
KOVAI MEDICAL CENTER & HOSPITAL

“Autoimmunity & Diarrhoea ”

ACM – Lecture series - 11th April 2024

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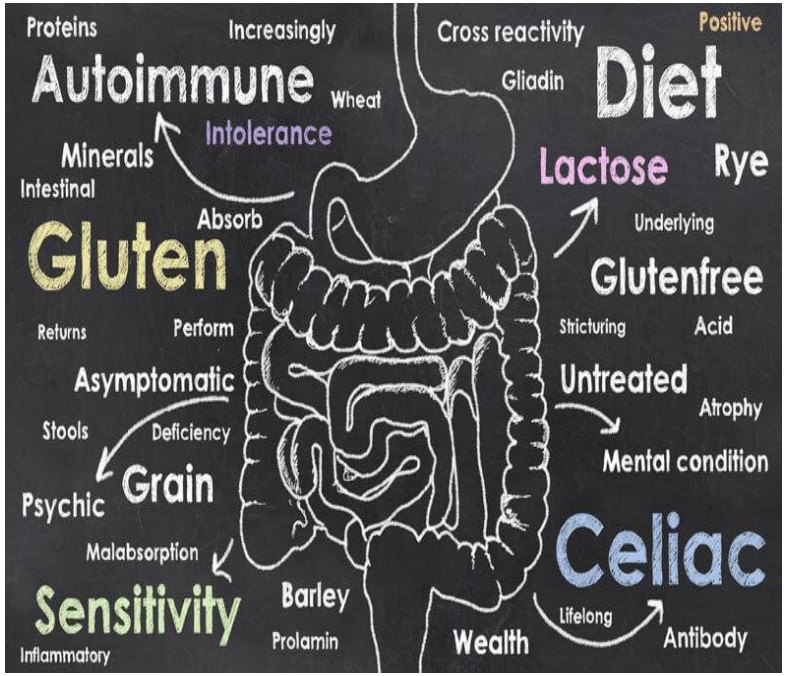
Objectives……

- Mechanism of Gastrointestinal Autoimmunity
- Gastrointestinal manifestations in various AI condition
- Autoimmune enteropathy

Introduction

- **Failure of immune tolerance causes self-attacking and autoimmune (AI) disorders.**
- **To date, more than 80 types of autoimmune diseases have been characterized, affecting approximately 5–8% of the world's population.**
- **The incidence and prevalence of autoimmune diseases has increased rapidly.**
- **Medical interventions can mitigate the symptoms but autoimmune diseases cannot be completely cured.**
- **Autoimmune diseases can be systemic or at local sites, including the gastrointestinal tract.**



Introduction

- **Autoimmune disorders associated with the digestive system, lead to a variety of gastrointestinal manifestations, such as oral ulcers, abdominal pain, diarrhea, and gastrointestinal bleeding**
- **Wide variation of gastrointestinal manifestations.**
  - **Presentation of AI disorders**
  - **Complication of treatment**
- **Moreover, evidence has suggested that persistent autoimmune inflammation and immunosuppressive therapy have been linked to increased cardiovascular risk or cancer**

Mechanism of GI- AI diseases

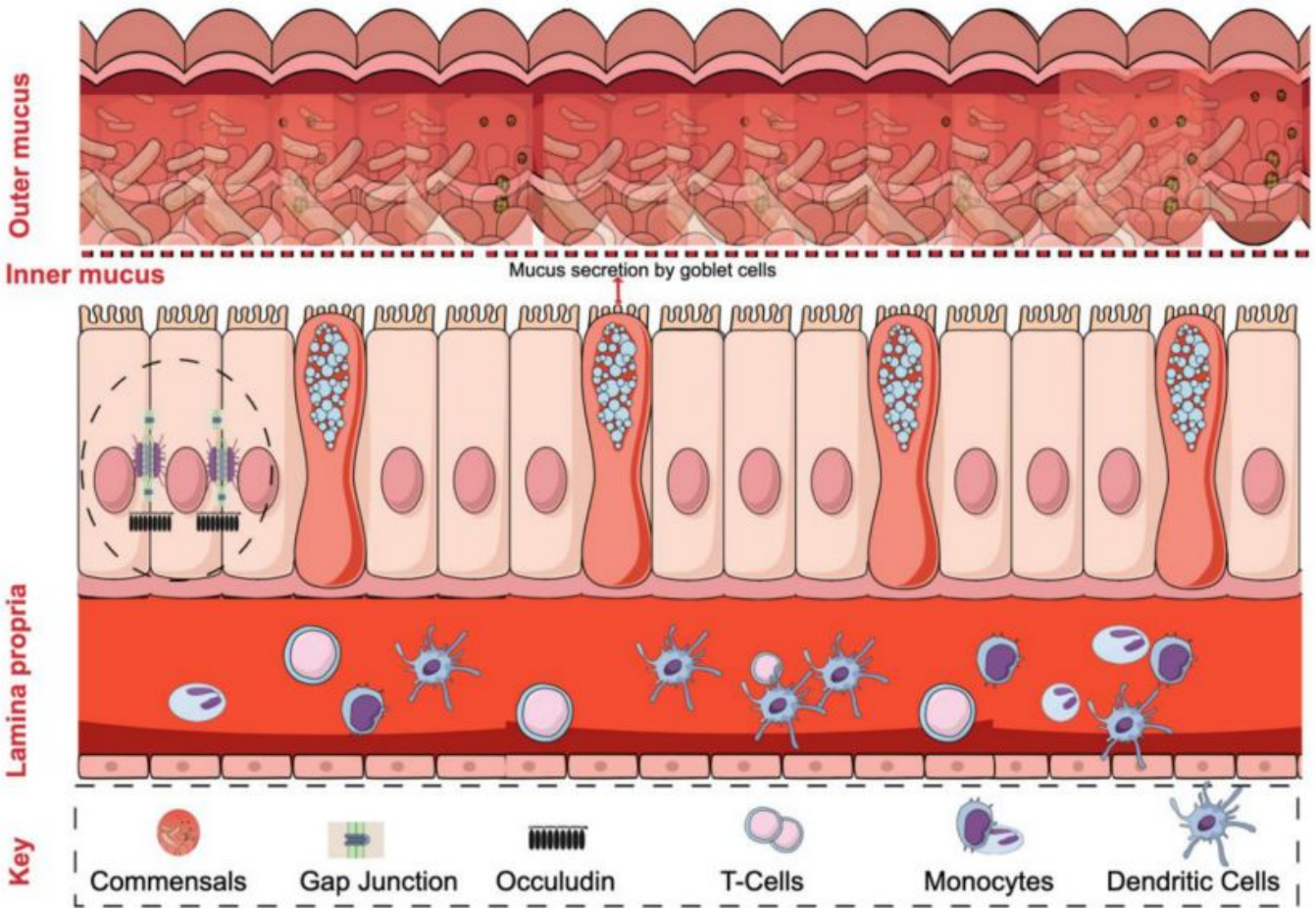
- Its complex with various causal factors, including genetic variation, immunological dysfunction, environmental factors, infections, diet and gut microbiota.
- Next-generation sequencing technology - genome-wide association studies (GWAS), have revealed hundreds of genomic variants that highly influence the risk of autoimmune diseases
- A balanced immune system is important for maintaining homeostasis by protecting the host from infection and preventing self-reactivity.
- Dysfunction of immune homeostasis causes inflammation, a key immunological determinant of autoimmune disorders.
- Abnormal inflammation, which causes substantial tissue damage, is strongly linked to autoimmune pathogenesis.

