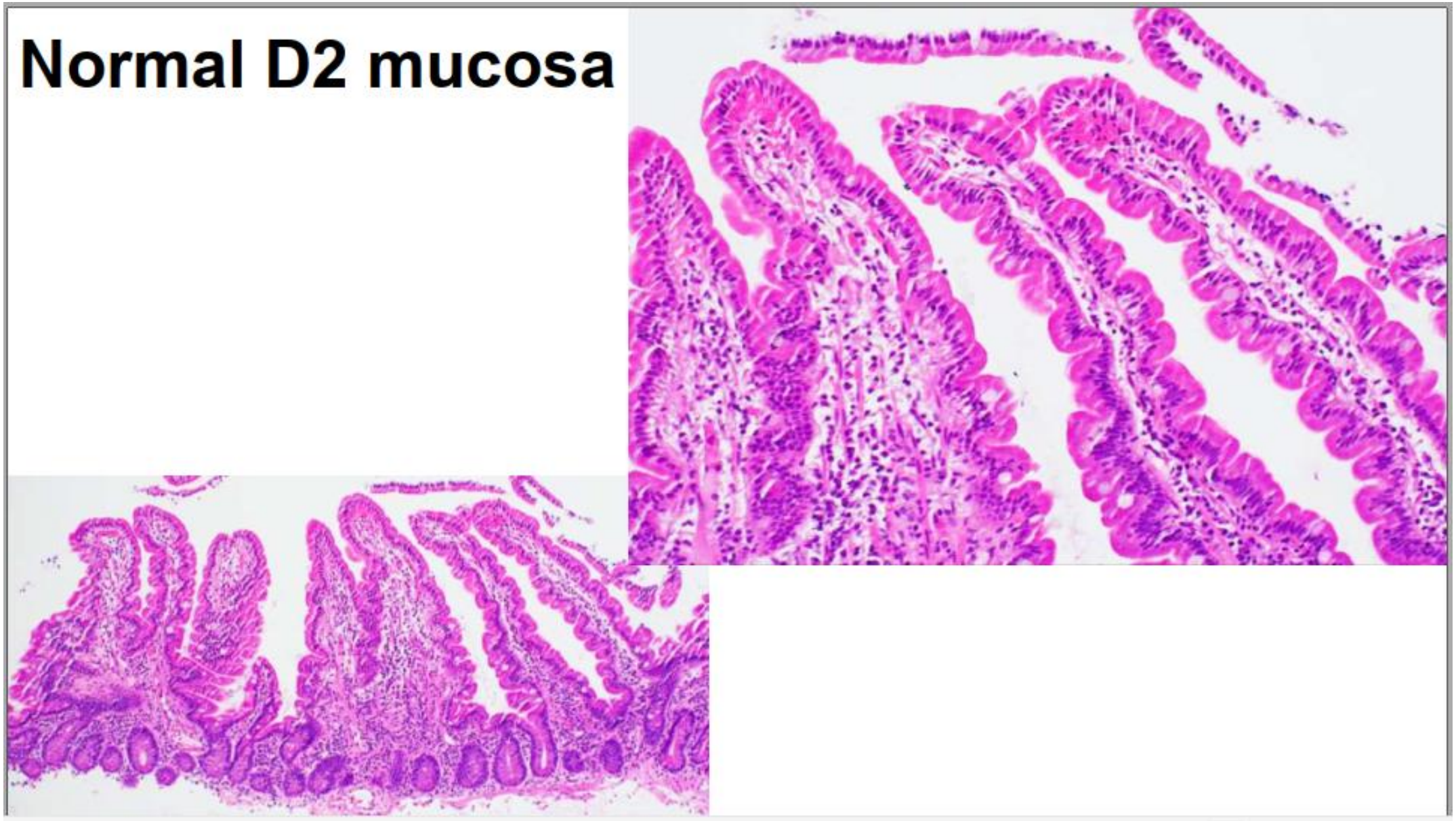
Liu X and Shen B. DDW 2024

Normal duodenal bulb mucosa

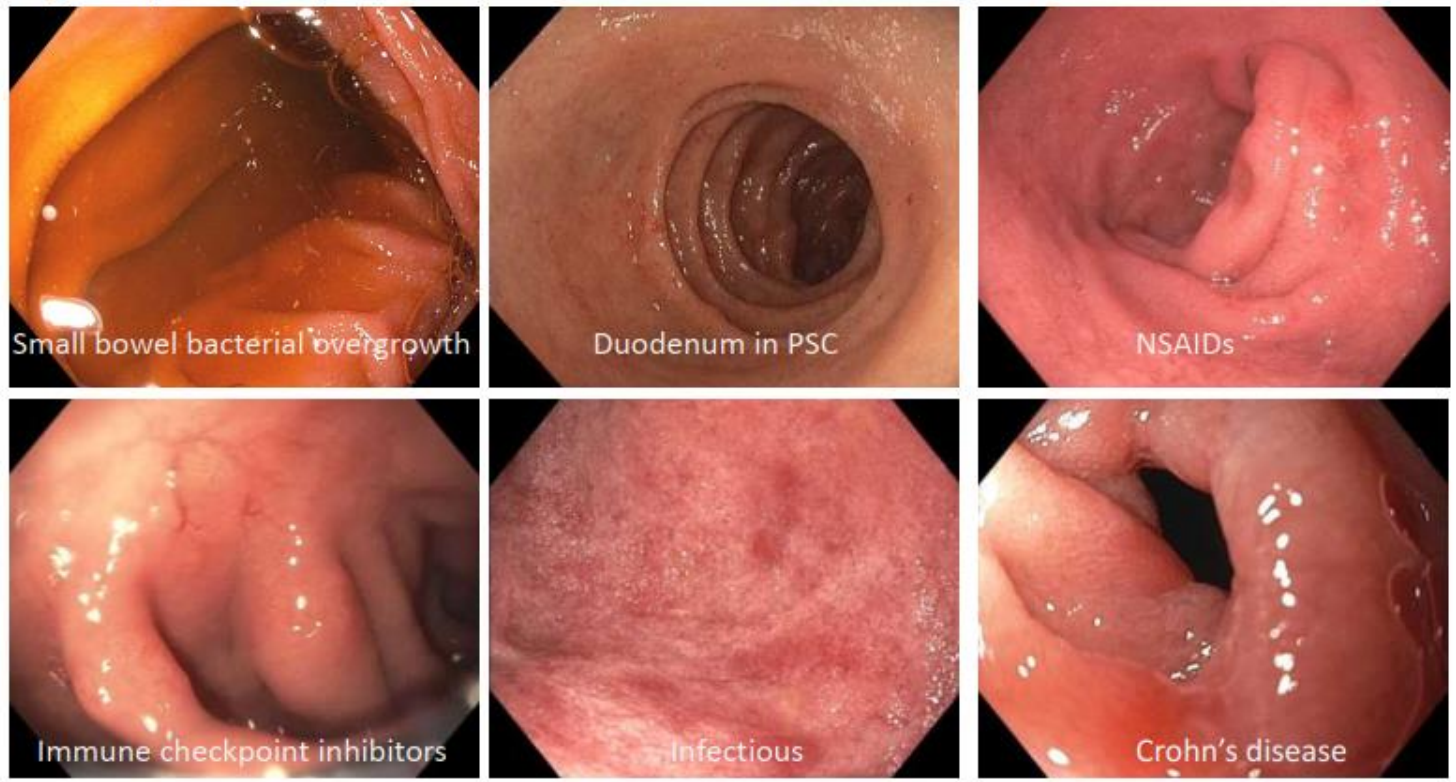




Normal D2 mucosa



Not All Villous Atrophy and Intraepithelial Lymphocytosis Result from Celiac Disease



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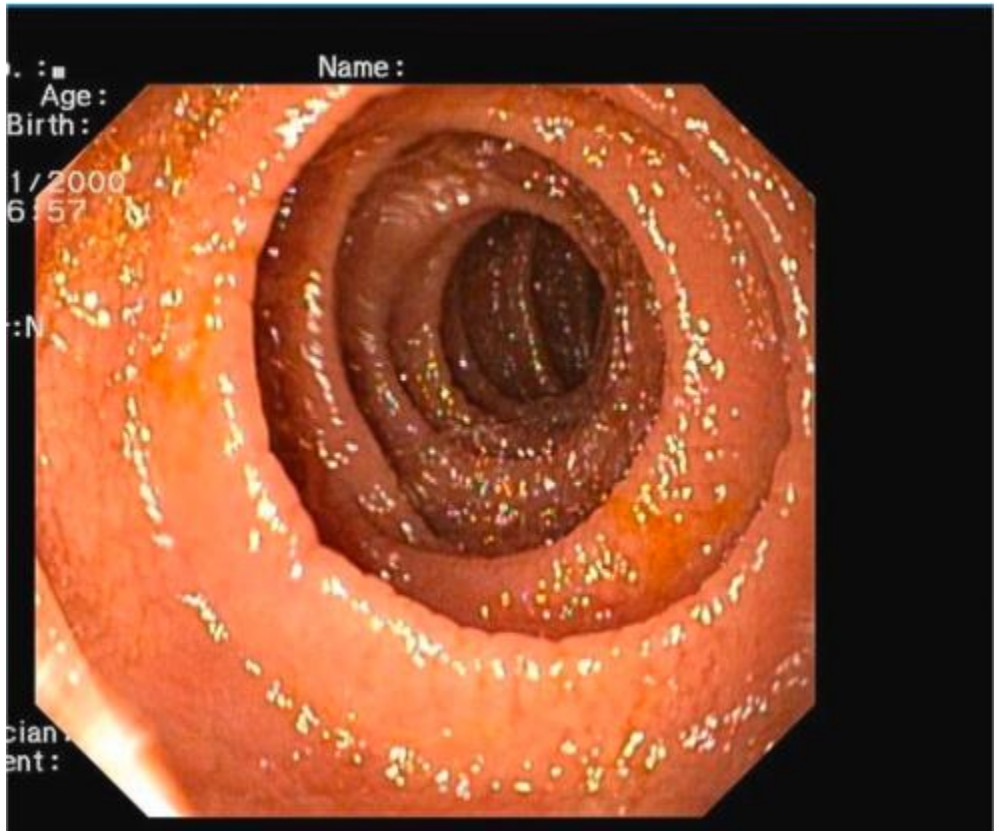
“Scalloping”



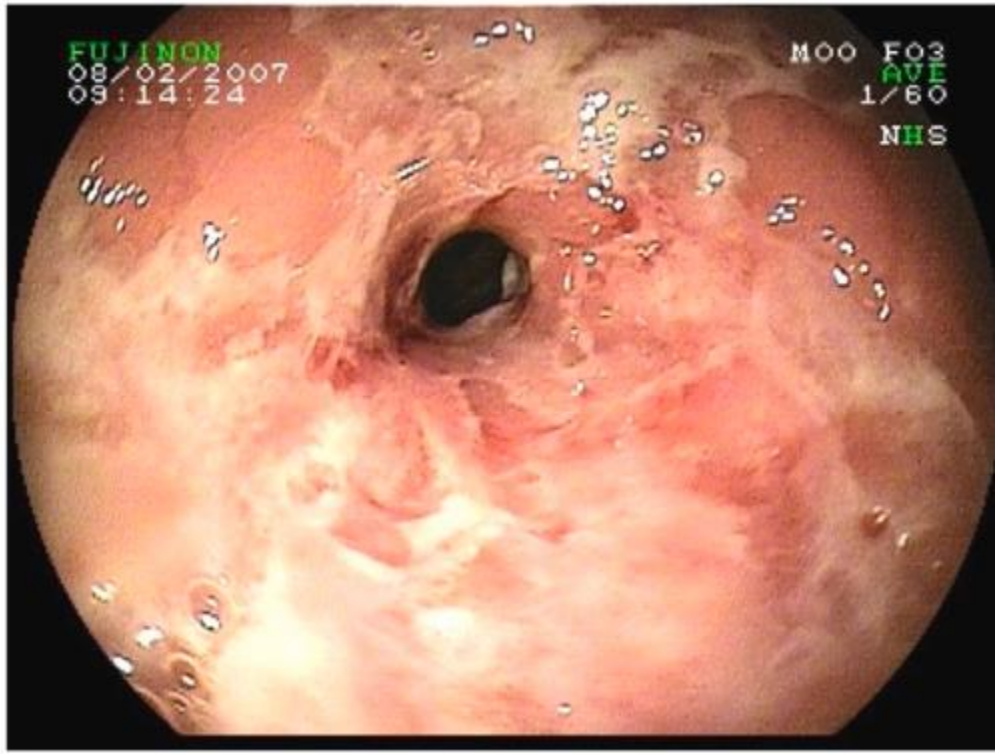


Shen B (Ed). Pouchitis and Ileal Pouch Disorders. Academic Press 2019

the duodenum in a patient with celiac disease displays mucosal cracks and scalloping folds



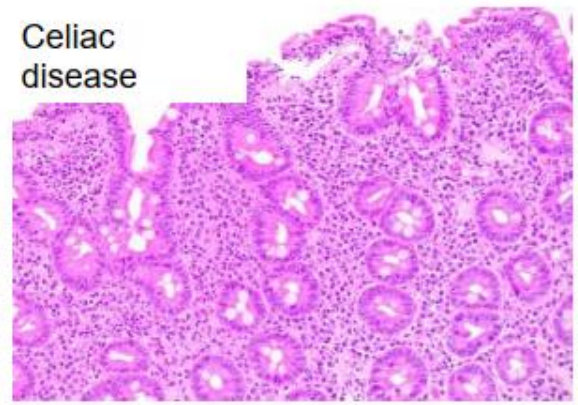
The duodenum in a patient with refractory celiac disease type II jejunitis with stenosis



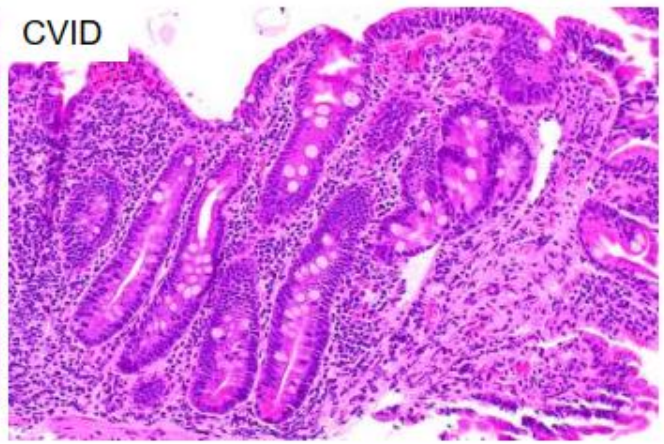
Not all villous blunting and intraepithelial lymphocytosis result from celiac disease



