December 1, 2022

Immune Deficiency Foundation

MISSION STATEMENT

The Immune Deficiency Foundation improves the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education, and research.

Immune Deficiency Foundation

IDF provides accurate and timely information, resources, and support for individuals with PI and their families.

Immune Deficiency Foundation

THANK YOU TO OUR SPONSORS

DISCLAIMER

Immune Deficiency Foundation (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.

Immune Deficiency Foundation

Managing GI Issues and Primary Immunodeficiency

Sarah C. Glover DO
Professor of Medicine
University of Mississippi
Jackson, MS

Faculty Disclosure

- Research support: Bristol Myers Squibb, CCFA, Janssen, Takeda, UCB, Gilead, AbbVie
- Speakers bureau in past: AbbVie, Takeda and Janssen
- Data safety monitoring board: Janssen

Objectives

- Immunology and the GI Tract
- Infectious GI Diseases, COVID-19, and microbiome
- Inflammatory GI Disease
- NLH
- Liver and Biliary Disease
- Cancer and Neoplasia
- Diet, Nutrition, and Probiotics
- COVID

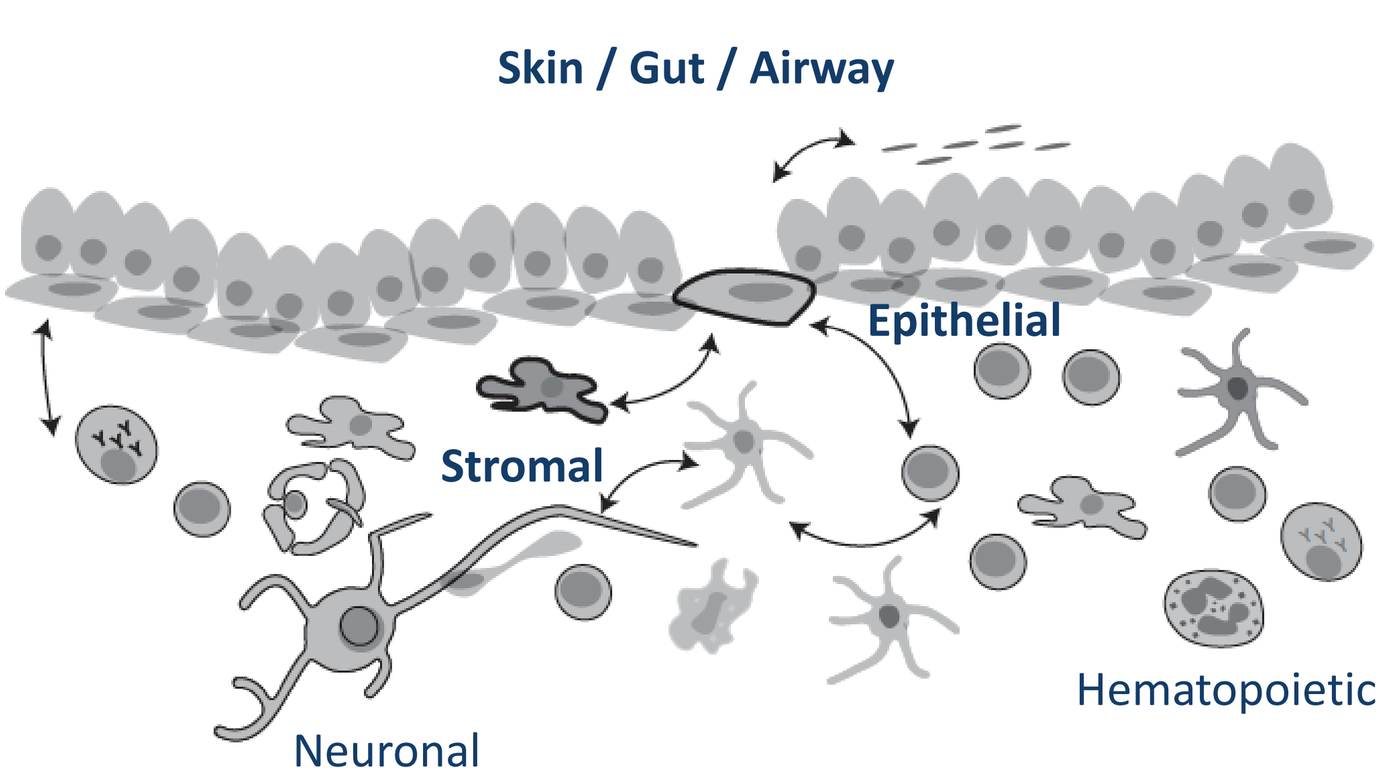
Barrier Tissue Adaptation and Memory

Input

Microbial

Abiotic

Injury



Output

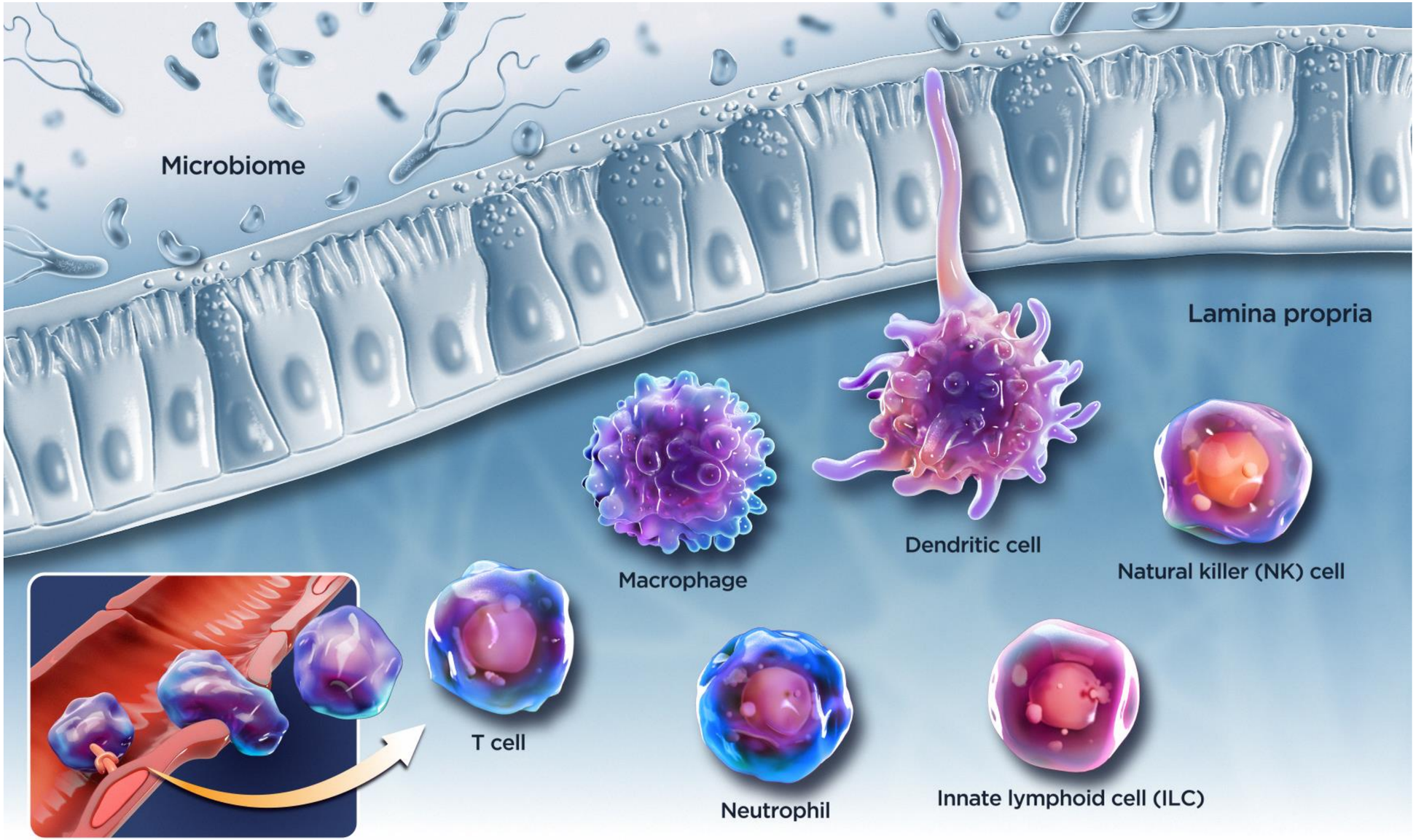
Defense

Metabolism

Repair

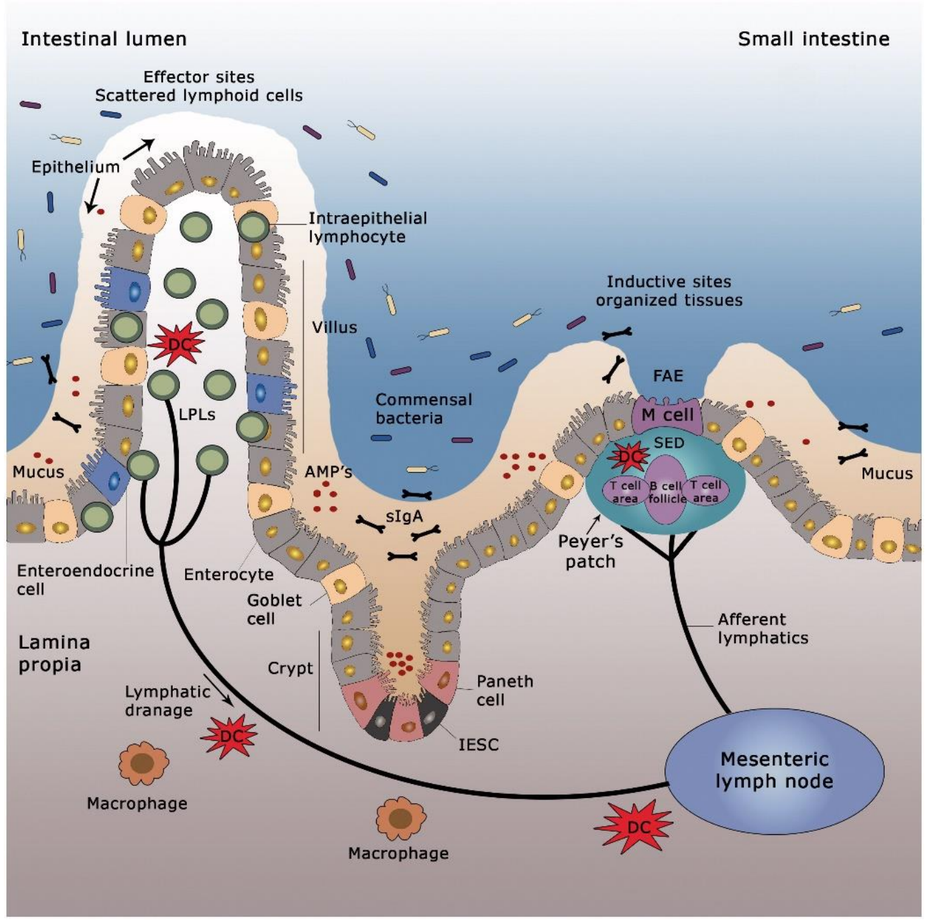
Ordovas-Montanes et al., (2020) Nature Reviews Immunology

The Normal Gut Barrier



1. Bamias G, et al. *Cytokine*. 2012;59:451-459. 2. Neurath M. *Nature Reviews*. 2014;14:329-342. 3. Dave M, et al. *Gastroenterol Clin N Am*. 2014;43:405-424.

Gut Barrier and GALT



Bani Ahluwalia, Maria K. Magnusson & Lena Öhman (2017) Mucosal immune system of the gastrointestinal tract: maintaining balance between the good and the bad, Scandinavian Jou of Gastroenterology, 52:11, 1185-1193, DOI: [10.1080/00365521.2017.1349173](10.1080/00365521.2017.1349173)

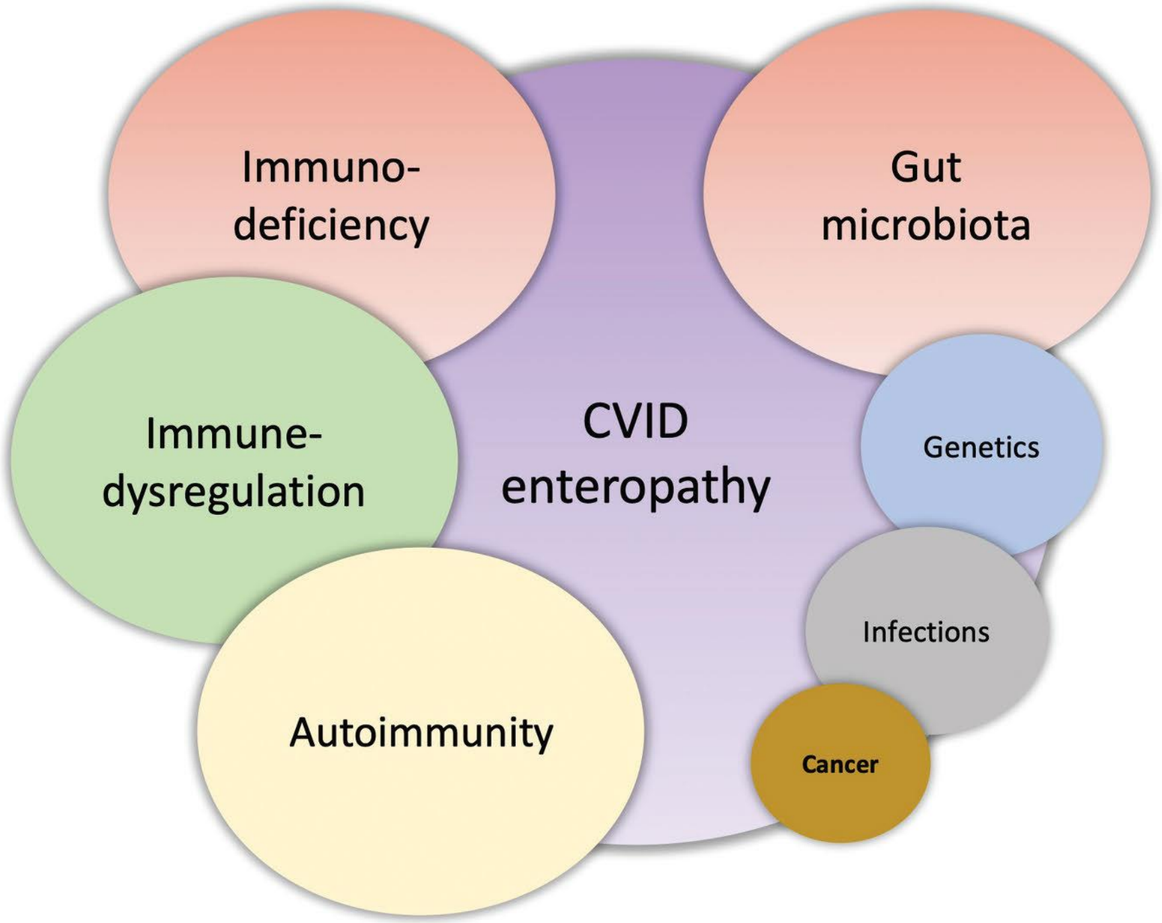
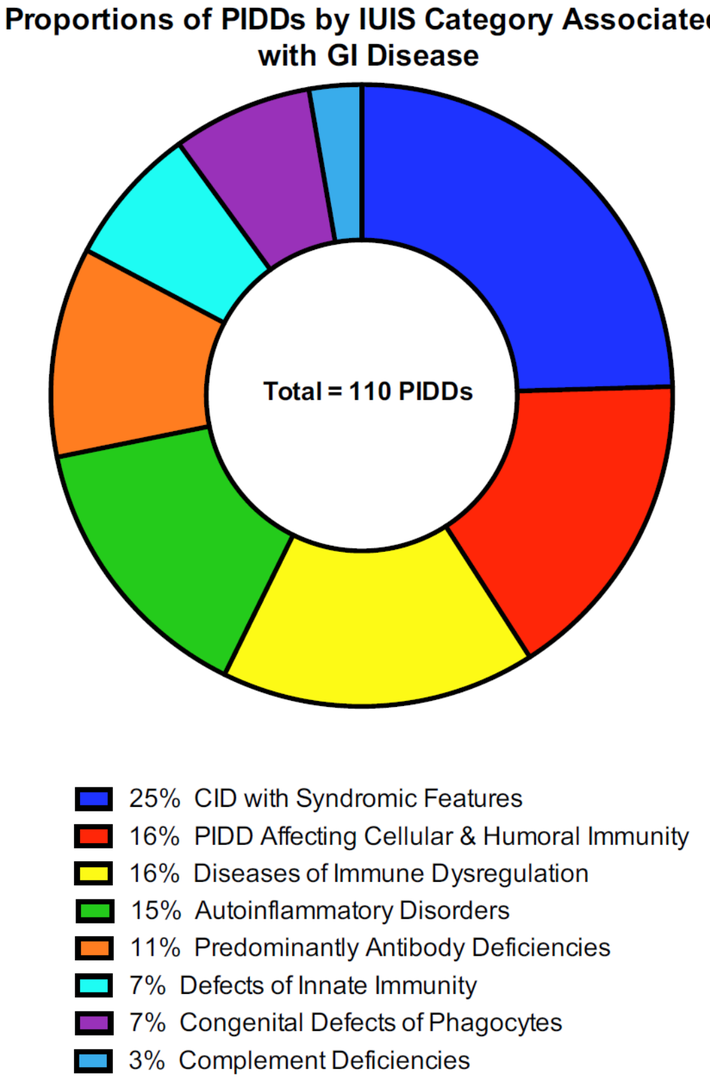


