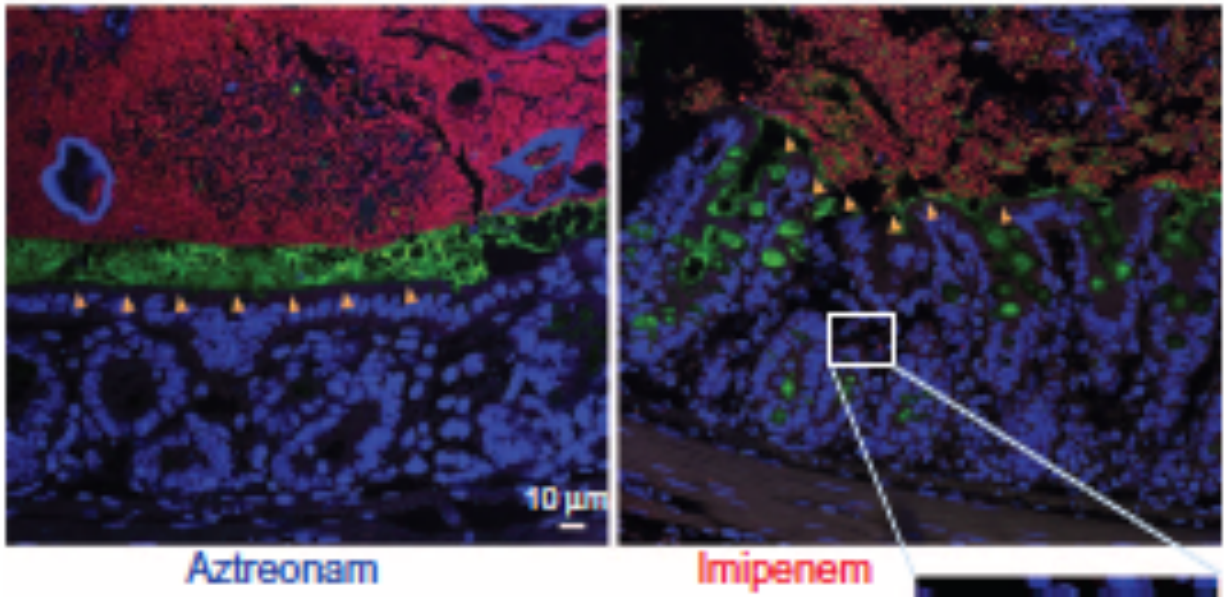


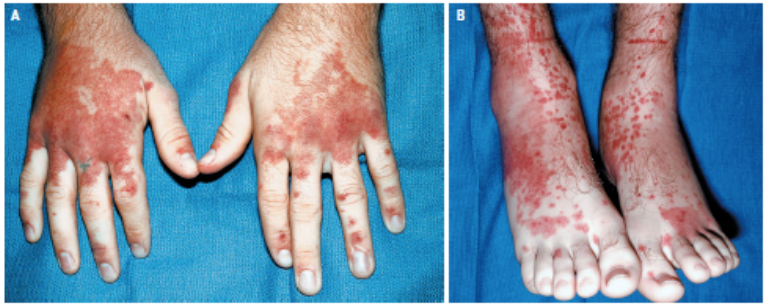
Ordensklinikum Linz
Barmherzige Schwestern Elisabethinen

Clinical Immunology

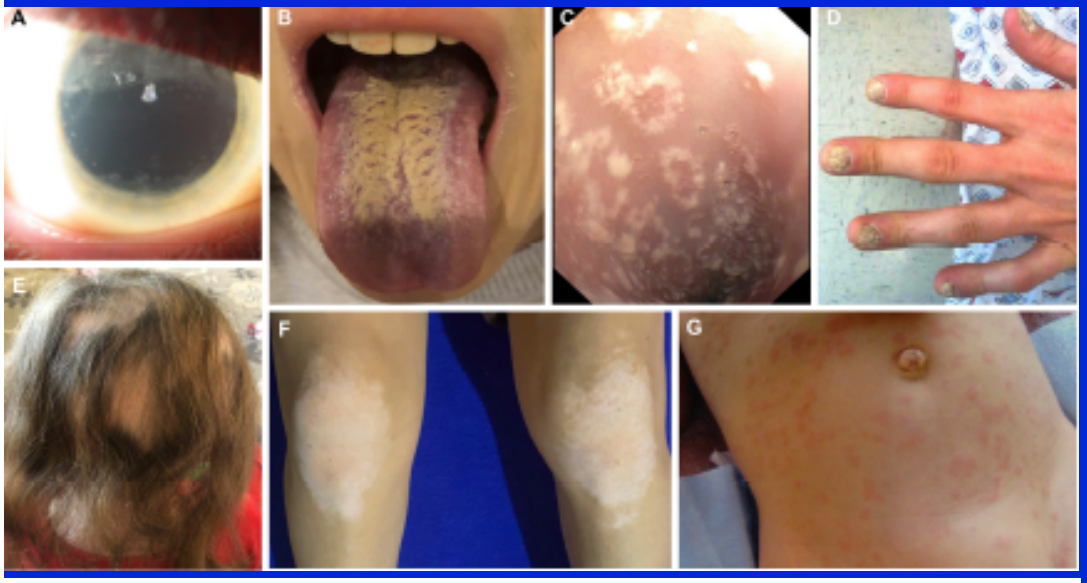
Part II: Autoimmunity & Immune Mediated Disease

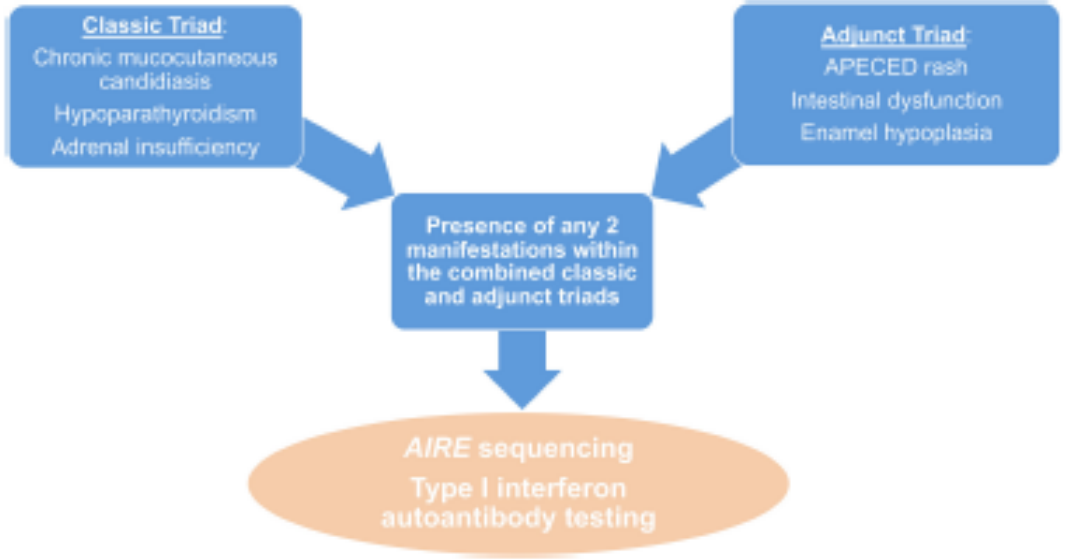
Harry Fuchssteiner 30/11/2023

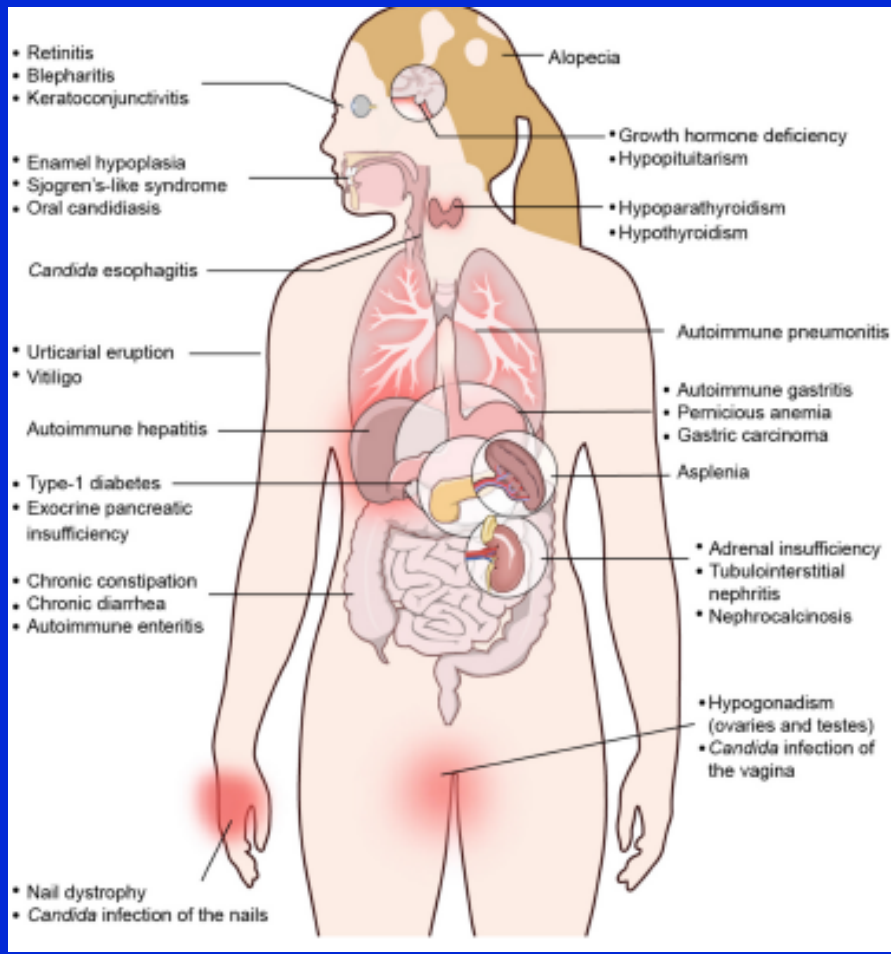
Innere Medizin 4, Ordensklinikum Linz – **BHS**



Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy







Ferre et al., Frontiers in Pediatrics 2021

Skin Manifestations of Primary Immune Deficiency

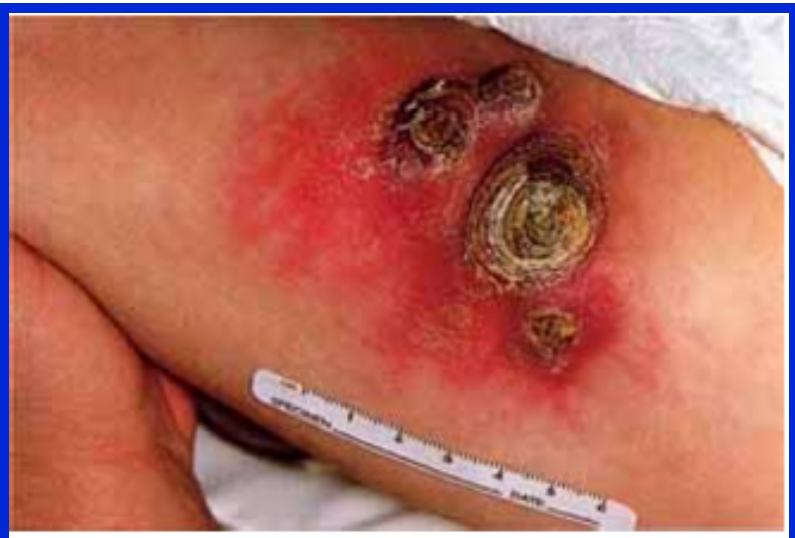
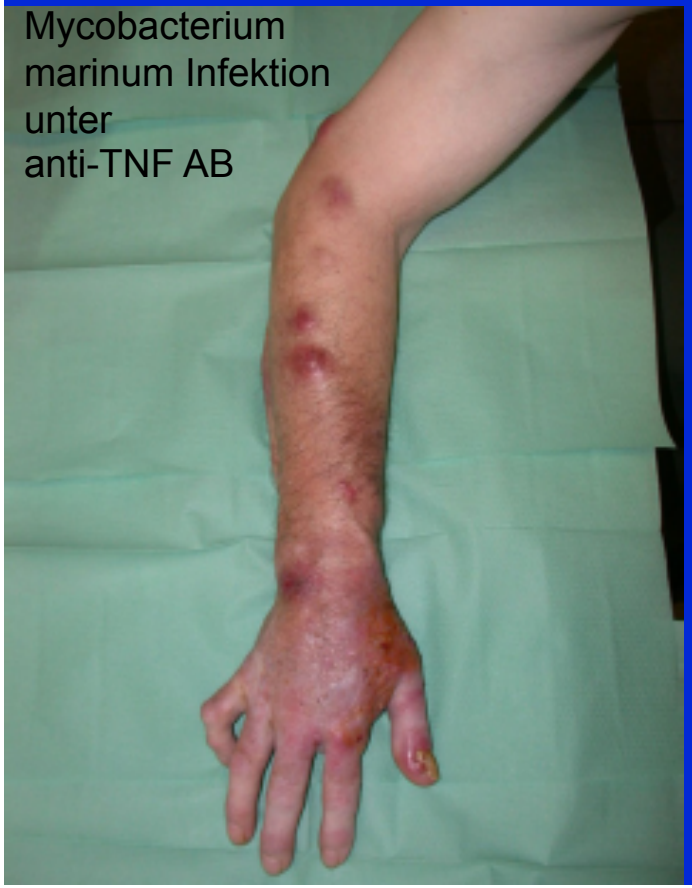


Fig. 4 Serratia abscess with absent pus formation in a patient with leukocyte adhesion deficiency type 1 (Courtesy of Dr. Steven M.

Segaet et al;
Am J Clin Dermatol 2017



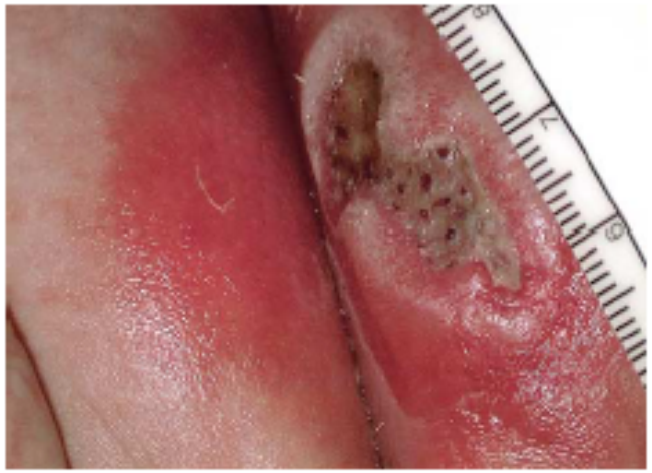
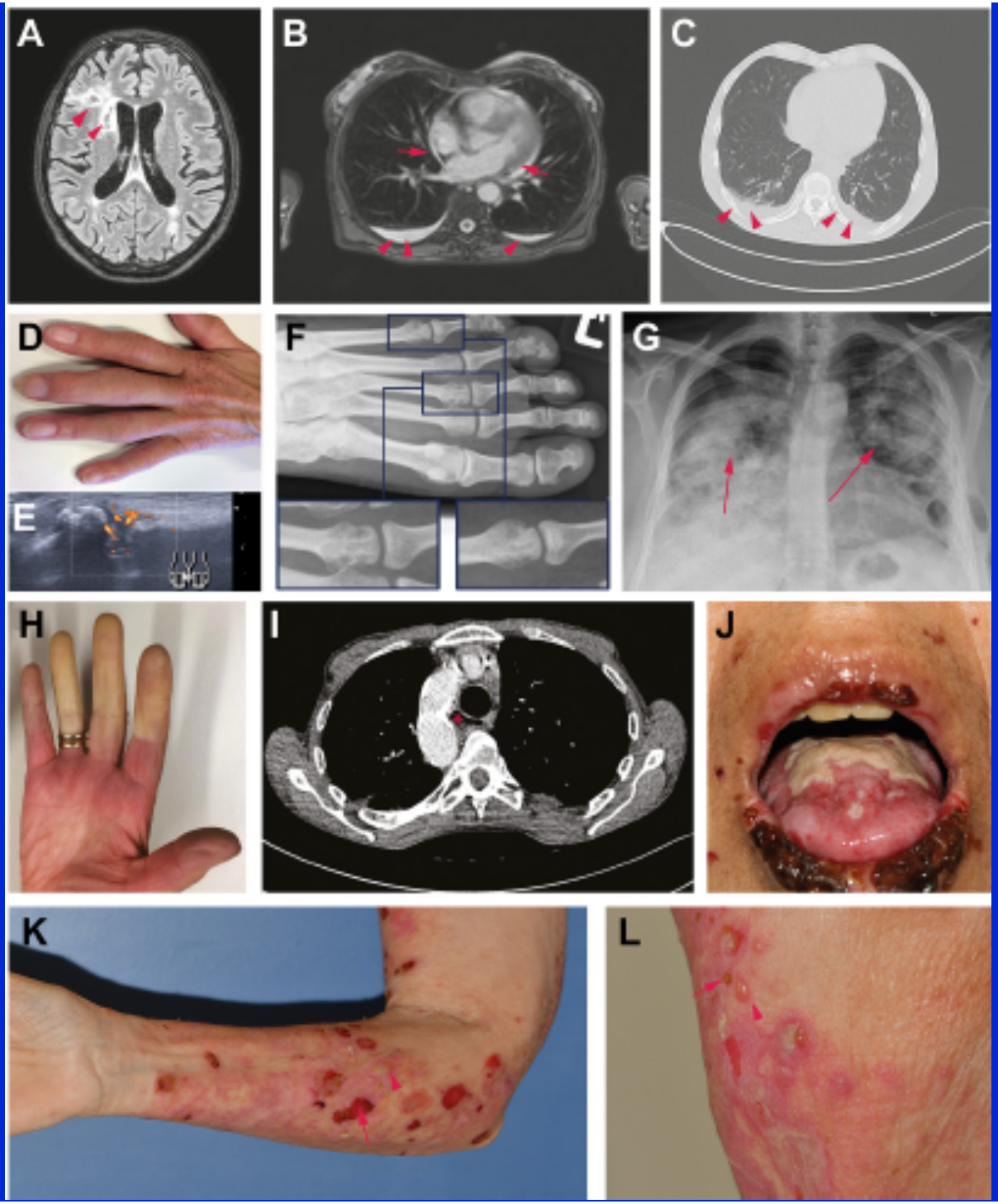


Fig 1. *Citrobacter freundii* ecthyma gangrenosum ulcer of right inferior buttock. *Reich et al., J AM ACAD DERMATOL 2004*

Nonpseudomonal ecthyma gangrenosum

Clinical Signs, Pathophysiology and Management of Cutaneous Side Effects of Anti-Tumor Necrosis Factor Agents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Systemic Lupus Erythematosus

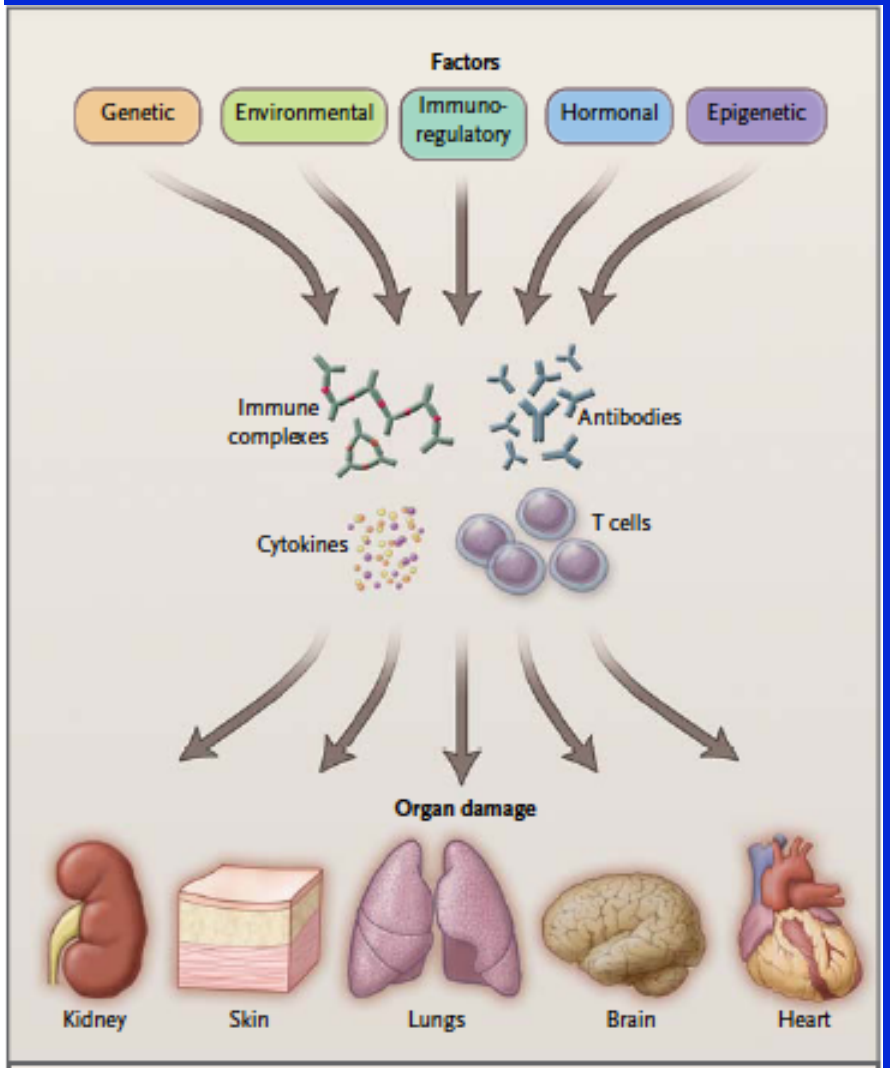


Figure 1. Overview of the Pathogenesis of Systemic Lupus Erythematosus.