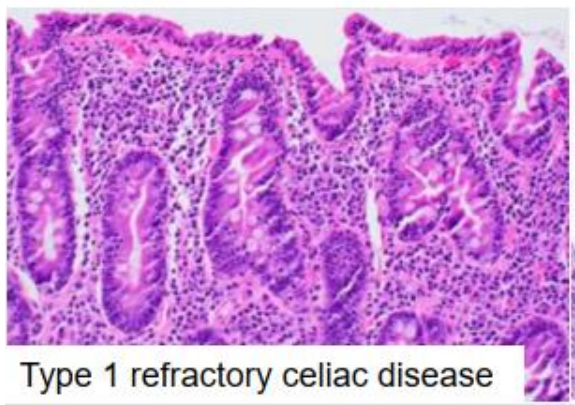
Tropical sprue



Celiac disease



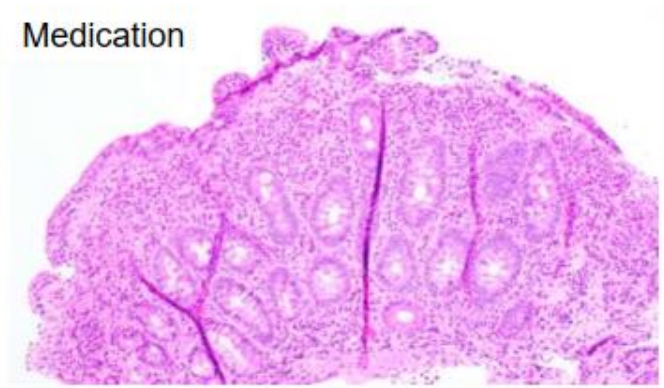
CVID



Type 1 refractory celiac disease

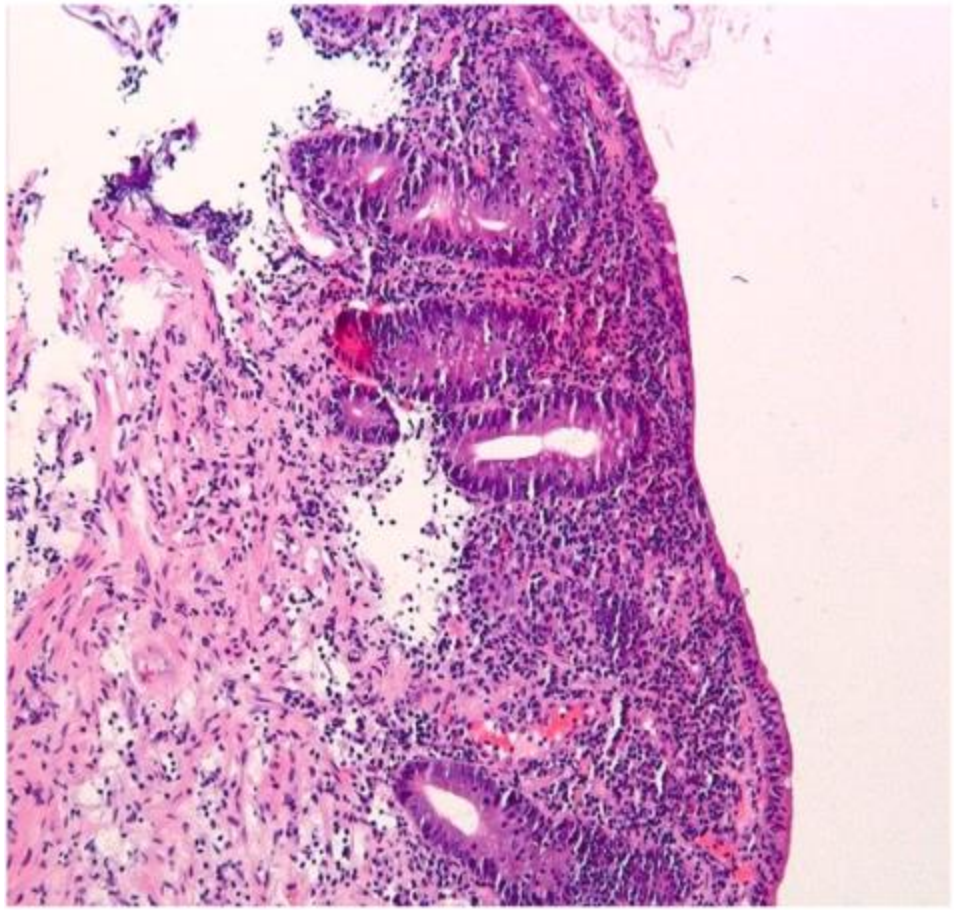


Type 2 refractory celiac disease

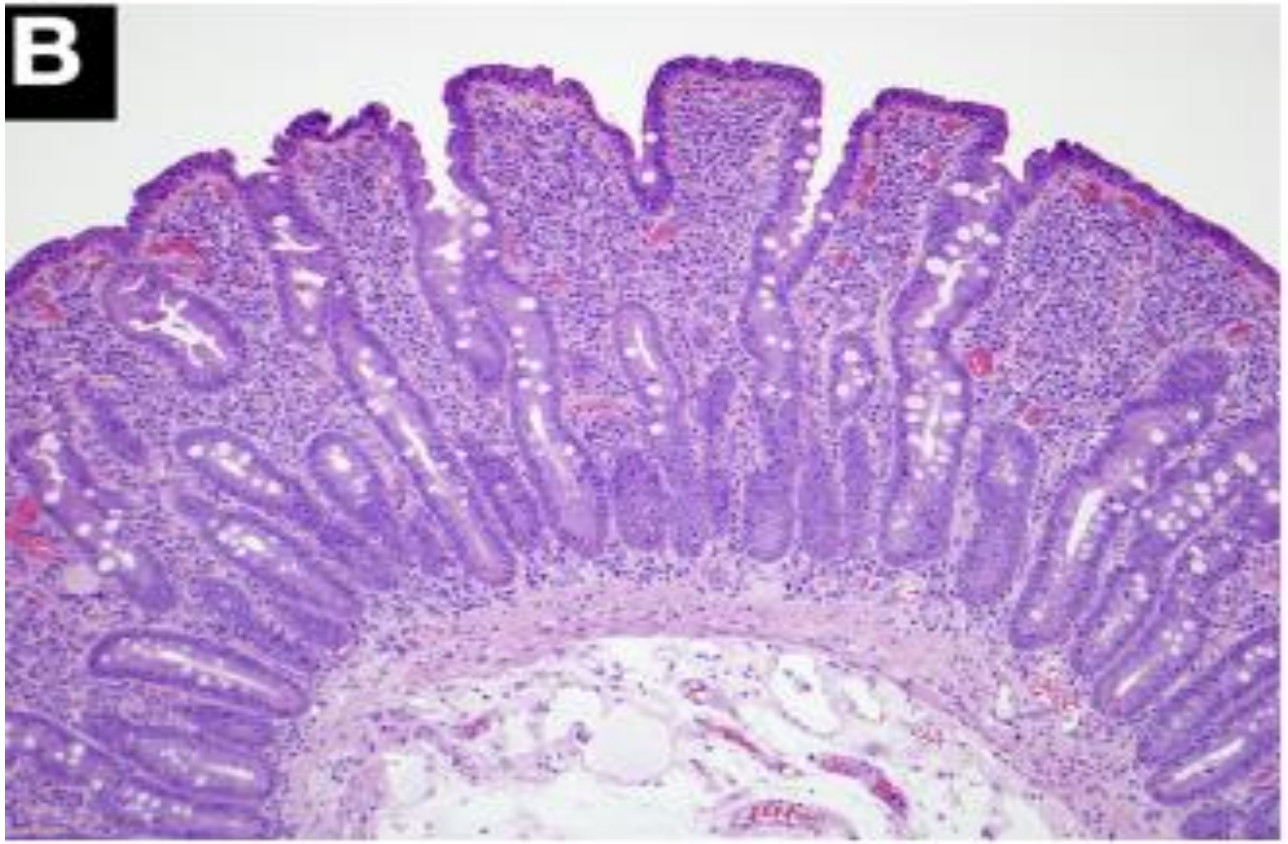


Medication

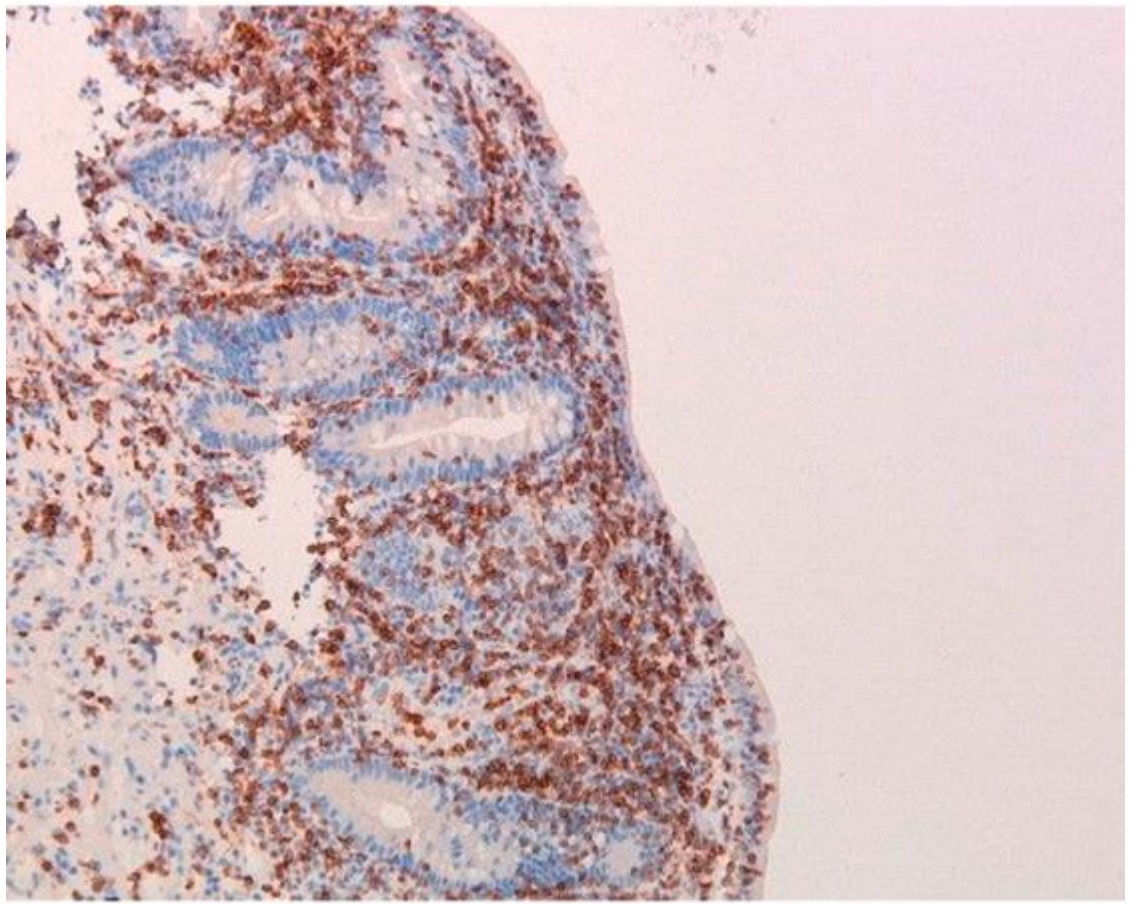
Hematoxylin and eosin stain of duodenal biopsy shows complete villous atrophy, crypt hyperplasia and intra-epithelial lymphocytosis (Marsh 3C)



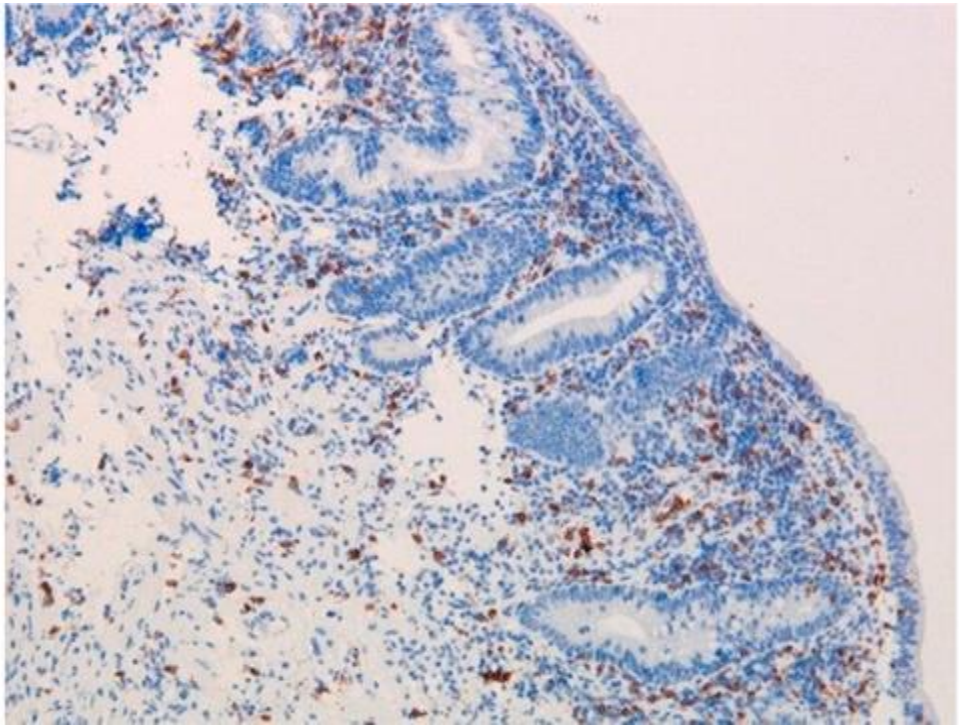
Duodenal Biopsy in refractory celiac type 1
Villous atrophy, increase intra-epithelial lymphocytes

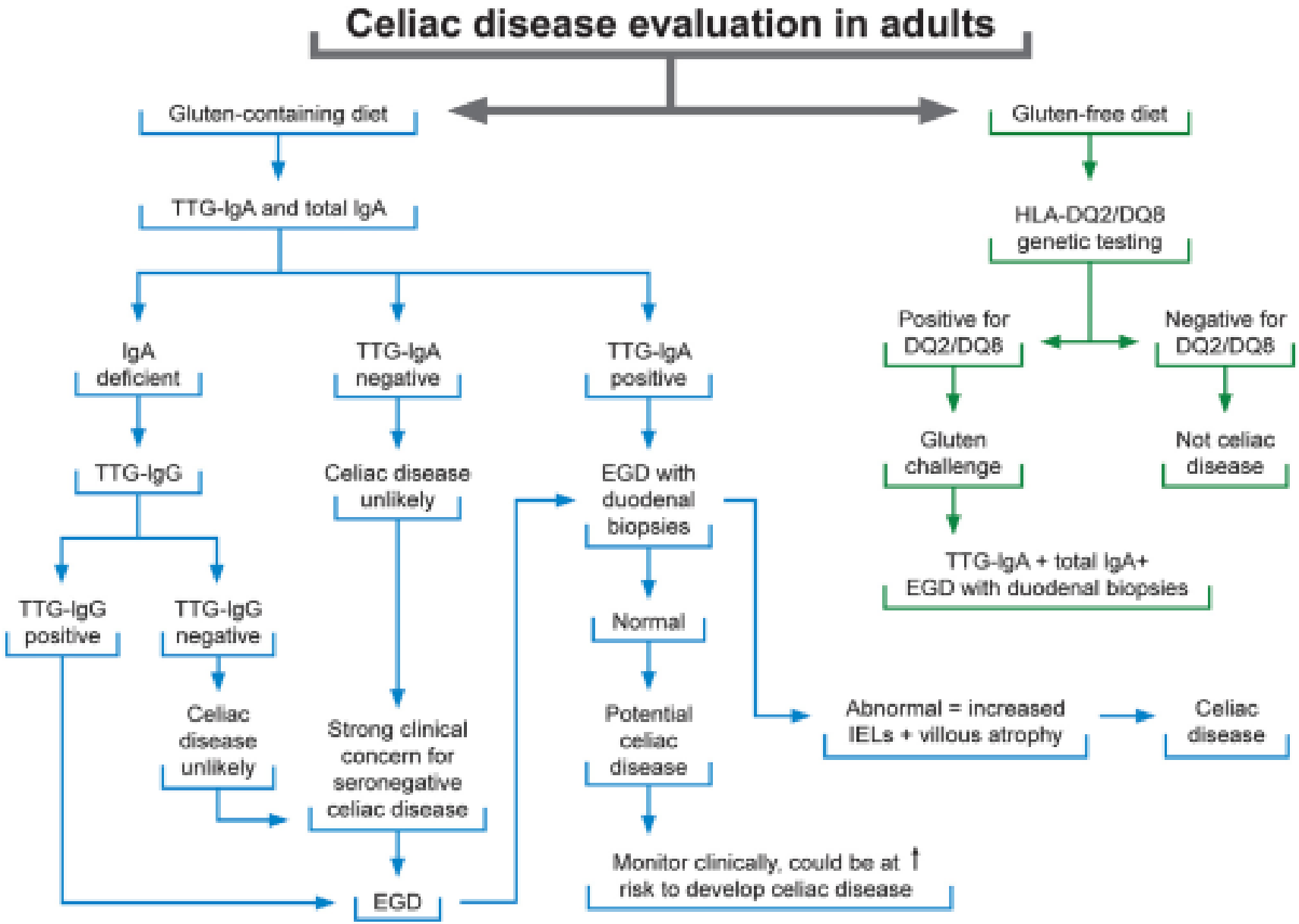


Refractory celiac disease
Same duodenal biopsies stained with CD3 and CD8



abundant expression of CD3 but not CD8 on intraepithelial lymphocytes, (premalignant) aberrant lymphocyte population in accordance with refractory celiac disease type II




Celiac disease evaluation in adults
Gluten-containing diet
Gluten-free diet
TTG-IgA and total IgA
HLA-DQ2/DQ8 genetic testing
IgA deficient
TTG-IgA negative
TTG-IgA positive
Positive for DQ2/DQ8
Negative for DQ2/DQ8
TTG-IgG
Celiac disease unlikely
EGD with duodenal biopsies
Gluten challenge
Not celiac disease
TTG-IgA + total IgA+ EGD with duodenal biopsies
TTG-IgG positive
TTG-IgG negative
Normal
Celiac disease unlikely
Strong clinical concern for seronegative celiac disease
Potential celiac disease
Abnormal = increased IELs + villous atrophy
Celiac disease
EGD
Monitor clinically, could be at † risk to develop celiac disease

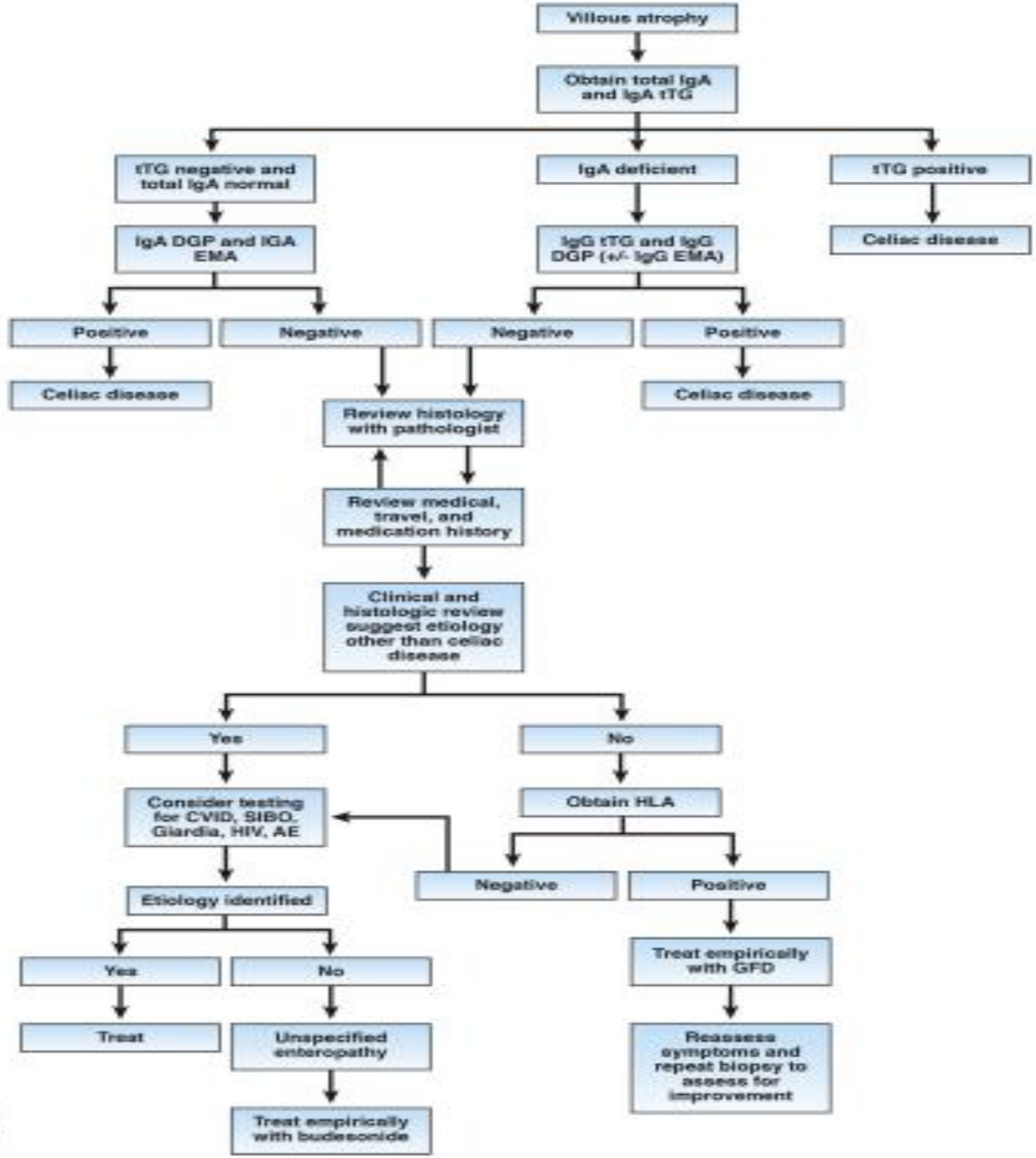


Figure 1. Approach to the patient with seronegative villous atrophy.

Histologic diagnoses

- Normal histology
- Celiac disease
- Collagenous sprue
- Intraepithelial lymphocytosis with preserved villous architecture
- Chronic active duodenitis
- Focal active duodenitis
- Granulomatous inflammation
- Erosion/ulceration
- Presence of infectious organisms
- Lack of plasma cells
- Lack of goblet cells and/or Paneth cells and/or endocrine cells



Etiologies/entities

- Celiac disease, refractory celiac disease (type 1, type 2)
- IBD (UC, Crohn's disease), post-colectomy enteritis
- Medications/drugs
  - NSAIDs, PPI, -sartan, ICIs
- Autoimmune enteropathy
- Lymphoproliferative disorders
- Stasis with bacterial overgrowth, infections
- Food allergy
- Systemic autoimmune disease
- Immunodeficiency
- Trauma, ischemia, etc.
- Idiopathic

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AUTOIMMUNE ENTEROCOLITIS

Clinical

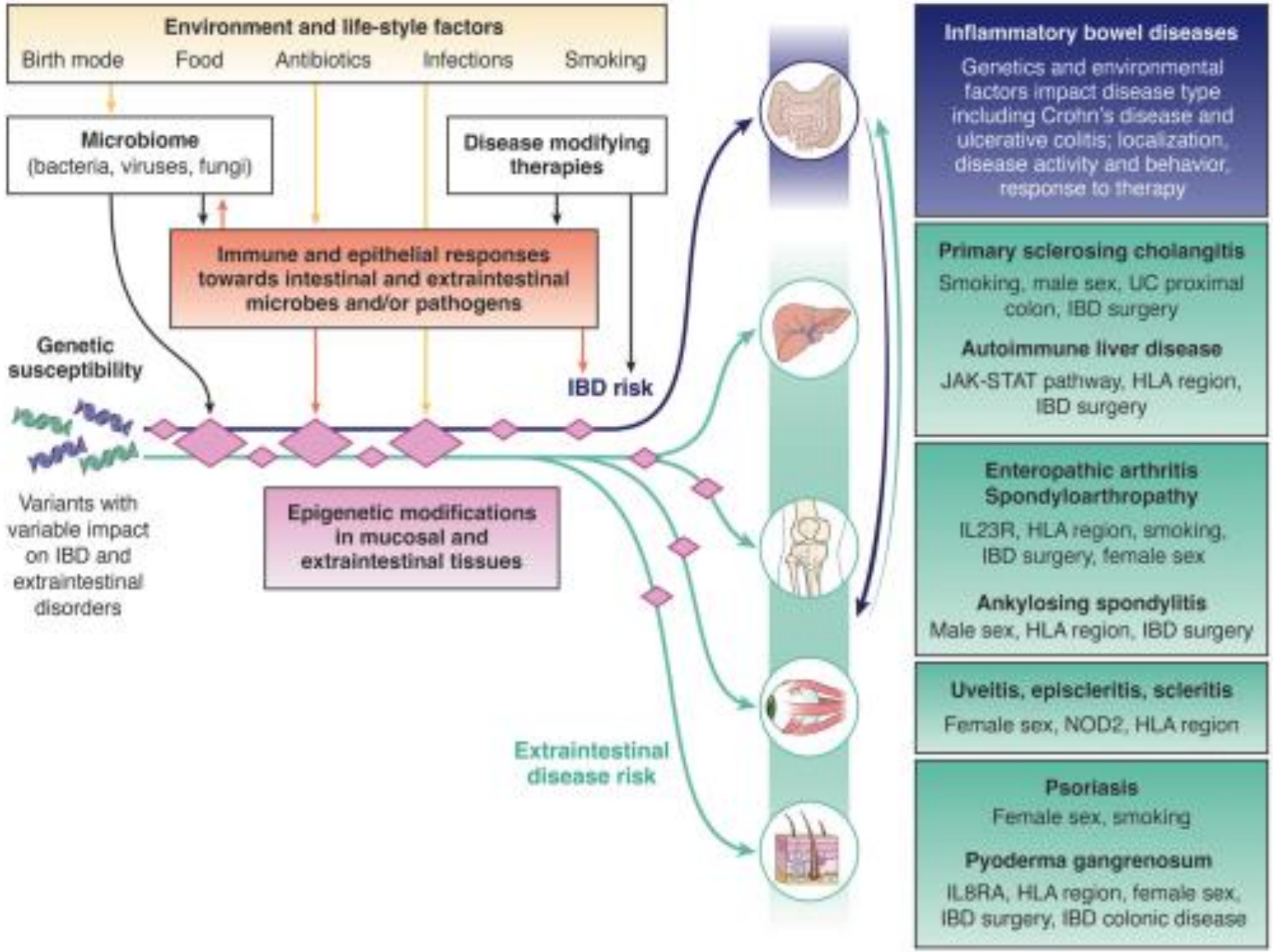
- These are difficult diagnoses that can go on for years
- Again collaboration with Pathology colleagues is needed
- Input from other specialties (hematology, rheumatology, and gastroenterology)
- Autoimmune diseases don't have to be exclusive

Pathology

- Variable histologic patterns. Loss of goblet cells, Paneth cells, endocrine cells possible. Active chronic enteritis pattern has broader differential.