Immunology behind GI Autoimmunity

- **T cell-mediated inflammatory responses are important drivers for immunopathogenesis in many autoimmune disorders.**
- **Pro-inflammatory CD4+ T helper (Th) cells play critical roles in promoting the pathogenesis and progression of autoimmune diseases.**
- **Pro-inflammatory cytokines produced by those cells are potent activators of other immune cells (e.g., neutrophils and macrophages) and non-immune cells (e.g., epithelial, endothelial cells and fibroblasts) to amplify the inflammatory response.**
- **Follicular helper T (Tfh) cells are also highly associated with a wide range of autoimmune diseases through their ability to enhance autoreactive B cells and CD8+ T cell responses.**
- **Further, dysfunction of regulatory T (Treg) cells which are the predominant T cell population maintaining self-tolerance, has been linked to most autoimmune manifestations**

Immunology behind GI Autoimmunity

- Lamina propria of the intestinal epithelial system underneath the intraepithelial cells holds a number of immune cells- T-cells, B-cells, macrophages, and dendritic cells etc.
  - Essential role in maintaining intestinal homeostasis .
- The components of the immune system like tumor necrosis factor-α (TNF-α), interleukins, and interferon-γ necessary for regulation of tight junctions TJs.
- Poor functioning of paracellular tight junctions, appear to be crucial ingredients presented in the pathogenesis of autoimmune diseases.
- TNF-α mediated activation of NF-κB an important regulator, and studies have shown that inhibition leads to protective effects against severe diarrhea

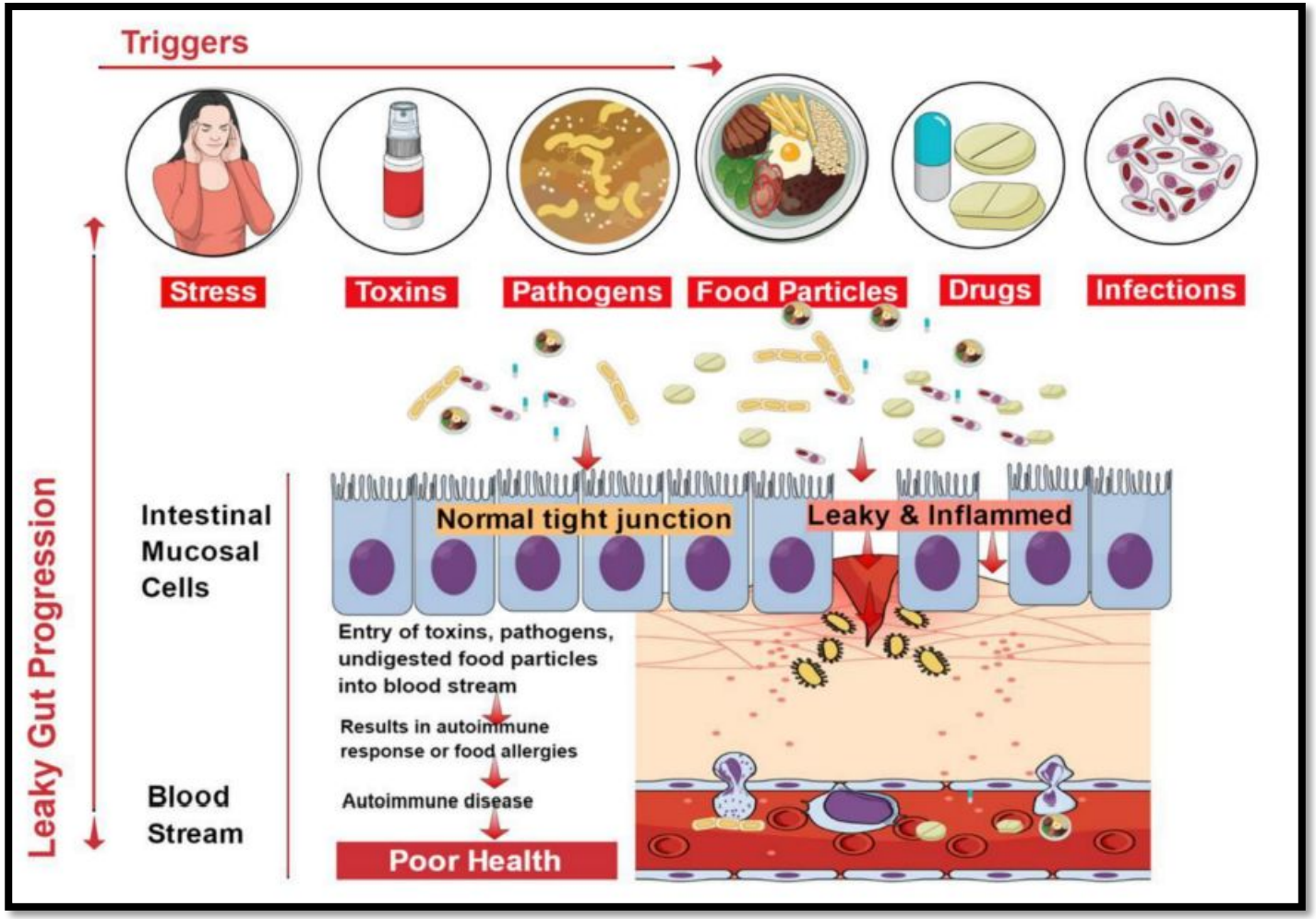


Bilal paray et al , Int J Med Sci , 2020

Environment & infections

- **Environmental stimulators, such as chemical toxins, solvents, organic pollutants, and heavy metals, are additional risk factors driving GI autoimmunity.**
  - **Several underlying mechanisms have been identified linking toxic chemicals to immune dysregulation.**
- **Various infectious agents can trigger autoimmune diseases in the gastrointestinal tract.**
  - **Multiple mechanisms by which pathogenic infections cause autoimmune disorders have been characterized, such as molecular mimicry, epitope spreading, bystander activation, and induction of inflammatory environment**