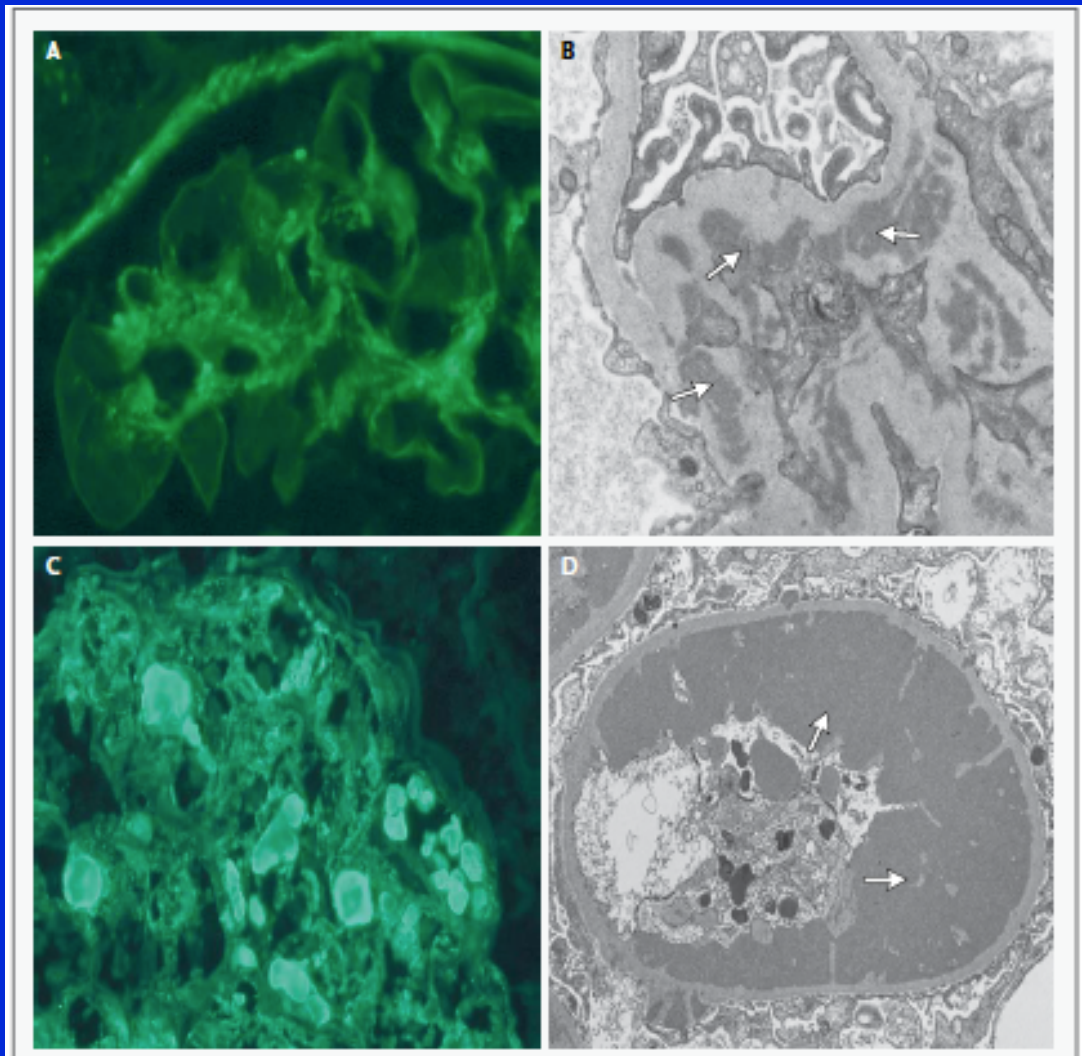
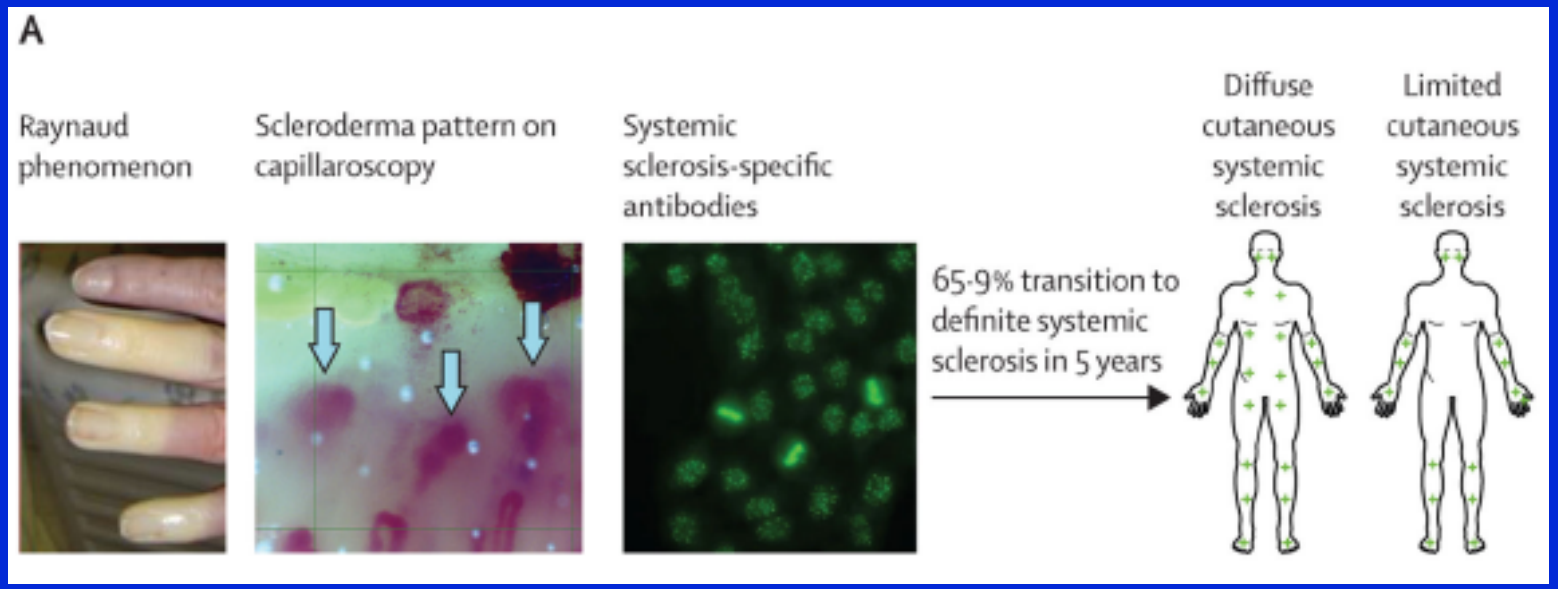


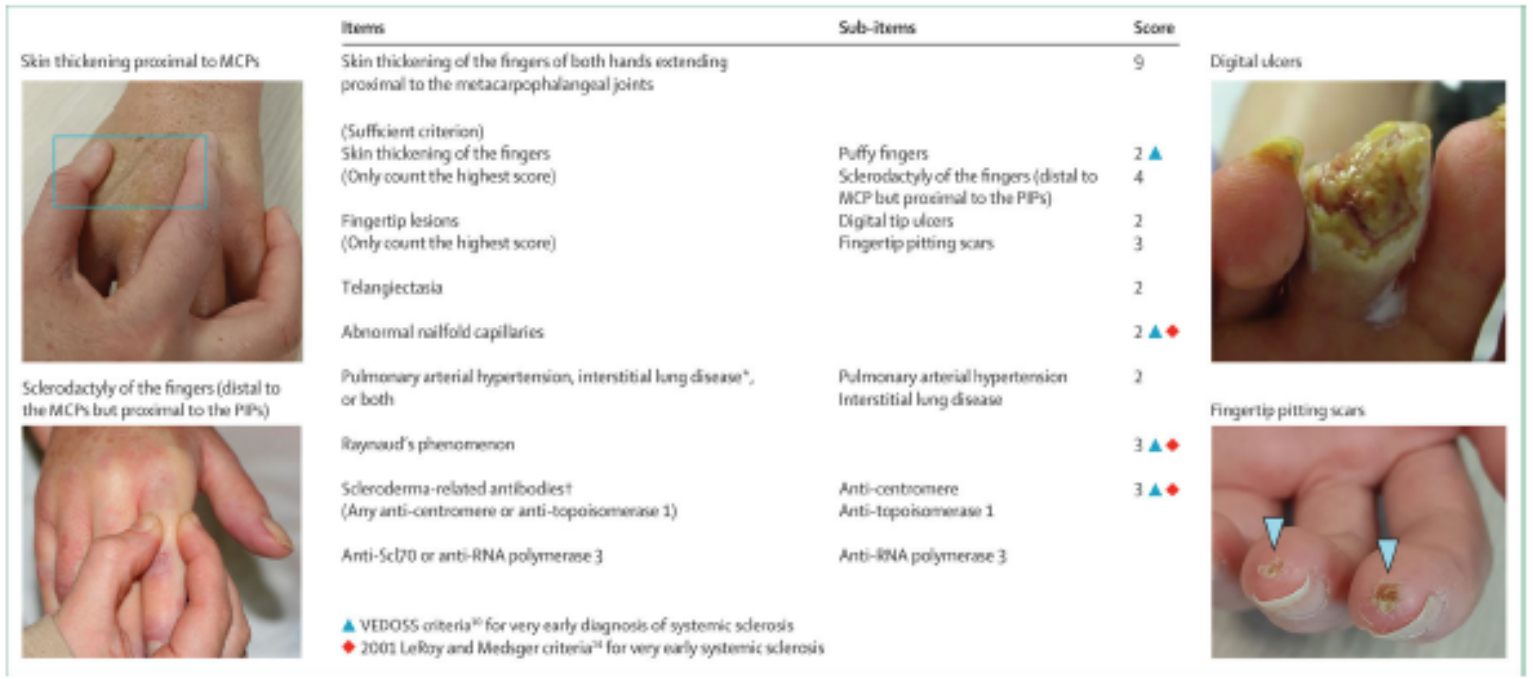
Figure 4. Features of Lupus Nephritis on Immunofluorescence Staining and Transmission Electron Microscopy.

Volkmann et al.