Autoimmune Enteropathy

- **A rare condition ,more common among infants and**
- **Children than among adults.**
- **It can occur as a primary process or due to another**
- **immune-mediated process.**
- **Symptoms include chronic diarrhea, malabsorption, weight loss.**
- **Extraintestinal manifestations include hemolytic anemia,**
- **nephritis, dermatitis, Thyroiditis and hepatitis**
- **have also been reported as autoimmune enteropathy.**


Environment and life-style factors
Birth mode
Food
Antibiotics
Infections
Smoking
Microbiome
(bacteria, viruses, fungi)
Disease modifying therapies
Immune and epithelial responses towards intestinal and extraintestinal microbes and/or pathogens
Genetic susceptibility
IBD risk
Variants with variable impact on IBD and extraintestinal disorders
Epigenetic modifications in mucosal and extraintestinal tissues
Extraintestinal disease risk
Inflammatory bowel diseases
Genetics and environmental factors impact disease type including Crohn's disease and ulcerative colitis; localization, disease activity and behavior, response to therapy
Primary sclerosing cholangitis
Smoking, male sex, UC proximal colon, IBD surgery
Autoimmune liver disease
JAK-STAT pathway, HLA region, IBD surgery
Enteropathic arthritis
Spondyloarthropathy
IL23R, HLA region, smoking, IBD surgery, female sex
Ankylosing spondylitis
Male sex, HLA region, IBD surgery
Uveitis, episcleritis, scleritis
Female sex, NOD2, HLA region
Psoriasis
Female sex, smoking
Pyoderma gangrenosum
IL6RA, HLA region, female sex, IBD surgery, IBD colonic disease

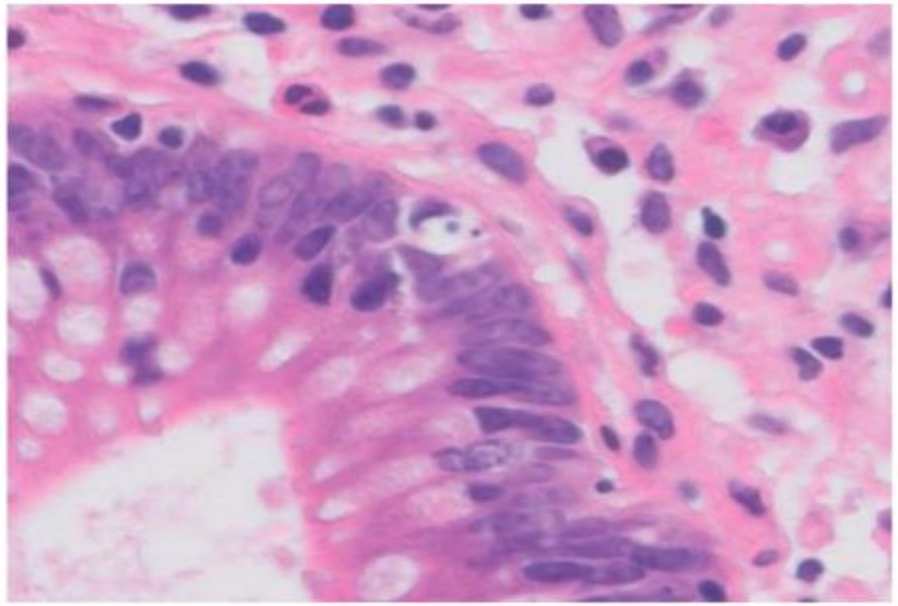
The etiology ,immunopathogenesis of adult-onset AIE

- **not known, but it is generally believed that immune dysregulation,**
- **Similar to that seen in the genetic syndromes in children,**
- **is responsible for the immunopathology in adult AIE.**
- **models, blockade of PD-L1, the ligand of the immune**
- **checkpoint regulator PD-1, leads to the development of**
- **Autoimmune enteritis, with T-cell infiltration, apoptosis of**
- **epithelial cells, and blunting of villi, which is reminiscent of**
- **that seen in human AIE.**

Definitions Of AIE

- **Adult AIE was defined as follows:**
- **(1) adult-onset protracted diarrhea (>6 weeks) not responsive to any dietary exclusion;**
- **(2) associated with specific small-bowel histology villous atrophy, minimal intraepithelial lymphocytes [IEL], increased crypt apoptotic bodies, or absence of goblet or Paneth cells**
- **(3) systematic exclusion of other causes of villous atrophy**

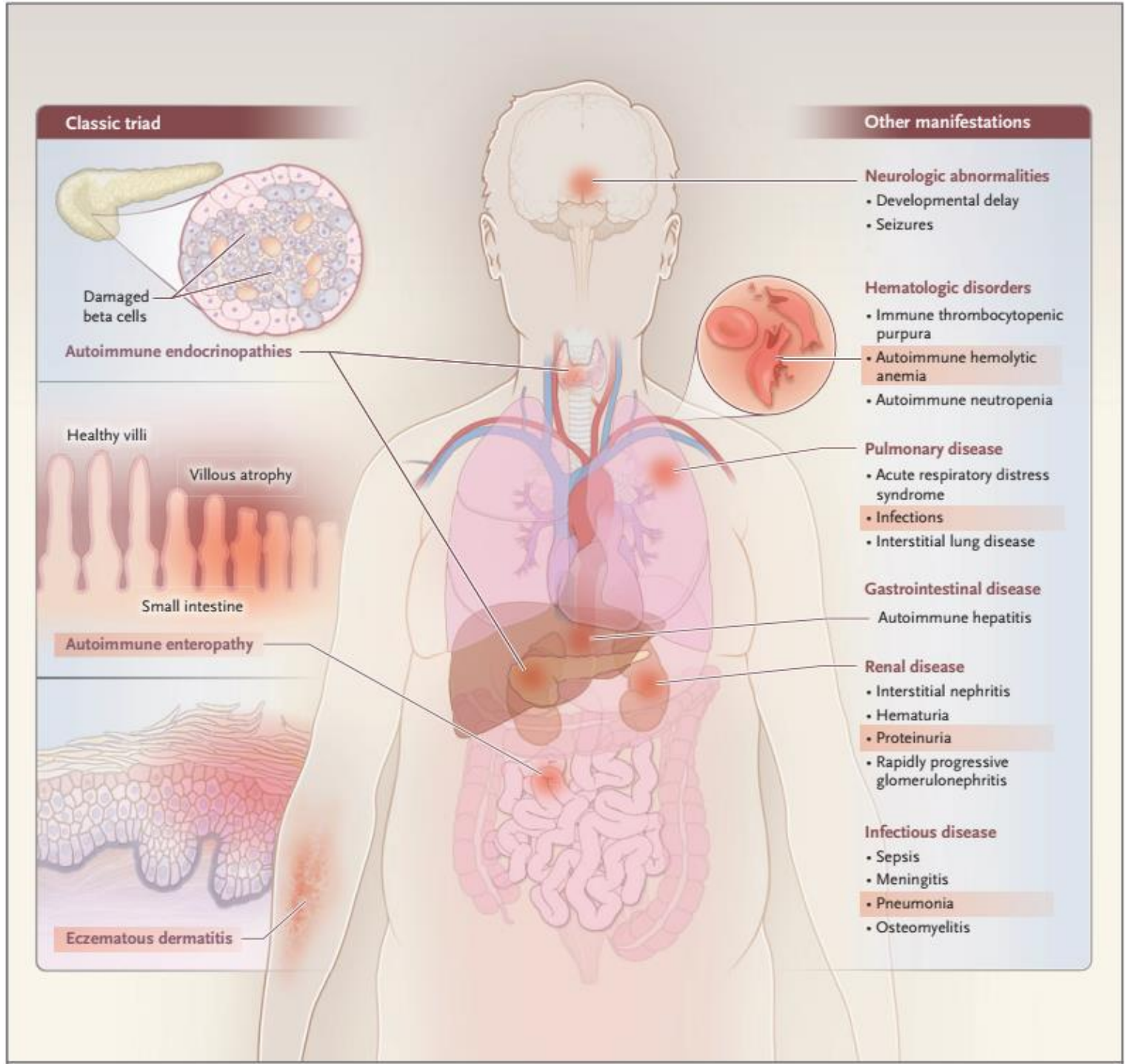
Hematoxylin and eosin staining of a duodenal biopsy with autoimmune enteropathy displaying apoptotic bodies.



AIE with Genetic Syndromes

- **The incidence of AIE in children is low, in the order of magnitude of**
- **0.1 per 100,000.**
- **AIE can occur in the context of identified genetic syndromes,**
- **the IPEX-syndrome (immune dysregulation, polyendocrinopathy,**
- **enteropathy, X-linked)**
- **caused by loss of function mutations in the FOXP3 gene on**
- **the X chromosome.**
- **The IPEX syndrome occurs only in males, whereas females are asymptomatic carriers**

- FOXP3 is widely expressed in CD4+/CD25+ subsets of T-cells and
- encodes for a transcription factor critical for the development and
- Function of regulatory T-cells.
- In addition to the gastrointestinal manifestations, insulin-dependent
- diabetes mellitus, hemolytic anemia, and eczema are characteristic
- features whereas thrombocytopenia, hypothyroidism, and
- glomerulonephritis can also occur.


Classic triad
Damaged beta cells
Autoimmune endocrinopathies
Healthy villi
Villous atrophy
Small intestine
Autoimmune enteropathy
Eczematous dermatitis
Other manifestations
Neurologic abnormalities
• Developmental delay
• Seizures
Hematologic disorders
• Immune thrombocytopenic purpura
• Autoimmune hemolytic anemia
• Autoimmune neutropenia
Pulmonary disease
• Acute respiratory distress syndrome
• Infections
• Interstitial lung disease
Gastrointestinal disease
Autoimmune hepatitis
Renal disease
• Interstitial nephritis
• Hematuria
• Proteinuria
• Rapidly progressive glomerulonephritis
Infectious disease
• Sepsis
• Meningitis
• Pneumonia
• Osteomyelitis

- Most children with IPEX receive hematopoietic stem cell
- transplants and one adult patient with therapy refractory
- disease was successfully treated with autologous stem cell
- transplantation
- So far, two patient with adult onset AIE have developed an EATL

Diagnosis of AIE

- **Due to the non-specific features of AIE, diagnosis is frequently**
- **delayed and patients may be initially misdiagnosed.**
- **The similarities with celiac disease can be particularly challenging.**
- **Adult AIE is often initially misdiagnosed as**
- **refractory CD (RCD), leading to delay in diagnosis,**
- **needless continuation of gluten-free diet (GFD).**
- **With similar presentations, how these 2 immune-mediated**
- **enteropathies fundamentally differ from each other is**
- **unclear.**

- Diarrhea in adult cases of AIE can be extremely voluminous
- And frequent. The diarrhea is persistent and non-bloody and
- is associated with significant weight loss and malabsorption.
- The duodenum is most commonly affected but involvement of
- stomach and colon have been described in 86% and 64% of cases,
- Similar to the pediatric population, adults with AIE can also suffer
- from other autoimmune conditions such as rheumatoid arthritis ,
- thymoma

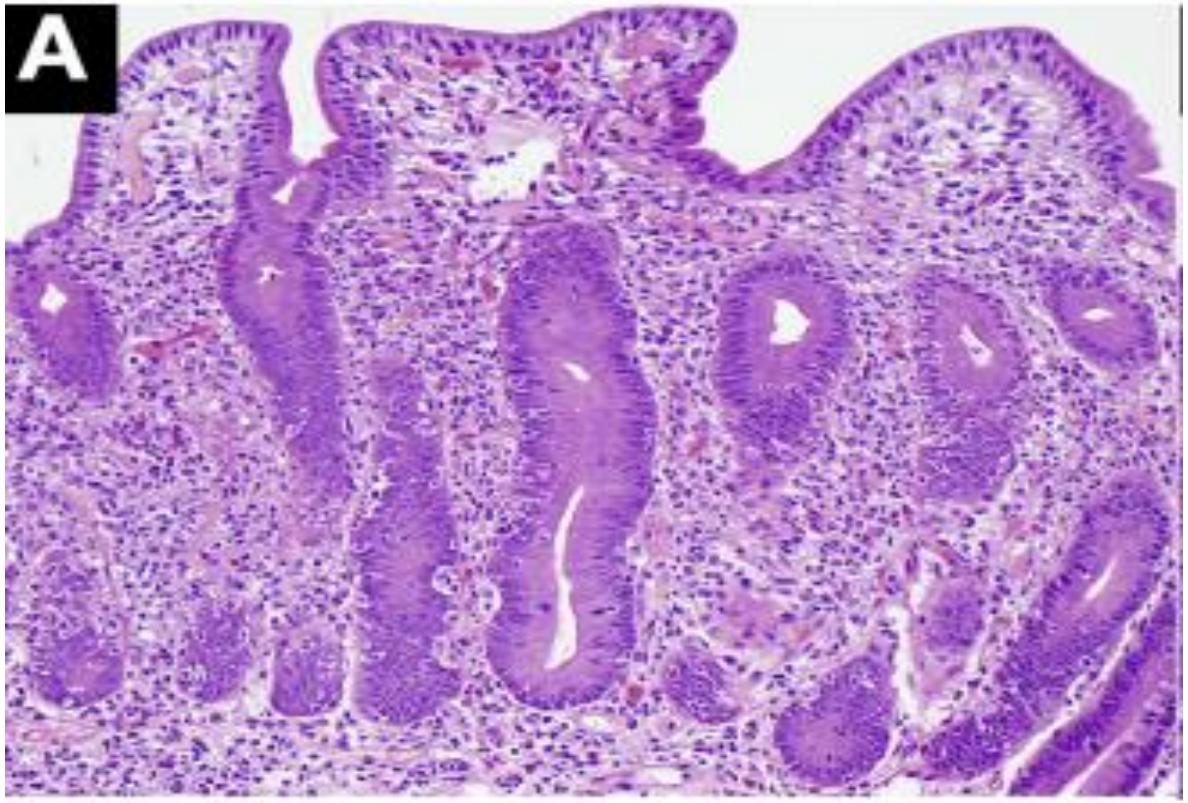
The histopathologic of AIE

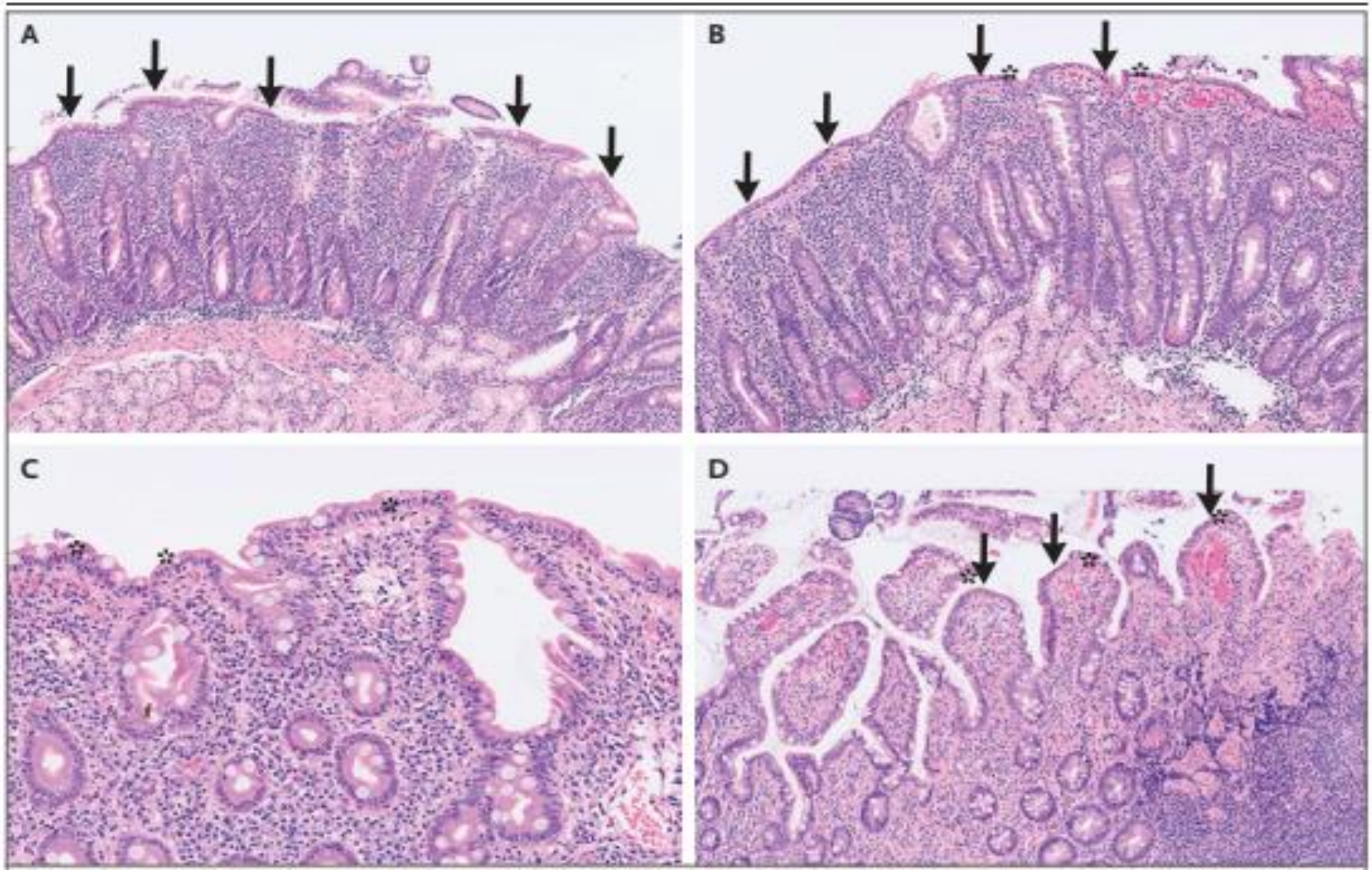
- **The common histopathologic presentation of AIE includes**
- **intestinal villous atrophy with variable lymphocytic**
- **infiltration,**
- **various features of follicular lymphoid hyperplasia,**
- **Cryptitis, graft-versus-host disease-like lesions,**
- **loss of Paneth and goblet cells.**
- **the presence of anti-enterocyte antibodies;**

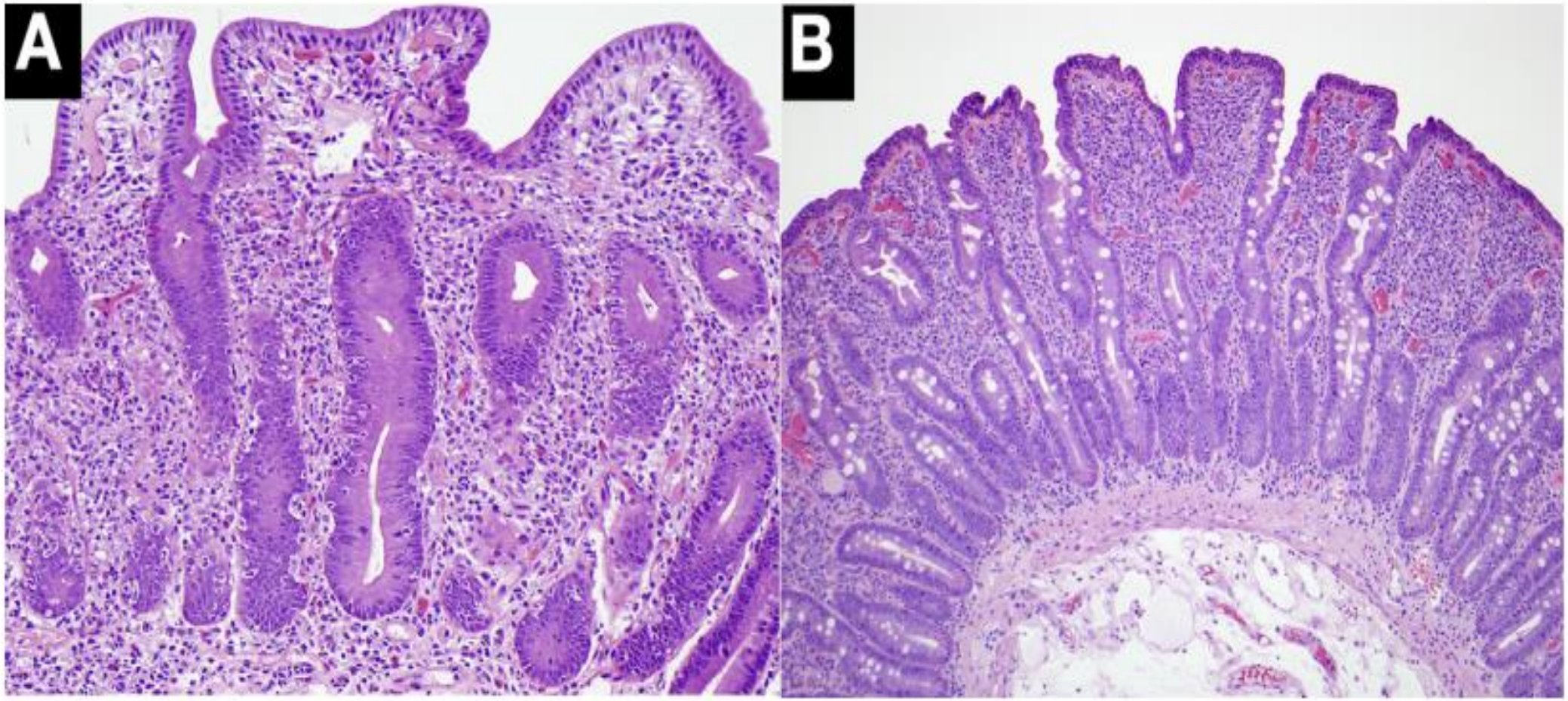
The histological presentation of autoimmune enteropathy

- **A new classification consisting of 4 types was proposed in 2017:**
- **(1) active chronic enteritis represents the most common form**
- **with a lympho-plasma-cellulair infiltrate located in the lamina**
- **propria which can be accompanied with epithelial apoptosis ,**
- **cryptitis**
- **(2) Celiac-like**
- **(3) graft-versus-host disease like, with prominent crypt epithelial**
- **Apoptosis with a relative absence of inflammation**
- **(4) mixed/no predominant pattern**

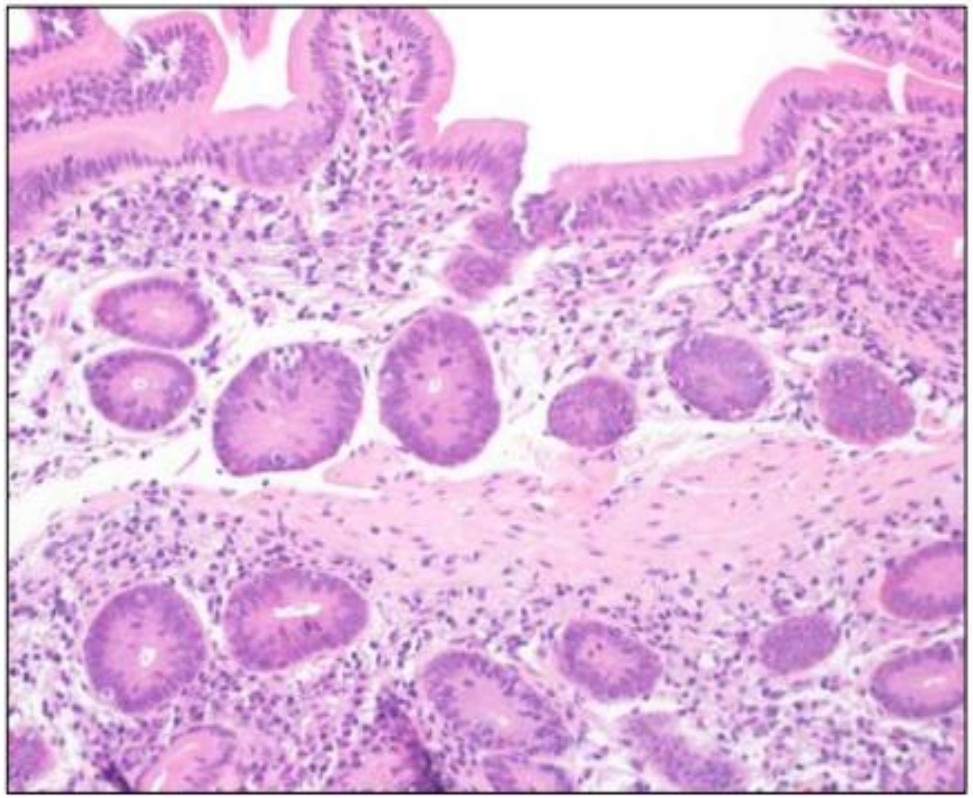
Duodenal biopsy in Autoimmune enteropathy
Villous atrophy with absence of Goblet,Panth cells



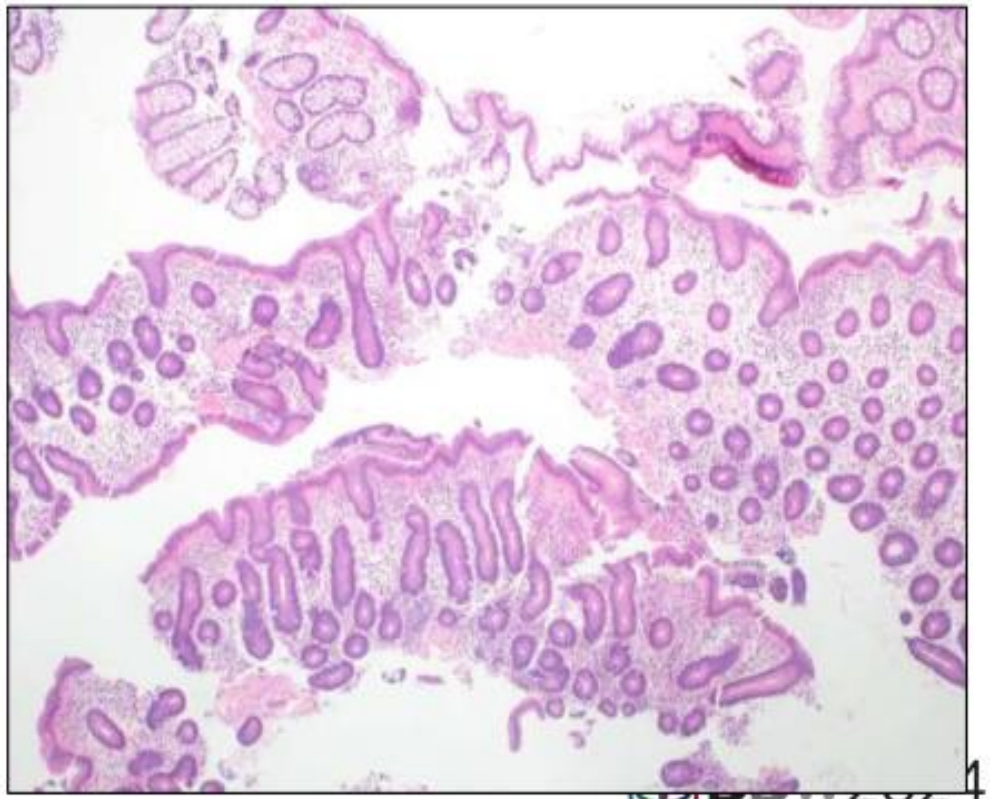

A
B
C
D


A
B

AUTOIMMUNE ENTEROCOLITIS



Ileum: Loss of goblet and Paneth cells.