Leaky gut and autoimmunity



Bilal paray et al , Int J Med Sci , 2020

Gut microbiome & Autoimmunity

- The gastrointestinal tract is now considered the largest immunological organ since it harbors 70% of the body's lymphocyte population
- The gut microbiota have been strongly correlated with digestive autoimmune disease
  - The dysbiosis—an abnormal microbiome immunity— affects both the innate and adaptive immune systems, promoting pro-inflammatory responses and autoimmunity
- Gut microbiota can also influence extraintestinal autoimmune disorders, such as rheumatoid arthritis (RA), type 1 diabetes (T1D), Inflammatory bowel disease (IBD) , Systemic lupus erythematosus (SLE) and experimental autoimmune encephalomyelitis (EAE)
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- Any practice that alters the composition of gut microbiota, such as dietary habit, physical activity, antibiotic or probiotics treatments and vaccinations, can affect digestive autoimmune diseases.
- It has been implicated that a high; fat, salt and sugar diet has a strong association with increased pathogenic Th17 cell differentiation and the development of autoimmunity.

Bilal paray et al , Int J Med Sci , 2020

Gut microbiome & Autoimmunity

Table 2 Ranking of the top 10 highest cited references

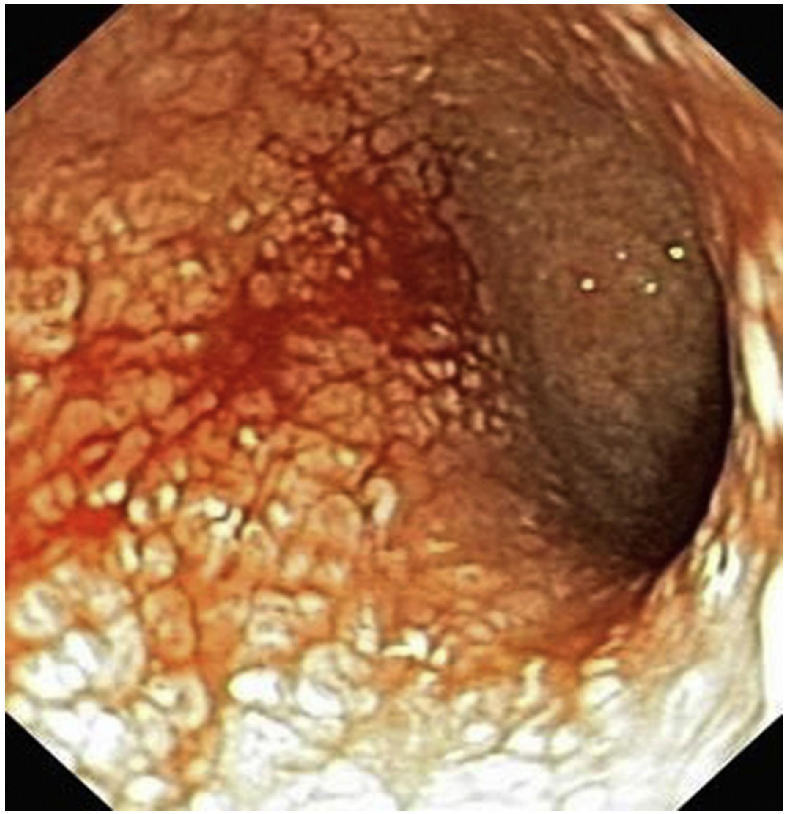
Rank	Year	Title	Journal	First author	Citations
1	2009	The gut microbiota shapes intestinal immune responses during health and disease	Nature reviews immunology	June L. Round	3045
2	2009	Induction of intestinal Th17 cells by segmented filamentous bacteria	Cell	Ivaylo I. Ivanov	2965
3	2014	Role of the microbiota in immunity and inflammation	Cell	Yasmine Belkaid	2307
4	2008	Innate immunity and intestinal microbiota in the development of type 1 diabetes	Nature	Li Wen	1393
5	2013	Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity	Science	Janet G. M. Markle	1145
6	2010	Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells	Immunity	Hsin-Jung Wu	1082
7	2014	The microbiome in inflammatory bowel disease: current status and the future ahead	Gastroenterology	Aleksandar D. Kostic	1024
8	2011	Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis	Proceedings of the national academy of sciences of the United States of America	Yun Kyung Lee	882
9	2017	Interactions between the microbiota, immune and nervous systems in health and disease	Nature neuroscience	Thomas C. Fung	849
10	2011	Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination	Nature	Kerstin Berer	808

Youao Zhang, Yongzheng Peng, Xu Xia. Clinical and Experimental Medicine (2023) 23:2813–2827