Figure 1. CVID enteropathy. A suggested etiology model of CVID enteropathy where the size of the circles reflects the suggested impact on the complex enteropathy phenotype.

Andersen and Jørgensen*. Expert Rev Clin Immunol.* Volume 18, Number 1, January 2022

Primary Immunodeficiency Syndromes and the GI Tract

- Of the more than 350 PIDDs, about 1/3 have some GI component
- GI symptoms and complications are often the initial sign of a PIDD
- GI symptoms may include:
  - Infectious diarrhea, inflammatory disease, liver/biliary disease, structural/oncologic disease, and malabsorption
- Treatment with replacement Ig in most cases does not reverse or prevent development of GI disease



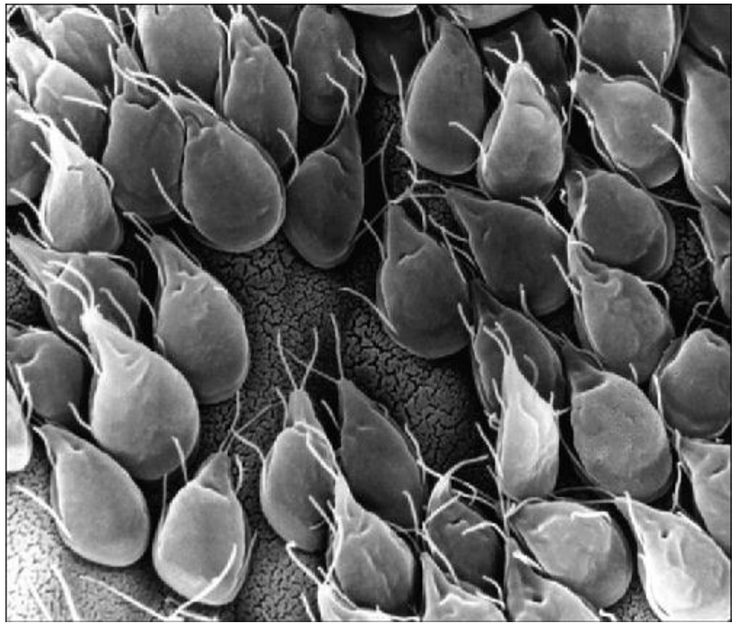
Hartono, S., Ippoliti, M.R., Mastroianni, M. et al. Clinic Rev Allerg Immunol (2018). https://doi.org/10.1007/s12016-018-8689-9

Infectious Diarrhea

- Defects in Humoral Immunity and Antibody production (B cells)
  - Increased risk of bacterial and viral infections
- Defects in T cells
  - Increased risk of viral and fungal infections
- Defects in T and B cells
  - Increased risk of bacterial, viral, and fungal infections
- Impaired phagocytosis
  - Increased risk of bacterial and fungal infections

What Infections to Look for?

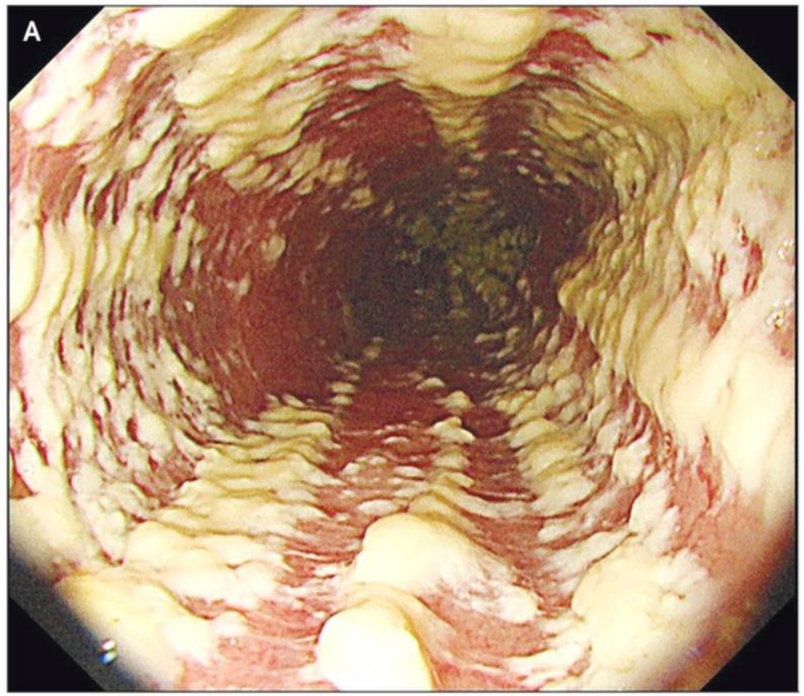
- CVID
  - Bacteria: Campylobacter, Salmonella, H. pylori
  - Viruses: CMV, norovirus
  - Fungal: Candida
  - Parasites: Cryptosporidium, Giardia lamblia
- Selective IgA Deficiency
  - Parasites: Giardia lamblia
- XLA & Hypogammaglobulinemia
  - Bacteria: Salmonella, Campylobacter, Shigella
  - Viruses: Rotavirus, coxsackievirus, echovirus
  - Parasites: Cryptosporidium, Giardia lamblia
- Diagnosis: GI PCR (institution dependent), Stool Cultures, Stool O&P
- SARS COV2



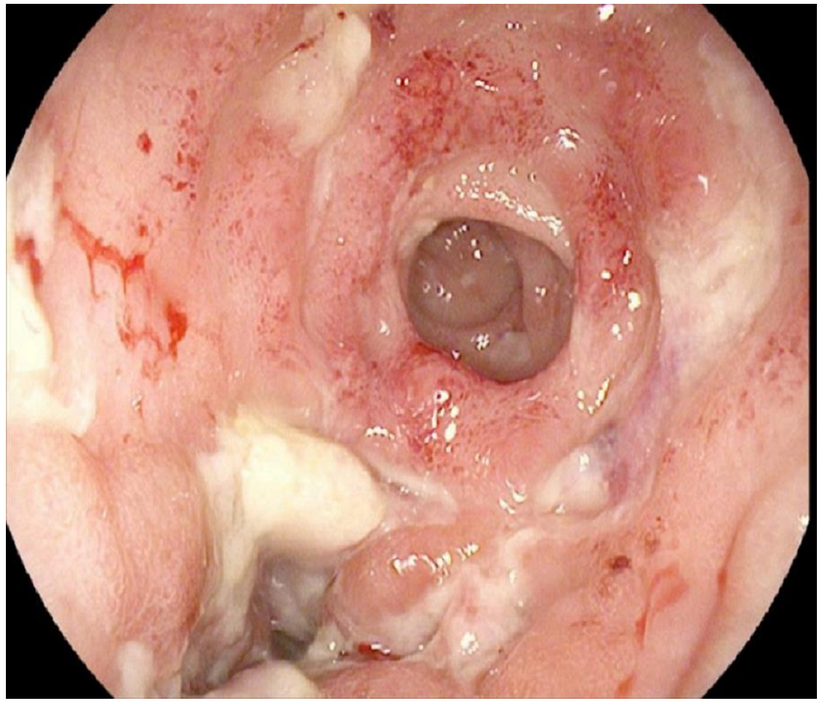
Treatments

- In general treatment is guided by results of lab testing and cultures
- In PI, treatment courses may need to be longer
  - Diarrhea despite eradication of infections suggests inflammatory or structural causes

Candida Esophagitis

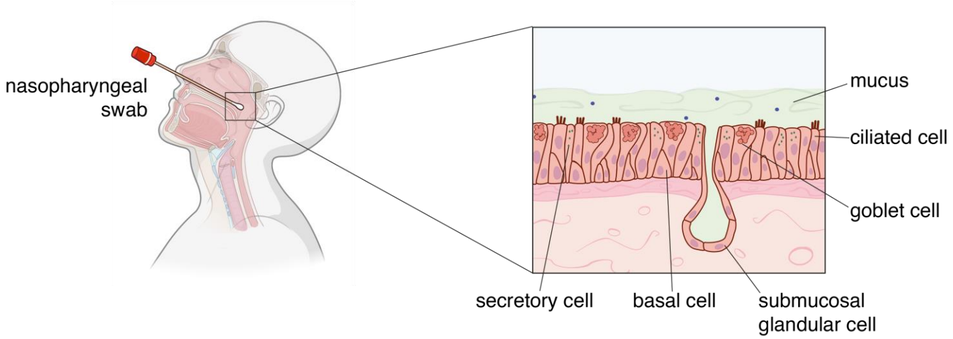


CMV Colitis

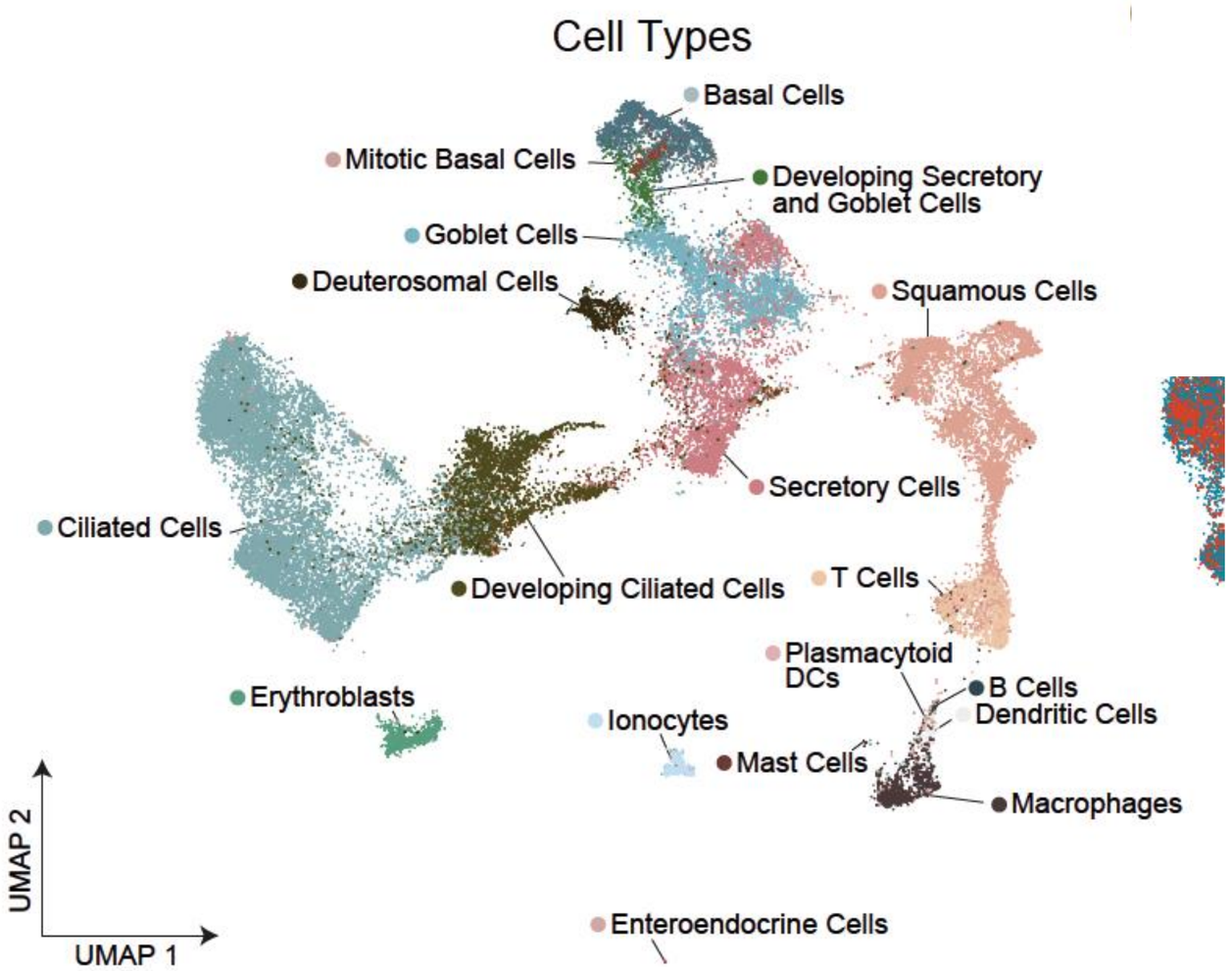


COVID-19

Covid-19: Nasopharyngeal Swab Cell Atlas

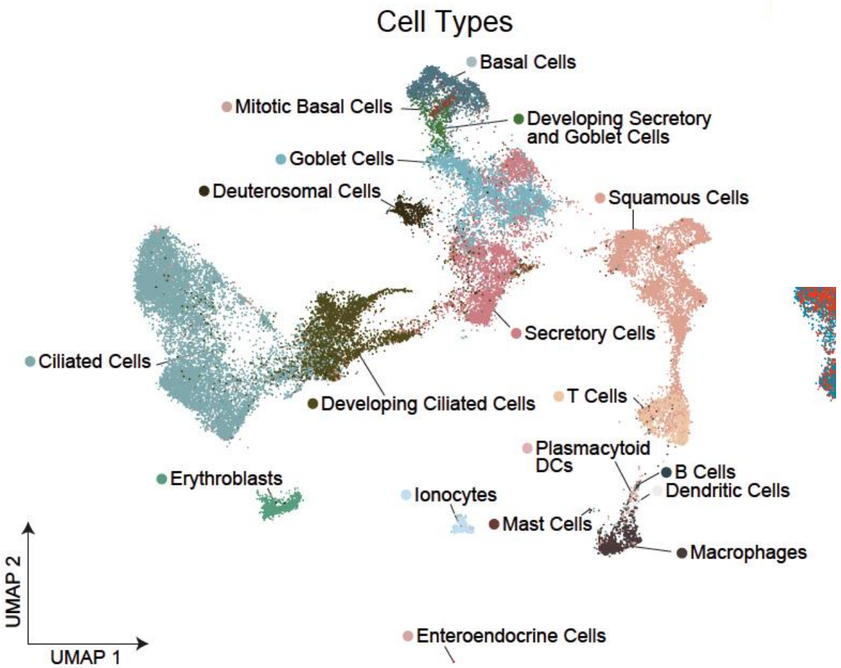


32,588 single cells total



Ziegler et al., (2021) Cell

Impaired local intrinsic immunity to SARS-CoV-2 infection underlies severe Covid-19