Patchy involvement of colon

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the underlying molecular mechanism

- **Genetic studies have revealed that several monogenic**
- **inborn errors of immunity**
- **Mucosal CD4+ T-cells from AIE patients secrete elevated**
- **levels of TNF-α ,**
- **there have been some reports of successful treatment of**
- **adult onset AIE with anti- TNF-α treatment which suggest**
- **that this proinflammatory cytokine plays a role in AIE**
- **isolated GI forms of AIE with presence of anti-enterocyte**
- **antibodies can occur in both children and adults**

Autoantibodies in AIE

- **directed against the enterocyte (AEA) or goblet cells (AGA).**
- **they target the intestinal brush border or the cytoplasm of**
- **enterocytes.**
- **Whether AEA play a pathogenic role is still under debate.**
- **These autoantibodies seem to appear after the onset of disease,**
- **AEA arise as a response to (auto)antigens that are released**
- **By damaged enterocytes.**

The treatment of AIE

- **involves immunosuppression To reduce inflammation in**
- **the small bowel.**
- **Various treatment strategies in AIE have been reported**
- **Prednisone and budesonide combinations have been**
- **used with variable success.**
- **When these therapies fail, potentially toxic agents,**
- **such as adalimumab, infliximab, or tacrolimus, are often**
- **tried with variable success rates**

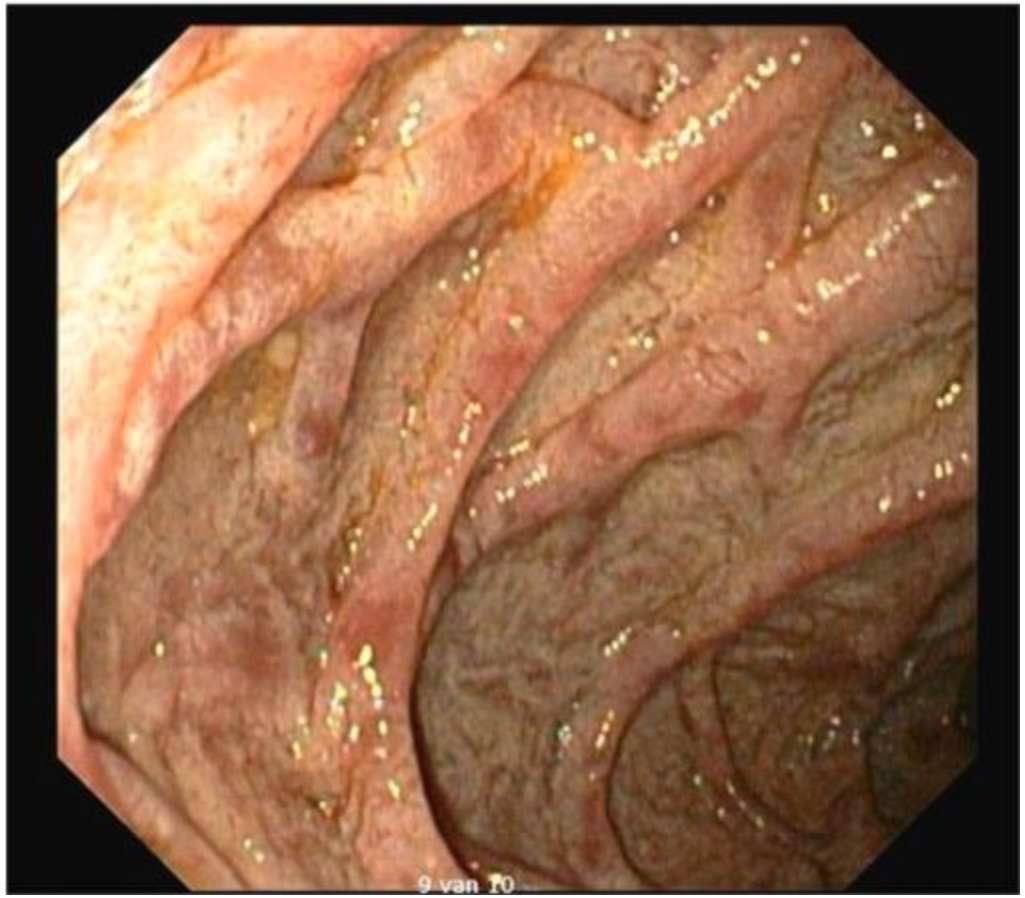
Common variable immunodeficiency syndrome (CVID)

- **characterized by an impaired antibody response which leads to**
- **insufficient production of immunoglobulins.**
- **the most common symptomatic immune deficiency disorder**
- **estimated prevalence between 1:25.000 and 50.000 .**
- **CVID results in recurrent infections as well as autoimmune**
- **complications.**
- **half of the patients with CVID experience chronic diarrhea**

the defective immunoglobulin production

- **Diarrhea as a result of Gastro-intestinal infections**
- **the defective immunoglobulin production**
- ***Giardia lamblia* leads to malabsorption duodenal villous atrophy.**
- **Villous atrophy is commonly present in patients with CVID**
- **and gastrointestinal symptoms**
- **The exact mechanism for the development of villous atrophy in**
- **CVID is however unknown as eradication of the pathogen does**
- **not always lead to mucosal and clinical recovery .**

duodenum in a common variable immuno-deficiency atrophic mucosa with mucosal cracks



Impaired secretion of IgA (sIgA)

- **Has been proposed to be at least Partly responsible**
- **sIgA is a key player in regulating intestinal Homeostasis**
- **SIgA prevents commensal bacteria in the small intestine**
- **From abundant contact with epithelial cells,**
- **it inhibit local production of nitric oxide which is an anti**
- **microbiocide with a potent pro-inflammatory effect**

Altered immune response

- **susceptible to dysregulation and contribute to intestinal**
- **inflammation**
- **Another interesting observation is that norovirus is an**
- **important pathogen for patients with CVID and a cause**
- **of CVID enteropathy.**
- **Analysis of duodenal biopsies revealed the presence of Norovirus**
- **in all 8 CVID patients with concomitant enteropathy and villous**
- **atrophy .**
- **Viral clearance, either spontaneously or with the use of ribavarin,**
- **was associated with symptom resolution and histological recovery**

Histological abnormalities in CVID

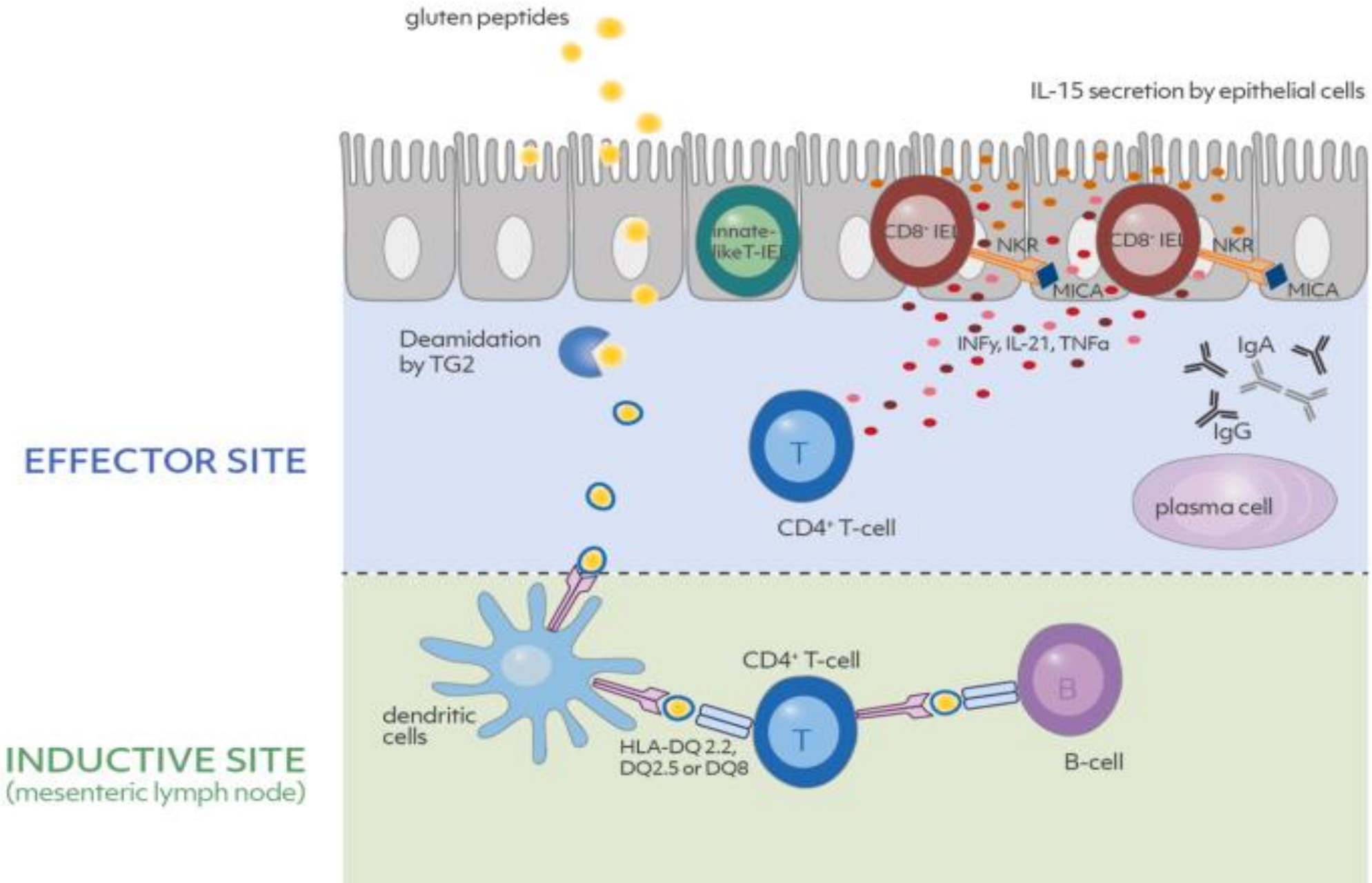
- **Intra-epithelial lymphocytosis, difficult to distinguish CD**
- **from CVID.**
- **Due to the impaired humoral immune response patients**
- **with CVID unable to produce antibodies of any kind,**
- **including CD-related antibodies.**
- **The histological hallmark of CVID is the absence or**
- **sparsity of plasma cells in the lamina propria.**

The treatment of villous atrophy in the context of CVID

- **complicated. Infection should be treated with**
- **the appropriate antibiotics or anti-parasitic therapy,**
- **often with a longer or more Repeated course than normal.**
- **Chronic intestinal norovirus infection should be evaluated**
- **And treated when the patient is symptomatic.**
- **Replacement of human immunoglobulin is useful for pulmonary**
- **infections , but appears to be of little use in clearing chronic intestinal infections .**

Celiac Disease

- **Has features of both a food intolerance and autoimmune disorder**
- **CD4+ T-cells induce B cell differentiation into plasma cells**
- **that secrete anti-tissue transglutaminase IgA antibodies (TGA).**
- **The events that culminate in the loss of tolerance to gluten in**
- **The small group of individuals that are HLA-DQ2 or DQ8 positive**
- **Poorly understood but changes in the microbiome,**
- **either caused by infections, antibiotic use or mode of delivery**
- **are under current scrutiny**


gluten peptides
IL-15 secretion by epithelial cells
innate-like T-IEL
CD8+ IEL
NKR
MICA
CD8+ IEL
NKR
MICA
Deamidation by TG2
INFγ, IL-21, TNFα
IgA
IgG
T
CD4+ T-cell
plasma cell
EFFECTOR SITE
INDUCTIVE SITE
(mesenteric lymph node)
dendritic cells
CD4+ T-cell
HLA-DQ 2.2, DQ2.5 or DQ8
T
B
B-cell

Gut microbiota changes in celiac disease

- Genes and gluten are necessary but insufficient to cause celiac disease (CeD)
- Altered gut microbiota has been implicated as an additional risk factor

Gut microbiota role

- Digestion of food
- Synthesis of nutrients and metabolites
- Modulating the immune system
- Maintainance of intestinal mucosa



Bacteroidetes
Proteobacteria

E Coli

Lactobacillus,
Bifidobacterium

Faecalibacterium
prausnitzii

Caminero & Pinto-Sanchez, Curr opinion Gastro 2020;
Caminero & Verdu AmJ Gastr Liv Physiol 2019; Constante M et al, Gastronterology 2022

CELIAC DISEASE CLINIC

McMaster University

Crohn’s disease

- **Crohn’s disease (CrD) is an inflammatory disease**
- **affect any part of the intestinal tract, with 80% of patients**
- **having involvement of the small intestine .**
- **The most common site of small intestinal inflammation is**
- **the terminal ileum, while the proximal small intestine is**
- **affected in only 5% of CrD patients.**
- **Involvement of proximal small intestine is more often seen**
- **in pediatric patients**

Crohn’s disease

- **The dysregulated inflammatory response in CrD results from**
- **The interaction of genetic, immunological, microbial and**
- **Environmental factors**
- **The majority of these genes are involved in the immune system.**
- **In CrD both the innate as well as the adaptive immune system**
- **play a role.**
- **Defective first line (innate) defense against luminal bacteria and**
- **increased intestinal permeability leads to increased exposure of**
- **The mucosal immune system to these bacteria**

Eosinophilic (gastro-)enteritis (EGE)

- **Clinical symptoms depend on the layer of the intestinal wall**
- **that is involved.**
- **Role for allergy is suggested as up to 75% of patients have an**
- **Atopic medical history ,**
- **Typical suggests a delayed-type of food hypersensitivity .**
- **EGE display an upregulation of Th2 response, by increased**
- **IL-4 and IL-5 production by peripheral blood T-cells,**
- **IL-13 secretion by T-cells derived from The duodenal lamina**
- **propria after these cells were stimulation with milk proteins**

Eosinophilic (gastro-)enteritis (EGE)

- **Peripheral eosinophilia is not required for EGE diagnosis disease**
- **as it is often not present and it does not correlate with disease**
- **Activity.**
- **When the mucosal and submucosal layer are predominantly**
- **involved, as is most frequently the case,**
- **patients present with abdominal pain, nausea, vomiting,**
- **diarrhea, malabsorption and weight loss.**
- **If the mucosal layer is predominantly inflamed this leads to**
- **Bowel thickening and patients can experience small bowel obstruction**

Graft-versus-host disease

- **Graft-versus-host-disease (GVHD) located in the gastrointestinal**
- **tract is a common complication of hematopoietic stem cell**
- **after solid organ transplantation and blood transfusion.**
- **Symptoms include nausea, vomiting and diarrhea, gastrointestinal**
- **bleeding, protein losing enteropathy, ileus.**
- **The histological abnormalities are classified into 4 grades:**
- **1) isolated apoptotic epithelial cells without crypt damage**
- **2) apoptosis with loss of individual crypts**
- **3) apoptosis plus loss of 2 or more adjacent crypts**
- **4) extensive crypt loss with mucosal denudation**

Graft-versus-host disease

- **No significant influx of inflammatory cells is present in GVHD.**
- **GVHD is caused by allo-reactive donor T-cells and leads to**
- **secretion of the proinflammatory cytokines IL-2, IL-12,**
- **interferon-γ and TNF-α .**
- **Damage to the mucosal barrier leads to translocation of microbial**
- **products and aggravates the inflammatory response.**
- **Paneth cells responsible for production of antimicrobial peptides**
- **by regulating microbiota composition are targeted by GVHD**
- **The degree of Paneth cell loss is directly associated with the**
- **severity of intestinal GVDH,**

Graft-versus-host disease

- **The cornerstone of treatment currently consists of**
- **Corticosteroid administration.**
- **In case of steroid-refractoriness various therapies**
- **including anti-T-cell antibodies (alemtuzumab, antithymocyte globulin), T-cell suppressive drugs (sirolimus, mycofenolate mofetil),**
- **anti-cytokine biologicals (TNF-α, IL-6) have all shown disappointing effects**

Post-colectomy enteritis with ulcerative colitis

- Only a handful cases reported; < 1% of patients who were post-colectomy for UC (7/829)
  - All patients had ulcerative pancolitis
  - Developed after a median of 33 (12-248) postoperative days
- Clinically life-threatening diarrhea, hemorrhage, weight loss, perforation
- Location: duodenum, jejunum, ileum, and pre-pouch and pouch in some patients

Yang Y, Liu Y, Zheng W, et al. BMC Gastroenterology. 19:61, 2019.

Horio Y, Uchino M, Hori K, et al. J Anus Rectum Colon 5:405-413;2021.

Post-colectomy enteritis with ulcerative colitis

Diffuse, superficial ulcerative mucosal inflammation

Multiple punched-out ulcers, multiple erosions, diffuse lesions, deep ulcer, etc.

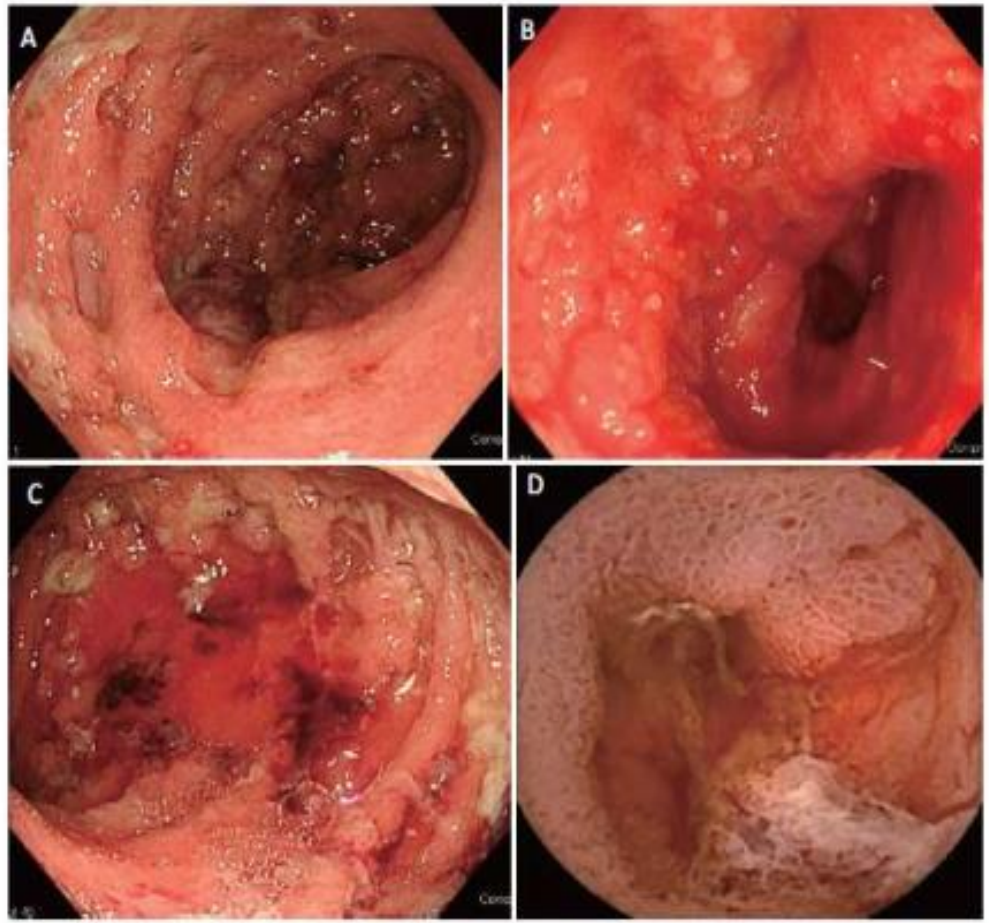
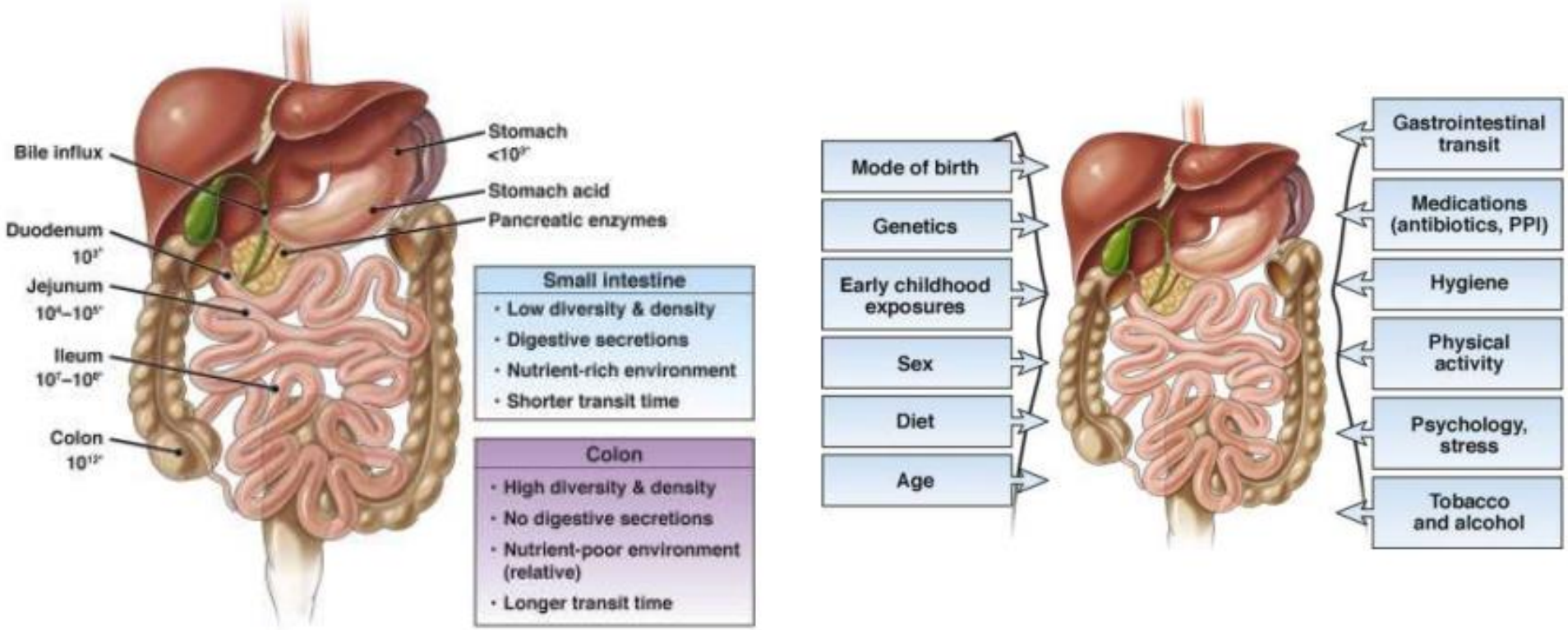


Figure 2. Representative findings of PCE. Friable and granular mucosa with A: punched-out ulcer, B: erosion and multiple aphthae, C: deep ulcer in the small intestine observed by endoscopy, and D: deep ulcer in the small intestine observed by capsule endoscopy.