Systemic sclerosis

Lancet. 2023 January 28;

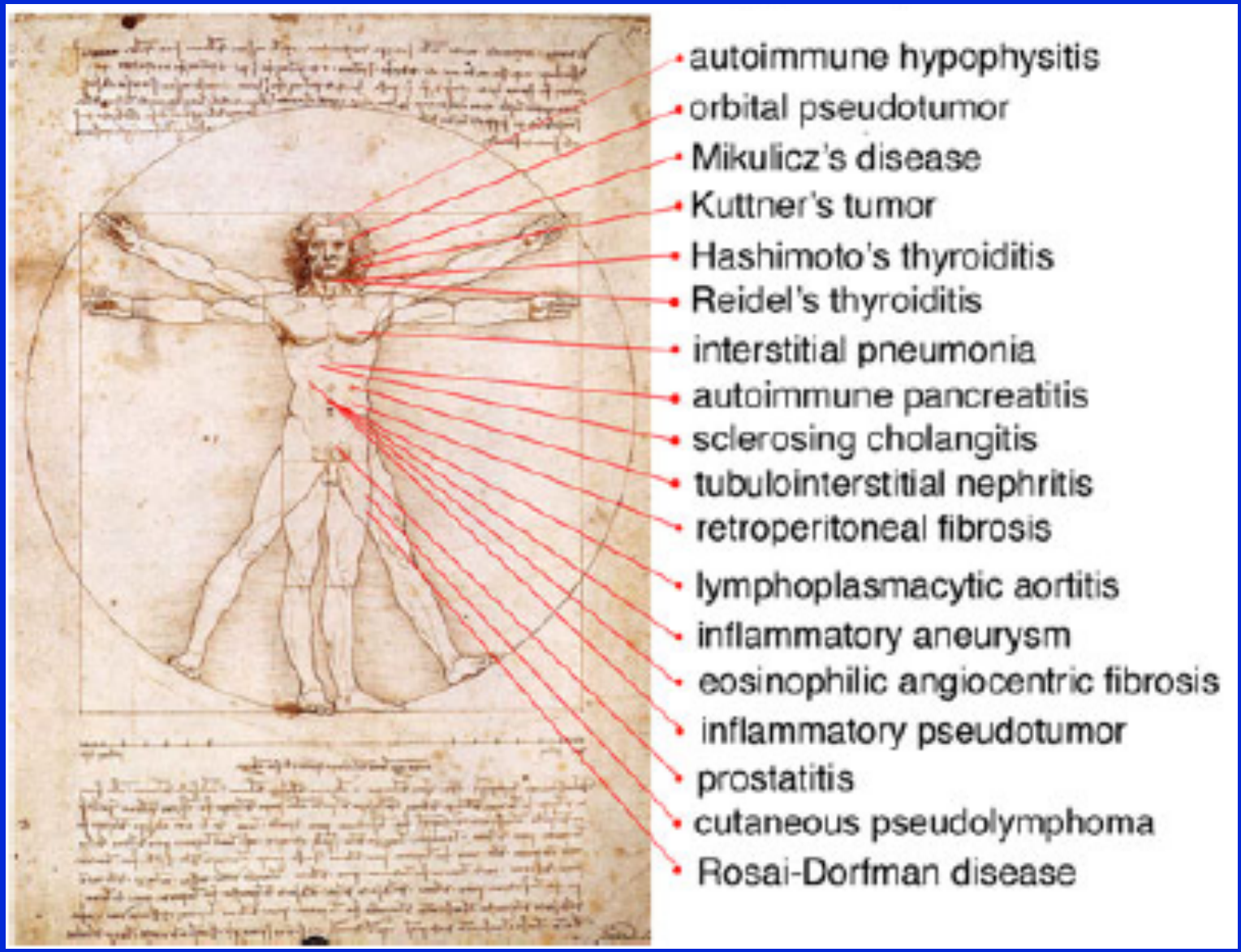




Items	Sub-items	Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
(Sufficient criterion)		
Skin thickening of the fingers	Puffy fingers	2 ▲
(Only count the highest score)	Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)	4
Fingertip lesions	Digital tip ulcers	2
(Only count the highest score)	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2 ▲◆
Pulmonary arterial hypertension, interstitial lung disease*, or both	Pulmonary arterial hypertension Interstitial lung disease	2
Raynaud's phenomenon		3 ▲◆
Scleroderma-related antibodies† (Any anti-centromere or anti-topoisomerase 1)	Anti-centromere Anti-topoisomerase 1	3 ▲◆
Anti-Scl70 or anti-RNA polymerase 3	Anti-RNA polymerase 3	

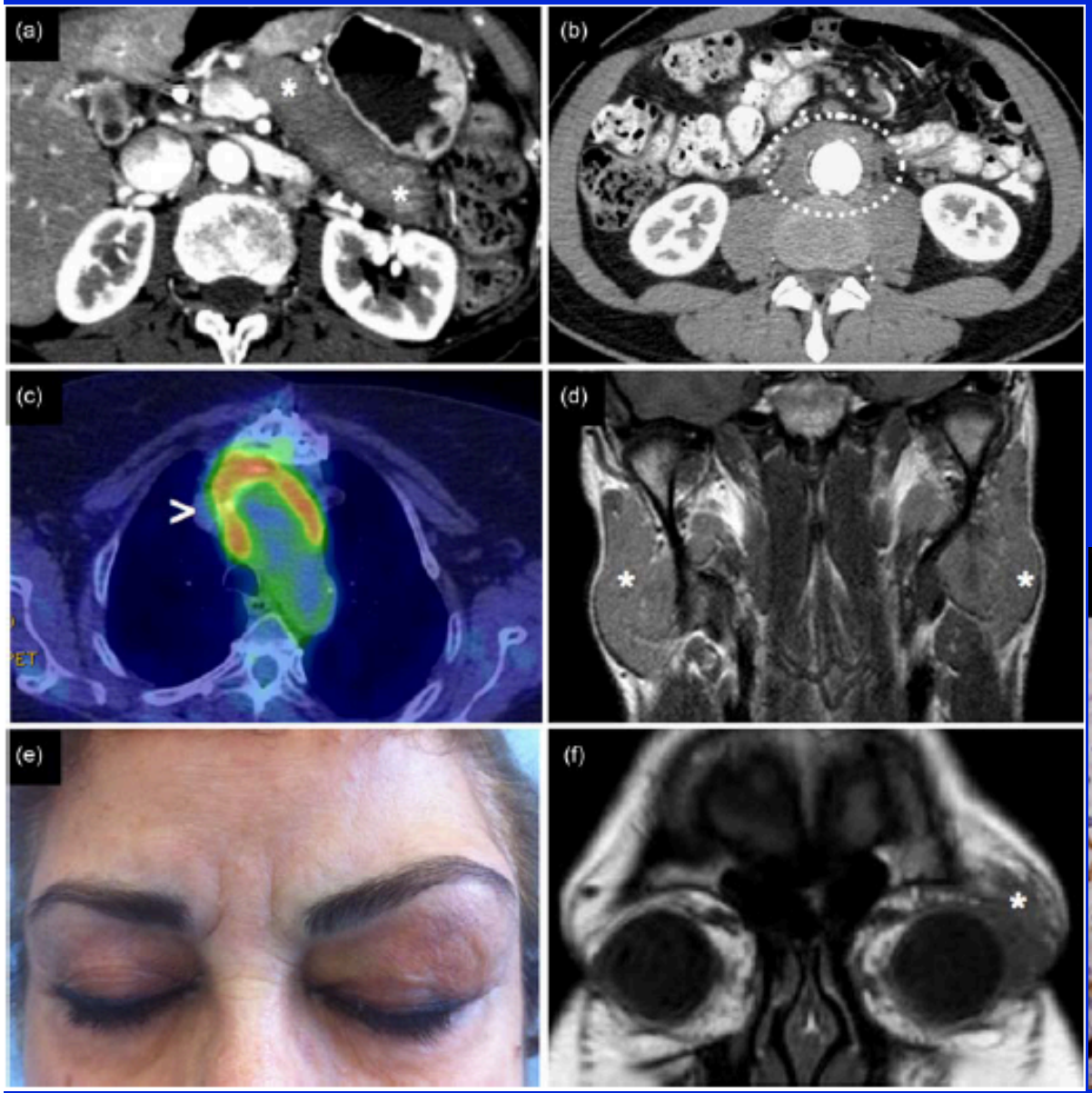
Figure 2: The 2013 American College of Rheumatology and European Alliance of Associations for Rheumatology Classification Criteria for systemic sclerosis

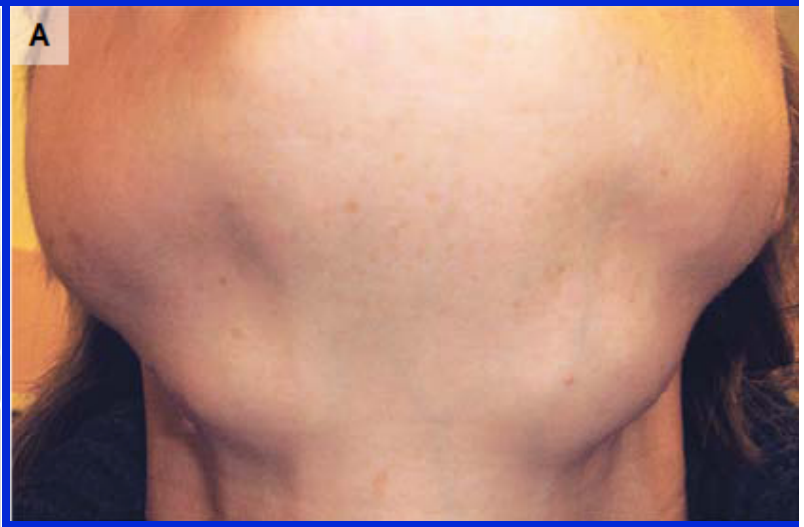
A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details