Open resource of Covid-19+ nasopharyngeal swabs

Identification of the full epithelial trajectory from frozen swabs

Identification of increases in goblet, deuterosomal, and secretory cells in Covid-19 patients

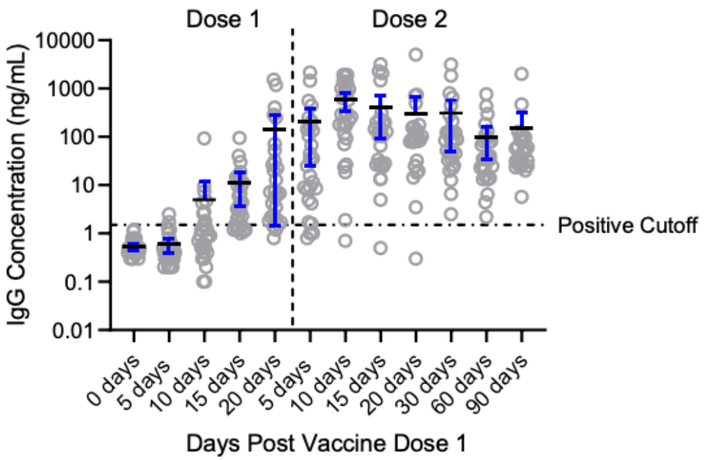
Identification of SARS-CoV-2 pos/neg strand reads at highest levels in goblet/secretory cells

Severe Covid-19 is characterized by a muted IFN-signature in the initial barrier tissue targeted by SARS-CoV-2

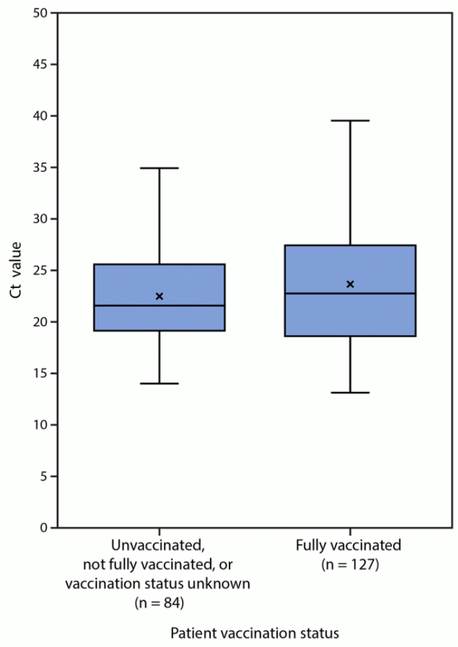
www.covid19cellatlas.org; Chan Zuckerberg Initiative Single-Cell COVID-19 Consortia (2020) medRxiv

Vaccines: early data on nasal mucosal immunity

Anti-Spike Nasal Antibodies post-Pfizer



Ct Values in Early Delta Wave "Provincetown" Study



Question: how does the inflammatory landscape or vaccination shift epithelial cell responses to challenge?

Mades et al., (2021) Scientific Reports; Brown et al., (2021) CDC Reports

Patient Cohort (total n = 124)

Ancestral Strain

- Control unvaccinated (n=15)
- COVID-19 unvaccinated (n=35)
  - mild-moderate WHO 1-5 (n=14)
  - severe WHO 6-8 (n=21)

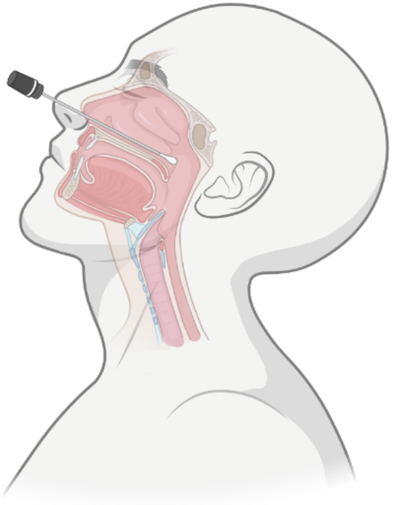
Delta

- Control vaccinated (n=15)
- COVID-19 unvaccinated (n=20)
  - mild-moderate WHO 1-5 (n=11)
  - severe WHO 6-8 (n=9)
- COVID-19 vaccinated (n=16)
  - mild-moderate WHO 1-5 (n=12)
  - severe WHO 6-8 (n=4)

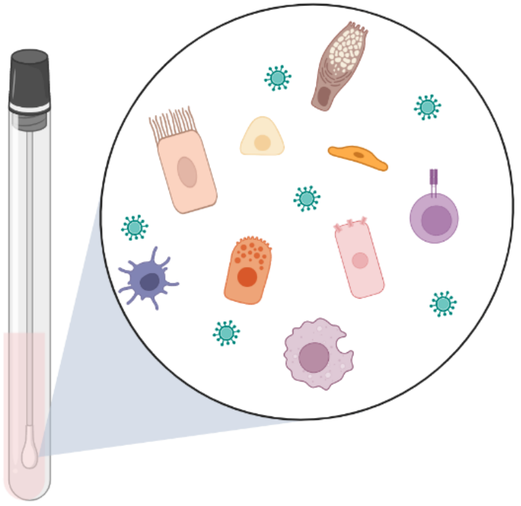
Omicron

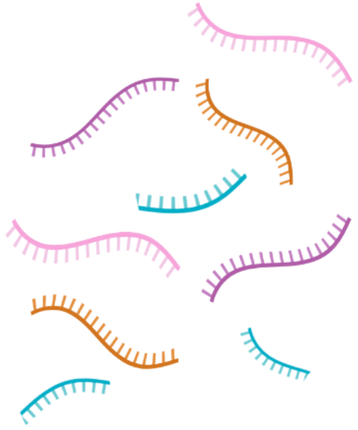
- COVID-19 unvaccinated (n=11)
  - mild-moderate WHO 1-5 (n=7)
  - severe WHO 6-8 (n=4)
- COVID-19 vaccinated (n=12)
  - mild-moderate WHO 1-5 (n=6)
  - severe WHO 6-8 (n=6)