Horio Y, Uchino M, Hori K, et al. J Anus Rectum Colon 5:405-413;2021.

Composition of GI Microbiota Along the Length of the GI Tract



Kastl AJ Jr, Terry NA, Wu GD, Albenberg LG. Cell Mol Gastroenterol Hepatol 2020;9:33-45
Shin A, Preidis GA, Shulman R, Kashyap PC. Clin Gastroenterol Hepatol 2019;17:256-274

The Definition of SIBO Expanded

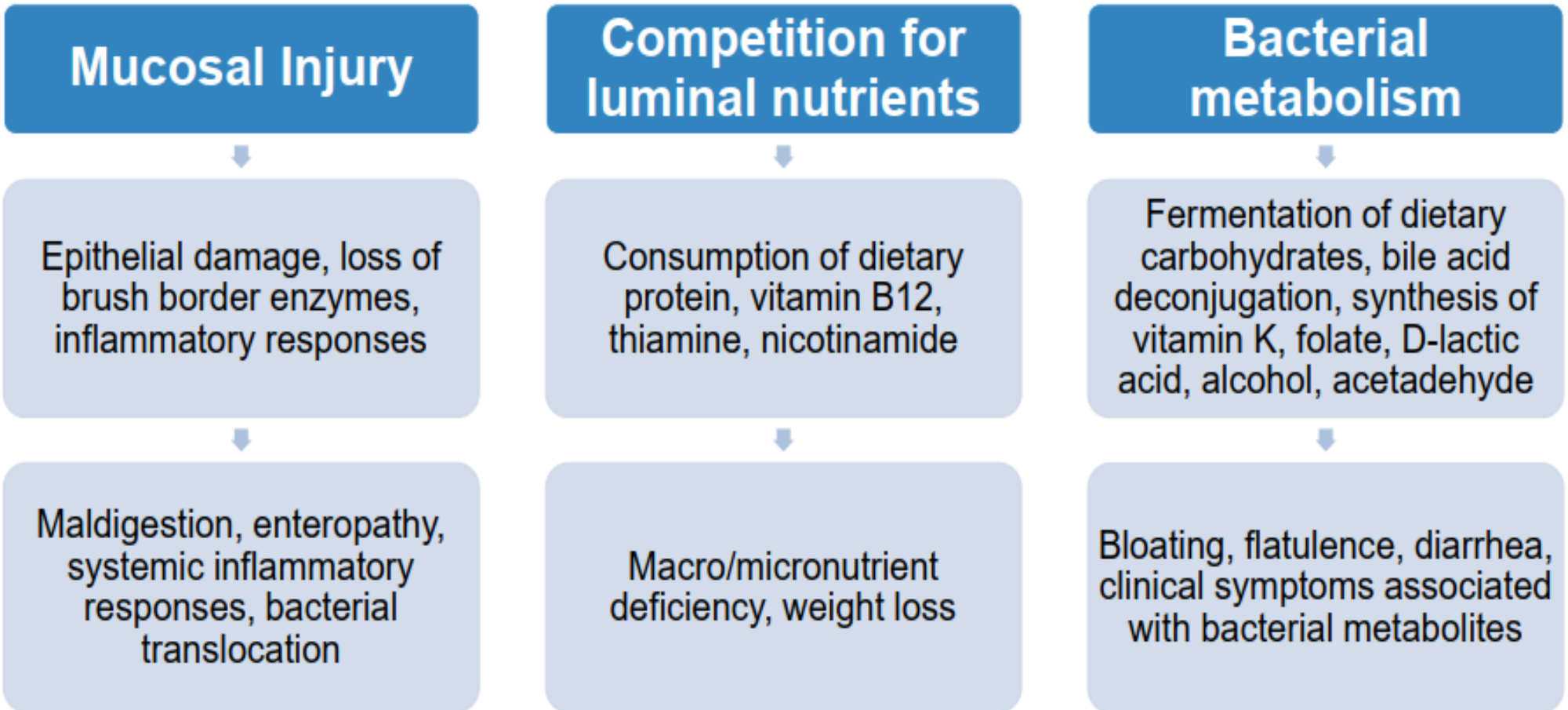
	Reports prevalence of SIBO
Normal populations	
Healthy study controls	0–20%
Dysmotility/gut wall injury	
Celiac disease	9–67%
Connective tissue diseases	43–55%
Crohn's disease	25–88%
Diabetes mellitus	8–44%
Hypothyroidism	54%
Nonspecific dysmotility	76%
Radiation enteropathy	26%
Ulcerative colitis	81%
Miscellaneous	
Chronic fatigue syndrome	81%
Chronic pancreatitis	34–92%
Drug-induced inhibition of acid secretion	26–75%
End-stage renal failure	36%
Fibromyalgia	93%
Irritable bowel syndrome	4–78%
Immunodeficiency syndromes	30–50%
Liver cirrhosis	17–36%
Obesity	17–41%
Parenteral nutrition	70%
Rosacea	46%

	Reports prevalence of SIBO
Neuromuscular diseases	
Muscular dystrophy	65%
Parkinson's disease	54%
Surgery	
Abdominal surgery	82%
Bilateral truncal vagotomy	93%
Gastrectomy	63–78%
Ileocaecal valve resection	32%
Roux-en-Y reconstruction	86%

- Traditionally defined as >10^5 CFU/mL of colonic-type bacteria
- Wide range of patients with increased bacterial counts < 10^5 CFU/mL
- Lower cut-offs proposed by others
- *True prevalence of SIBO is unknown*

Grace et al. Aliment Pharmacol Ther 2013;38:674-88

Pathophysiological Effects of SIBO



SIBO: Risk factors

Loss of Protective Mechanisms

Immune Deficiencies

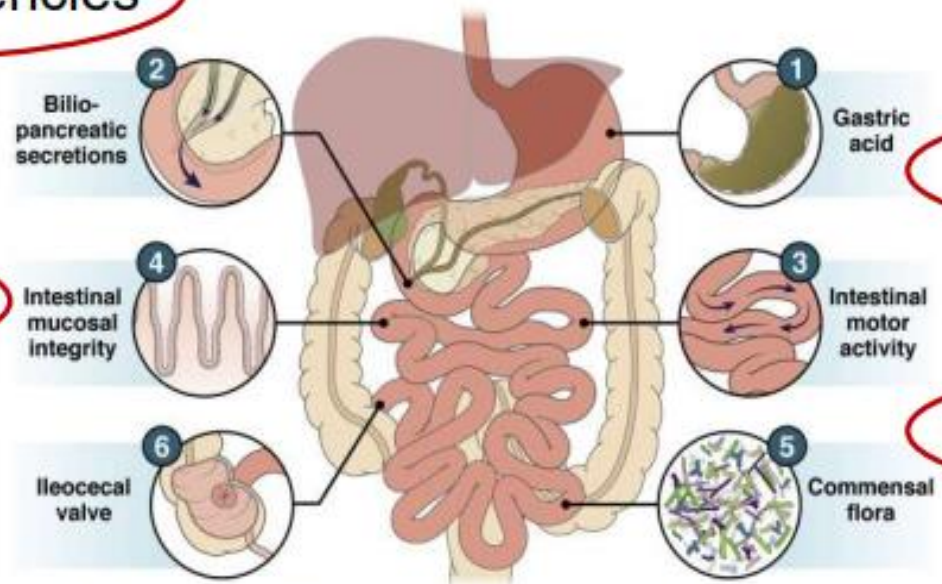
Hypochlorhydria

Altered Anatomy

Intestinal dysmotility

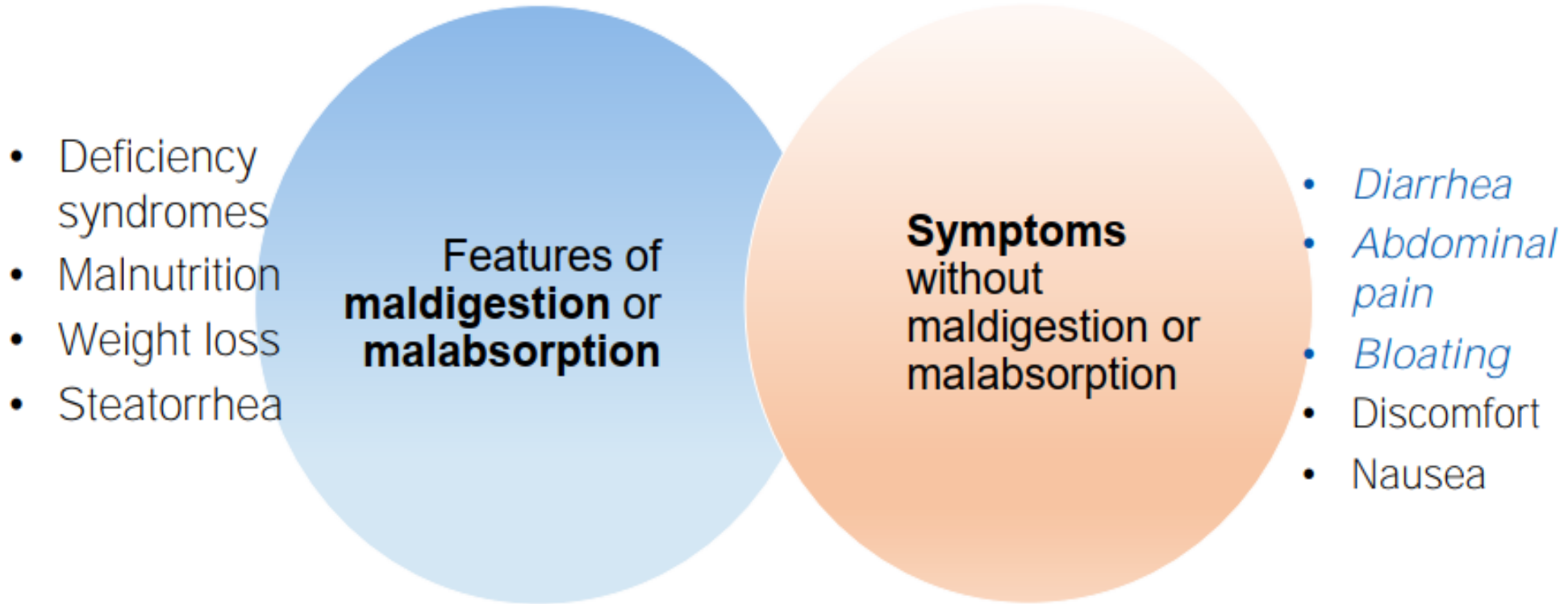
Multifactorial Causes

Medications



Bushyhead D, Quigley EMM. Gastroenterology 2022;163:593-607

Clinical Features Associated with SIBO



Indolent T-cell lymphoproliferative disease

- **the gastrointestinal tract are rare clonal T-cell diseases**
- **that more commonly occur in the intestines and have a**
- **protracted clinical course.**
- **There is a strong male predominance, as 73% of the cases so**
- **far described were males. The median age is around 50 years,**
- **Lesions can occur anywhere in the gastrointestinal tract,**
- **with common involvement of the small intestine**

Indolent T-cell lymphoproliferative disease

- **The immunophenotype is heterogeneous,**
- **can be either CD4+, CD8+, or CD4-/CD8-.**
- **Genetic alterations, were identified in (80%)**
- **lymphoproliferative disorders and involved frequent**
- **alterations of the JAK-STAT pathway genes.**
- **The diagnosis is challenging and such cases can be misinterpreted**
- **as IBD or an aggressive peripheral T-cell lymphoma .**
- **Chemotherapy because of an initial diagnosis of peripheral**
- **T-cell lymphoma is generally ineffective.**

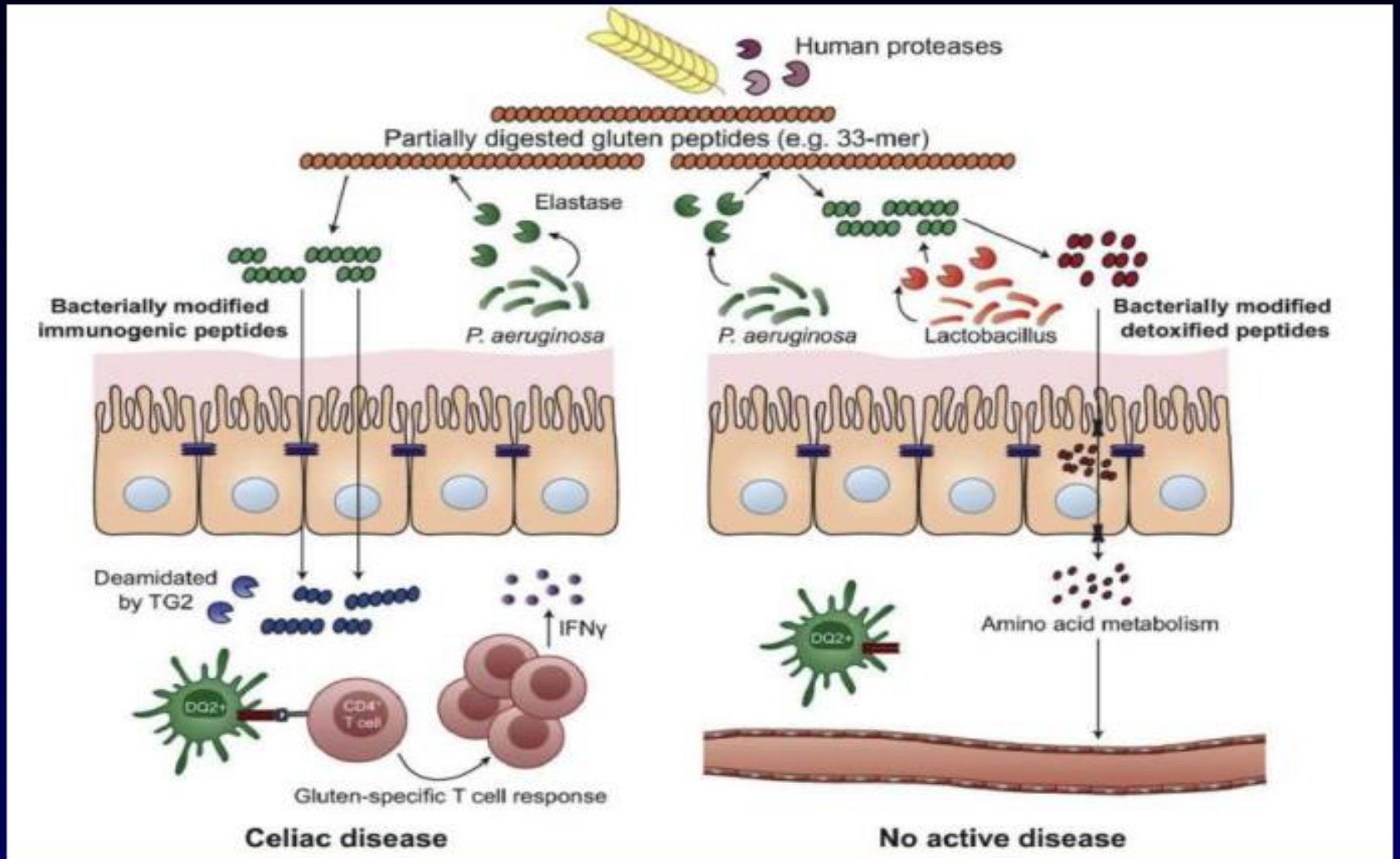

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Vladimir Gluten
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Thank you

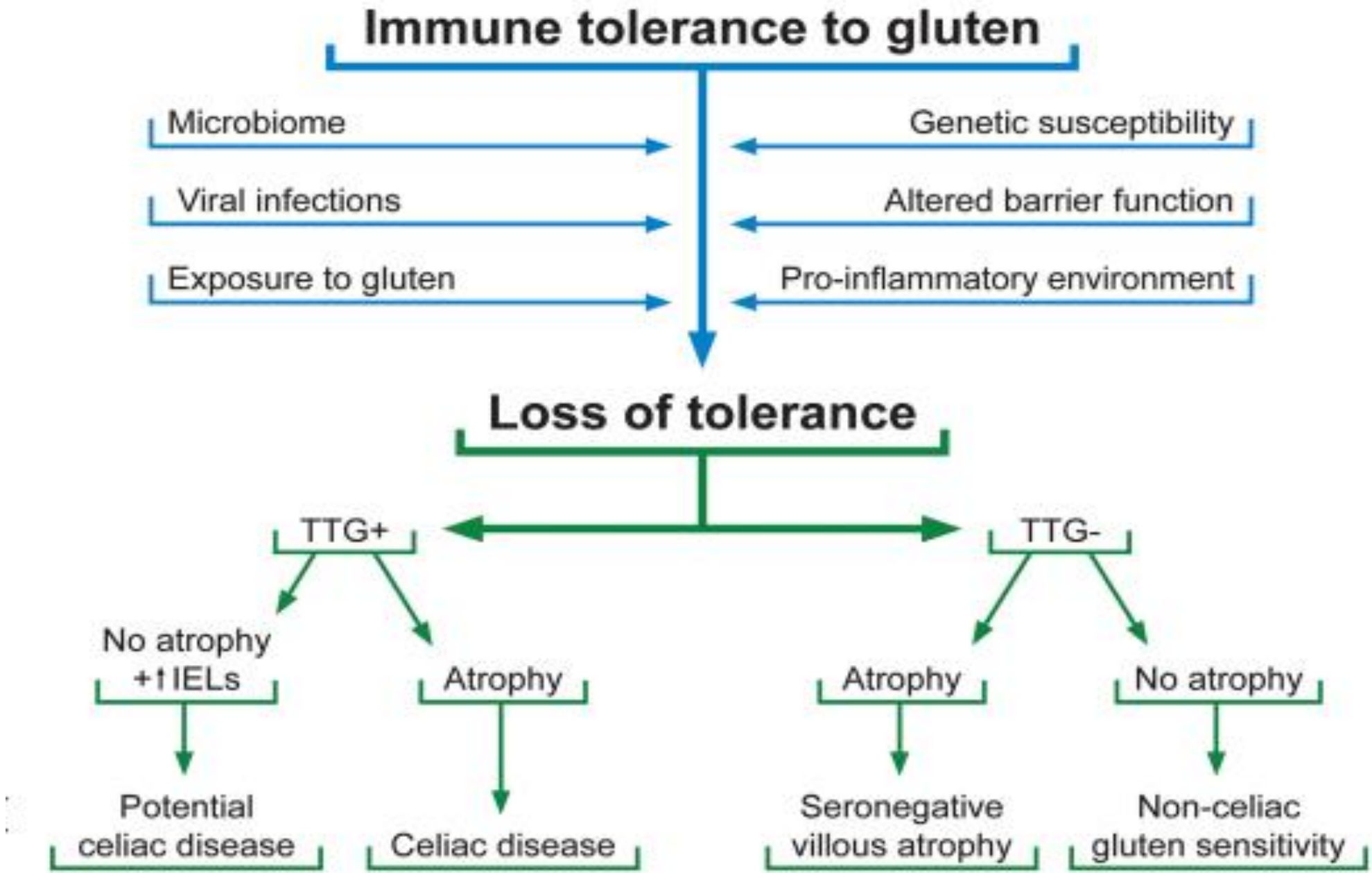
Enteropathy

Take Home Points

- Historically SIBO identified among individuals with anatomical abnormalities and/or severe dysmotility
- Heterogeneous clinical consequences, symptoms, features
- Recognized as a potential source of symptoms in a variety of GI diseases and disorders
- Extending our definition of SIBO to small intestinal dysbiosis
- Evidence for biological plausibility, correlation with symptoms, response to treatment
- Deeper understanding of host-microbe relationships and small intestinal microbiome in health and disease required



Caminero A al, Gastroenterology 2016

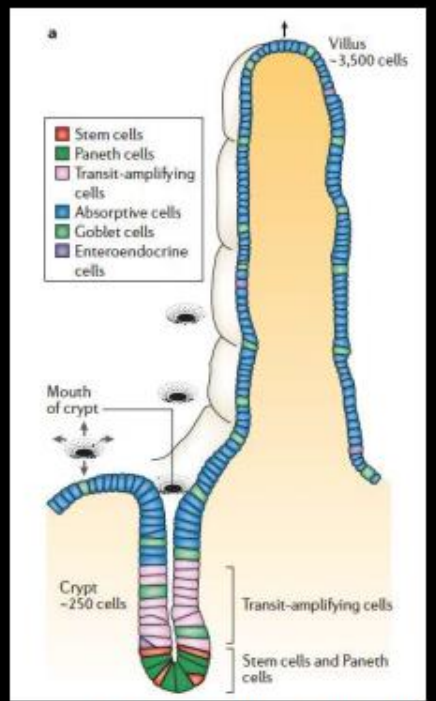

Immune tolerance to gluten
Microbiome
Viral infections
Exposure to gluten
Genetic susceptibility
Altered barrier function
Pro-inflammatory environment
Loss of tolerance
TTG+
TTG-
No atrophy
+↑IELs
Atrophy
Atrophy
No atrophy
Potential
celiac disease
Celiac disease
Seronegative
villous atrophy
Non-celiac
gluten sensitivity