Autoimmunity & Diarrhoea (GI manifestations

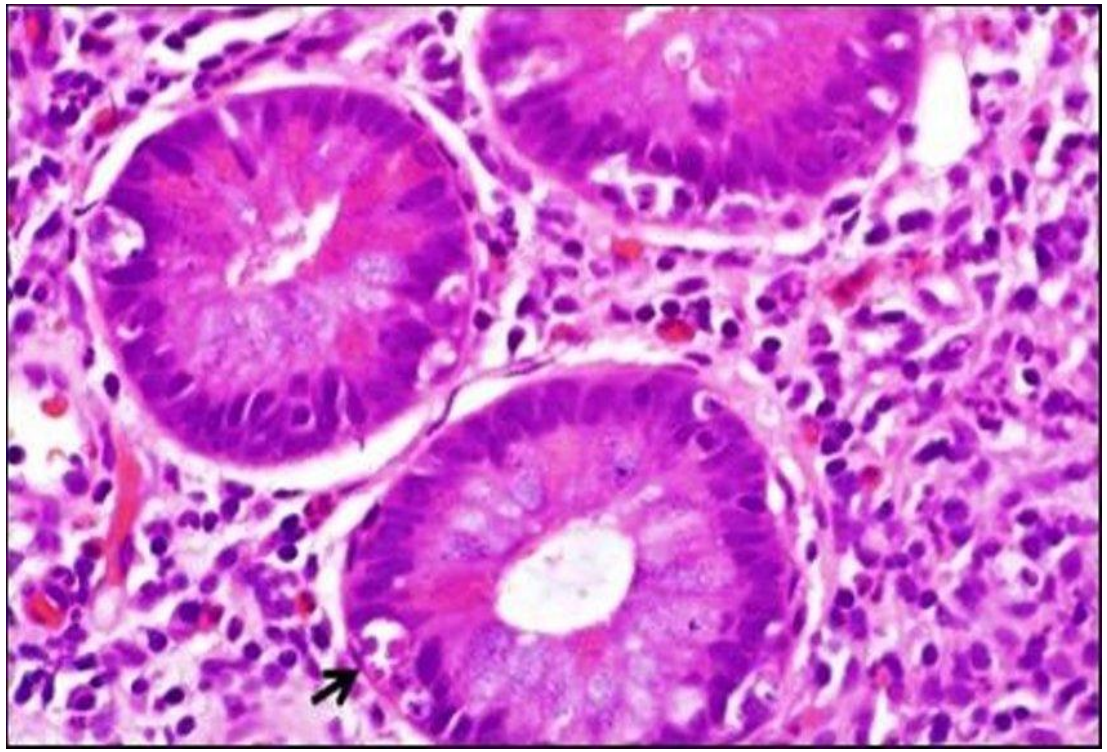
Autoimmune enteropathy

- **Autoimmune enteropathy (AIE)** is a rare cause of severe diarrhea associated with immune dysregulation and characterized by the presence of antibodies and autoimmune disorders.
- It manifests with **chronic and intractable diarrhoea in infants** following an uncomplicated gestation and neonatal period.
- It is generally believed to **predominantly affect males**
- **Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome**, caused by a mutation in the **FOXP3 gene**, and **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome**, caused by mutations in the **AIRE gene**, frequently cause AIE.



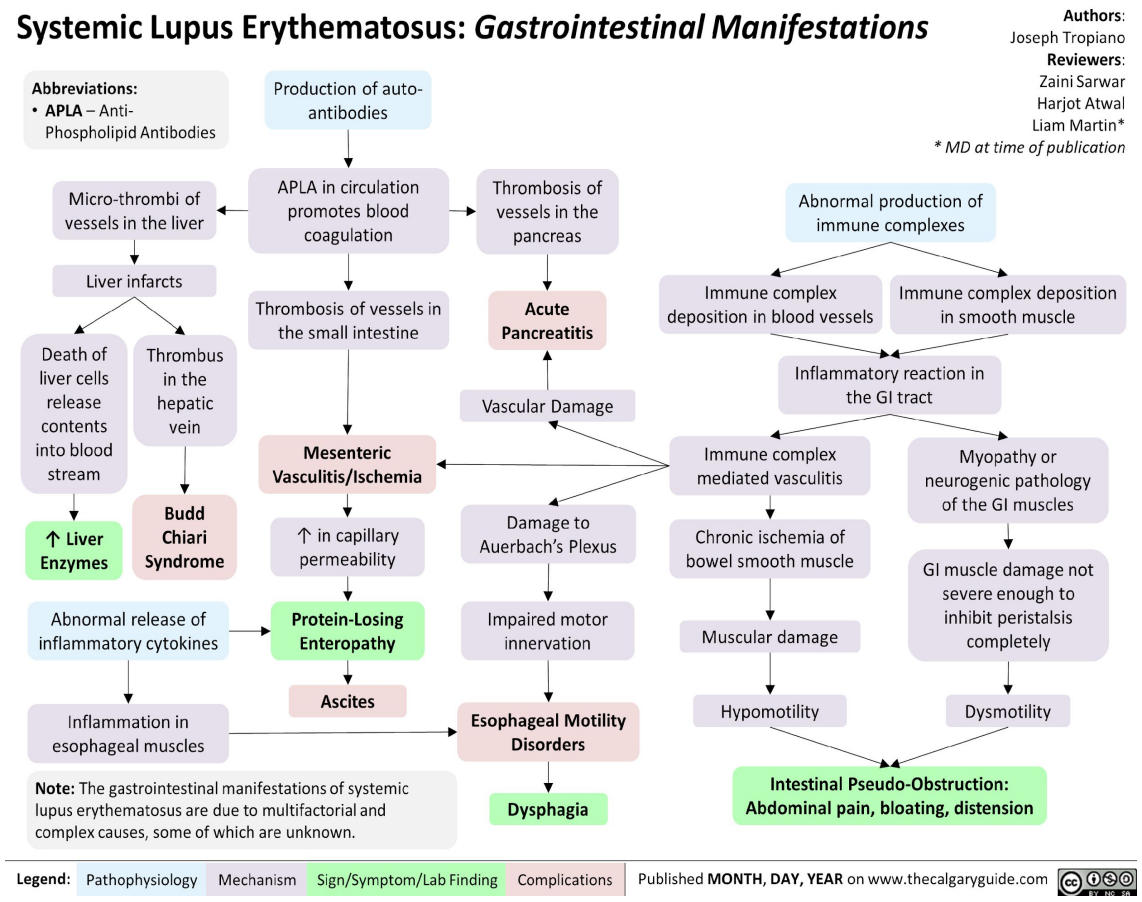
Autoimmune enteropathy

- Involves the **small intestine predominantly** and sometimes gastric and colonic involvement.
- **Histological examination** - villous atrophy with crypt hyperplasia and a marked T cell infiltrate in the intestinal mucosa. **Crypt apoptosis is characteristic of AIE**
- Nutritional support to ensure adequate growth **and immunosuppressive therapy, with corticosteroids** being the first-line treatment.
- In cases where steroid therapy fails, **alternative immunosuppressive agents** are used, such as cyclosporine, tacrolimus, sirolimus or mycophenolate.