Nasopharyngeal swabs

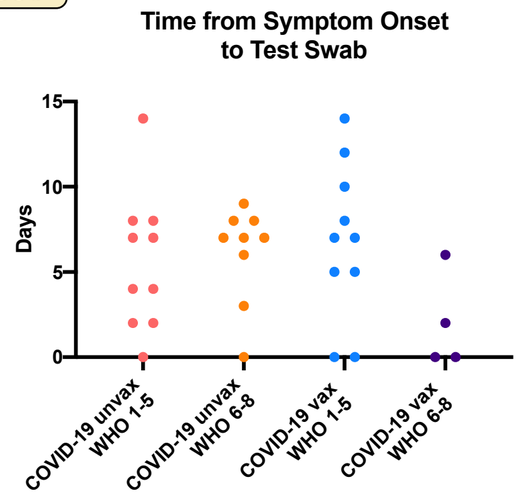


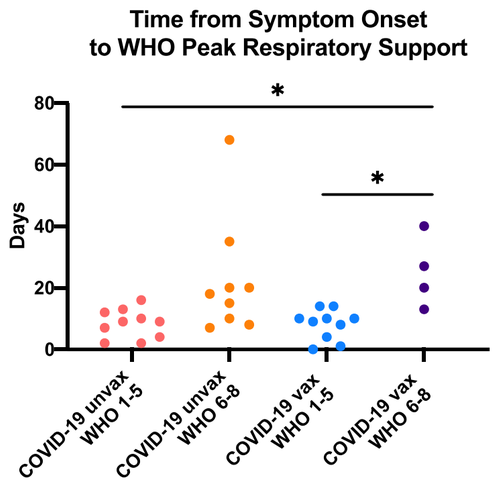
scRNA-seq of host + viral transcripts



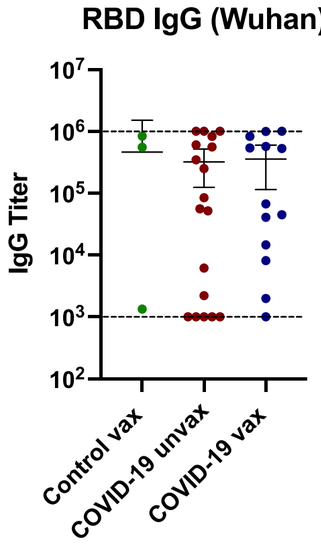


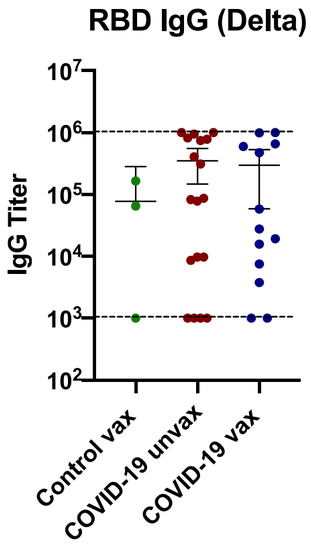
Delta

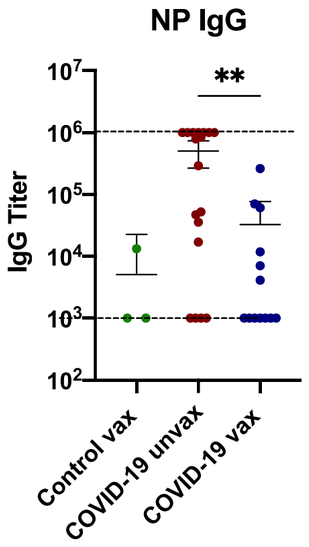




Sampling Kinetics

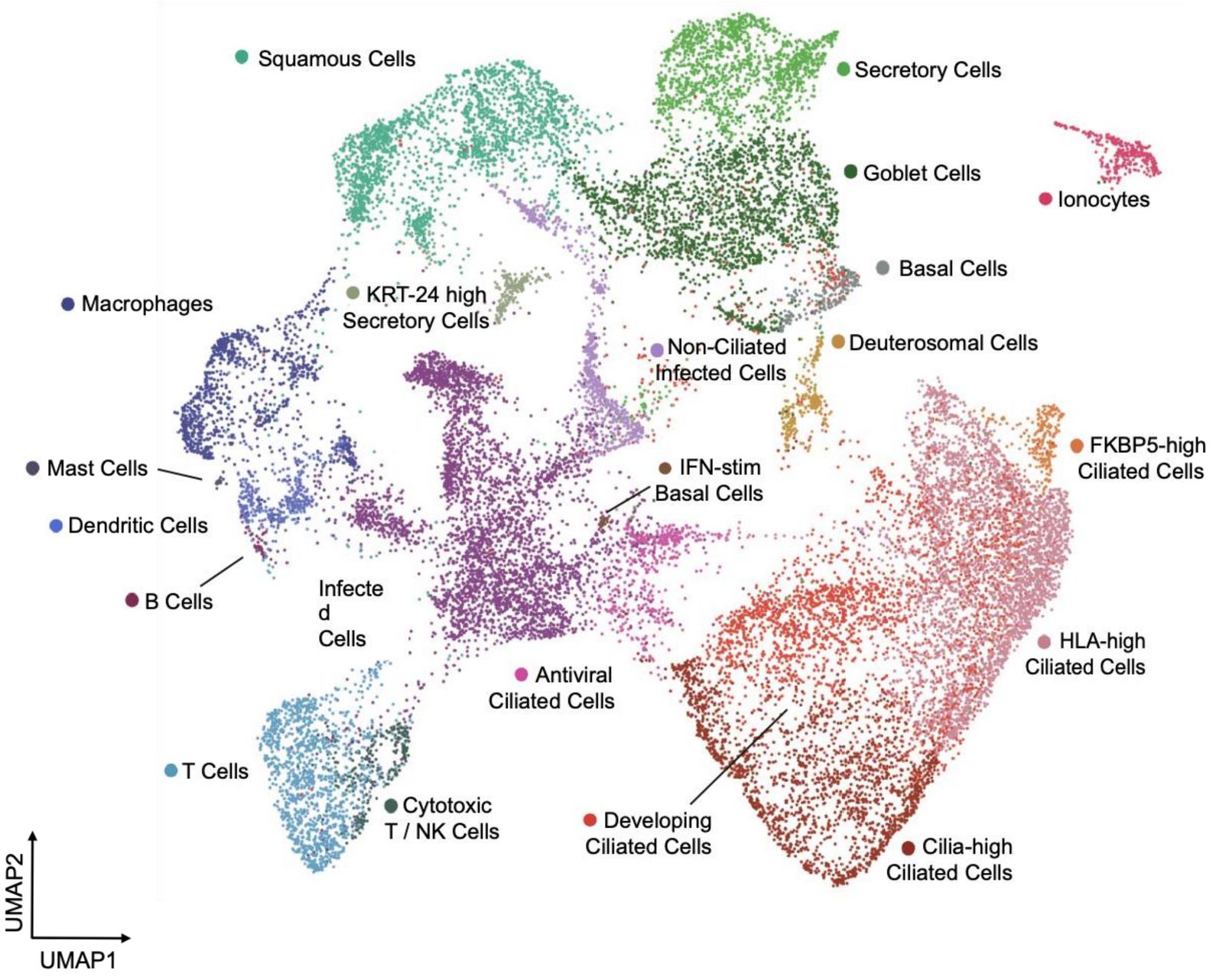


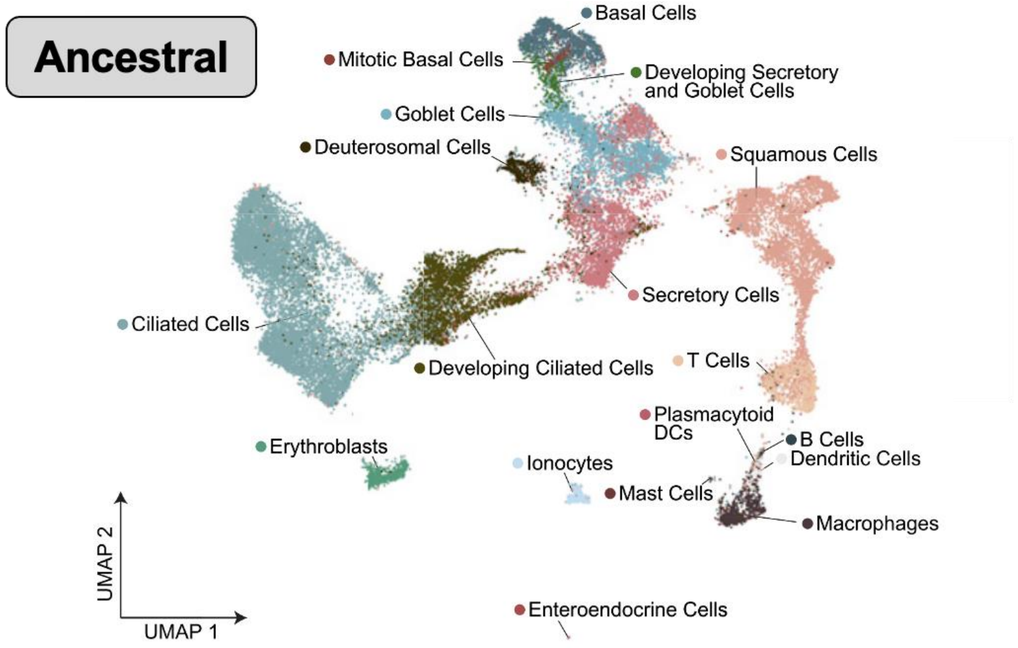


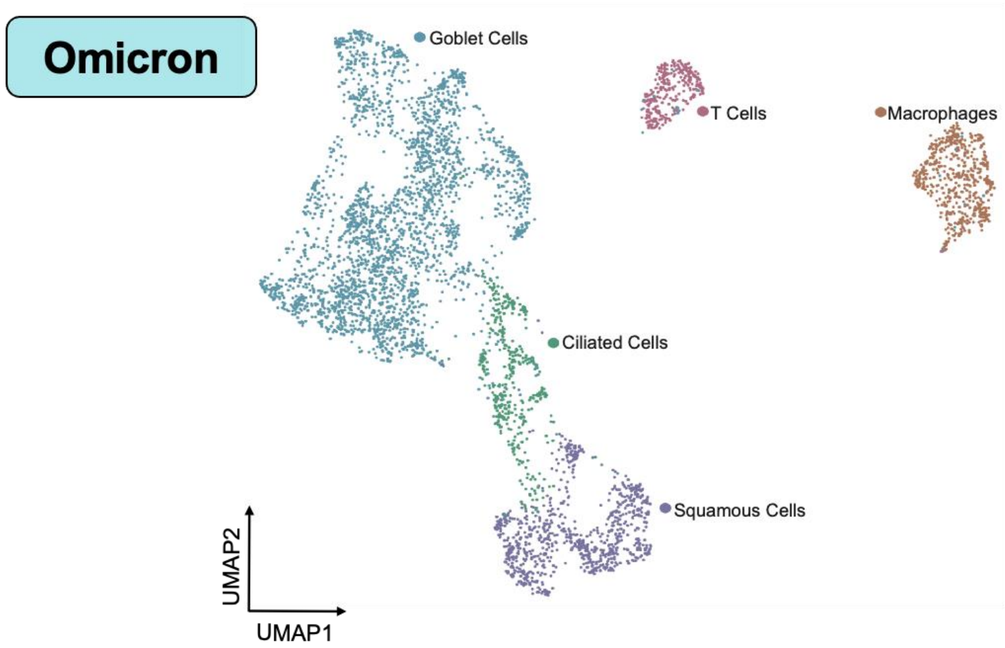


Plasma antibody levels

Delta

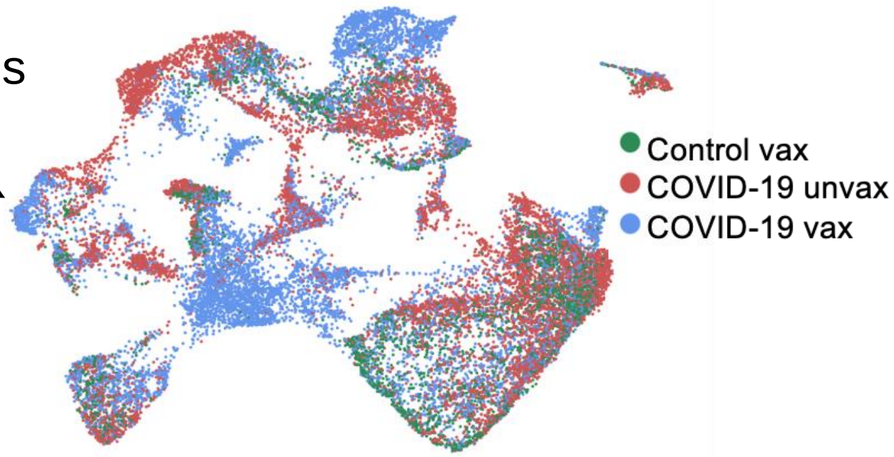

Squamous Cells
Secretory Cells
Goblet Cells
Ionocytes
Basal Cells
Macrophages
KRT-24 high Secretory Cells
Non-Ciliated Infected Cells
Deuterosomal Cells
FKBP5-high Ciliated Cells
Mast Cells
IFN-stim Basal Cells
Dendritic Cells
B Cells
Infected Cells
HLA-high Ciliated Cells
Antiviral Ciliated Cells
T Cells
Cytotoxic T / NK Cells
Developing Ciliated Cells
Cilia-high Ciliated Cells
UMAP2
UMAP1

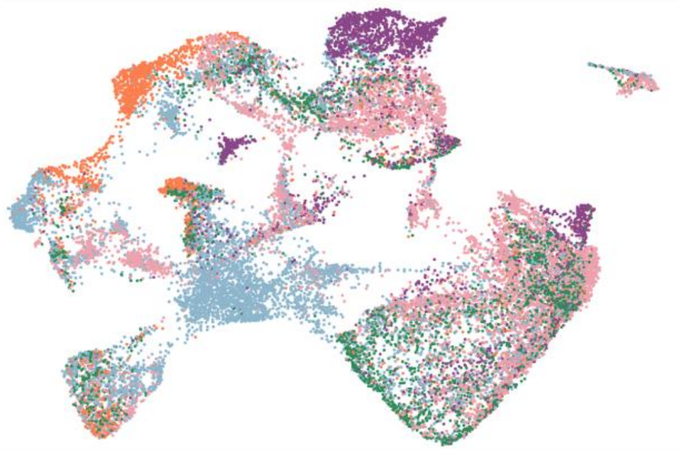

Ancestral
Basal Cells
Mitotic Basal Cells
Developing Secretory and Goblet Cells
Goblet Cells
Deuterosomal Cells
Squamous Cells
Secretory Cells
Ciliated Cells
Developing Ciliated Cells
T Cells
Plasmacytoid DCs
B Cells
Dendritic Cells
Erythroblasts
Ionocytes
Mast Cells
Macrophages
Enteroendocrine Cells
UMAP 2
UMAP 1


Omicron
Goblet Cells
T Cells
Macrophages
Ciliated Cells
Squamous Cells
UMAP2
UMAP1

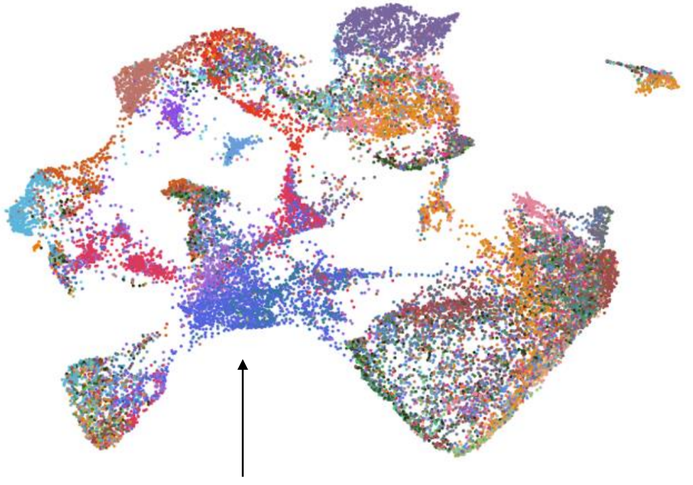
Secretory Cells

Macrophages



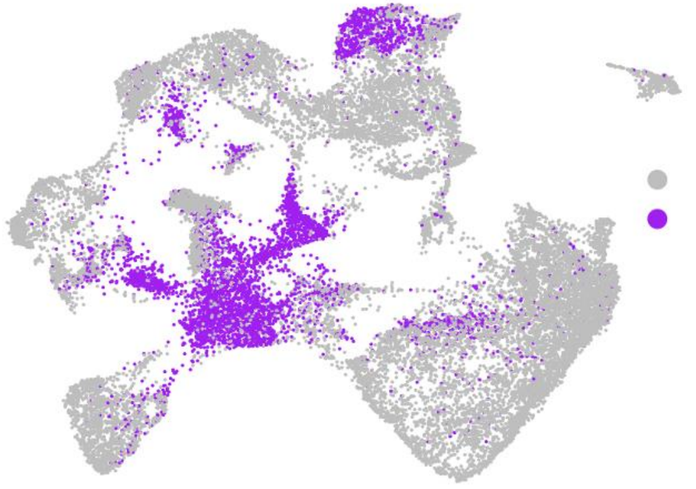


Participant



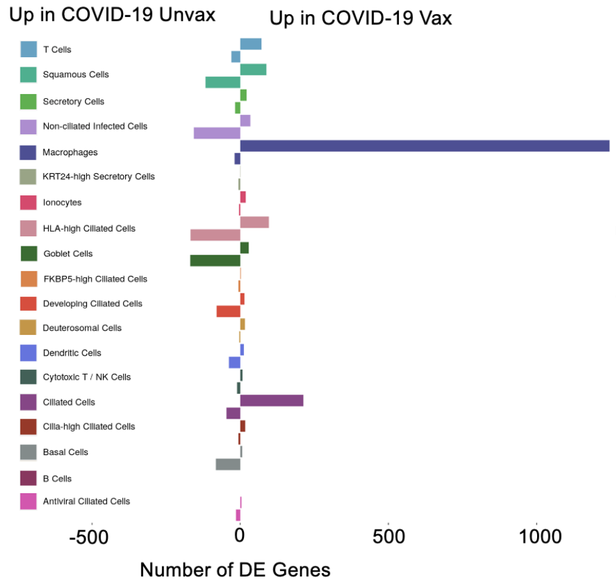
Anti Viral Ciliated Cells

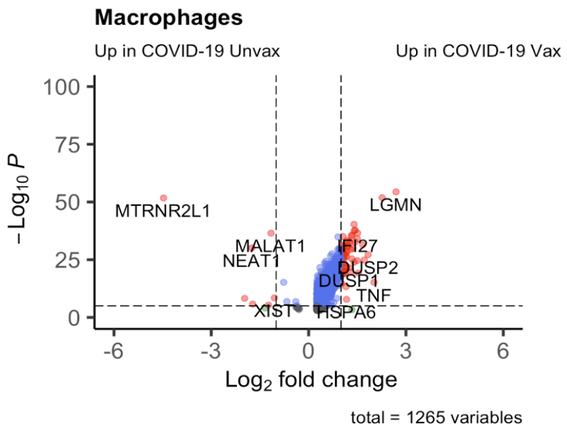
SARS-CoV-2 RNA



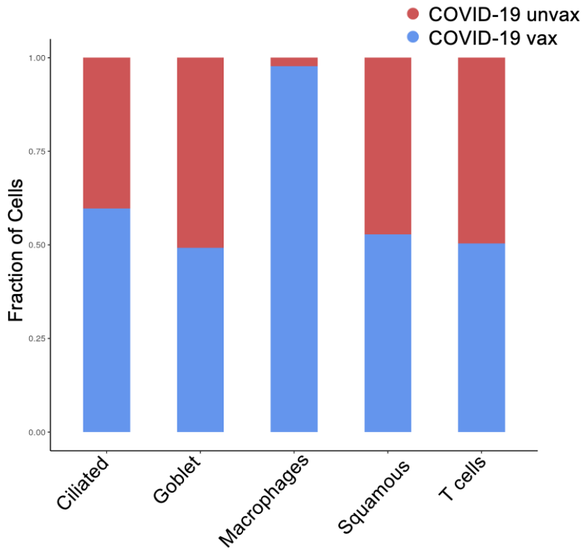
Macrophages in vaccinated patients display phenotypic and numerical changes