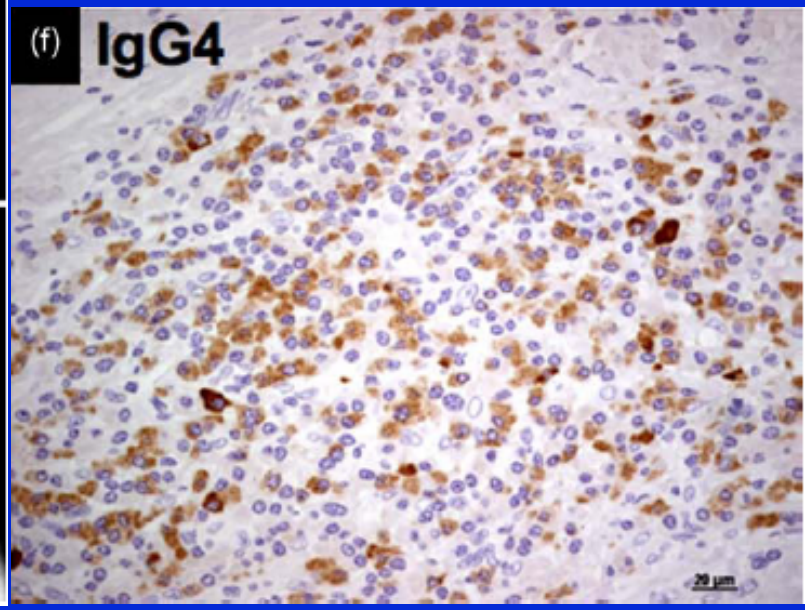


Umehara et al., Mod Rheumatol 2012

Immunology of IgG4-related disease

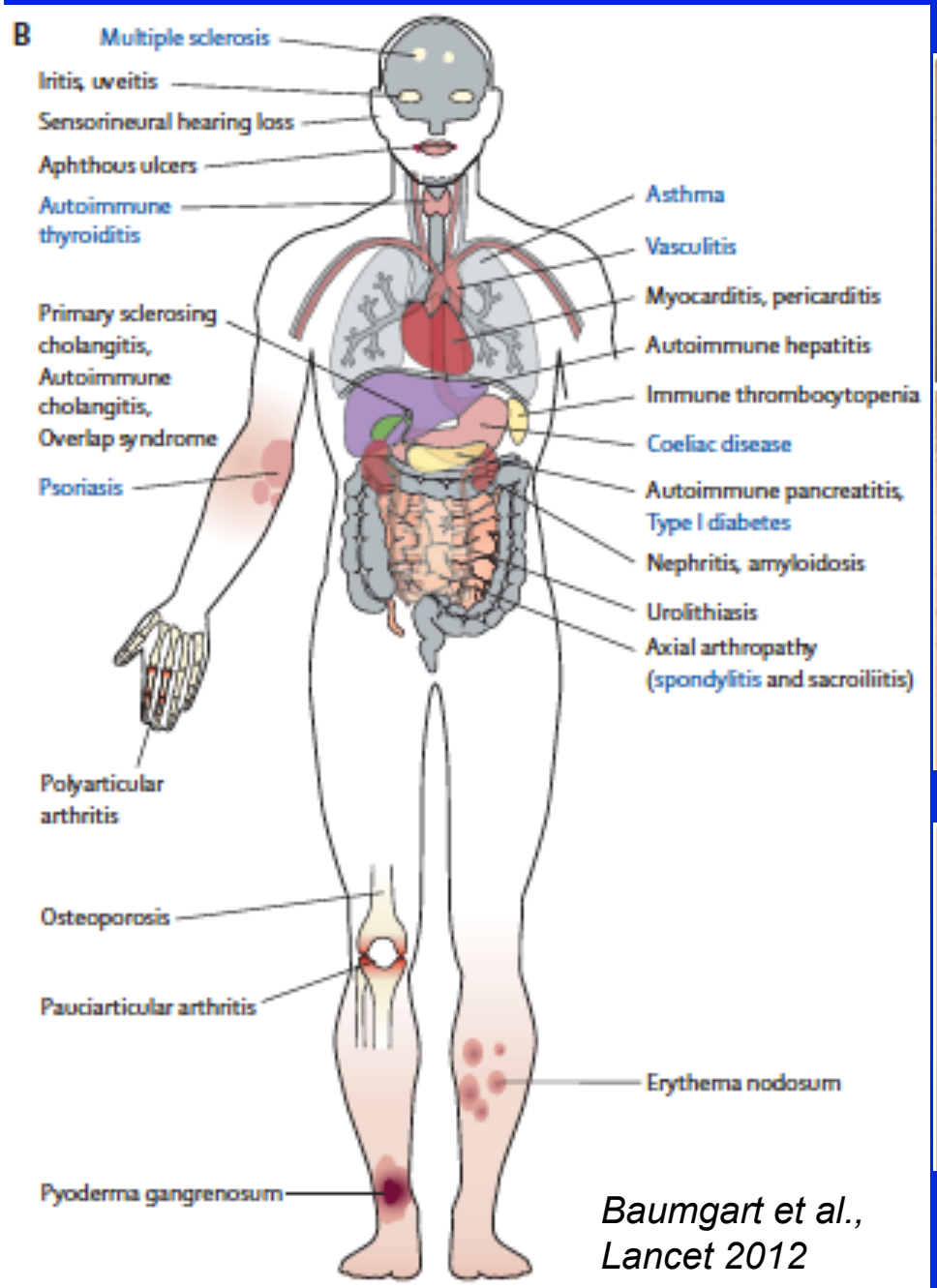




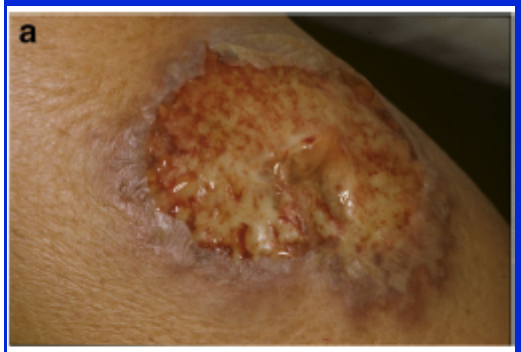


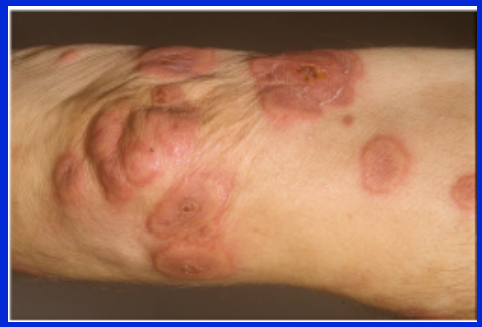
Della-Torre et al., Clinical and Experimental Immunology 2015