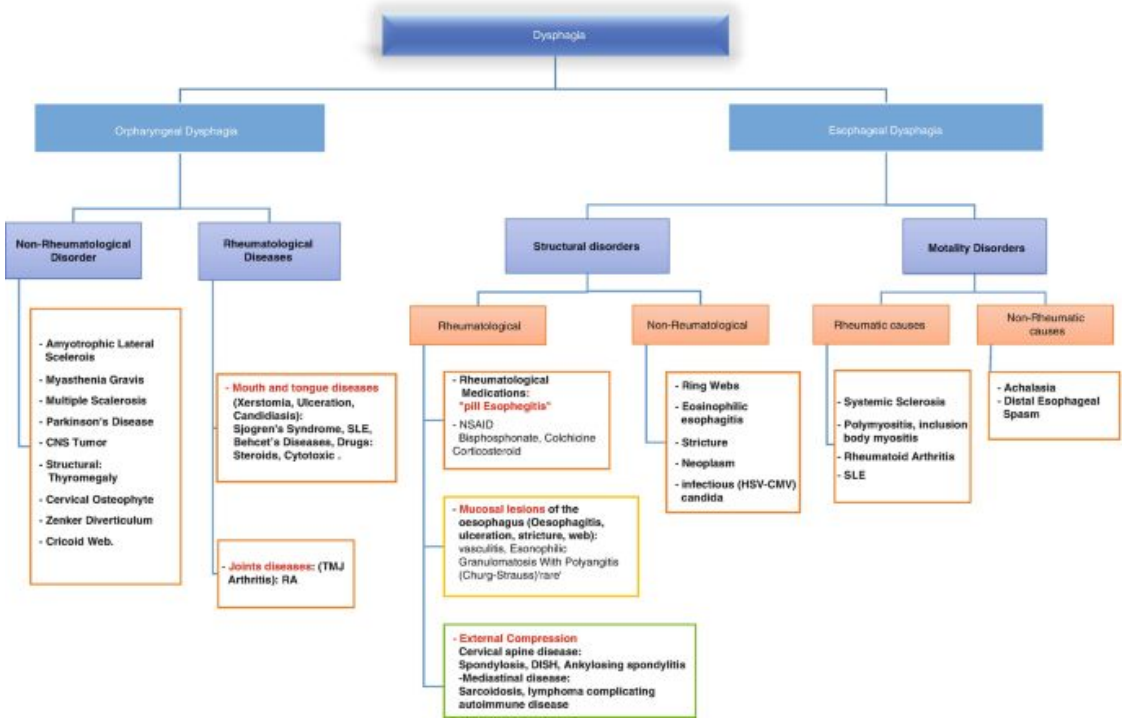
Systemic lupus erythematosus

- Gastrointestinal manifestations of SLE are common.
  - Due to primary gastrointestinal disorders, complications of therapy or SLE itself.
  - Any part of the gastrointestinal tract may become involved in SLE.
- **Lupus enteritis** - alimentary tract lesions in SLE
- Gastric ulceration with perforation may occur in SLE. Gastric antral vascular estasia may cause a "**watermelon stomach**" appearance
- **Small and large intestinal abnormalities** in SLE include dysmotility, vasculitis and malabsorption
- **Protein-losing enteropathy** is an unusual manifestation of SLE, although its clinical manifestations and management are not well understood. The association of SLE with inflammatory bowel disease is rare



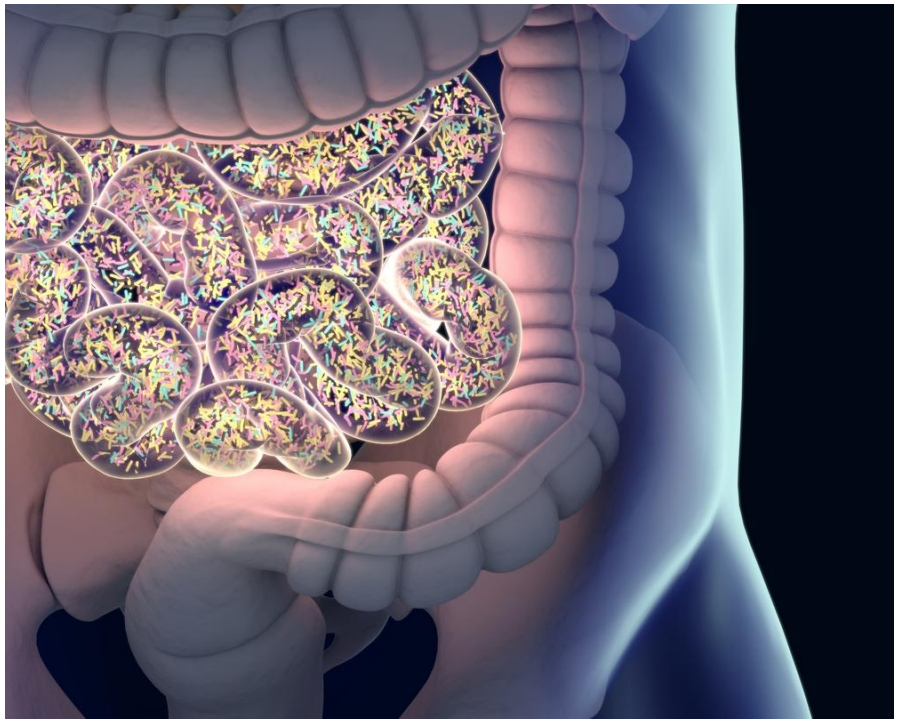
Rheumatoid arthritis

- In RA , Colonic inflammation may be accompanied by a subepithelial collagen band and the histologic picture of collagenous colitis.
- The thick collagen containing colonic wall cannot allow adequate water resorption, resulting in a typical presentation of profuse diarrhea, possibly associated with pain, flatulence and weight loss.
- Secondary amyloidosis may occur in patients with long-standing rheumatoid arthritis
  - may involve any portion of the gastrointestinal tract
  - may be manifest by Chronic diarrhea
  - can be diagnosed by endoscopic gastroduodenal biopsies.