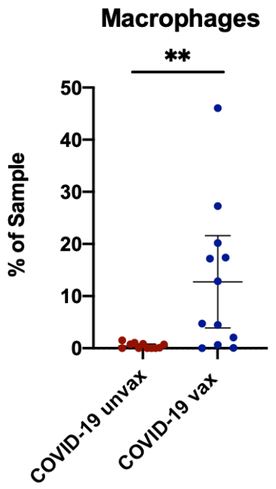
Delta





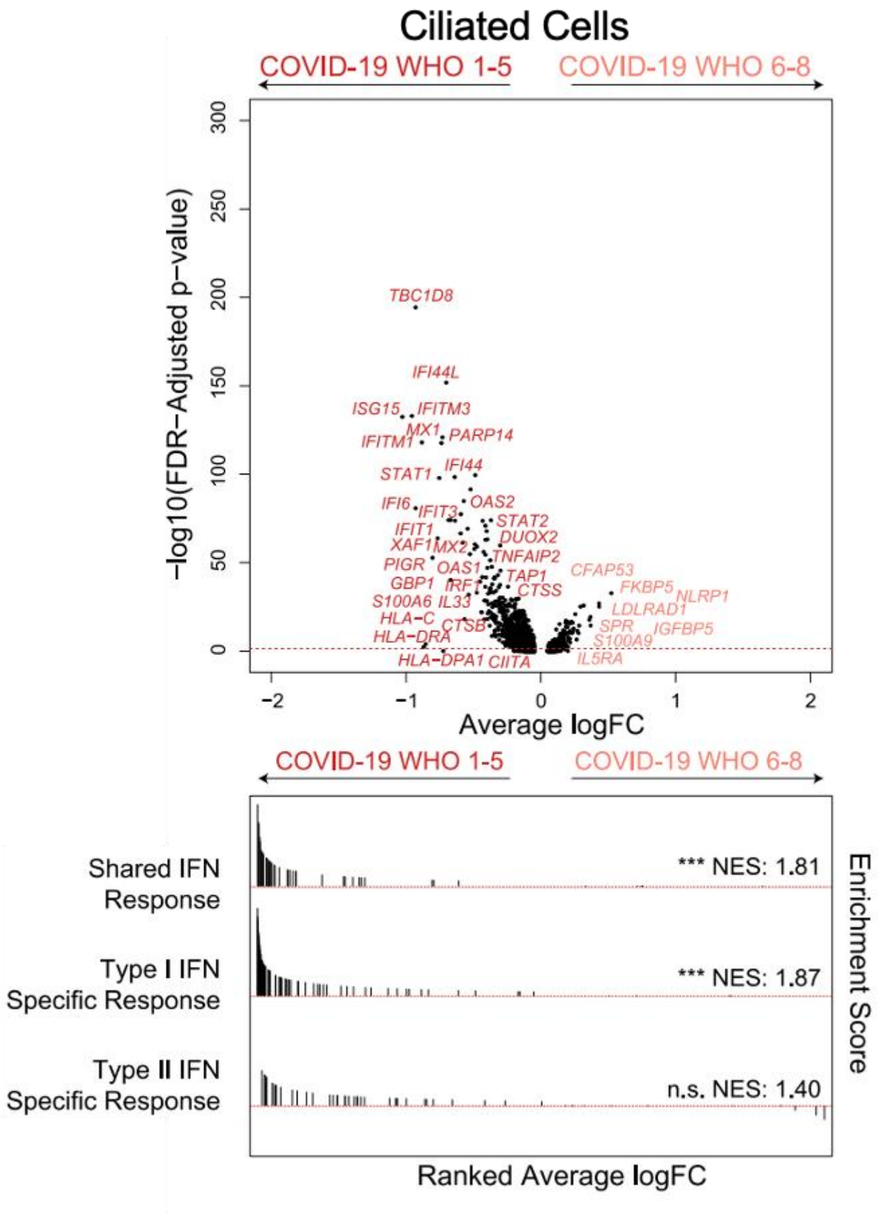
Omicron



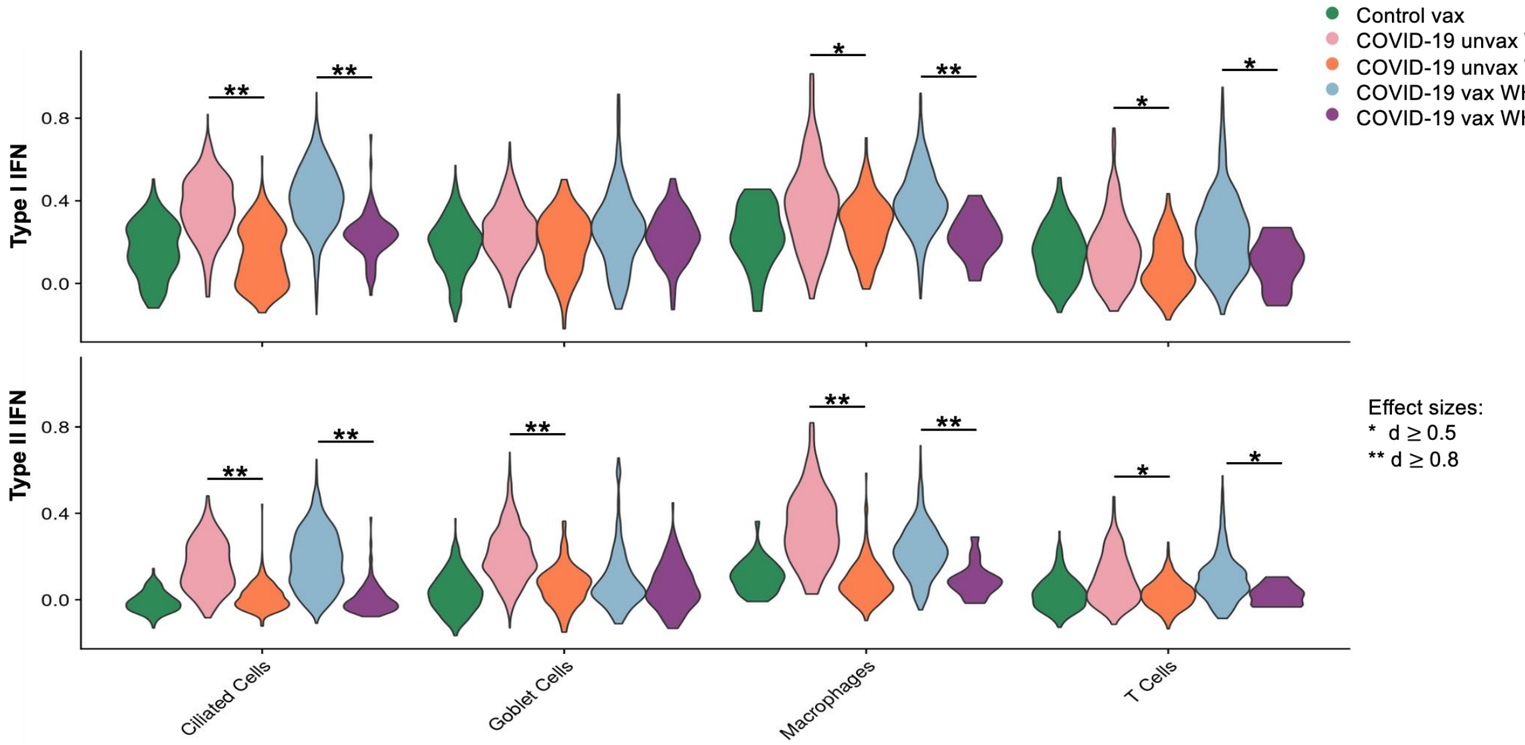


Severe COVID-19 is associated with low IFN response score in the nasal mucosa

Ancestral



Delta



Post covid and GI Tract

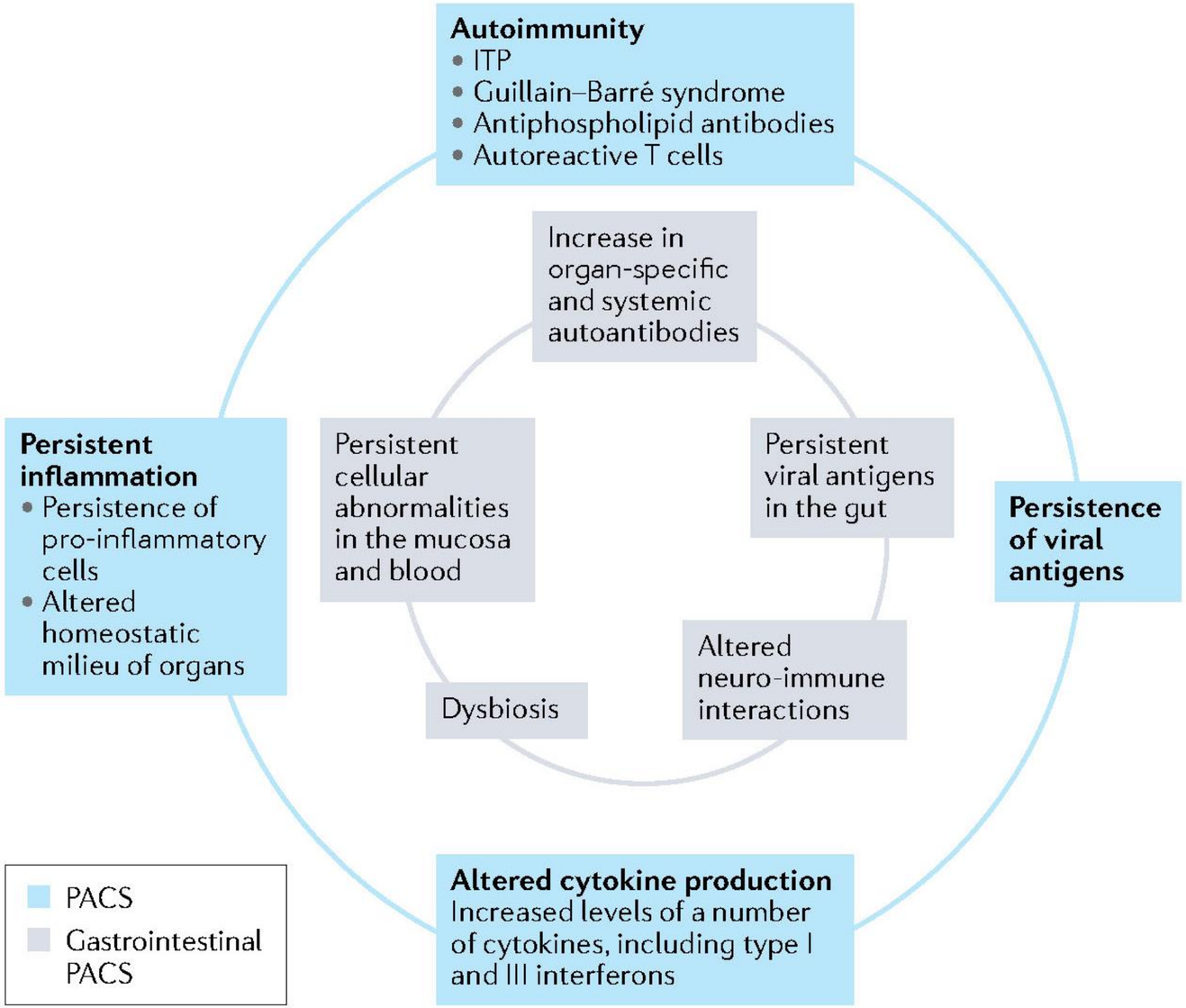


Fig. 1 | **The pathophysiology of PACS and gastrointestinal PACS.** The external blue circle represents proposed pathophysiological mechanisms in post-acute COVID-19 syndrome (PACS). The internal grey circle represents gastrointestinal-PACS-specific pathophysiological mechanisms. ITP, idiopathic thrombocytopenic purpura.

Meringer and Mehandru. Nat Rev Gastroenterol Hepatol. Volume 19, Number 6, June 2022

Primary Immunodeficiency and the Microbiome

- The microbiome in PID appears to play a crucial role in helping the host’s immune system maintain hemostatic control in the intestine.
- Symbiotic flora is affected significantly in primary immunodeficiencies with more dysbiosis in the microbiome.
- Primary immunodeficiency disorders are associated with microbial dysbiosis, systemic inflammation, particularly in the presence of immune dysregulation conditions.
- The gut microbiome is a promising area of study in PID.

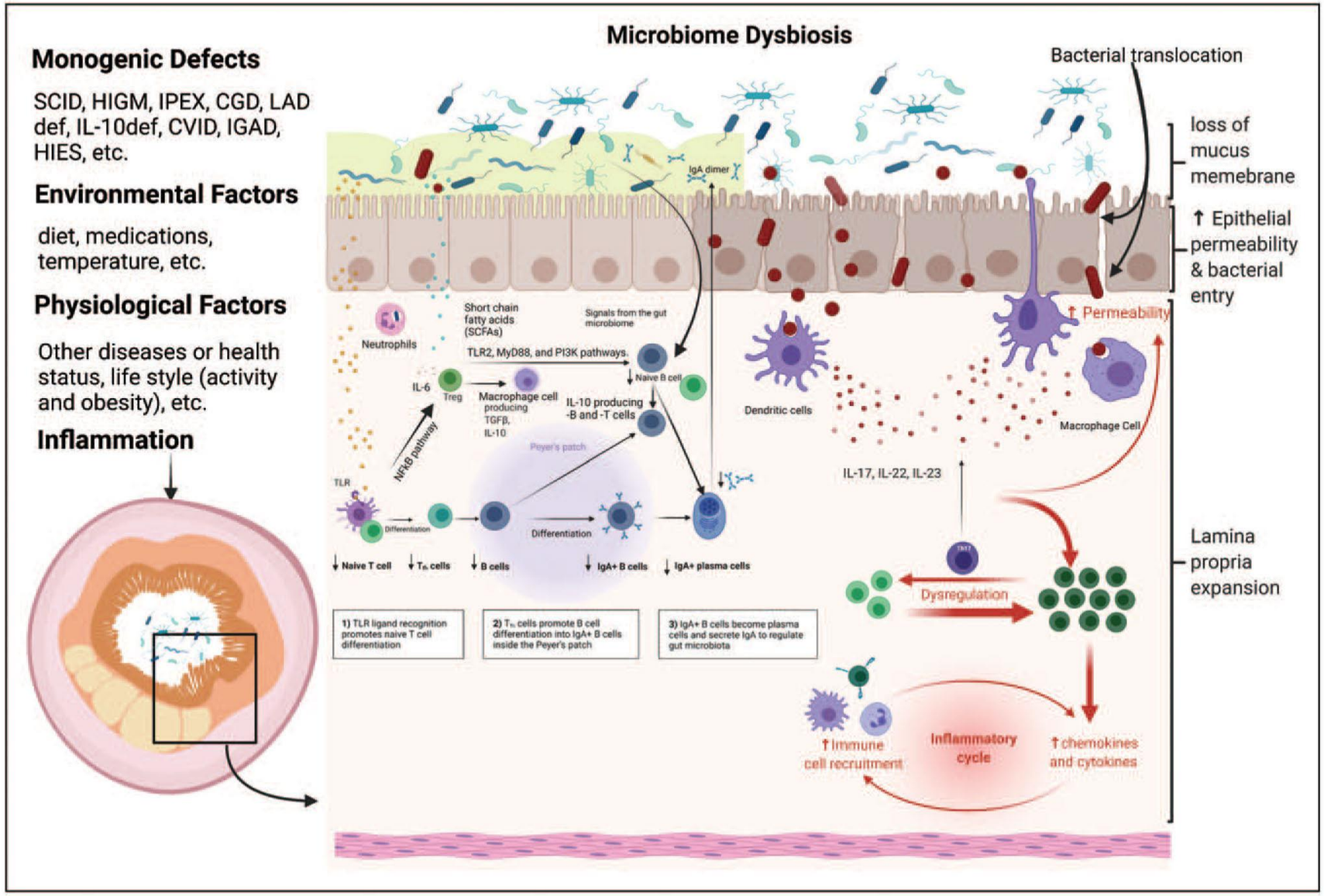
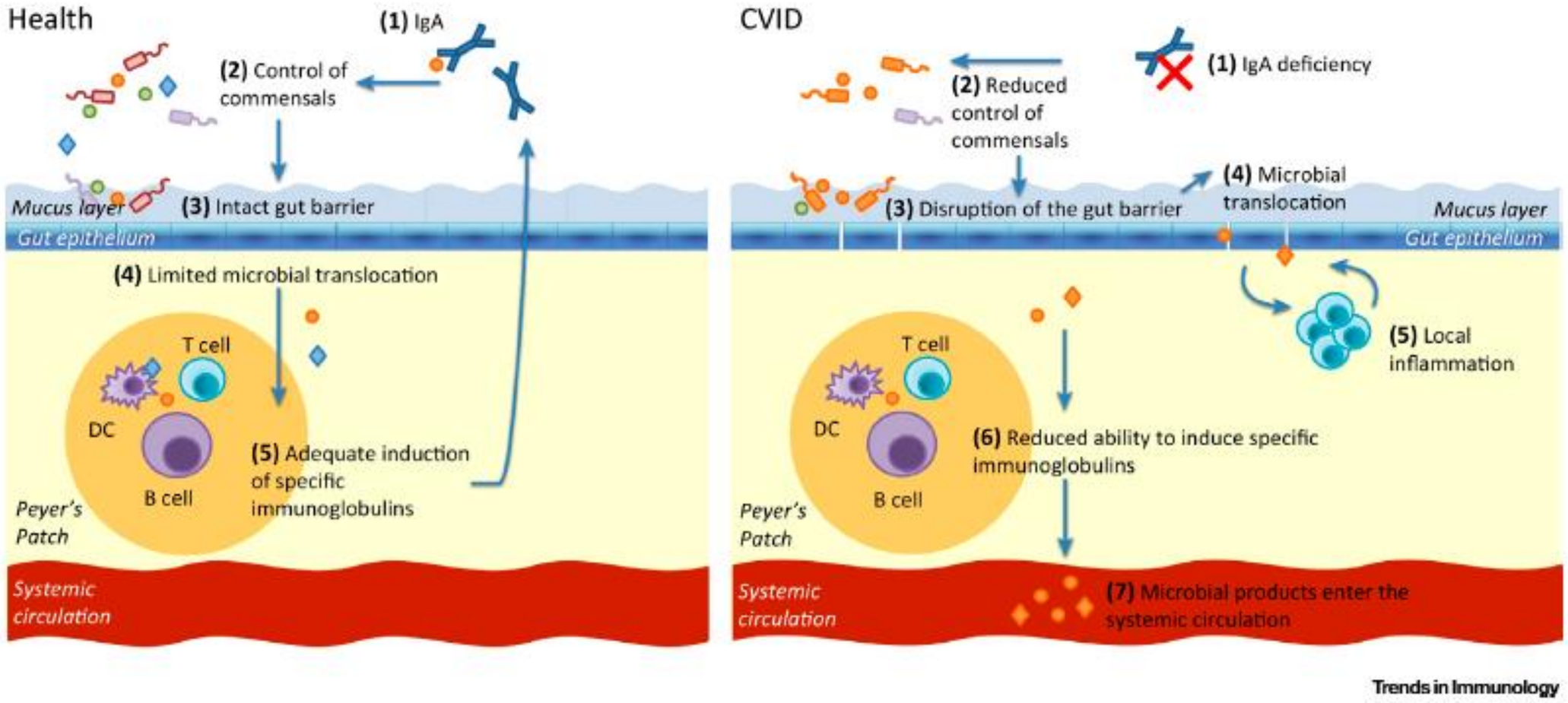