- shows marked villous blunting (arrows) and lymphoplasmacytic
- expansion of the lamina propria.
- A specimen of duodenal mucosa obtained at presentation
- shows marked villous blunting , lymphoplasmacytic expansion of
- the lamina propria, and an increase in intraepithelial lymphocytes.
- A specimen of ileal mucosa obtained at presentation (Panel D)
- shows findings similar to those observed in the duodenum, with mild
- villous blunting (arrows), lymphoplasmacytic expansion of the lamina
- propria, and an increase in intraepithelial lymphocytes (asterisks)

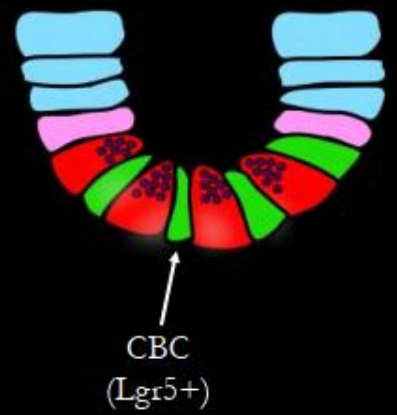
The intestinal epithelium regenerates every 2-5 days and is maintained by stem cells located at the base of the crypt



Bjerknes & Cheng,
Methods Enzymol, 2006



Crosnier C et al, Nat Rev Genet, 2006

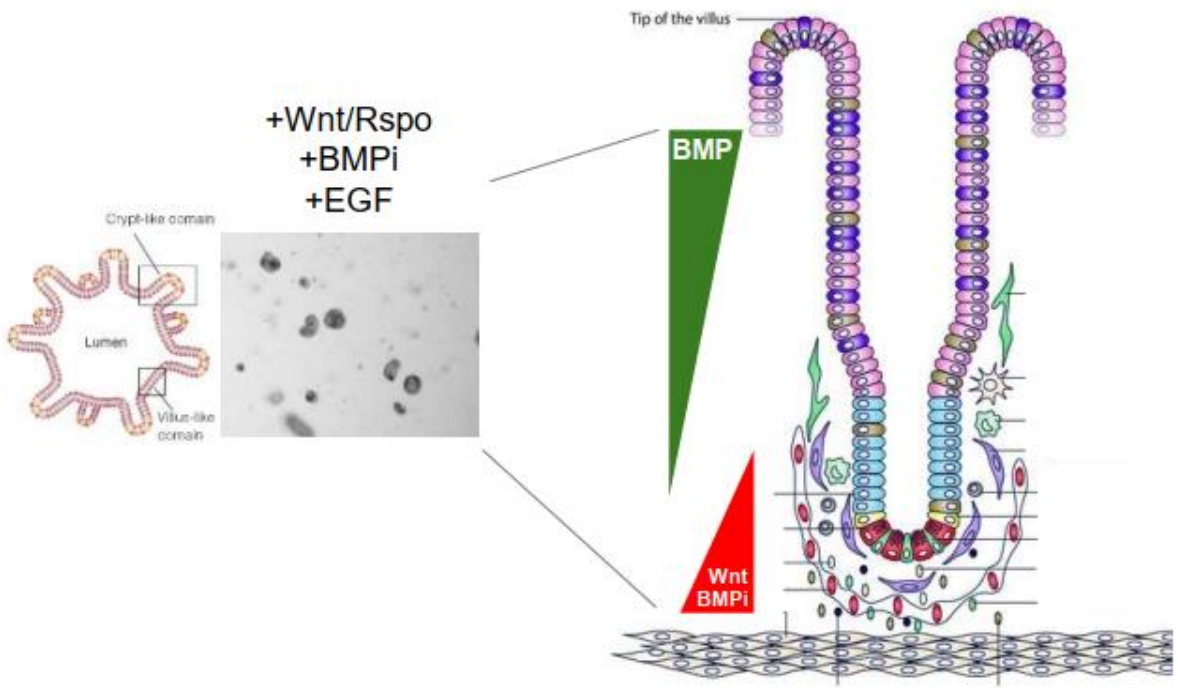


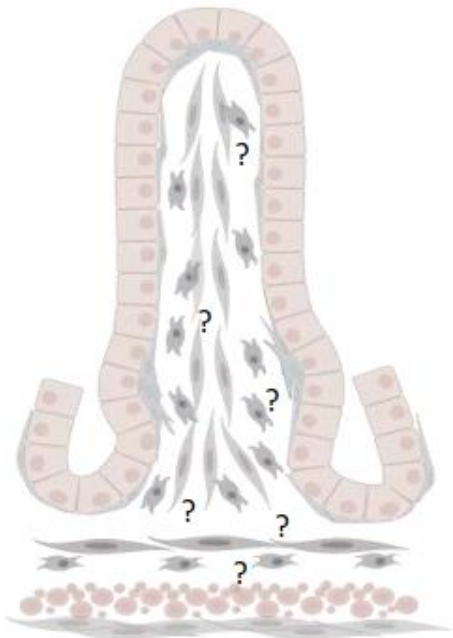
CBC
(Lgr5+)

Cedars Sinai

UCSF

What are the mesenchymal sources that maintain key signaling gradients in the niche?





Sailaja et al., J Physiol. 2016

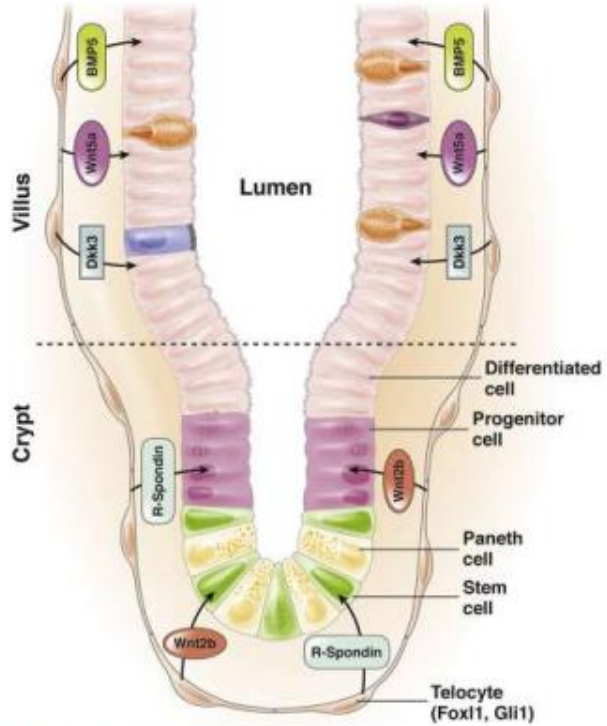
causes of villous atrophy

- **1- CD or RCD ,based on combination of celiac serology,**
- **HLA typing, histopathology features, and response to GFD,**
- **2- drug-induced enteropathy (based on history of starting**
- **medication and its correlation with symptoms, duration**
- **of treatment, histopathology and effect after discontinuation),**

causes of villous atrophy

- **3- common variable immunodeficiency associated**
- **enteropathy based on total immunoglobulin titers**
- **histopathology presence of plasma cells, lymphoid**
- **aggregates,**
- **4- collagenous sprue and colitis (based on histopathology),**
- **5- intestinal lymphoma.**

Signals of the intestinal stem cell niche



Kaestner KH, *CMGH* 2019

Spatiotemporal control of growth and differentiation occurs through WNTs/WNTi, RSPO, BMPs/BMPi, and EGF ligands

Multiple Wnts expressed along axis, but not necessarily redundant

Wnt2b

- Expression detected in intestinal mesenchyme and epithelia
- Emerging as a distinct participant in developmental and injury response mechanisms
- Specific roles of Wnt2b in the ISC niche are unclear

Bacterial proteases to degrade gluten in celiac disease

- The human GI tract (oral cavity to rectum) harbours bacteria that express enzymes that cleave immunogenic gluten peptideswith modest efficacy and mainly at neutral pH (Rothia and Lactobacilli)
- Some may enhance gluten immunogenic peptide availability (Pseudomonas), and thus modulate CeD activity
- The most active glutenases (prolyl-endopeptidases, PEPs) are from external microbial sources, and are usually active at acidic (gastric) pH
- The combination of Sph. caps. PEP and germinating barley EP-B2 (ALV-003) reduces immunogenic gluten >90% in real life clinical trials
- Genetic engineering of PEPs via in silico modeling and targeted mutagenesis has yielded even more effective acid pH glutenases: Kuma030 (TAK-062) that has been validated ex vivo and in patients in vivo
- These glutenases have the potential to inactivate large quantities of gluten and will be an important adjunct to mucosa-targeted therapies for CeD

Summary

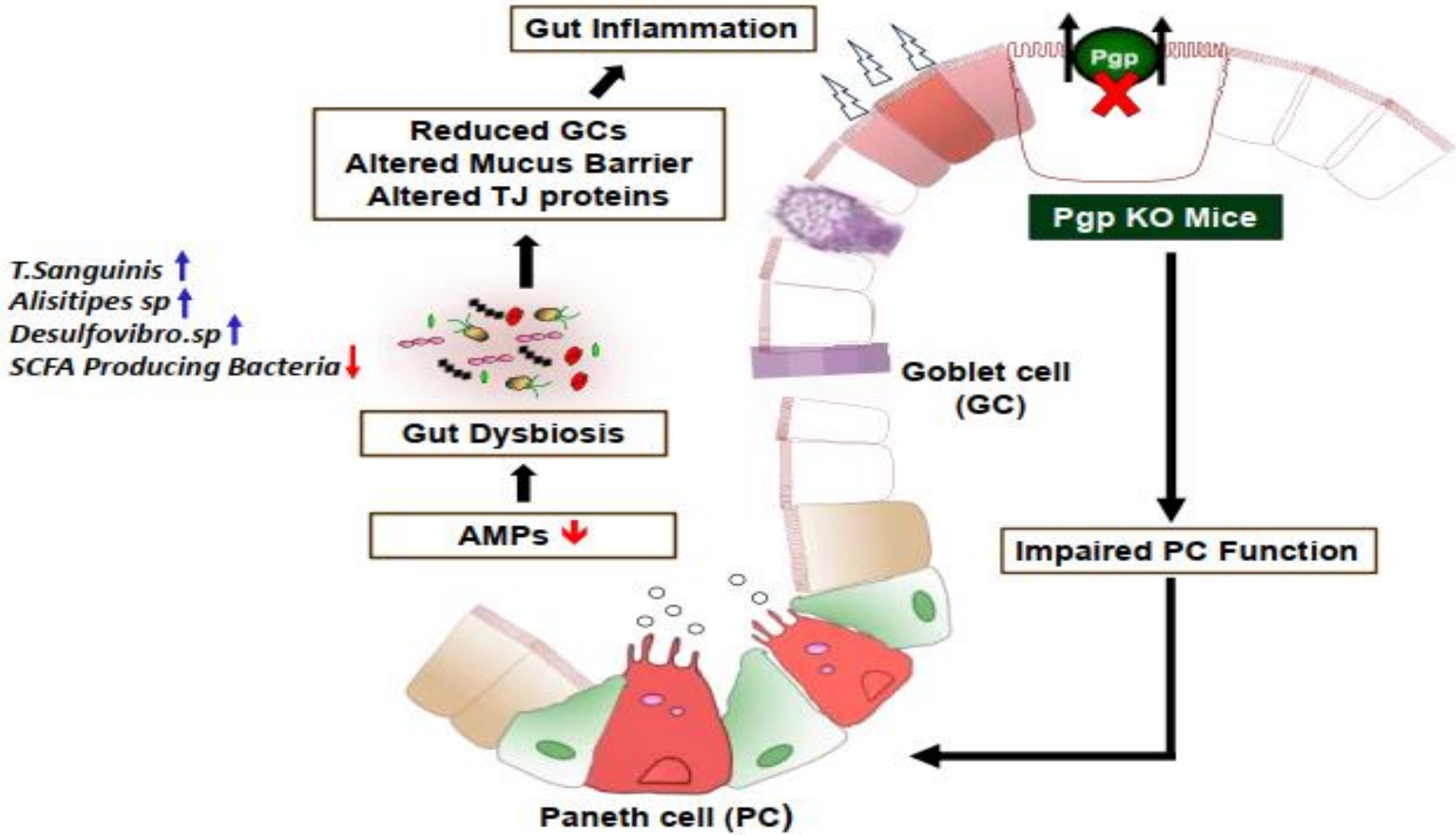
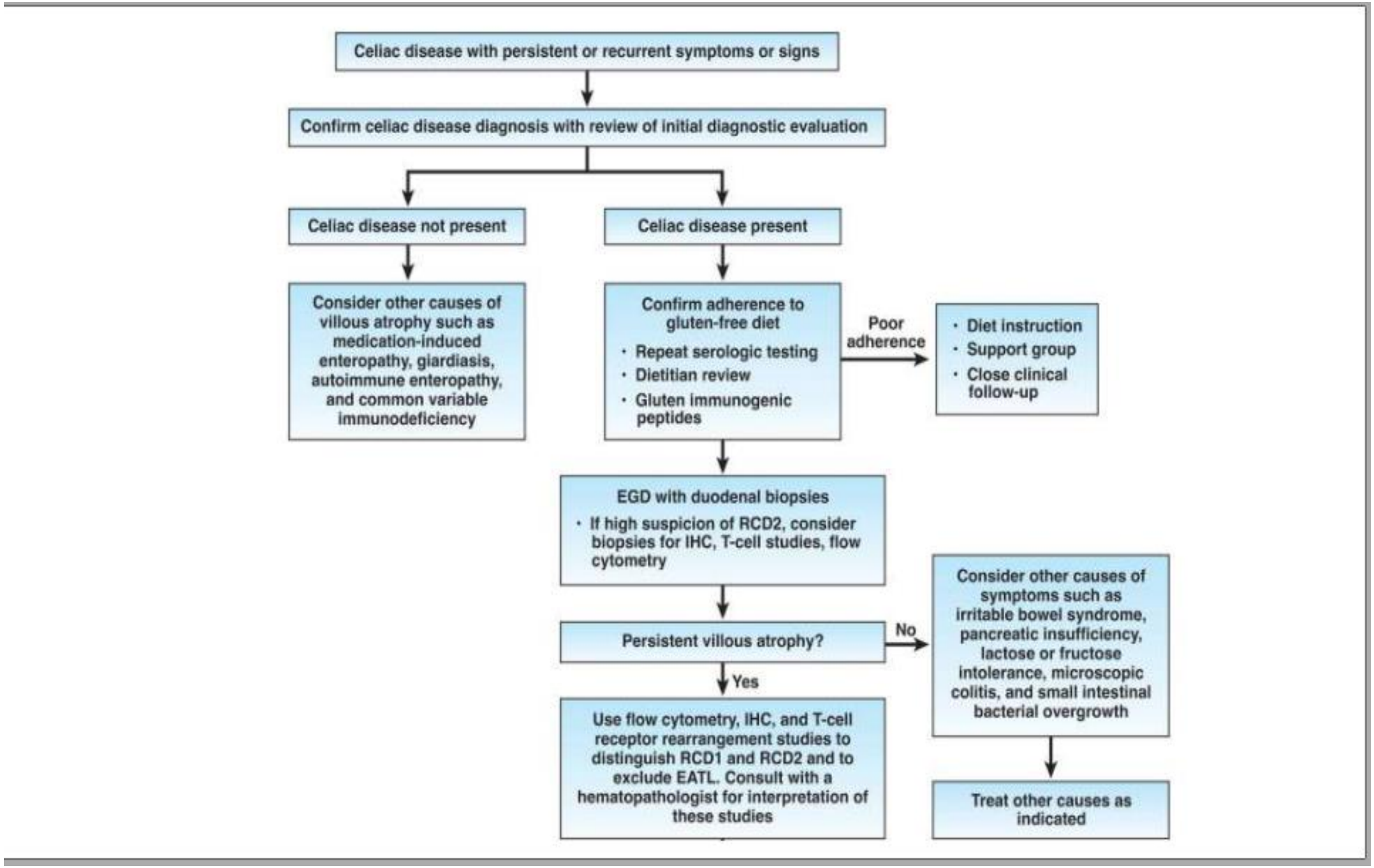
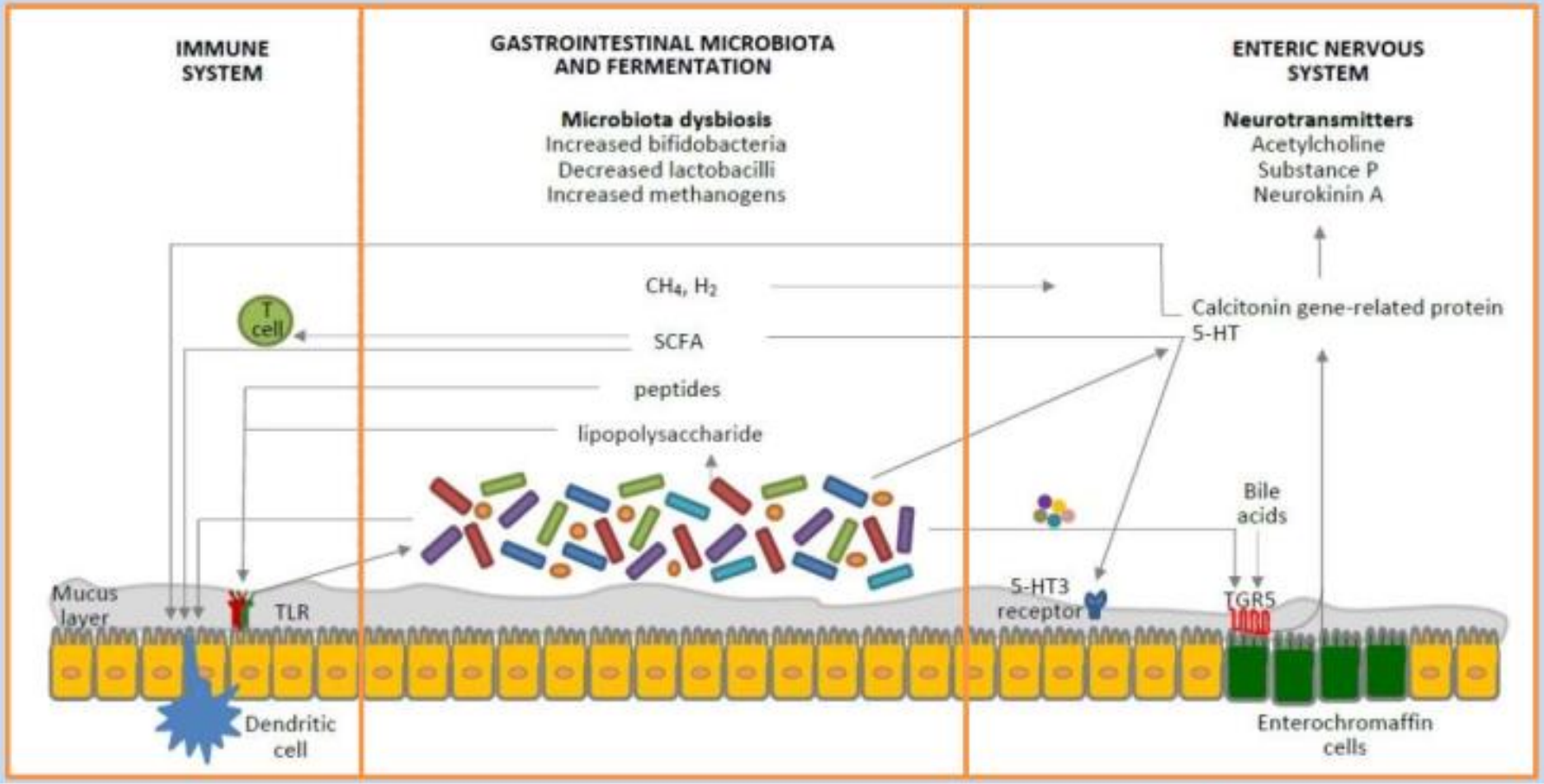

Gut Inflammation
Reduced GCs
Altered Mucus Barrier
Altered TJ proteins
T.Sanguinis ↑
Alisitipes sp ↑
Desulfovibro.sp ↑
SCFA Producing Bacteria ↓
Gut Dysbiosis
AMPs ↓
Pgp
Pgp KO Mice
Goblet cell
(GC)
Impaired PC Function
Paneth cell (PC)

Table 1. Etiologies of Seronegative Villous Atrophy

Etiology
Immune-mediated
Serongative CeD
Common variable immune deficiency
Autoimmune enteropathy
Intestinal lymphoma
Sarcoidosis
Infectious
Parasitic infections (*Giardia lamblia*)
Tropical sprue/environmental enteropathy
Whipple disease
Small intestinal bacterial overgrowth
Tuberculosis
HIV enteropathy
Iatrogenic
Medications
Olmesartan
Azathioprine
Mefenic acid
Methotrexate
Mycophenolate mofetil
Chemotherapy
Graft vs host disease
Radiation enteritis
Transplanted small intestine
Inflammatory
Crohn's disease
Collagenous sprue
Eosinophilic enteritis


Celiac disease with persistent or recurrent symptoms or signs
Confirm celiac disease diagnosis with review of initial diagnostic evaluation
Celiac disease not present
Celiac disease present
Consider other causes of villous atrophy such as medication-induced enteropathy, giardiasis, autoimmune enteropathy, and common variable immunodeficiency
Confirm adherence to gluten-free diet
• Repeat serologic testing
• Dietitian review
• Gluten immunogenic peptides
Poor adherence
• Diet instruction
• Support group
• Close clinical follow-up
EGD with duodenal biopsies
• If high suspicion of RCD2, consider biopsies for IHC, T-cell studies, flow cytometry
Persistent villous atrophy?
No
Yes
Consider other causes of symptoms such as irritable bowel syndrome, pancreatic insufficiency, lactose or fructose intolerance, microscopic colitis, and small intestinal bacterial overgrowth
Use flow cytometry, IHC, and T-cell receptor rearrangement studies to distinguish RCD1 and RCD2 and to exclude EATL. Consult with a hematopathologist for interpretation of these studies
Treat other causes as indicated