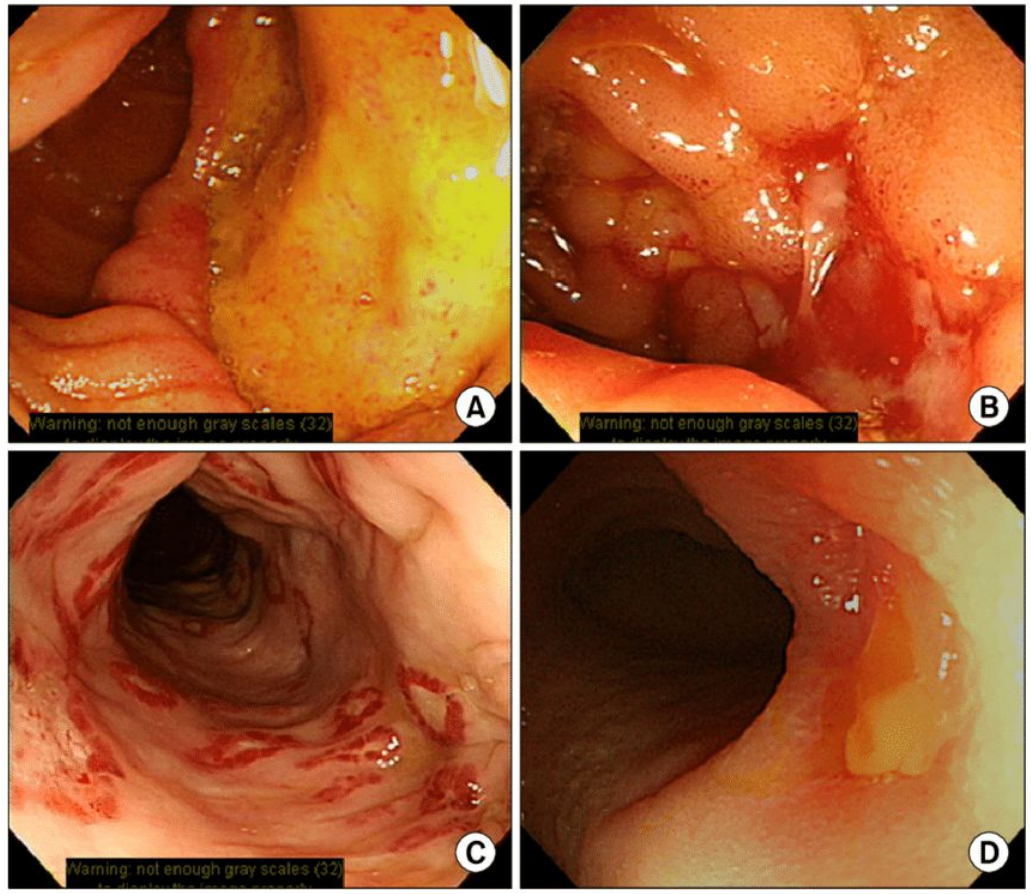
Sjogren's syndrome

- **Patients with Sjögren syndrome may have involvement of their entire gastrointestinal tract.**
- **Gastrointestinal manifestations include jejunitis, sigmoiditis, and inflammatory bowel disease.**
- **Malabsorption due to lymphocytic infiltrates of the intestine rarely occurs in patients with Sjögren syndrome, and oesophageal dysmotility has been reported in 36% to 90% of patients**



Behcet's disease

- **Behçet's disease causes inflammation and ulceration throughout the digestive tracts** that are identical to the aphthous lesions in the mouth and genital area.
- Oral apthae are painful, shallow, round to oval ulcers with discrete borders which often occur in crops.
- Mucosal apthae more frequent in esophagus than in stomach and duodenum.
- Esophageal involvement may manifest as ulcers, varices and less often perforation.
- **Ulceration** may occur anywhere in the gastrointestinal tract from the mouth to the anus.
- **Segmental mucosal ulceration** in the ileocecal and colonic area may appear after several years of recurrent aphthosis and present in the form of acute complications (perforation, massive hemorrhage) or **by prolonged bloody diarrhea**.

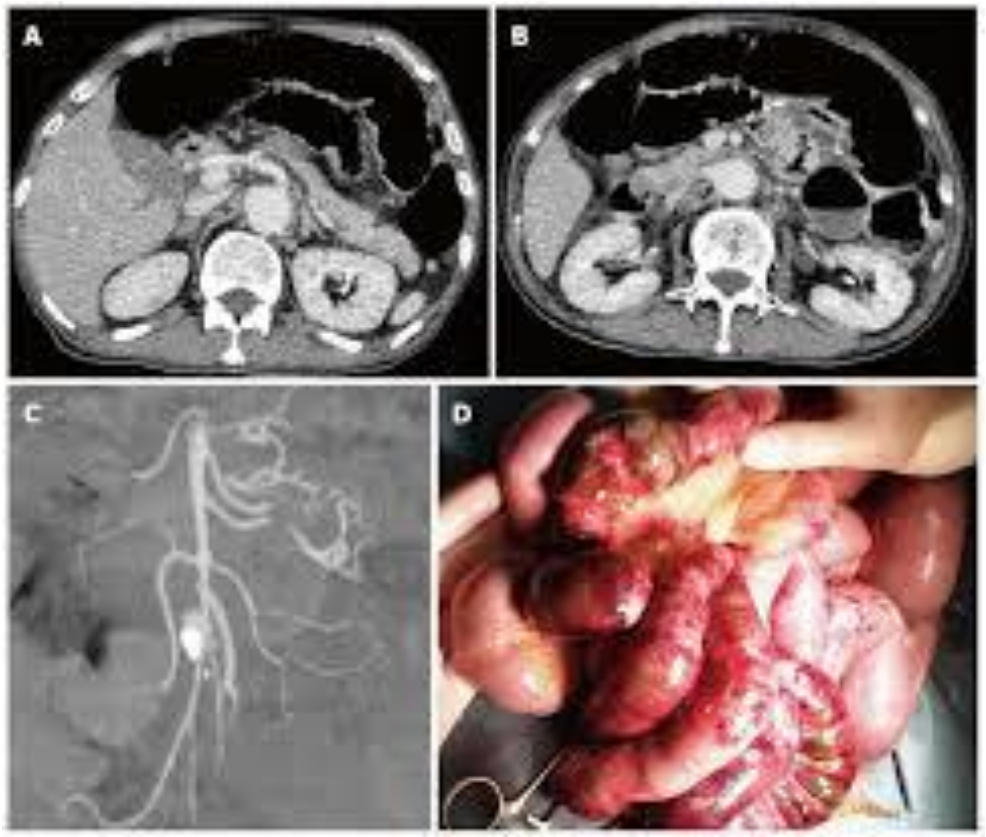


Progressive systemic sclerosis

- Scleroderma can **decrease motility** anywhere in the gastrointestinal tract
- **Dysmotility of small intestine** may cause **chronic pseudo-obstruction**.
- The small intestine can also become involved, leading to **bacterial overgrowth and malabsorbtion** of bile salts, fats, carbohydrates, proteins, and vitamins.
  - Malabsorbtion occurs as a consequence of bacterial over growth in **stagnant intestinal fluid.**
- The colon can be involved, and can cause **pseudo-obstruction or ischemic colitis**

Polyarteritis nodosa

- The signs and symptoms of systemic vasculitis involving the gastrointestinal tract result from mesenteric ischemia.
- The most common gastrointestinal symptom is acute abdominal pain which occurs in 23-70% of patients.
- The pain is vague, non-specific and is thought to be secondary to bowel ischemia, most commonly in the small bowel.
- Hematemesis, melena and hematochezia may also occur.
- Gastrointestinal ulceration may be found in 6% of patients and the most common site is the jejunum.
- Perforation occurs in 5% and bowel infarction in 1.4% of patients with polyarteritis nodosa.