FIGURE 1. The interaction between cellular and humeral processes in microbial dysbiosis. The figure above shows various interactions that may lead to inflammation in PID-associated microbial dysbiosis Refs. [2,16,17▪,18▪▪]. Created with BioRender.com.

Al-Nesf et al. Curr Opin Pediatr
Volume 33, Number 6, December 2021

Key Figure

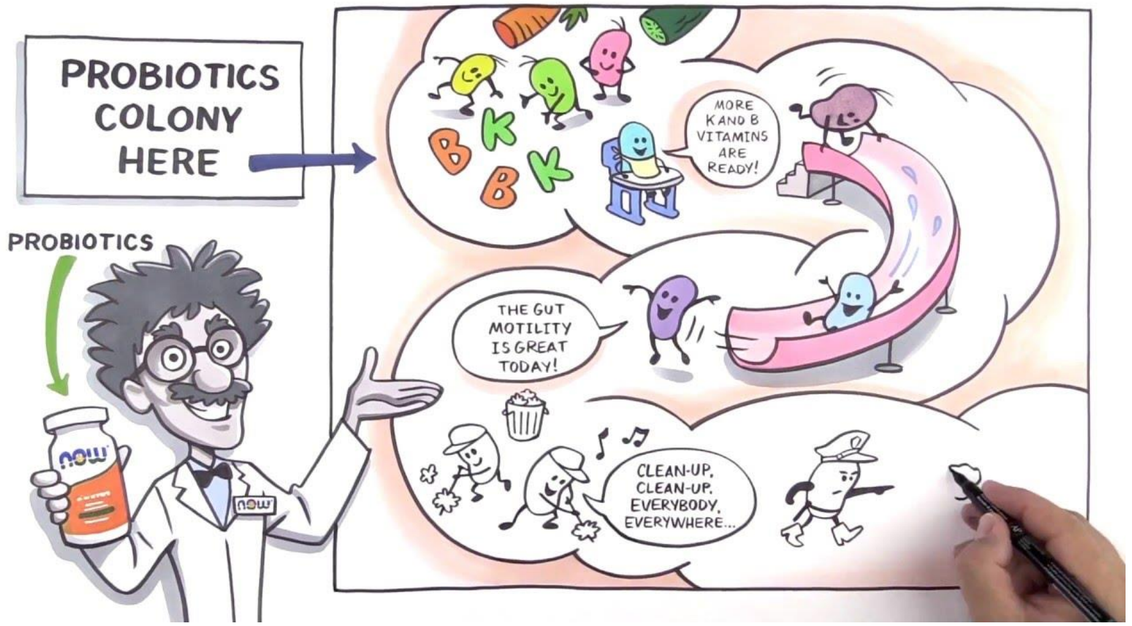
Control of the Microbiome in Health and CVID



Trends in Immunology, March 2017, Vol. 38, No. 3

Probiotics? Not yet.

- No studies evaluating the role of probiotics in PIs
- No data to confirm harm
- In IBD literature, there is a lack of efficacy and increased risk of bacteremia in patients with weakened immunity.



FDA Approves First Fecal Microbiota Product

Rebyota Approved for the Prevention of Recurrence of Clostridioides difficile Infection in Adults

“Today’s approval of Rebyota is an advance in caring for patients who have recurrent *C. difficile* infection,” said Peter Marks, M.D., Ph.D., director of the FDA’s Center for Biologics Evaluation and Research. “Recurrent CDI impacts an individual’s quality of life and can also potentially be life-threatening. As the first FDA-approved fecal microbiota product, today’s action represents an important milestone, as it provides an additional approved option to prevent recurrent CDI.”

Inflammatory & Autoimmune GI Disorders

- May be presenting illness in some PI patients
- Immune dysregulation →inappropriate immune response → autoimmunity or uncontrolled inflammation
- Celiac, IBD, Pernicious anemia/Gastritis, Autoimmune liver disease

Table 1 Primary immunodeficiency disorders with gastrointestinal manifestations

From: Inflammatory and infectious manifestations of immunodeficiency in the gastrointestinal tract

Feature	Common variable immunodeficiency	Selective IgA deficiency	Chronic granulomatous disease
Immunologic defect	Hypogammaglobulinemia	Decreased mucosal immunity	Impaired destruction of phagocytosed microorganisms
Key histologic features	Chronic active colitis with crypt architectural distortion. Variably severe villous defect. Absent or decreased plasma cells. More pronounced intraepithelial inflammation in deep mucosa compared with surface. Lymphoid hyperplasia. Increased apoptosis in glands and crypts. Lymphocytic or collagenous colitis pattern of inflammation.Granulomata.	May appear normal. Shortened small intestinal villi with crypt hyperplasia. Intraepithelial lymphocytosis. Lymphoid hyperplasia.	Shortened small intestinal villi. Chronic active colitis with crypt architectural distortion. Granulomata. Pigmented lamina propria macrophages.
Associated gastrointestinal disorders	*Cytomegalovirus, Cryptosporidium*. *Salmonella spp*., *Giardia lamblia* infections. Esophageal candidiasis. Extranodal B-cell lymphomas.	*Giardia lamblia* and *Strongyloides* infections. Celiac disease. Inflammatory bowel disease. Gastric adenocarcinoma.	Invasive fungal infections, particularly *Aspergillus spp*. Bacterial infections, particularly *Salmonella spp*.

Table 3. Histopathological findings of endoscopic biopsies in PID patients with antibody deficiencies

	Histopathological findings	Selective IgA deficiency	CVID	IgG subclass deficiency	Hypogammaglobulinemia	Agammaglobulinemia	PIK3CD
Esophagus	Esophagitis	4/8	4/7	–	–	–	1/2
Stomach	*H. pylori* (–) gastritis	2/8	2/7	1/1	1/1	1/2	1/2
	H. pylori (+) gastritis	2/8	–	–	–	–	–
	Atrophic gastritis	1/8	–	–	–	1/2	1/2
	Focally enhanced gastritis	–	1/7	–	–	–	1/2
	İntestinal metaplasia	–	–	–	–	–	–
Duodenum	Duodenitis	–	1/7	–	1/1	2/2	–
	Villous atrophy	4/8	1/7	–	–	–	1/2
	İncreased İEL	4/8	2/7	–	–	–	1/2
	Apoptosis	–	–	–	–	–	1/7
	Lymphoid hyperplasia	–	2/7	–	–	–	1/7
İleum	İleitis	–	1/7	–	–	–	–
	Villous flattening	–	1/7	–	–	–	–
	Lymphoid hyperplasia	–	–	–	–	1/2	1/2
Colon	Colitis	–	3/7	–	–	1/2	1/2
	Apoptosis	–	–	–	1/1	–	–
	Drop-out necrosis	–	–	–	–	1/2	–
	Lymphoid hiperplasia	–	–	–	–	–	1/7

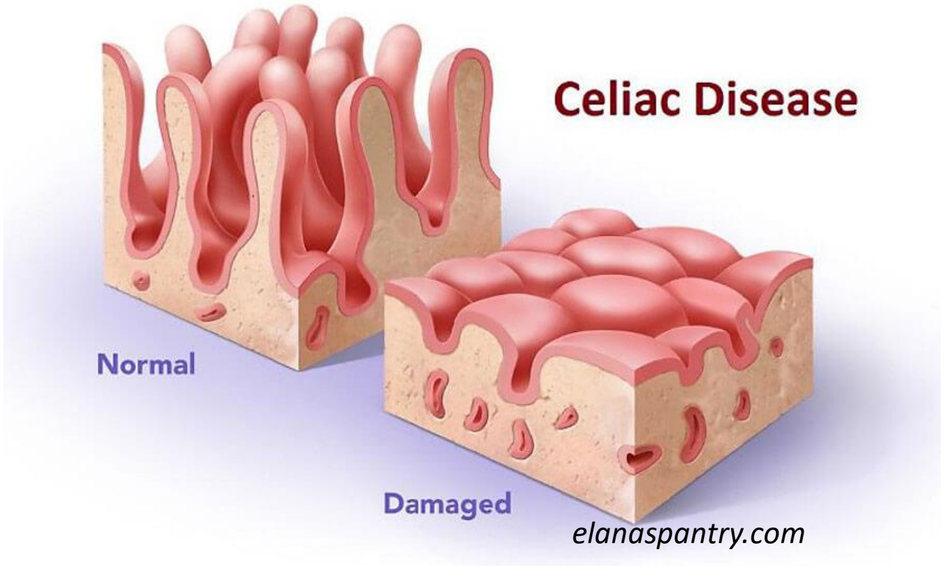
Dig Dis 2019;37:45–52

Celiac Disease aka Celiac Sprue

- Autoimmune disease due to inappropriate immune response to gluten
- Endoscopy shows inflammation and villous blunting in the first part of small intestine
- Can be asymptomatic but may result in malabsorption, weight loss, diarrhea, anemia, bloating and abdominal pain
- Increased risk in CVID, selective IgA Deficiency

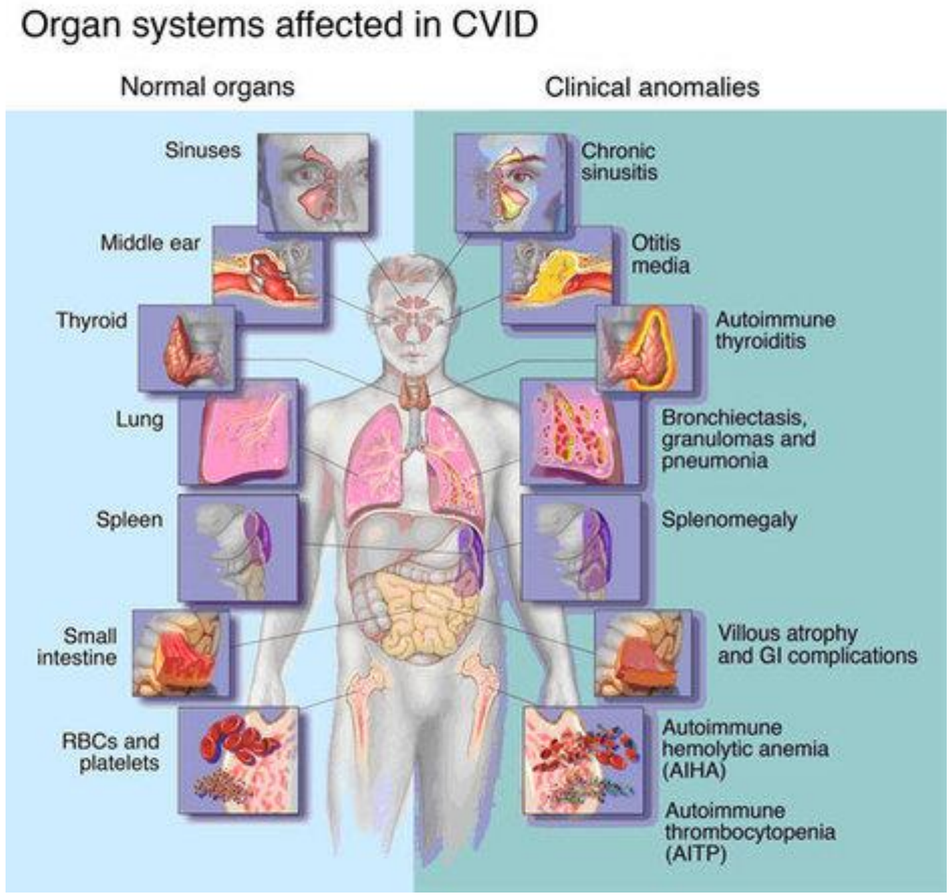
Celiac Disease and Celiac-like Disease

- Selective IgA Deficiency
  - Diagnosis more difficult as blood tests typically look for IgA related antibodies.
    - Recommended to check tTg-IgG
  - 5-15x increased risk compared to normal (other studies as high as 35x)
  - Treatment = gluten free diet



Celiac Disease and Celiac-like Disease

- CVID:
  - Diagnosis usually made by endoscopic biopsy in patients with symptoms
  - Consider gene testing for HLA-DQ2/8
  - Gluten free diet does not work → typically requires glucocorticoids and immune modulators
  - Severe disease → malabsorption with nutrient deficiency