Extraintestinal Manifestations

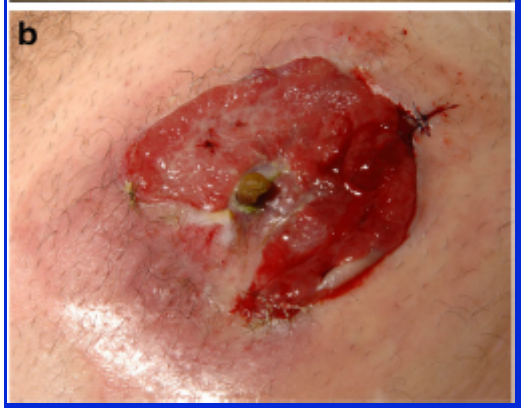


Baumgart et al., Lancet 2012

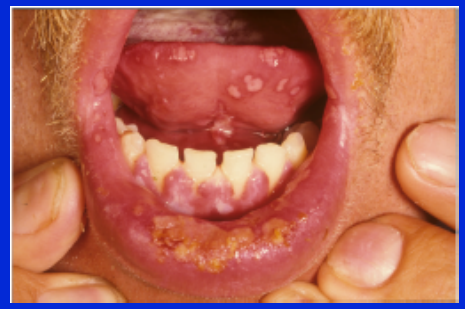




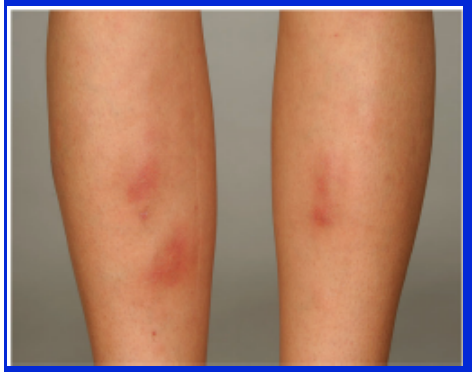
Sweet`s syndrome



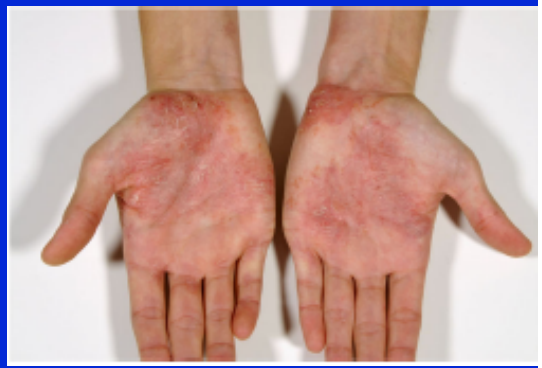
Pyoderma gangrenosum



Aphtous ulcers



Erythema nodosum

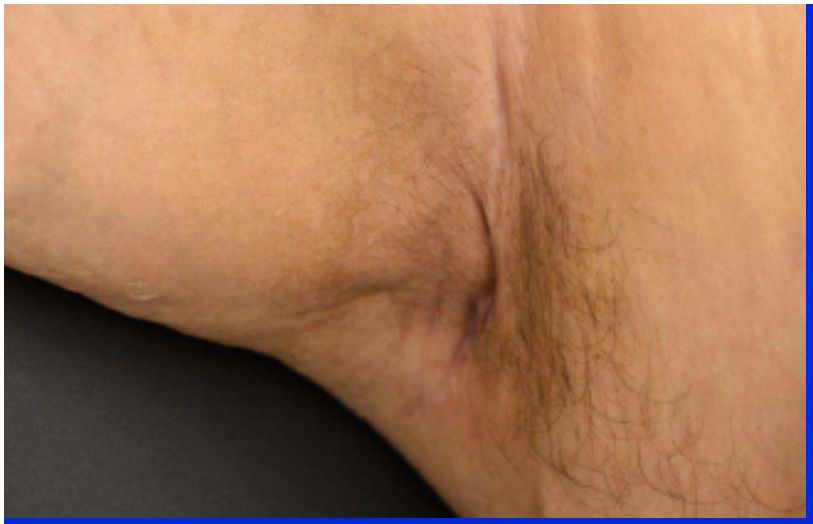


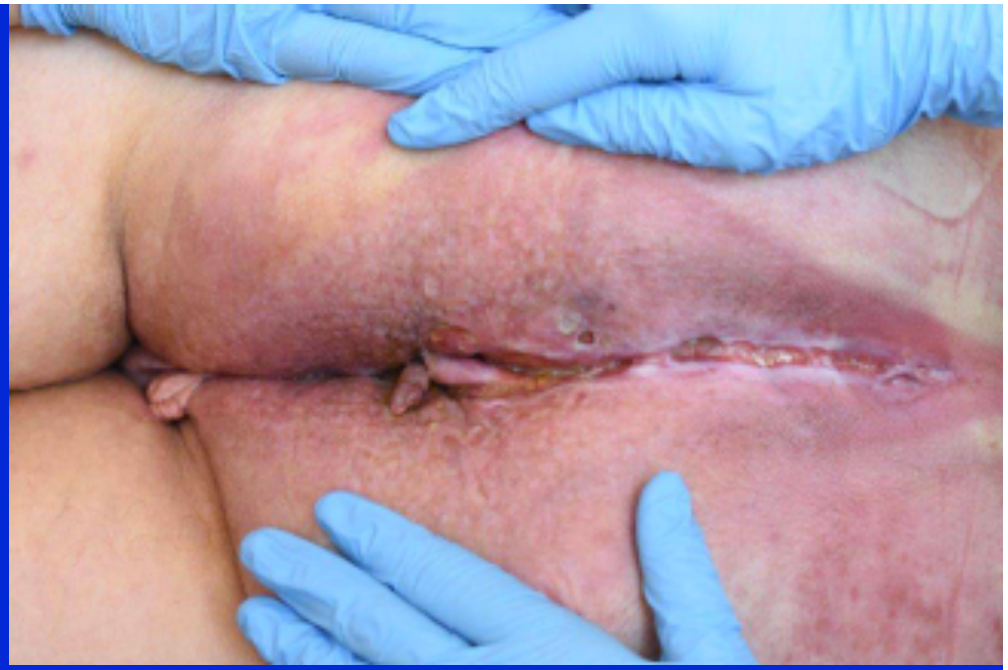
TNF induced Psoriasis

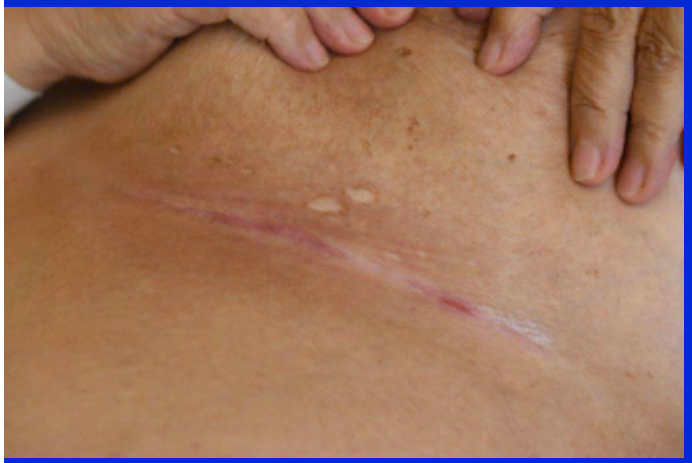
Skin Manifestations of Inflammatory Bowel Disease

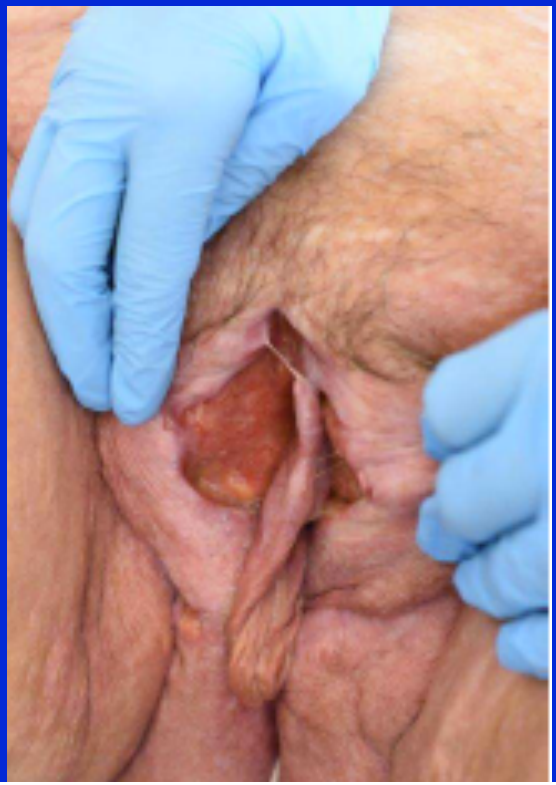
Thomas Greuter[1] · Alexander Navarini[2] · Stephan R. Vavricka[1,3]

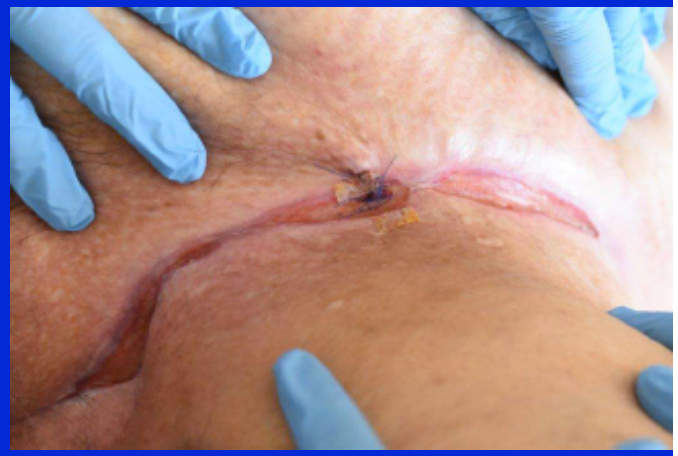
Clinic Rev Allerg Immunol (2017)