Kawasaki disease

- **Kawasaki disease is a syndrome that usually occurs in infants and children.**
- **It is characterized by an exanthem, enanthem, fever, lymphadenopathy, and polyarteritis of variable severity.**
- **Patients with Kawasaki disease presented oral mucosal changes (erythema or dryness or fissuring of the lips), strawberry tongue and erythema of the oropharynx.**
- **Gastrointestinal manifestations include abdominal pain, vomiting and diarrhea.**
- **Small bowel obstruction may occur as a result of ischemia with stricture with adhesion formation**

Inflammatory muscle disorders

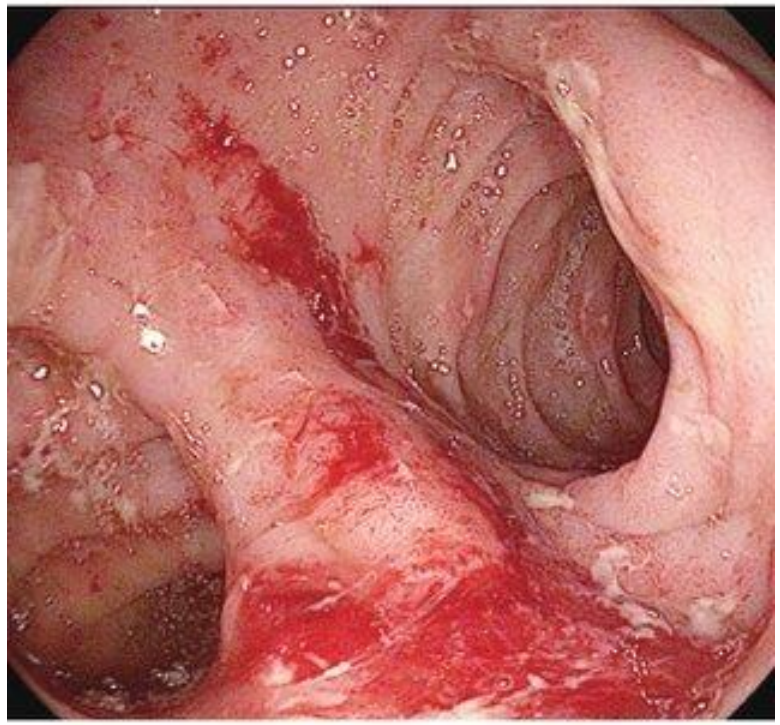
- Polymyositis and dermatomyositis are systemic autoimmune diseases characterized by inflammation of striated and, to a lesser extend, smooth muscle
  - The most common gastrointestinal manifestations of idiopathic inflammatory myopathies are related to motor abnormalities
  - the most serious and life-threatening problems are secondary to ischemic vasculopathy.
- Gastric and esophageal emptying is compromised in many patients, who may complain of dysphagia, aspiration, regurgitation, early satiety, and bloating.
- Patients may have difficulty in swallowing and nasal regurgitation, abnormal esophageal and gastrointestinal peristalsis, reduced gastrointestinal motility, hiatal hernia with reflux esophagitis with resultant stricture formation, dilated atonic esophagus associated with delayed gastric emptying and intestinal mucosal thickening.
- Inflammatory process leads to changes in the endothelium of small arteries and capillaries which may cause ischemia and necrosis in any part of gastrointestinal tract, resulting in ulceration, perforation or hemorrhage.
- Inflammatory myopathies have an association with inflammatory bowel diseases
- Constipation is the complication

Giant cell arteritis

- **Giant cell arteritis is a large vessel arteritis with strong predilection for the cranial and in particular, the temporal arteries.**
- **Giant cell arteritis rarely involves other sites**
- **Aortitis occurs in approximately 10% of patients**
- **There are case reports of intestinal gangrene and acute pancreatitis**

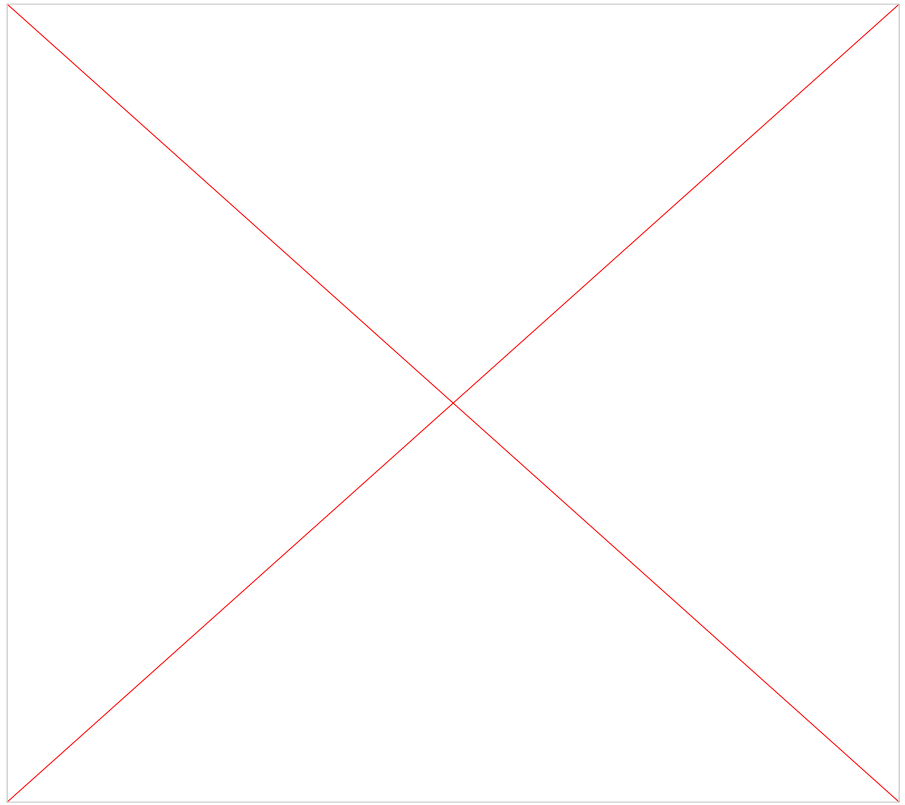
Henoch-Schönlein purpura

- **Henoch-Schönlein purpura is the most common systemic vasculitis in children with IgA mediated immune complex deposits affecting small vessels.**
- **Gastrointestinal signs and symptoms have been reported in 75% of cases.**
- **The most common presenting symptom is dull periumbilical pain.**
- **Nausea and vomiting are common as well.**
- **The main cause of abdominal pain is ulceration of the bowel mucosa which is more marked in the second part of the duodenum, but less frequently seen in the stomach, jejunum, colon and rectum**



Takayasu arteritis

- **Takayasu arteritis is a chronic vasculitis of unknown etiology.**
- **Women are affected in 80 to 90 percent of cases, with an age of onset that is usually between 10 and 40 years.**
- **The inflammatory processes cause thickening of the walls of the affected arteries. Narrowing, occlusion, or dilatation of involved portions of the arteries in varying degrees results in a wide variety of symptoms.**
- **The involvement of the descending abdominal aorta and its branches leads to gastrointestinal symptoms including abdominal pain, nausea, diarrhea and hemorrhage.**
- **Stenotic and saccular aneurismal lesions of intraabdominal arteries are reported**