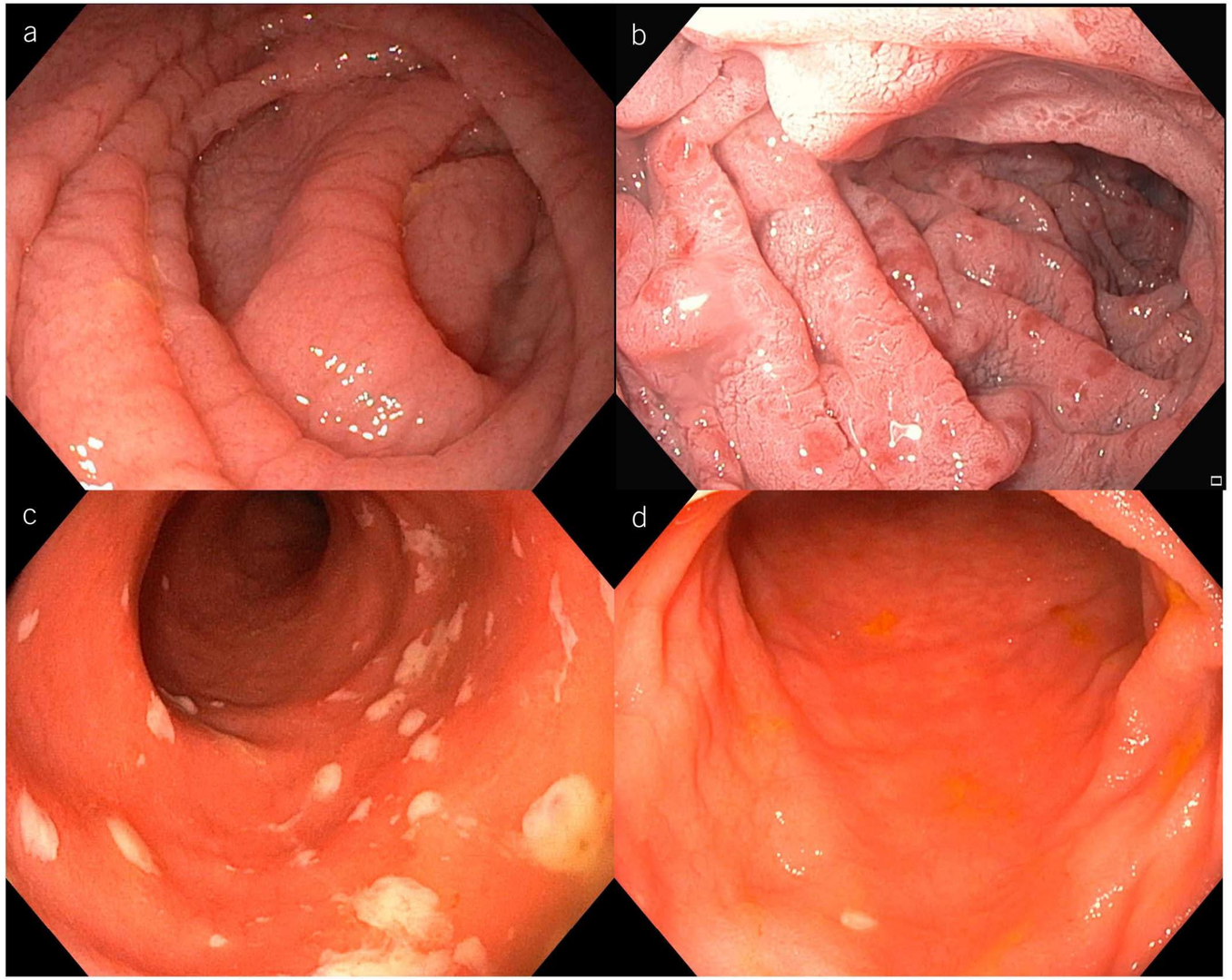
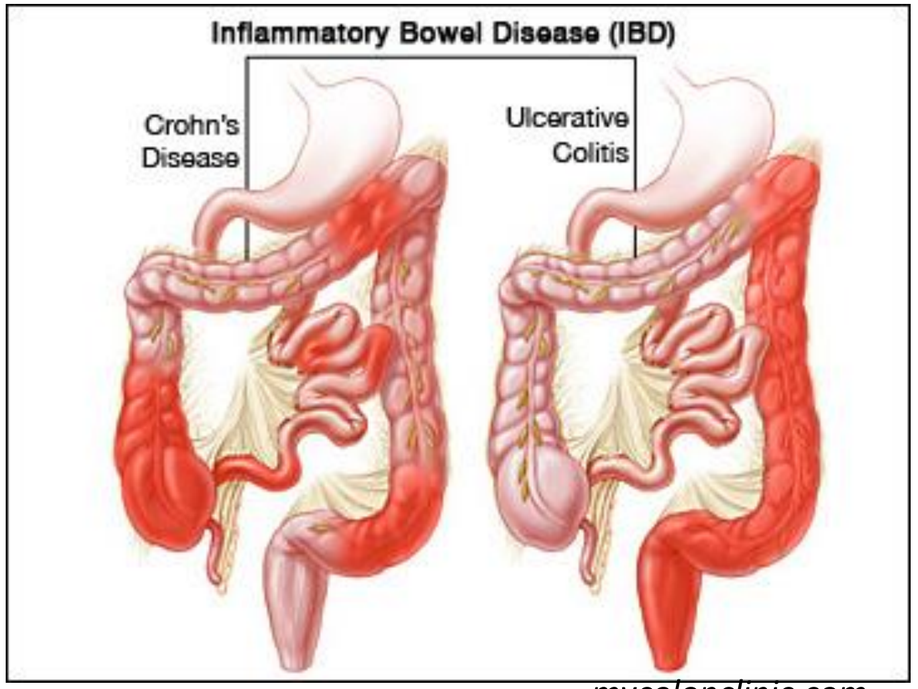


Figure 2. Panel showing examples of the variety of endoscopic appearance of CVID-induced changes of the GI tract: (**a** and **b**) duodenal scalloping as seen in CVID-induced enteropathy mimicking celiac disease, (**c**) colitis, and (**d**) terminal ileum ulcer. CVID, common variable immunodeficiency; GI, gastrointestinal.

Hashash et al. Am J Gastroenterol. Volume 117, Number 11, November 2022

Inflammatory Bowel Disease and IBD-like Disease

- Traditional IBD - Two major types: Crohn Disease and Ulcerative Colitis
- Disease characterized by diarrhea, abdominal pain, bloody stools, vomiting, weight loss
  - Ulcerative Colitis – continuous inflammation of the intestine from anus to proximal parts of the colon, but limited to colon.
  - Crohn’S Disease – may segmentally affect any part of the GI tract, resulting in abdominal pain and malnutrition. Can lead to fistulas and strictures.



mycolonclinic.com

Inflammatory Bowel Disease and IBD-like Disease

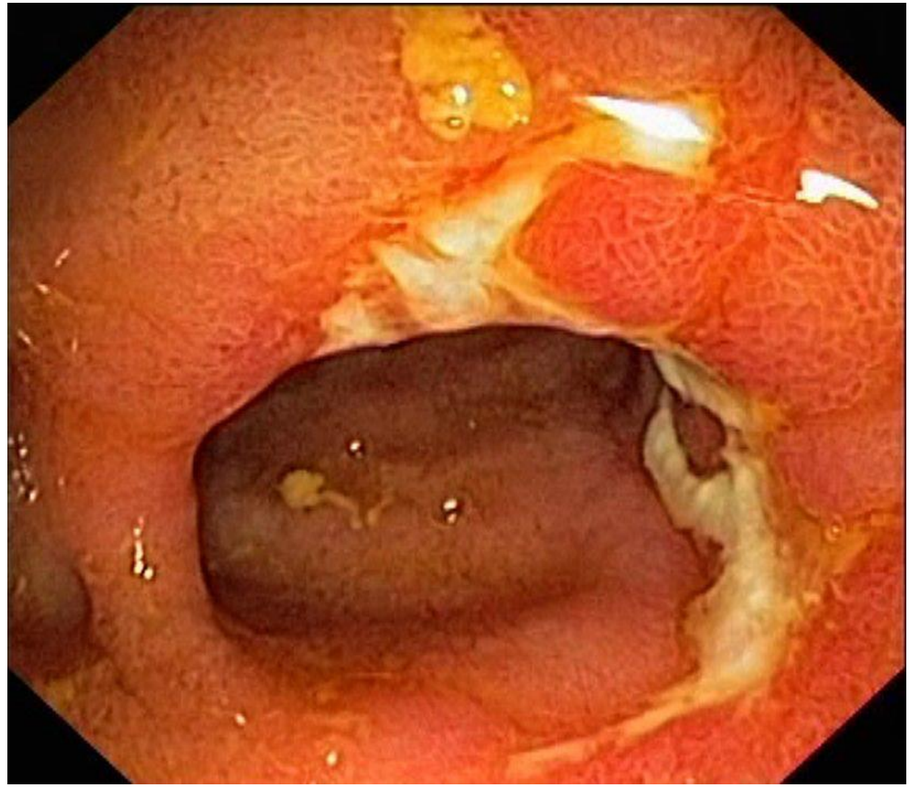
- IBD may be sign of underlying PIDD
- Some types of PID (especially those with Antibody Defects and Chronic Granulomatous Disease) are at increased risk compared to immunocompetent patients
  - Selective IgA Deficiency – studies show 5x increased risk of classic IBD
  - Often IBD-like disease in PID does not improve with traditional IBD medications

Inflammatory Bowel Disease and IBD-like Disease

- X-Linked Agammaglobulinemia
  - IBD/enteritis diagnosed in up to 10% of patients
    - Historically, patients can develop small bowel strictures and transmural intestinal fissures
    - Unlike Crohn disease, no granulomas or plasma cells are seen when strictures are surgically removed
  - Treatment: IVIG may help, Majority of patients (74%) required parenteral nutrition in retrospective review by Barmettler et al, 2017.

IBD-like Disease

- CVID – associated with IBD-like illness that can affect both large and small bowel
  - Ig replacement therapy does not seem to improve course
- Endoscopy – indistinguishable
- Biopsies from endoscopy can differentiate CVID from typical IBD (next slide)
- Treatment: Same as IBD arising in non-PI patients



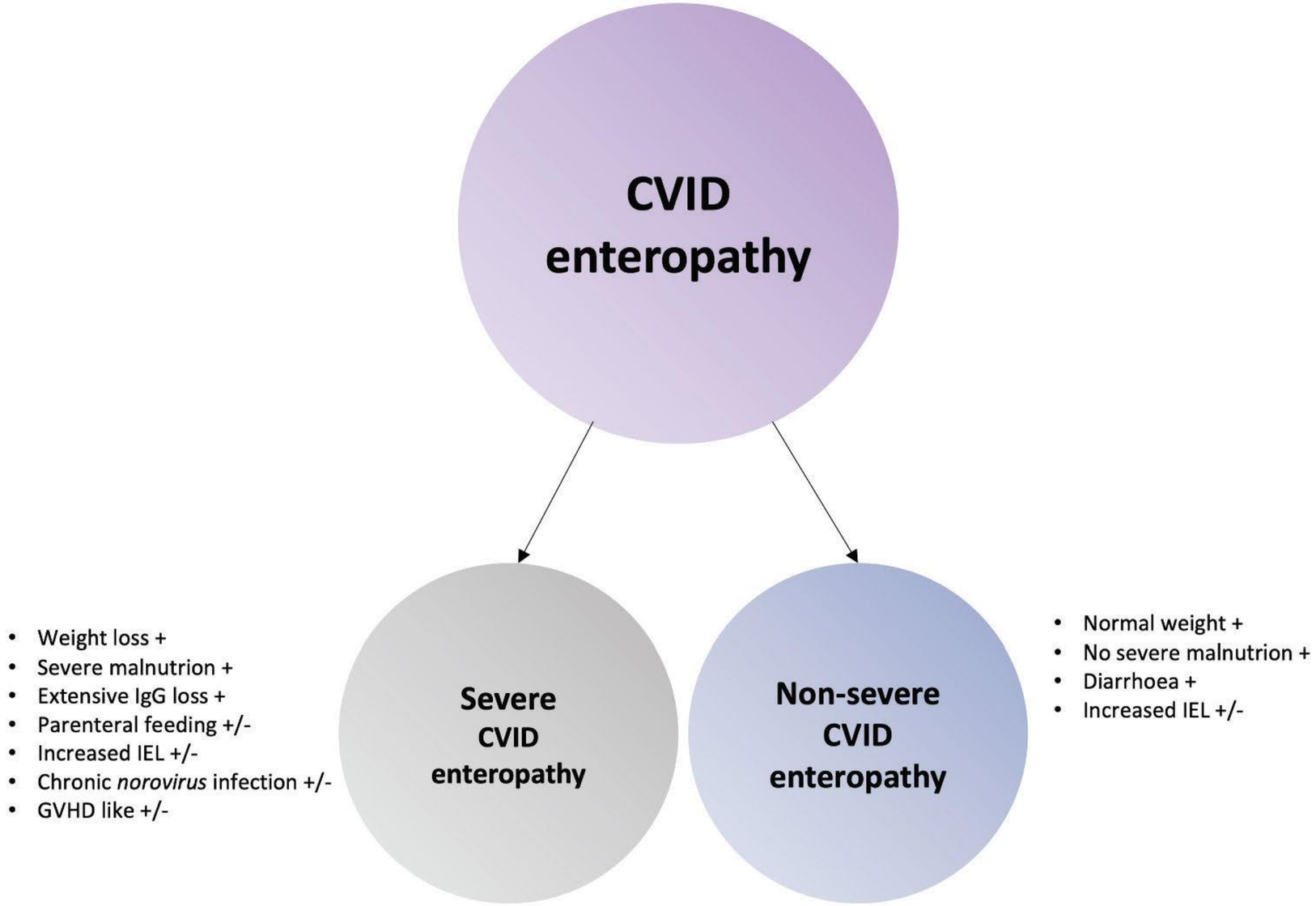
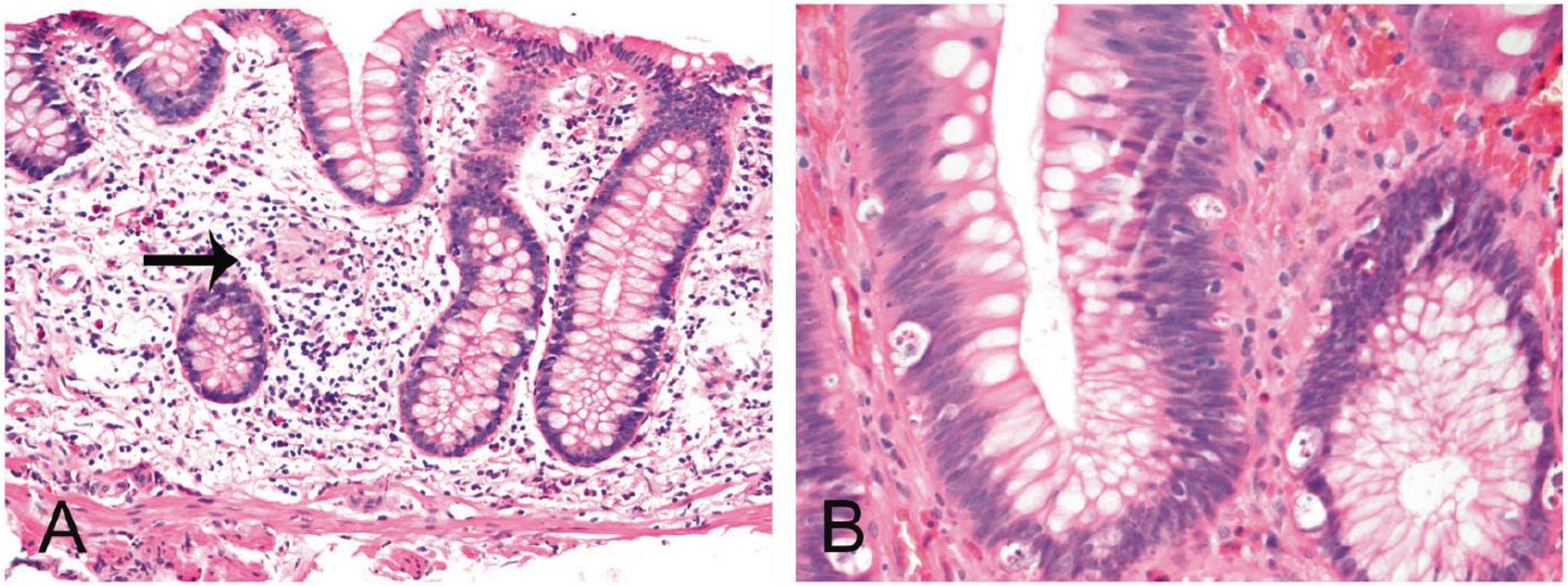


Figure 2. CVID enteropathy sub-classes. CVID enteropathy divided into the two subclasses: Severe CVID enteropathy and Non-severe CVID enteropathy.