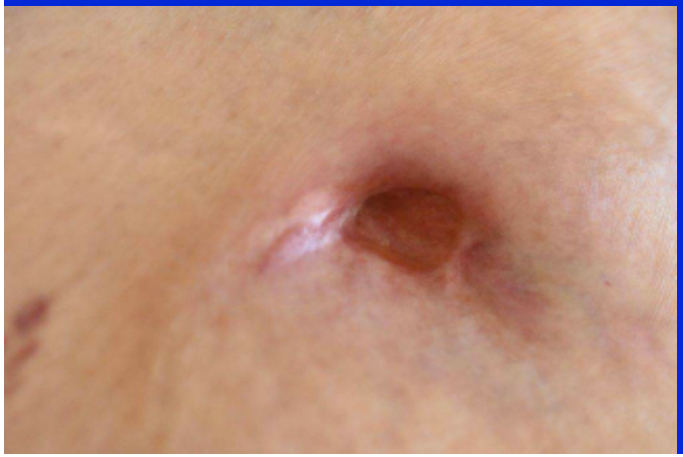






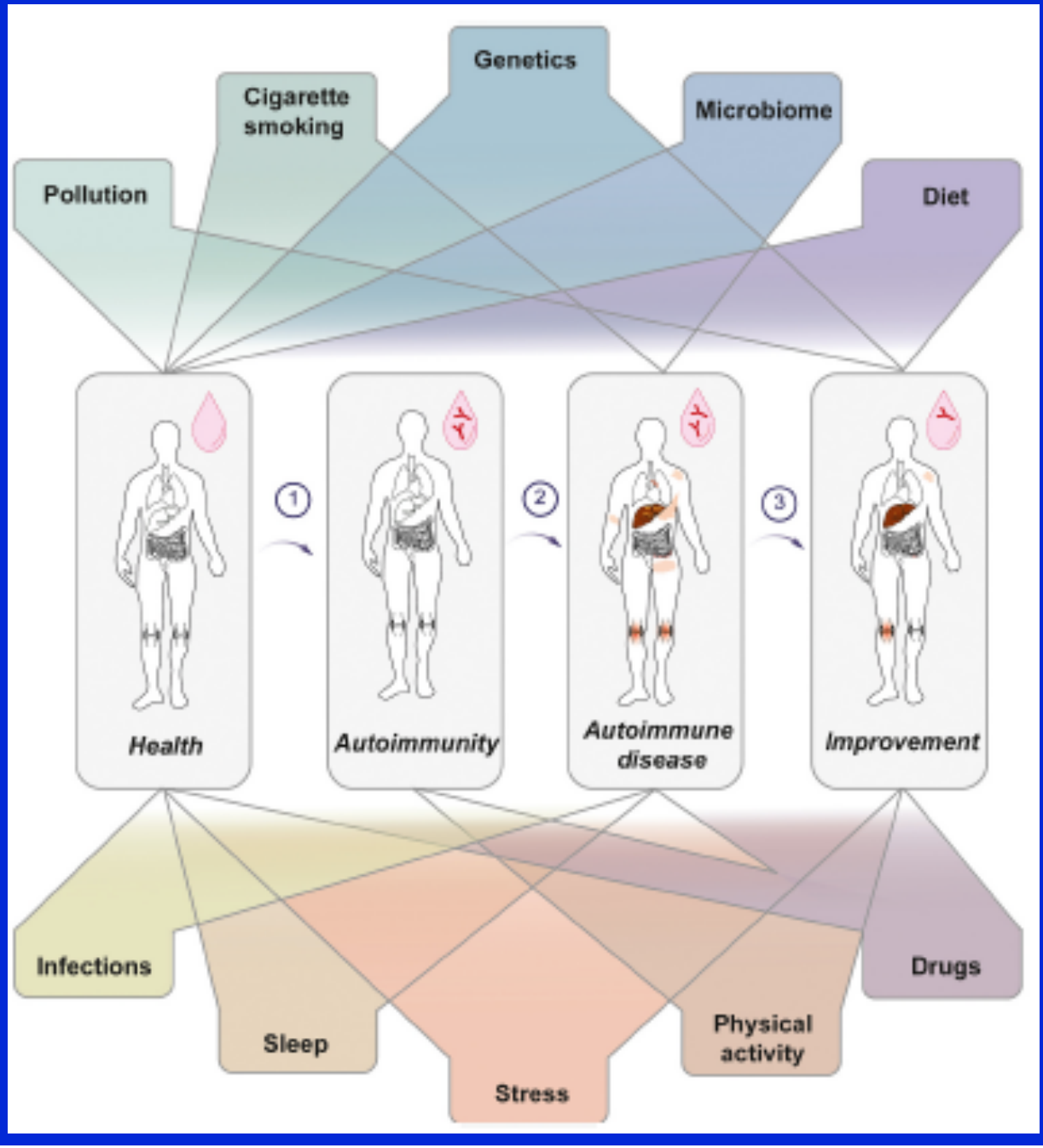




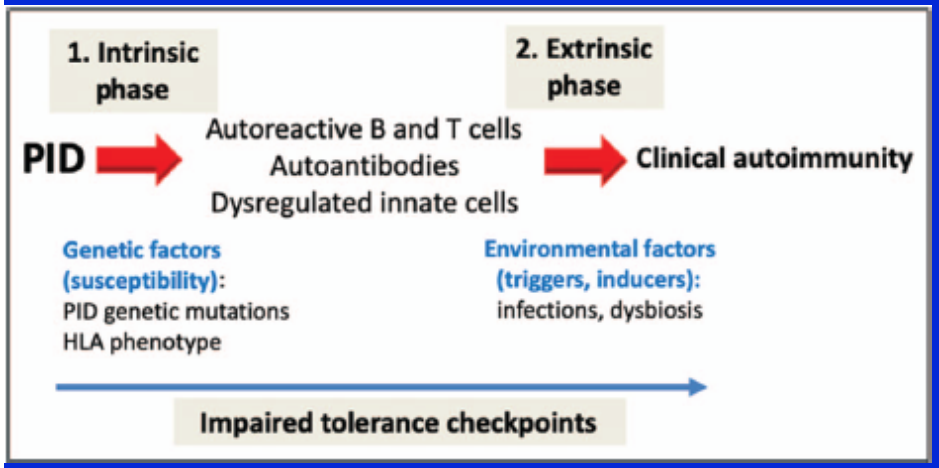


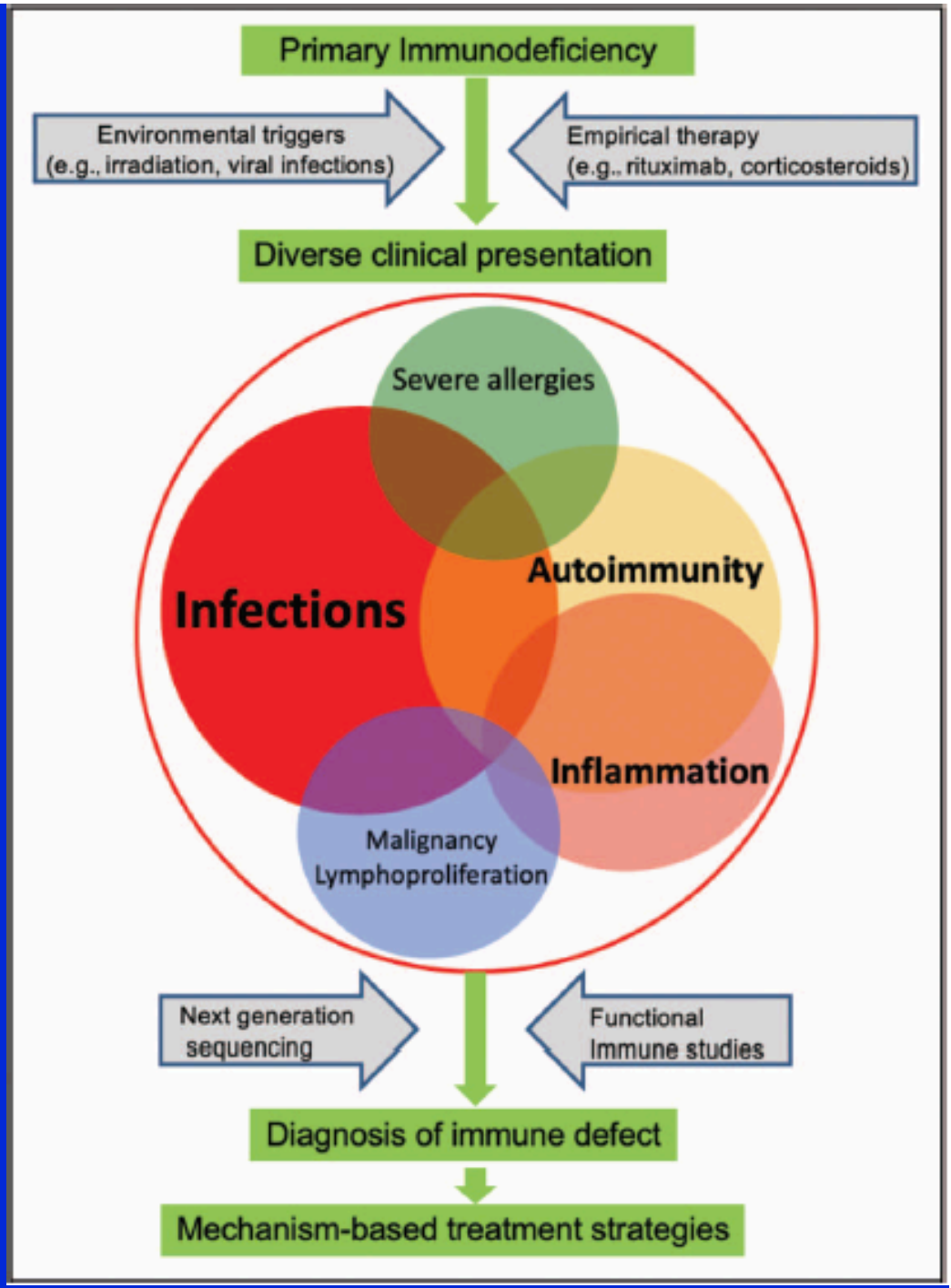
Patientin HR
60a; BMI 40;
Haut: Kutaner Crohn
Endo: unauffällig

Autoimmune pre-disease



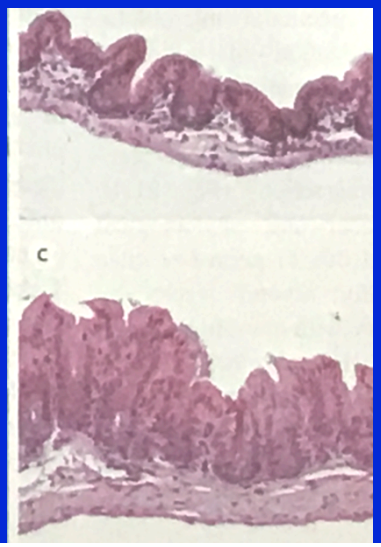
Autoimmunity as a continuum in primary immunodeficiency





Gnothobiology
germ free mice - immunopathology

- Peyer`s patches ↓
- Lymph follicels ↓
- Spleen size ↓
- secretory IgA ↓
- CD 8 T cytotoxity ↓
- Lymphocyte homing ↓
- IEL ↓
- T_H 17 function ↓

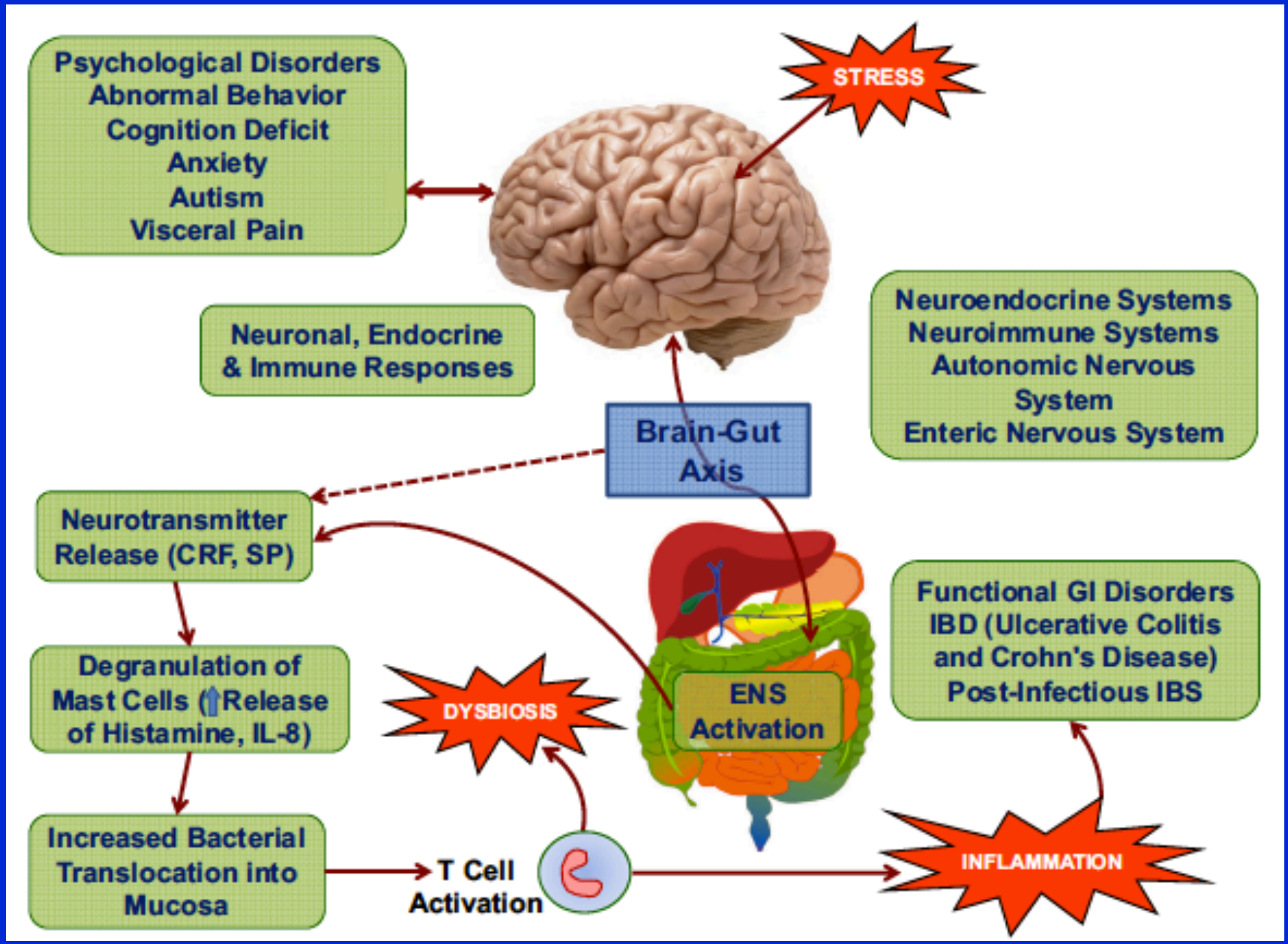


Infection ↑

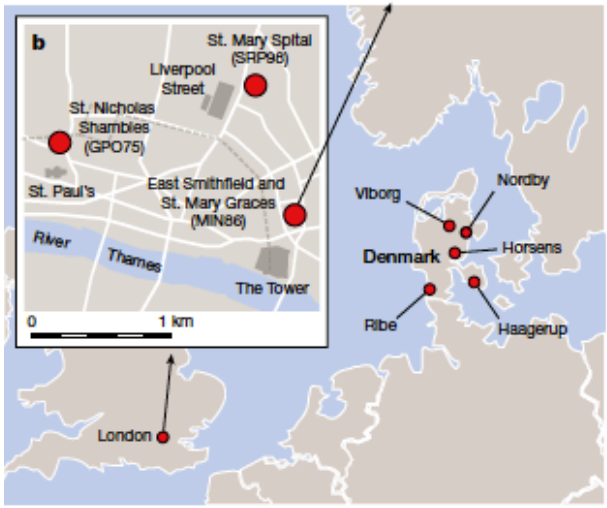
T cell Autoimmunity ↓
(EAE, IBD, Arthritis)