Probiotics, gut motility, disorders of gut brain interaction: mechanisms of action



Dimidi, Advances in Nutrition. 2017; 8: 484–94

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Summary

Probiotics have been shown to be effective in a range of disorders of gut brain interaction in adults, although effect sizes are generally quite small

Varying context, varying findings:

- Studies show species- and strain -specific effects, but there are rarely sufficient numbers of trials of individual probiotic strains to enable meta-analyses that allow us to make recommendations at the strain level
- Other factors are associated with response, including microbiome, host physiology and host diet

Preliminary evidence of a role for gut microbiome in response to dietary therapy (including probiotics), but additional evidence for a role of microbiome metabolites

The etiology ,immunopathogenesis of adult-onset AIE

- **Ipilimumab is a monoclonal antibody against CTLA-4 that**
- **induces a T-cell response used for treatment of metastatic**
- **melanoma.**
- **The drug is well known for gastrointestinal side effects that**
- **includes enterocolitis which initiated by T-cell activation in the gut .**
- **Other immune checkpoint inhibitors such as anti-programmed**
- **death-1 antibodies (anti-PD-1, pembroluzimab, nevolimab) are**
- **associated with a similar risk of immune mediated entero-(colitis)**

The etiology ,immunopathogenesis of adult-onset AIE

- **These immune checkpoint inhibitors are also able to induce**
- **an new onset of severe CD as was observed in a patient**
- **recently started on ipilimumab.**
- **Development of CD has previously been described in patients**
- **Using interferon α and interferon β 1, suggesting that these**
- **drugs contribute to CD development in genetically susceptible patients**

Bile Acid Diarrhea: Background

- Also known as: bile acid malabsorption (BAM)
- Results when there are excess bile acids (BA) in the large intestine causing watery, loose stools and increased motility
- Fecal urgency and incontinence very common

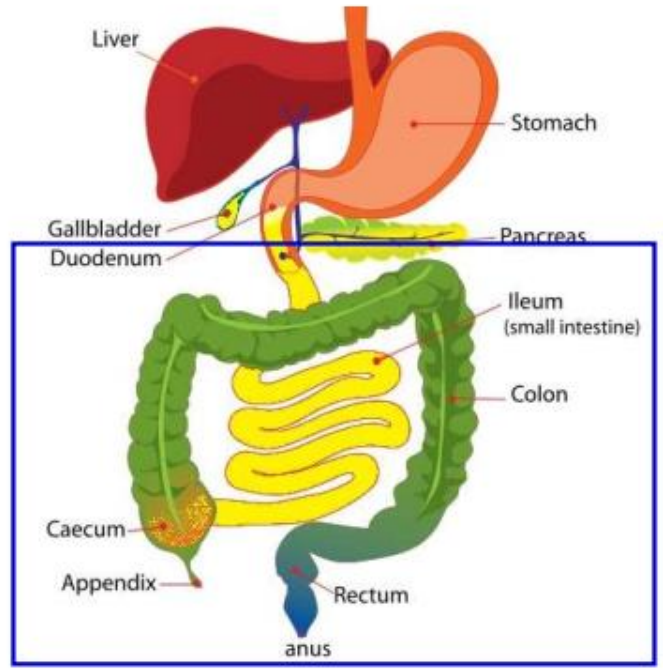


Image credit: Mariana Ruiz/Wikimedia

Cause of Bile Acid Diarrhea

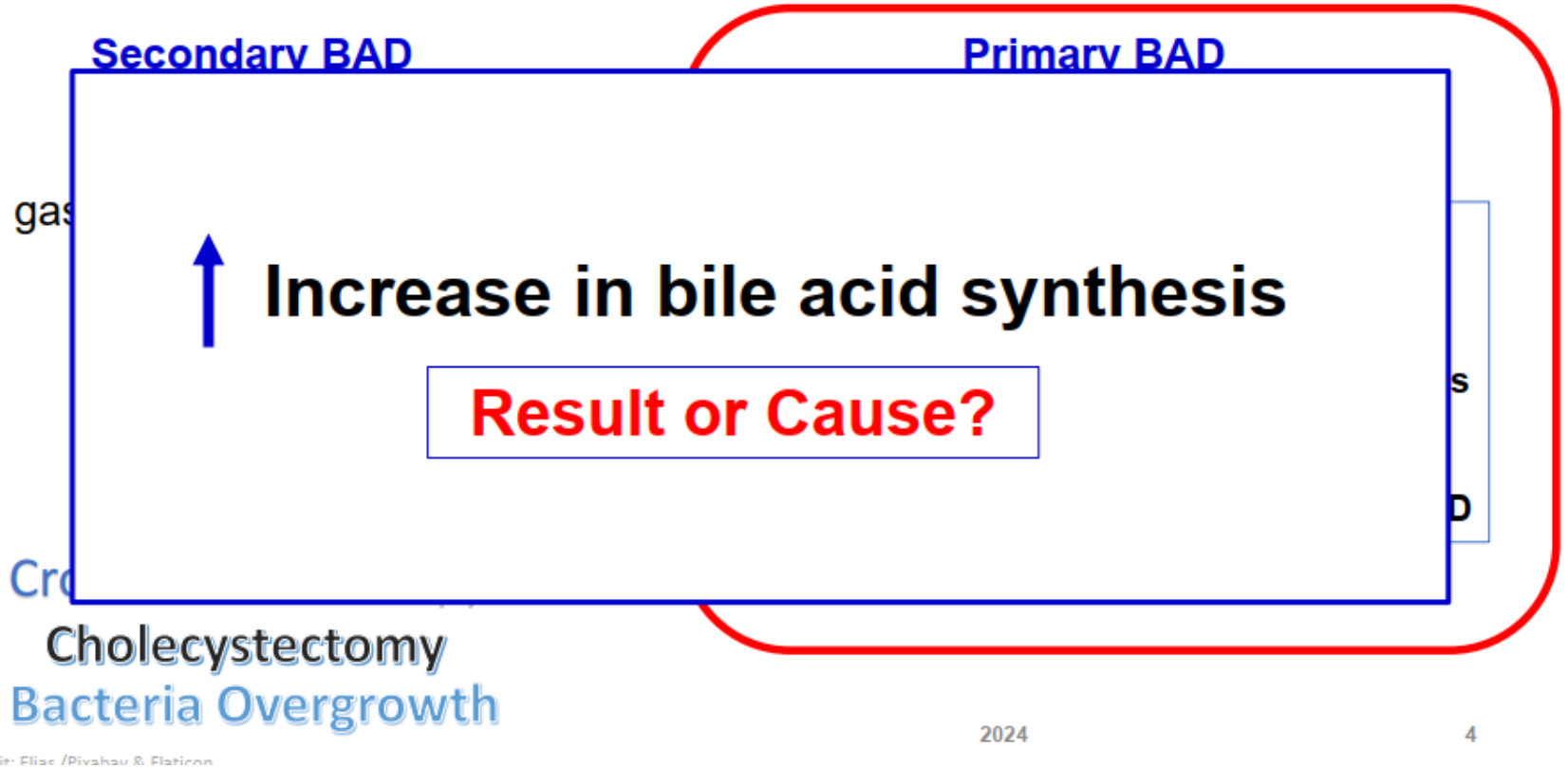
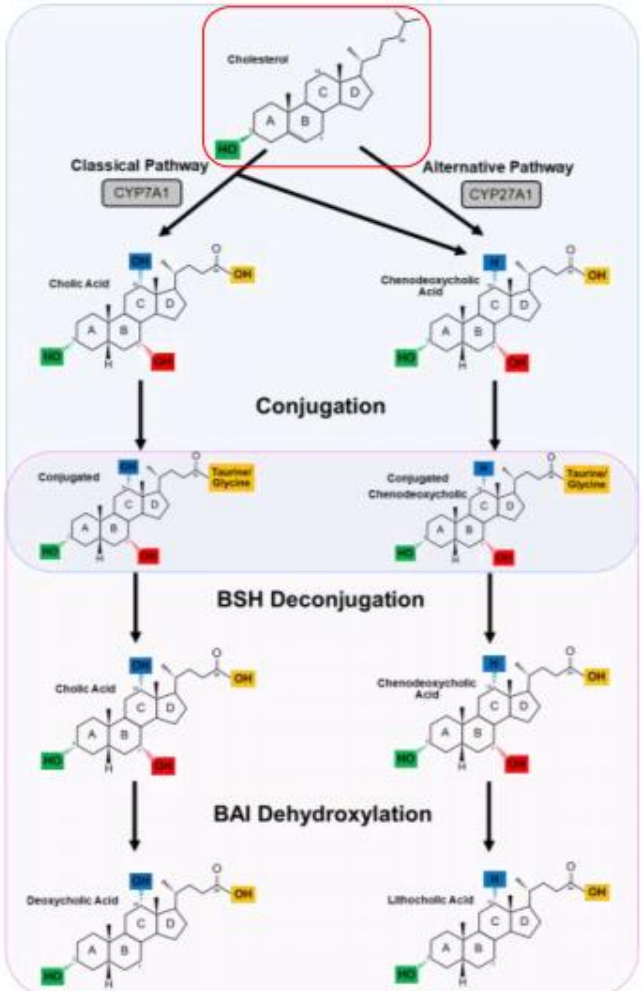


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Bile Acid Synthesis



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Human Transformation

Bacterial Transformation

Bile Acids

Primary

- Cholic acid (CA)
- Chenodeoxycholic acid (CDCA)

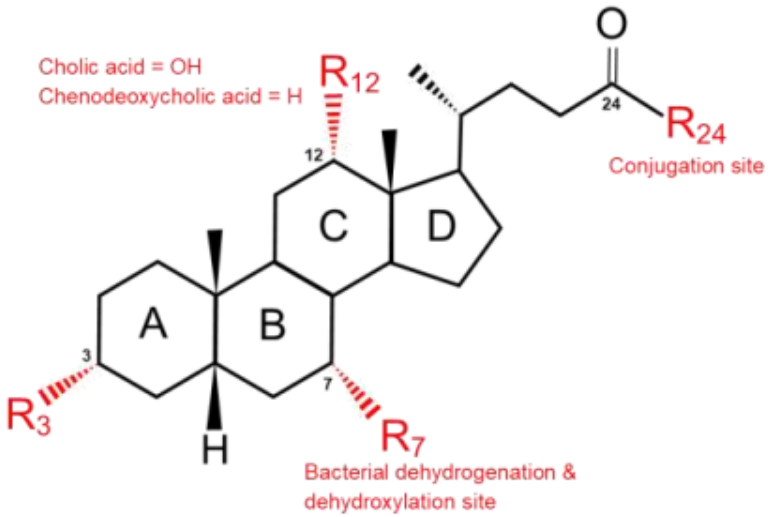
Conjugated to an amino acid (glycine or taurine) in the liver

Secondary

Primary BAs are

- Deconjugated
- Dehydroxylated
- Dehydrogenated (reversible)

into secondary bile acids **by bacteria** in the small intestine and colon

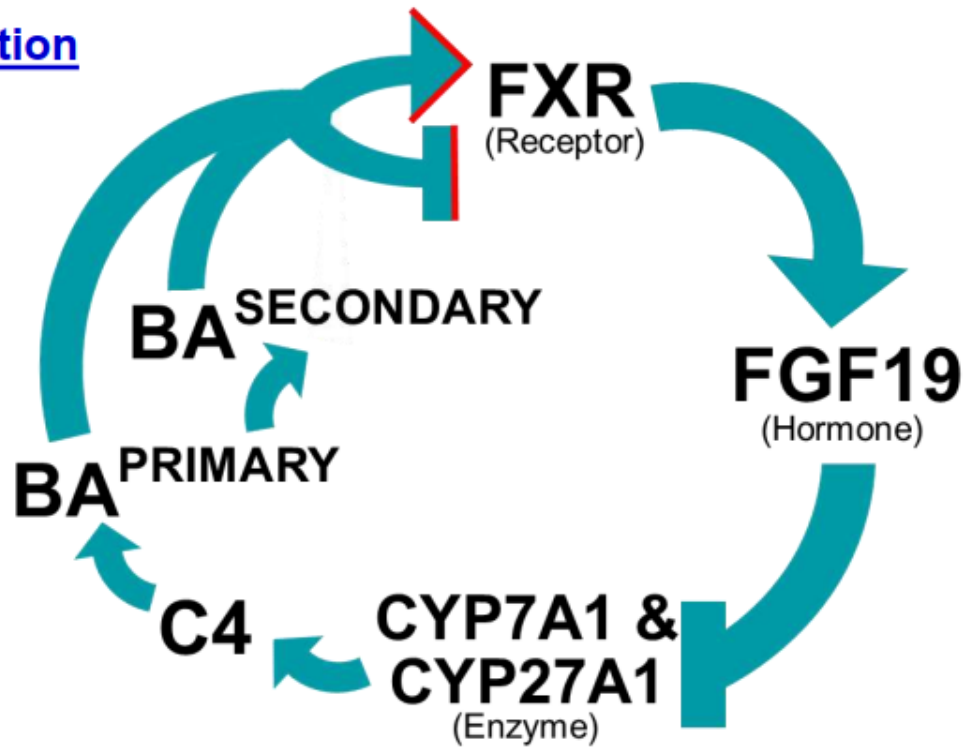


Name	R_3	R_7	R_{12}	R_{24}
Cholic Acid	OH (α)	OH (α)	OH	OH
Chenodeoxycholic Acid	OH (α)	OH (α)	H	OH
Deoxycholic Acid	OH (α)	H	OH	OH
Lithocholic Acid	OH (α)	H	H	OH

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Possible Significance

Bile Acid Regulation



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Conclusion

- Identified **variations in bile acids** in the stool of SeHCAT-diagnosed Primary BAD subjects compared to healthy subjects
- Indicates likely **significant differences in bile acid metabolism** by the fecal microbiome
- **Further specific extended bile acids studies** are needed to enhance understanding of Primary BAD pathogenesis, diagnosis, and treatment

- The estimated prevalence is 0.6% with a female to male ratio of 2:1
- CD affect people of European descent, as originally studies have
- shown rates of CD of up to 5.6% in specific North African
- The clinical presentation of patients with CD varies widely
- between asymptomatic to a severe malabsorption syndrome.
- Celiac disease can occur at all ages and 40% of patients are being
- diagnosed Above the age of 40 years .
- The incidence has been steadily rising over the last 50 years, which
- can only partly be attributed to heightened awareness and better diagnostic modalities

- The etiology is a complex interaction between genetic,
- environmental and immune factors that is not fully understood.
- Epidemiological studies have shown that first degree relatives
- have a 5–20% risk of disease and a high degree of concordance
- in monozygotic twins of approximately 70% points towards a
- strong genetic preponderance
- Positivity for the HLA class II alleles HLA-DQ2 or DQ8 is a
- prerequisite to develop disease but not sufficient since 30–40% of
- The Caucasian population is carrier of one or both of these alleles

- Revealing the functional consequence of these
- genetic polymorphisms will provide further insight
- in the pathogenesis of this disease .
- The HLA association in celiac disease can be explained by
- the ability of HLA-DQ2 to bind the proline-rich gluten
- peptides that have survived gastrointestinal digestion.
- After intestinal absorption of gluten peptides the enzyme
- tissue transglutaminase is responsible for deamidation of
- these gluten peptides into negatively charged molecules

- Deamidation is crucial in converting poorly immunogenic
- wild-type gluten peptides to highly immunogenic antigens
- for CD4+ T-cells .
- The peptides are then presented by HLA-DQ2 or DQ8 antigen
- presenting cells to gluten specific CD4+ T-cells, which leads to
- activation of lamina propria T-cells that subsequently excrete
- proinflammatory cytokines such as IFNγ and IL-21

- IL-21 playing a role in T-cell dependent B-cell responses .
- Interleukin 15 (IL-15) produced by epithelial cells stimulates
- expansion of intraepithelial lymphocytes (IELs) as well as
- upregulation of the activating NKG2D receptor which
- licenses these cytotoxic IELs to kill intestinal epithelial cells

- What drives the expression of IL-15 is an unanswered question,
- but may be related to epithelial stress triggered by
- microbiota-derived innate signals or by peptides present in
- wheat or gluten .
- During disease activity numbers of both αβ T-cells and γδT-cells
- are increased in the duodenal epithelium.
- In contrast to numbers of αβ T-cells that correlate with disease activity,
- the γδ T-cell population remains enlarged in all stages of the disease

The histological presentation of autoimmune enteropathy

- **The histological pattern of autoimmune enteropathy is variable**
- **With variety of presentations that often are indistinguishable**
- **from other inflammatory disorders**
- **Originally partial or complete blunting of the villi, deep crypt**
- **lymphocytosis, increased crypt apoptosis, and minimal surface**
- **intraepithelial lymphocytosis,**
- **described as histological patters in AIE**

histopathologic pattern of AIE

- **This mixed histopathologic pattern combined**
- **with inefficacy of gluten-free diet allow**
- **differentiating AIE from celiac disease.**
- **Treatment remains challenging because AIE**
- **patients are only variably improved by steroids**
- **and immunomodulators**

- Recently it has
  been shown that tissue resident, innate-like γδ T-cells are irretrievably lost in CD, and the vacant immunologic space is filled with circulating γδT-cells that together permanently alter the γδ T-cell compartment in CD patients The long lasting hypothesis of a viral infection triggering the onset of disease is
  supported by murine studies showing that mice carrying HLA-DQ8, which develop gluten-specific CD4+ T-cells, lose tolerance to gluten when infected by a rotavirus

- Also recent epidemiological studies in children at risk of CD
- showed the appearance of transglutaminase antibodies within the
- three months following an episode of gastrointestinal infection
- whereas risk of CD decreased in children vaccinated against
- rotavirus before three months of age
- For screening purposes serological markers such as tissue transglutaminase
- IgA antibodies (TGA) and anti-endomysium antibodies (EMA) are useful tests
- with a combined sensitivity and specificity of 98% and 100% respectively .

- Yet, it should be kept in mind that 2%–3% of CD patients
- lack these antibodies
- Endoscopic abnormalities in CD include scalloping folds,
- reduced duodenal folds and mucosal cracks or a mosaic
- pattern
- Nevertheless, these endoscopic findings lack sensitivity,
- specificity
- Histology will display intra-epithelial lymphocytosis, crypt
- hyperplasia ,villous atrophy to a various extent, which is
- defined accordingly to the modified Marsh criteria .

underlying immune dysregulation

- **AIE is increasingly being recognized in adults,**
- **its characterization remains limited to a handful of case**
- **reports and small case series.**
- **its varied heterogeneous clinical associations and presentations**
- **suggest that adult AIE represents a collection of several entities**
- **unified by underlying immune dysregulation.**
- **From here we will focus on these adult forms of AIE**

- Intestinal TGA deposits measured in biopsy specimen
- appear more sensitive than serological test as these deposits
- can be found in seronegative CD patients
- These intestinal TGA deposits slowly decrease upon a GFD
- In addition, measuring TGA in culture supernatants of duodenal
- biopsies from CD patients appears even more sensitive and specific

- However, these techniques are laborious and costly and
- not used in daily clinical practice.
- A recently developed technique to detect gluten specific T-cells
- in biopsies and blood with the use of HLA-DQ2.5-gluten tetramer
- technology holds great promise since this technique is able
- to detect such cells even years after the instigation of a gluten
- free diet

Refractory celiac disease

- **After initiation of a GFD the majority of CD patients experience**
- **clinical improvement within weeks despite the fact that villous**
- **Atrophy can persist over a long period (6 months–5 years, median of**
- **1.3 years) in more than 40% of patients on a GFD**
- **Persisting or recurring of symptoms are most often due to**
- **(inadvertent) gluten contamination**
- **Refractory celiac disease (RCD) is defined as persisting symptoms and**
- **concomitant histologic abnormalities despite a strict gluten**
- **free diet for at least 12 months as objectified by normalization of antibodies .**
- **Extensive work-up may be necessary to eliminate other**
- **enteropathies which cannot be treated with a GFD**

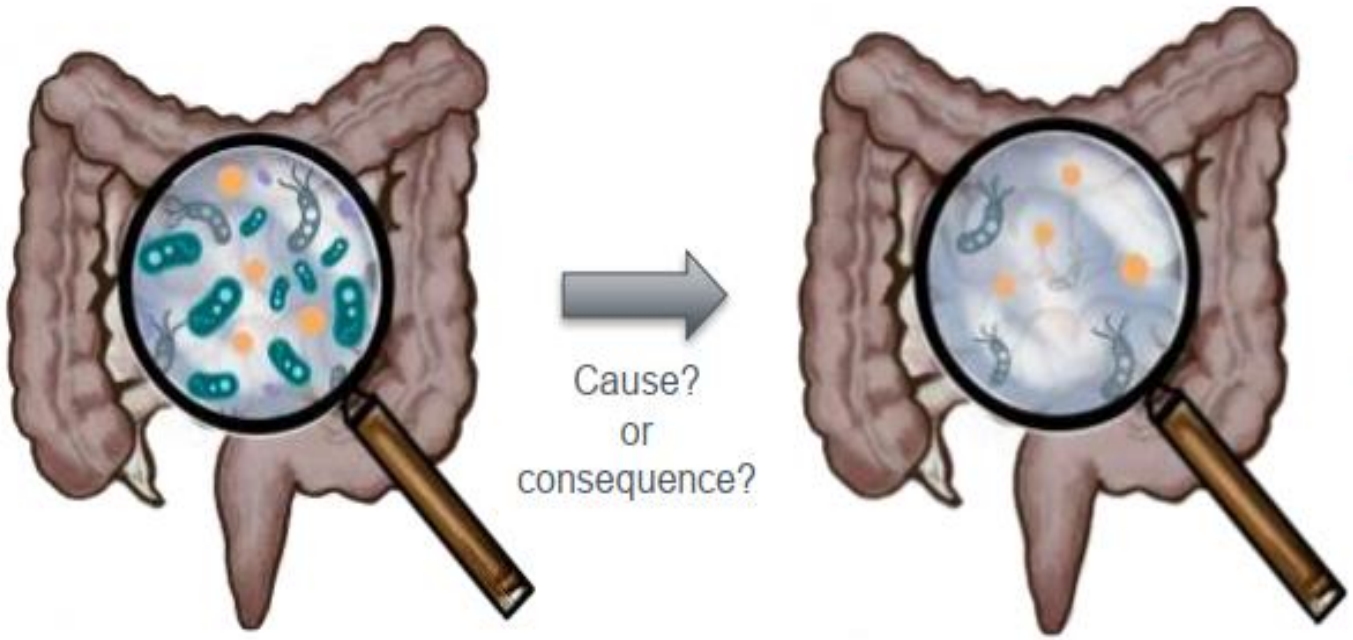
- RCD affects women two to three times more often than men,
- usually affects individuals over 50 years of age
- RCD can be distinguished based on the absence (RCDI) or presence
- (RCDII) of a premalignant, clonal population of intra-epithelial
- lymphocytes (IELs) with a distinctive phenotype.
- Primary non-responsiveness to a GFD in newly diagnosed patients
- is observed in 30% of RCDI and 50% of RCDII
- Population based studies show a low prevalence of RCD
- in CD patients, varying between 0.31% and 0.70%

- This is in line with findings from tertiary referral centers that
- evaluate CD patients non-responsive to a GFD and only a
- minority of these patients (1–23%) are in fact diagnosed with
- RCD
- The premalignant, clonal population of IELs in RCD comprise a
- lineage negative subset that is distinct from T, B, NK and
- lymphoid tissue inducer cells .