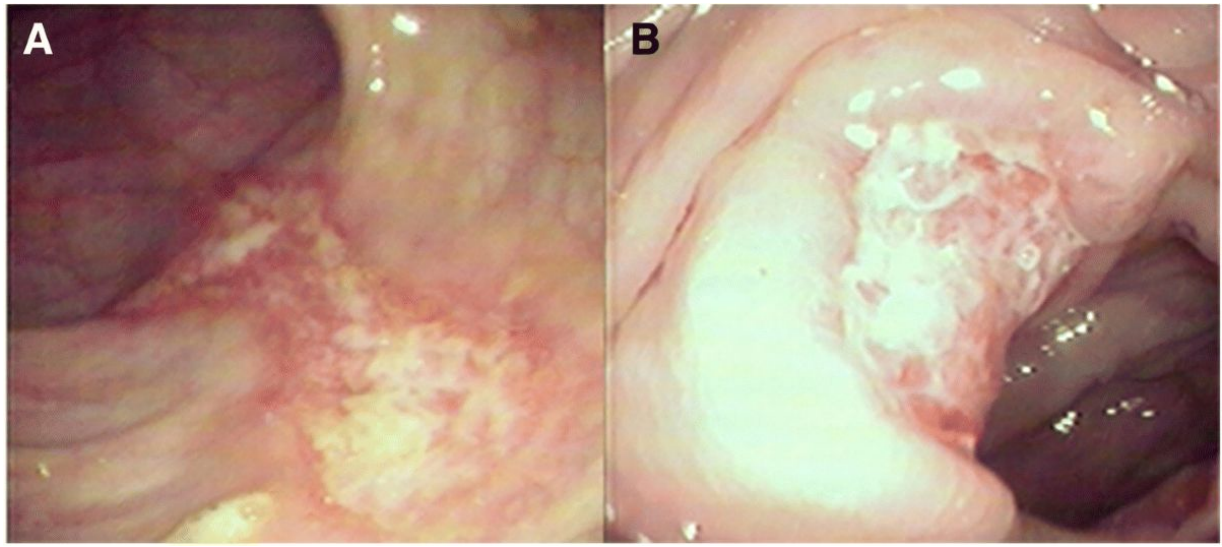


Churg-Strauss syndrome

- **Churg-Strauss syndrome is an allergic angiitis and granulomatous necrotizing vasculitis that occur almost exclusively in patients with asthma.**
- **The syndrome is most common in patients aged 30-50 years and has no gender predilection.**
- **Patients are typically asthmatic and present with eosinophilia, fever, and allergic rhinitis.**
- **Gastrointestinal involvement occurs in about 50% of patients.**
- **Eosinophilic gastroenteritis may be the prodrome of Churg-Strauss syndrome.**
- **Common gastrointestinal symptoms included abdominal pain, bloody stools, diarrhea and occasional nausea and vomiting**
- **Multiple ulcers may be seen and may lead to perforation.**
- **The small intestine is the most common site of involvement and is most commonly perforated,**
- **Necrotizing granulomatous vasculitis of the mesenteric artery may occur and lead to mucosal ischemia.**

Wegener granulomatosis

- **Wegener granulomatosis** is a systemic autoimmune disease characterized by granulomatous vasculitis of the upper and lower respiratory tracts, glomerulonephritis, and small-vessel vasculitis.
- The histopathologic hallmark of Wegener granulomatosis is a necrotizing vasculitis of small arteries and veins with granuloma formation.
- Gastrointestinal manifestations of Wegener granulomatosis are less common, with only scattered case reports of oropharyngeal mucosal lesions and gingivitis, gastric ulcer, small intestinal perforation, colonic ulceration, nonhealing perianal ulcers.



Spondyloarthropathies

- The spondyloarthropathies are a group of interrelated chronic inflammatory rheumatic diseases that includes ankylosing spondylitis, the arthritis associated with inflammatory bowel disease (IBD), and reactive arthritis.

- The spondyloarthropathies are also strongly associated with the HLA-B27 gene.
  - HLA-B27 also appears to enhance the invasion of enteric pathogens that are known to trigger reactive arthritis.

- Ulcerative colitis and regional enteritis (Crohn's disease) are the most frequently encountered types of idiopathic IBD that are associated with arthritis or spondylitis

Management of GI symptoms in AI

- Traditional therapeutic drugs for autoimmune diseases are generally nonspecific immunosuppressants, such as nonsteroid anti-inflammatory drugs (NSAIDs), steroid anti-inflammatory drugs (SAIDs) and disease-modifying antirheumatic drugs (DMARDs).
- Immunological drugs targeting inflammatory cytokines, receptors, intracellular molecules and kinase pathways have been developed and revolutionized the treatment of autoimmune diseases.
- Novel therapeutic targets are also under evaluation, such as TGFβ-SMAD signalling, cell adhesion or migration molecules and the NLRP3 inflammasome .
- Various novel immunotherapies engaging in T-cell immunity have recently been applied in autoimmune diseases and demonstrated promising therapeutic efficacy
- In reference to immunotherapies in cancer, engineered chimeric antigen receptor (CAR)-T cells and chimeric autoantibody receptor (CAAR)-T cells are developed to target autoreactive B cells or T cells in autoimmune diseases.
- In addition, strategies to induce T_{reg} cell expansion and function or generate CAR-T_{reg} cells have been extensively studied in preclinical autoimmune models

Lina Sun & Baojun Zhang , BMC Immunology , 2023

Healing the leaky gut

- The process of healing the gut with both short-term and long-term measures.
- Short-term measures to heal the gut include discontinuing foods rich in gluten, dairy, and sugar from the diet
- In the long term, maintaining good gut health is crucial to the prevention of autoimmune diseases
  - Addition of prebiotics & Probiotics helps in establishing the gut flora by creating a fresh system of operation in the gut
    - Treatment with Bacteroides fragilis has been shown to decrease the pathogen translocation that further ameliorates the diseased state
    - The introduction of probiotics (most of the lactobacilli) modulates the gut microbiota and decreases the occurrence of autoimmune diseases such as IBD and T1D .
    - The most common prebiotic supplement derived from plants is inulin. The supplementation of diet with inulin enhances the growth of Bifidobacterium spp., besides improving glucose homeostasis

Bilal paray et al , Int J Med Sci , 2020

Take home ……..

- Gut microbiome associated with Autoimmunity
- Range of Gastrointestinal manifestations in AI diseases
- Treatment of AI diseases with restoring the Gut microbiota with Pre & Probiotic