CVID Enteropathy



Panarelli et al., 2018

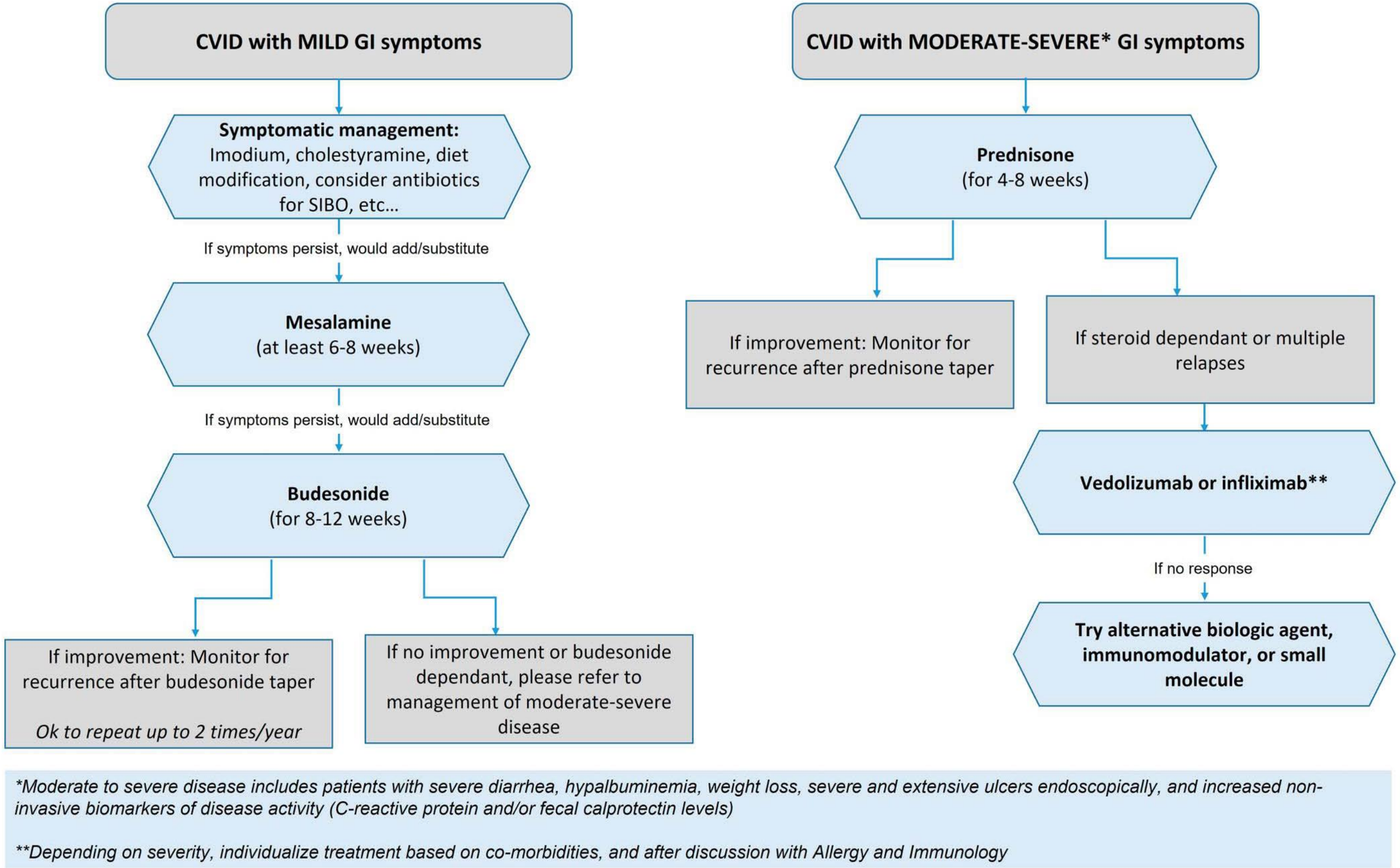


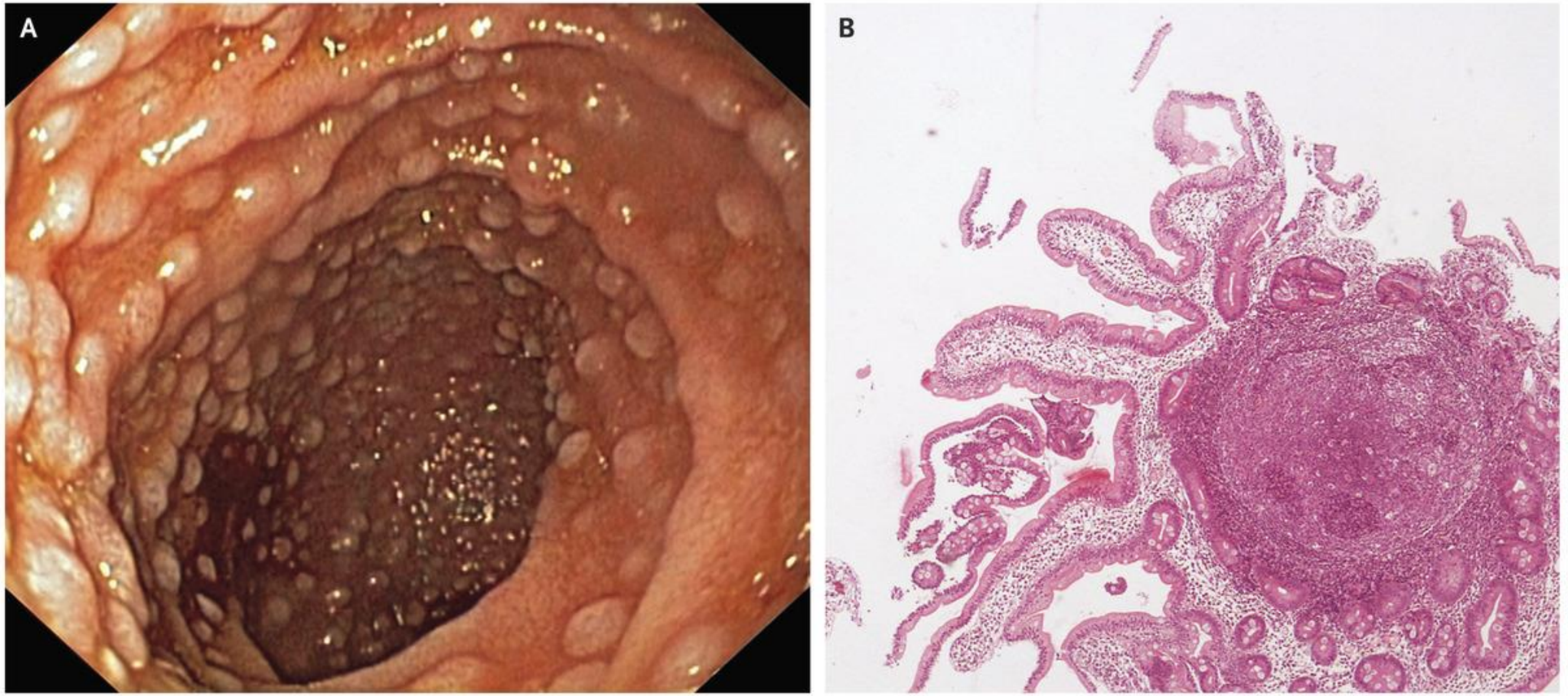
Figure 4. Proposed treatment algorithm for patients with CVID. CVID, common variable immunodeficiency; GI, gastrointestinal; SIBO, small intestinal bacterial overgrowth.

AJG 2022 117(11) 1743-1752

Nodular Lymphoid Hyperplasia

- A benign condition characterized by multiple small nodules (2-10mm in diameter) arising within the GI tract
- Most commonly seen in the small intestine, but also in the stomach, colon, or rectum.
- Typically asymptomatic, can be an incidental finding on endoscopy
- Associated with all antibody-deficiency syndromes except XLA
- Occasionally may be associated with abdominal pain, diarrhea, bleeding, intussusception, malabsorption or intestinal obstruction

Nodular Lymphoid Hyperplasia



Sharma, Ahuja (2016); Nodular Lymphoid Hyperplasia. N Engl J Med 2016; 375:e3.
DOI: 10.1056/NEJMicm1514403

Liver and Biliary Disease

- Liver disease common in PI – Rodrigues et al, 2005: 147pts with PI, liver involvement in nearly 24%
  - Among the 35 patients, 63% had hepatomegaly, 60% had sclerosing cholangitis
    - CVID → Increased risk of autoimmune liver disease: primary biliary cirrhosis, autoimmune hepatitis. Also nodular regenerative hyperplasia with pulmonary HTN.
    - CGD → Risk of liver abscess (infections from *S aureus* and *Pseudomonas aeruginosa*), chronic hepatitis
    - Hyper-IgM →Liver disease seems to be somewhat related to *Cryptosporidium* infection
      - Associated risk of progressive sclerosing cholangitis which can lead to bile duct or liver cancer
      - Requires careful monitoring with LFTs, GGT

Other Considerations and Cancer

- CVID – associated with gastritis, pernicious anemia (B12 deficiency)
  - Increased risk of gastric adenocarcinoma and lymphoma (typically NHL)
  - Recommend EGD at time of diagnosis and possibly routinely thereafter. Also suggest testing for *H.pylori*
- Hyper-IgM
  - Higher incidence of pancreatic, liver, and biliary malignancy
  - Recommend routine screening with LFTs & GGT, treatment of Cryptosporidium
- Selective-IgA Deficiency
  - Moderately increased risk of gastrointestinal malignancy

Liver disease or splenomegaly	Obtain abdominal ultrasound for elevated liver enzymes or consider screening abdominal ultrasound every 1–2 yr; new data suggest performing yearly liver ultrasound with dopplers and liver ultrasound with transient elastography
Gastric cancer	Initial screening: consider endoscopy at diagnosis of CVID, especially in the presence of risk factors, including upper GI symptoms, diarrhea, positive *Helicobacter pylori* breath test, iron deficiency, or low vitamin B_{12} (46,49) Routine follow-up: endoscopy every 24 mo (46,50) For abnormal histology (46): Atrophic gastritis or intestinal metaplasia: repeat in 12 mo Dysplasia: repeat in 6 mo

CVID, common variable immunodeficiency; GI, gastrointestinal; PCR, polymerase chain reaction; TIBC, total iron-binding capacity.

**For colon cancer screening, follow national guidelines.

AJG 2022 117(11) 1743-1752

Nutrition and Diet

- Malnutrition and Failure to Thrive are key features of PIs
  - Patients have limited food intake, malabsorption of nutrients, increased nutrient losses
    - Study in 50 CVID patients with GI symptoms showed biological evidence of malabsorption in 54% of patients
  - Screen for malnutrition at diagnosis and regularly thereafter
    - Iron deficiency
    - Folic Acid
    - Zinc, Selenium
    - Magnesium
    - Calcium/Vit-D
    - Vitamins A, B12, E, K
    - Stool alpha-1-antitrypsin (for protein losing enteropathy)
    - Fecal elastase

Micronutrients

- Diarrhea and inadequate dietary intake may lead to micronutrient deficits
  - Lab testing may be confusing as these levels change with inflammation
  - A daily multivitamin is likely to be of benefit in PI patients with GI symptoms
  - Vitamin D has immunomodulatory properties and is essential for bone health.
    - In IBD patients low Vitamin D levels correlate with active disease and inflammation

Diet

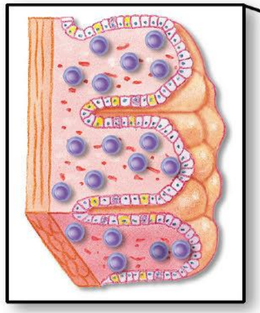
- For patients with gluten sensitive celiac disease → Gluten Free Diet
- Otherwise there is no specific diet for PI patients
  - All patients should have an individual (nutritional) approach based on their specific personal situation
    - Preferably with a dedicated dietician or nutritionist
  - Food Journal
  - No dietary studies have been performed on PI patients, thus Specific-carbohydrate diet is our best guess based on patients with IBD

Other Considerations

- Bile acid loss
- Lactose deficiency-can be primary or secondary
- Sucrase deficiency-can be primary or secondary
- Mast cell activation-can be primary or secondary

Liver:
- Granulomas
- Nodular regenerative hyperplasia

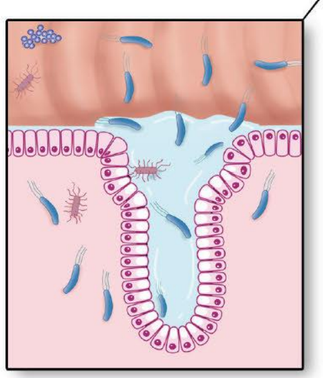
Small intestine:
"Celiac-like disease"
- Villous atrophy
- Intraepithelial lymphocytes



Stomach:
- Metaplasia
- Gastric cancer
- Chronic gastritis

Colon:
- IBD-like findings
- Unspecific colitis
- Microscopic colitis
- GVHD-like findings

Gut microbial dysbiosis:
- Reduced microbial diversity
- Increased gut permeability of bacterial products



Small and large intestine:
- Granulomas
- Absence of plasma cells
- Non-specific inflammation
- Nodular lymphoid hyperplasia

THANK YOU!

Sarah C. Glover, DO
The University Medical Center School of Medicine

Immune Deficiency Foundation

From all of us at IDF

Thank You!

Abe Frances CHRIS Lorraine Jarey ANGELA Katherine Rachel
Lynn Nathaniel Elizabeth Chuck Fri Stephanie Karen Zach
Emma Kathy Alissa Jennifer Brian Cheryl Val Tawny Aimee Sarah Christopher
Amy Julieann Adam Wanda STEPHANIE Colleen Becca Maura Doreen Kim Jamie

You make the IDF community stronger

Immune Deficiency Foundation