- Lack of surface expression of CD3, CD8 and the T-cell
- receptor (TCR) in combination with intracellular expression of
- CD3 and surface expression of the natural killer (NK) receptor
- NKP46 separates these cells from normal IELs.
- Indeed these cells that are active in RCD patients on a GFD appear
- to be gliadin (gluten) independent .
- Furthermore, there is marked heterogeneity in cytokine
- Responsiveness
- of the aberrant cell lines among RCDII patients as most respond
- to IL-15, but others to IL-21 and or IL-2

Microbial proteases in gastrointestinal disease?

- Microbial proteases are structurally and functionally highly diverse compared to human proteases.
- Considered virulent factors in infectious agents.



- Inflammatory bowel disease
- Irritable bowel syndrome
- Celiac disease

Several studies have described alterations ("dysbiosis") in common GI conditions

- In clinical practice three methods are used to identify this clonal
- aberrant cell population;
- TCRG clonality analysis and phenotypical analysis using
- immunohistochemistry or flow cytometry
- Common TCRG clonality analysis is however sensitive nor specific
- Additional analysis of the TCRB gene rearrangement pattern improves
- sensitivity, but is not yet widely available

- Immunohistochemistry uses the aberrant phenotype of these
- cells that loose both CD3 and CD8 on cell surface, but still
- contain CD3 in the cell cytoplasm.
- Flow cytometric analysis allows a much more accurate
- identification of IEL subsets, including the aberrant IEL
- population, and is superior to immunohistochemistry,
- as well as TCRG clonality analysis in identifying pathologically enlarged IEL populations

The main clinical problem in patients with IME

- **the most important discovery has been the identification of**
- **Olmesartan use as a cause of enteropathy With severe**
- **Malabsorption and its associated complications.**
- **the increased risk of developing an aggressive (EATL)**
- **enteropathy-associated T-cell lymphoma, observed in**
- **CD patients, CD patients refractory to a gluten free diet (GFD) ,**
- **in patients with AIE, even though it concerns a small absolute risk,**
- **has led to distress among patients and clinician**

Inflammatory response in celiac disease

- Gluten peptides that are preserved despite digestion are able to cross the intestinal epithelium, and subsequently undergo deamidation by the enzyme tissue transglutaminase (TG2). The negatively charged peptides now fit well on the HLA-DQ 2.2, DQ2.5 and DQ8 molecules that are present on antigen presenting cells (APC's) such as dendritic cells. After stimulation by these APC's, primed gluten specific CD4+ T cells migrate from the mesenteric lymph node towards the lamina propria and produce proinflammatory cytokines (IFNγ, IL-21, TNFα). In addition, gluten peptides induce expression of IL-15 and stress molecules on enterocytes.

- Together these cytokines initiate enterocyte killing by intraepithelial CD8+ cytotoxic T-cells. Stressed epithelial cells also upregulate expression of major histocompatibility complex class I chain-related gene A (MICA) that costimulate cytotoxic CD8+ T-cells that express natural killer receptors (NKR). Gluten reactive CD4+ T-cells stimulate B-cells to become tissue transglutaminase antibody and deamidated gliadin peptide antibody producing plasma cells. When abundantly secreted, these antibodies can be found in the peripheral blood. Fig. 1B**.** Refractory celiac disease type II (RCDII) is characterized by a clonal population of innate like T-IEL with an unusual phenotype

- They lack expression of surface CD3-TCR complexes and CD8 but they contain intracellular CD3
and display clonal rearrangement of TCR genes. They also express NK receptors, notably NKp46. These cells are hyper responsive to IL-2, IL-15 and IL-21, possibly to
JAK1 and STAT3 gain of function mutations (gof), and will dominate the gut epithelium. IL-15 is mainly produced by epithelial cells, while the source of IL-2 and IL-
21 secretion is unclear; yet the association with HLA-DQ 2.5 homozygosity suggests that CD4+ T-cells are somehow involved despite the absence of gluten exposure.
The clonal innate-like T-IEL contain high levels of intracellular granzyme B, and are able kill enterocytes. In addition, the clonal innate-like T-IEL population is prone to gain additional chromosomal mutations, and therefore is at risk to progress to an enteropathy-associated T-cell lymphoma.

Refractory celiac disease type I

- RCDI is defined by persistent villous atrophy despite a strict GFD longer than 1 year that leads to concomitant symptoms such as diarrhea, steatorrhea, abdominal pain, weight loss and-or nutritional deficiencies. Establishing the diagnosis of RCDI can be difficult as a diagnostic test is lacking and the diagnosis is based on exclusion of other concomitant diseases that can result in similar symptoms [57]. Since a relatively high percentage of RCDI patients was HLA-DQ2 and -DQ8 negative in some studies, it cannot be fully excluded that some of these patients may have suffered from other diseases than (R)CD

- Another challenge in the diagnosis of RCDI is that persistent villous atrophy is frequently present in asymptomatic CD patients and those patients are referred to as slow responders and are generally believed not to require additional immunosuppressive treatment.
- For instance, after one and five years of following a GFD respectively up to 80% and 40% of adult-onset CD patients still display villous atrophy [59–65]. So distinguishing patients with persistent villous atrophy without symptoms (slow responders) from those with symptoms (RCDI) might sometimes be controversial as for instance abdominal pain or diarrhea could well be caused by concomitant disease.

- While the 5-year survival in RCDI patients is similar as compared to the general population, symptoms and-or nutritional deficiencies may warrant immunosuppressive treatment
- Budesonide, prednisone or a combination of prednisone with azathioprine are effective in inducing clinical and histological remission .
- The risk of developing an EATL in RCDI is low as these patients lack an premalignant aberrant IEL population

Refractory celiac disease type II

- RCDII is characterized by a clonally expanded IEL population with an aberrant (cytCD3+ CD7+ sCD3- CD4- CD8-) phenotype [41]. In patients with an EATL the same T-cell clone has been identified in both the aberrant IEL population and the EATL, which has led to the believe that aberrant IEL are precursor EATL cells [74,75]. RCDII seems an inappropriate name as some patients present with an aberrant IEL population at the time of CD diagnosis and therefore are strictly not yet refractory to a GFD [76]. During (capsule) endoscopy it is not uncommon to find an ulcerative jejunitis in these patients.

- Aberrant clonal IELs derive from a small subset of unusual innate-like IELs present in the normal intestine [47,52,77]. The proliferation of these cells is gliadin-independent since dominant TCR clones in RCDII patients show sequences distinctive from gliadin restricted T-cells [48]. Gluten specific CD4+ T-cells isolated from CD duodenal biopsy specimens produce IL-2 and IL-21 that are able to trigger proliferation of these aberrant IELs (Fig. 1b [78]. In addition, IL-15 has an anti-apoptotic effect on aberrant IELs and somatic JAK1 or STAT3 gain-of-function mutations (or both), which confer hyper-responsiveness to IL-15, further augmenting the massive expansion of this cell population

- The expression of the natural killer (NK) marker NKp46 on aberrant IELs, in presence of IL-15 leads to enterocyte killing which may explain the severe ulceration often seen in these patients [77]. RCDII enterocytes
  also strongly express MICA, a ligand for NKG2D that is present on aberrant IELs which may further contribute to this uncontrolled inflammation [50,80]. In addition, a genetic association study (GWAS) in RCDII patients identified a genetic polymorphism that may control expression of FAM188B, and by doing so tamper with tumour surveillance

- Approximately half of the RCDII patients develop an EATL within 5 years [42–44]. EATL are often located extra-intestinally which is in agreement with the finding that IELs are able to disseminate and can be found in the epithelium of the stomach and colon, as well as the bronchi and the skin [83,84]. Prognostic factors for the development of an EATL in a patient are the stage of cell maturation defined by the completion of the TCRB rearrangement, the scarcity of T-cell clones, as well as CD30 expression on aberrant IELs

- The 5 year survival in RCDII patients is poor (44–58%) which, in addition to severe malabsorption is mainly due to the development of an EATL [42–44]. There is a clear genetic association with both RCDII and EATL with HLA-DQ2.5 homozygosity, suggesting a predisposing role of a strong anti-gluten responses [50,58]. Yet, there are conflicting results regarding the protective effect of a GFD on the development of EATL [86–88]. It should be noted that the majority of EATLs arise in non-recognized CD patients (primary EATL) instead of (R)CD patients (secondary EATL) [89]. Currently it is unclear whether EATLs that develop from clonal aberrant IELs in RCDII patients differ phenotypically or genetically from EATLs that develop in CD patients without these clonal aberrant IEL populations.

- In attempt to eradicate the premalignant aberrant IEL population treatment various chemotherapeutic agents have been tried with limited success, probably because these cells have a low proliferative rate [50]. Cladribine, a purine analogue that induces T-cell depletion, has shown to decrease the risk of EATL development in RCII patients [90]. Cladribine is able to induce histological recovery but does not fully eradicate the aberrant IEL population.(80, 81) Histological recovery appears the best prognostic factor for a decreased risk of EATL development in these patients, probably because it represents absence of ongoing inflammation

- In case of non-responsiveness to cladribine
  therapy, autologous stem cell transplantation has beneficial effects in patients that are eligible for this intense treatment [92]. A recent double-blind placebo controlled trial evaluating the effect of anti-IL-15
  treatment did not find a difference between the groups in terms of the primary endpoint of aberrant intraepithelial lymphocyte reduction from
  baseline but appeared to have a positive impact on clinical symptoms

- This protein participates in interactions between membrane
- associated proteins and other cytoplasmic proteins involved in
- cytoskeletal arrangement, tight junction formation and in
- the regulation of paracellular enterocyte permeability
- and thus provide a plausible pathogenic mechanism for disease.
- Although many patients succumb before the age of three due to
- Either severe enteropathy or fatal infections unless they receive a
- hematopoietic stem cell transplant, some present with a milder
- form and survive to adolescence

Autoimmune enteropathy

- **In the late 1970s an adolescent was described with diarrhea and**
- **autoantibodies binding to the cytoplasm of the intestinal epithelium,**
- **which responded to immunosuppressive therapy .**
- **In the same period, familial syndromes were described with intractable**
- **diarrhea in the presence of other autoimmune disorders.**
- **In 1985 Unsworth and Walker-Smith were the first to use the term**
- **autoimmune enteropathy (AIE) for intractable diarrhea in the pediatric**
- **population, weight loss from malabsorption and immune-mediated**
- **intestinal damage in the absence of immunodeficiency**

Crohn’s disease

- Dendritic cells and macrophages in CrD respond with production of pro-inflammatory cytokines TNF-α, IL-12 and IL-23. TNF-α prevents apoptosis of T-cells and secondarily increases the intestinal permeability [160]. IL-12 induces CD4 helper T-cell into a Th1 differentiation that produce IFN-y, IL-2 and IL-21. IL-23, which shares the IL-12p40 subunit with IL-12, induces a Th17 differentiation which leads to secretion of the pro-inflammatory Th17 cytokine thereby further enhancing inflammation [161]. ASCA have been used as a serological marker for CrD to differentiate it from UC, as it serves as a parameter for increased intestinal permeability [162]. Sensitivity and specificity are however limited

- Treatment consists of classical immunosuppressive drugs such as prednisone (systemic or topical), thiopurines as well as monoclonal antibodies that intervene in various parts of the immunopathogenesis.
  The first and most widely used MAB are anti-TNFα blockers. Other monoclonal antibodies that block the pro-inflammatory response are anti-IL12/IL23 blockers (ustikinimab) and JAK-inhibitors (tofacitinib). Furthermore, integrin-inhibitors (vedolizumab) prevent migration of lymphocytes to the gut-associated lymphoid tissues.

Eosinophilic (gastro-)enteritis (EGE)

- **Eosinophilic gastrointestinal disorders are a group of diseases**
- **That include eosinophilic esophagitis, eosinophilic gastritis,**
- **Eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis.**
- **eosinophilic gastroenteritis is an uncommon and heterogeneous disease**
- **characterized by eosinophilic infiltration of the gastrointestinal tract in**
- **the absence of secondary causes.**
- **Patients can present with a variety of symptoms, depending on**
- **the site of inflammation and the depth of eosinophilic infiltration,**
- **can be predominantly mucosal, muscular or serosal.**

- A first step in treatment it is advocated to evaluate the presence of sensitization by food skin testing and-or specific IgE [163]. When sensitization is present a trial of food elimination can be initiated. When
sensitization is not objectified or food elimination failed, in severe cases
immunosuppressive drugs such as budesonide and thiopurines appear
effective

Celiac disease

- **Celiac disease (CD) is a gluten sensitive T-cell mediated**
- **Enteropathy in genetically susceptible individuals.**
- **Gluten is the common denominator for staple proteins**
- **found in wheat, barley, and rye.**
- **They comprise hundreds of proteins with repeated sequences**
- **rich in proline (e.g. gliadin) and glutamine which renders them**
- **highly resistant to enzymatic breakdown.**

- Review histologic findings with experienced pathologists who specialize in gastroenterology.
- Serologic tests are essential for an accurate diagnosis of celiac disease.
- For patients with suspected celiac disease but negative results from
- serologic tests, total IgA level should be measured;

- patients should also be tested for antitissue transglutaminase,
- IgA against deamidated gliadin peptide, and endomysial antibody (IgA).
- Patients with total IgA levels below the lower limit of detection
- and IgG against tissue transglutaminase or deamidated gliadin
- peptide, or endomysial antibody, should be considered to have celiac disease with selective IgA deficiency rather than seronegative celiac disease.

- Patients’ diets should be carefully reviewed and duodenal biopsies should be collected and analyzed at the time of serologic testing to determine exposure to gluten and accuracy of test results.
- Thorough medication histories should be collected from patients, with attention to angiotensin II receptor blockers, such as olmesartan, along with travel histories to identify potential etiologies of villous atrophy. This will guide additional testing

- Patients should be analyzed for disease associated variants in human leukocyte antigen genes; results must be carefully interpreted. Negative results can be
  used to rule out celiac disease in seronegative patients
- Patients with suspected celiac disease
  who are seronegative but have villous atrophy and genetic risk factors for celiac disease must undergo endoscopic evaluation after 1–3 years on a gluten-free diet to evaluate improvements in villous atrophy. A diagnosis of seronegative celiac disease can then be confirmed based on clinical and histologic markers of improvement on the gluten-free diet.

- Seronegative patients with an identified cause for enteropathy should be treated accordingly; a follow-up biopsy might or might not be necessary.
- Patients with persistent signs and symptoms who do not respond to a gluten-free diet, and for whom no etiology of enteropathy is ultimately identified
- should be treated with budesonide.

Eosinophilic (gastro-)enteritis (EGE)

- EGE can occur in all age-groups with a peak incidence between 30 and 40 years of age without a clear sex predisposition [164]. Genetic susceptibility is illustrated by the finding that 10% of EGE patients has a first degree relative with EGE [165]. Furthermore, a role for allergy is suggested as up to 75% of patients have an atopic medical history [163]. Eosinophils are present in intestinal mucosa in the physiological state, but numbers within a healthy individual vary depending on the segment of the GI-tract [166]. For example, eosinophils are more abundant in the appendix and cecum. Furthermore, numbers of eosinophils vary among individuals depending on region, climate, season, age, infections and food allergens

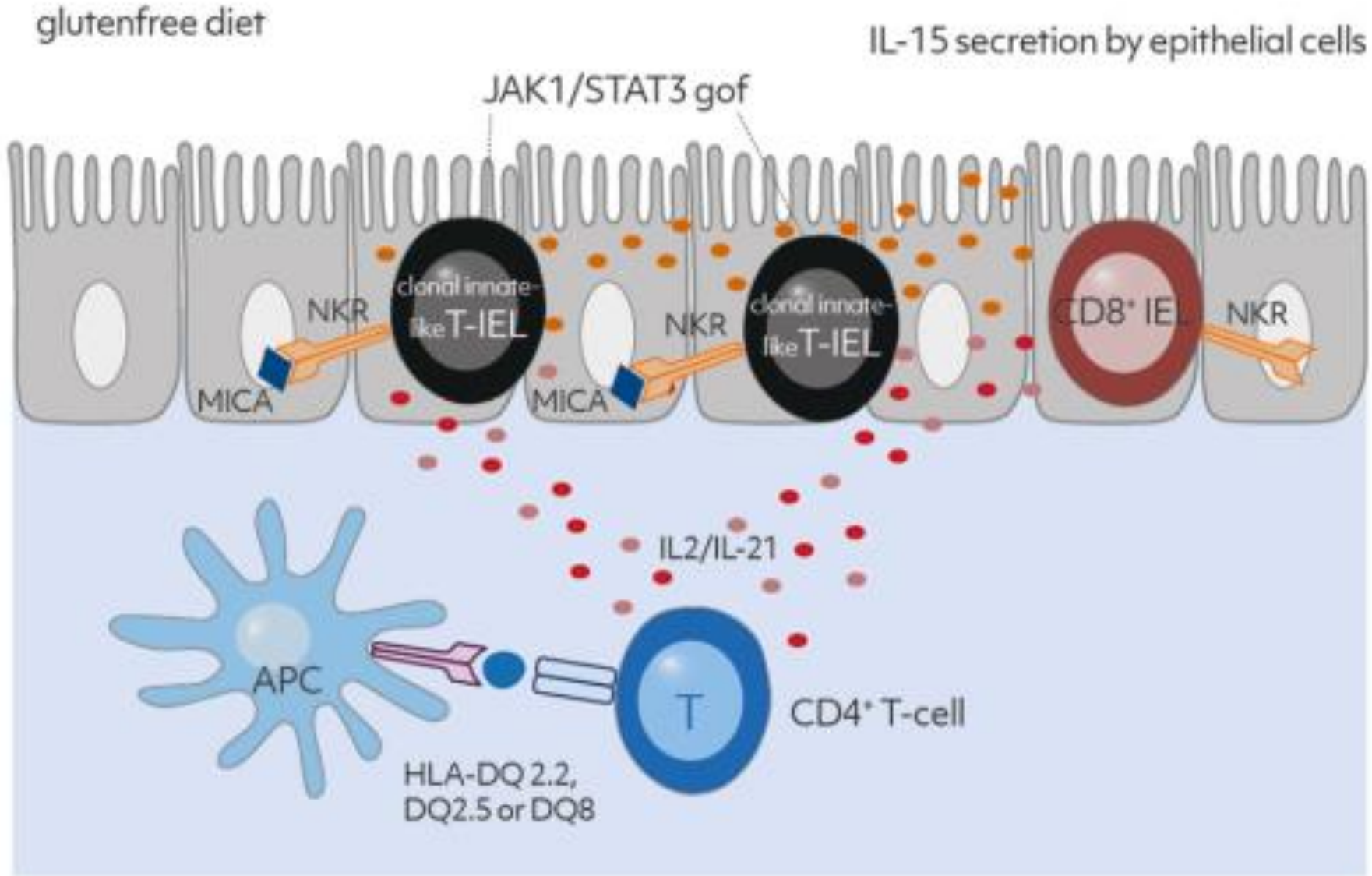
Angiotensin II receptor blocker Associated Enteropathy

- **Olmesartan, an angiotensin II receptor blocker used**
- **For treatment of hypertension, has been associated with a**
- **severe enteropathy . More than 100 cases of olmesartan-associated**
- **enteropathy (OAE) have been described.**
- **it might be quite common in patients with unexplained enteropathy**
- **Patients usually present with non-bloody diarrhea and weight loss,**
- **but severe dehydration with electrolyte imbalances and acute renal failure have been reported**

Angiotensin II receptor blocker Associated Enteropathy

- **Men and women are equally affected in the seventh and**
- **eight decade of life, when the prevalence of hypertension**
- **Some have reported a substantial concomitant presence of**
- **extra-intestinal autoimmune disease which indicates a genetic susceptibility**
- **Histopathology can mimic AIE, especially with respect to**
- **intra-epithelial lymphocytosis within or close to normal limits,**
- **loss of Paneth and goblet-cells, and crypt apoptosis.**
- **subepithelial collagen deposition are reported**

- Mycophenolate mofetil is another drug that has been associated with new onset diarrhea and villous atrophy in four patients who used this drug to prevent rejection after renal transplantation, with complete recovery of symptoms after cessation of the drug [132]. More recently,
  watery diarrhea and apoptotic enteropathy has been associated with the
  use of methotrexate, capecitabine and TNFα inhibitors, indicating that clinicians and pathologists should be aware of the expanding spectrum
  of drugs that can cause apoptotic enteropathy


glutenfree diet
IL-15 secretion by epithelial cells
JAK1/STAT3 gof
NKR
clonal innate-like T-IEL
MICA
NKR
clonal innate-like T-IEL
MICA
CD8⁺ IEL
NKR
IL2/IL-21
APC
T
CD4⁺ T-cell
HLA-DQ 2.2, DQ2.5 or DQ8

AIE with Genetic Syndromes

- **The APECED syndrome ,autoimmune phenomena,**
- **polyendocrinopathy, candidiasis, and ectodermal dystrophy,**
- **known as autoimmune polyglandular syndrome 1 (APS-1),**
- **is another rare monogenic autoimmune disease, with an**
- **autosomal recessive inheritance.**
- **The responsible gene, AIRE (autoimmune regulator), encodes**
- **a protein involved in architectural organization of the thymic**
- **Microenvironment essential normal processes of T-cell**
- **intra-thymic negative selection**

the underlying molecular mechanism

- **identification of the underlying molecular mechanism**
- **is crucial to treat unresponsive patients.**
- **Genetic studies have revealed that several monogenic inborn**
- **errors of immunity, notably NFKB1 ,CTLA4 (cytotoxic T-lymphocyte**
- **-associated protein 4)**
- **haploinsufficiency, and LRBA (LPS responsive beige-like**
- **Anchor protein) deficiency**
- **may manifest by AIE only at adulthood**