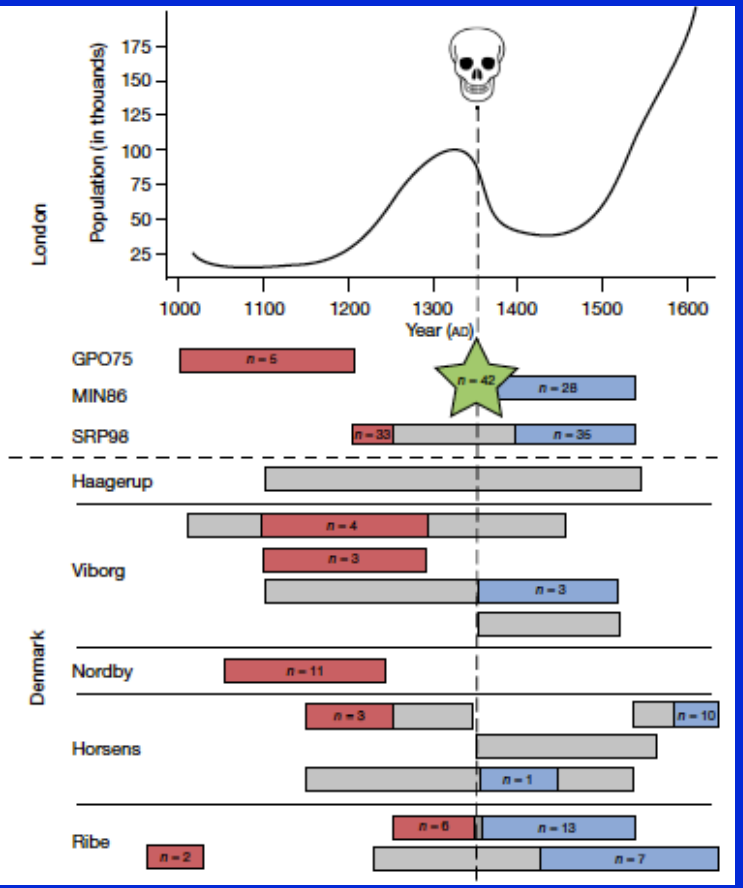
Aus Dirk Haller: The Gut Microbiome in Health and Disease, Springer 2018; und Smith et al.: Principles of Mucosal Immunology, Garland Science 2013

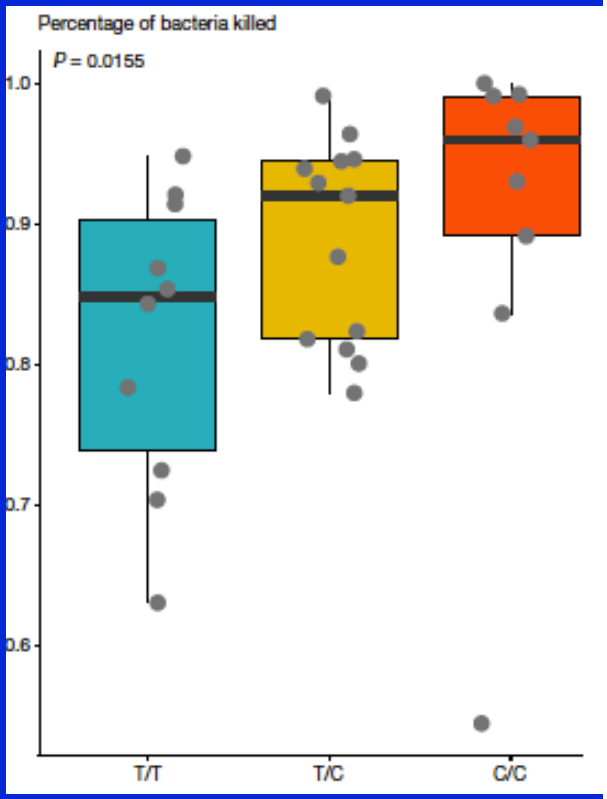
Mechanisms by which Stress Affects the Experimental and Clinical Inflammatory Bowel Disease (IBD): Role of Brain-Gut Axis



positive selection. The selected allele for one of these variants, rs2549794, is associated with the production of a full-length (versus truncated) *ERAP2* transcript, variation in cytokine response to *Y. pestis* and increased ability to control intracellular *Y. pestis* in macrophages. Finally, we show that protective variants overlap with alleles that are today associated with increased susceptibility to autoimmune diseases, providing empirical evidence for the role played by past pandemics in shaping present-day susceptibility to disease.







Evolution of immune genes is associated with the Black Death

www.nature.com

Accepted: 14 September 2022

Citation: Gracia-Ramos, A.E.; Martin-Nares, E.; Hernández-Molina, G. New Onset of Autoimmune Diseases Following COVID-19 Diagnosis. *Cells* **2021**, *10*, 3592.

New Onset of Autoimmune Diseases Following COVID-19 Diagnosis

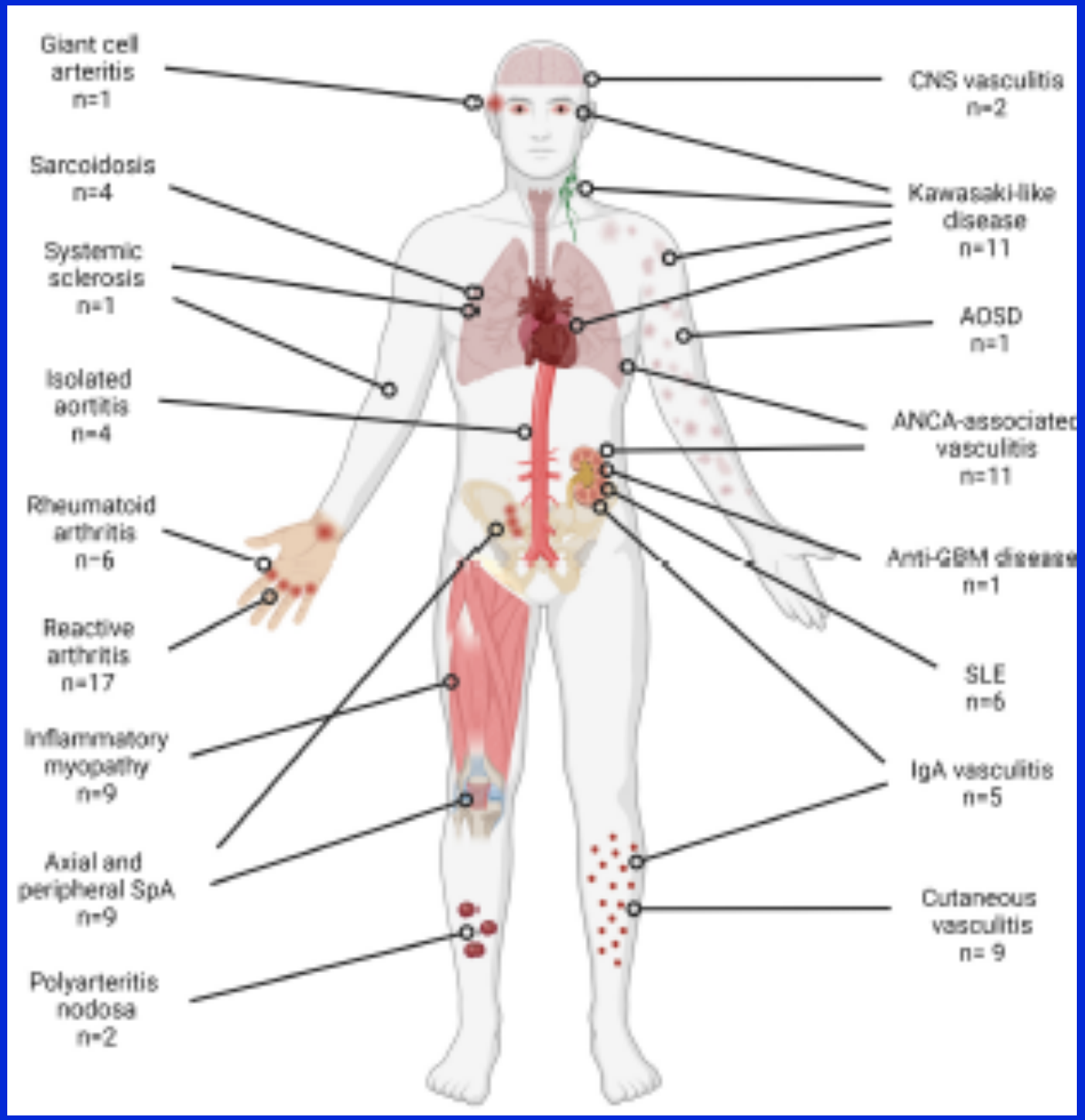
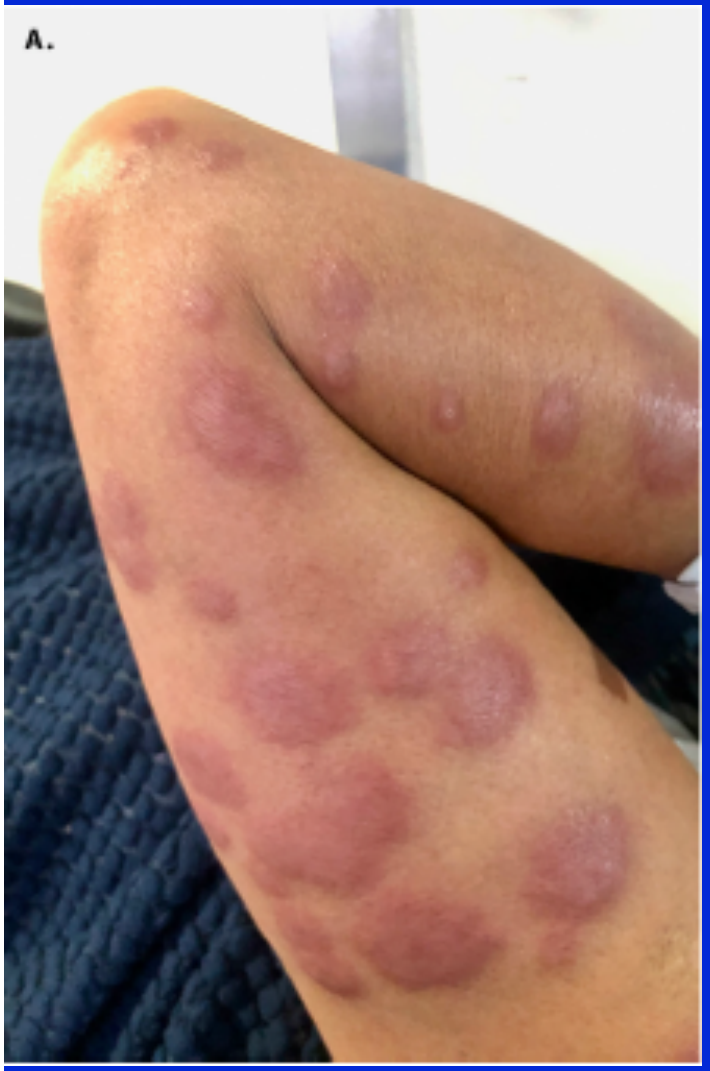
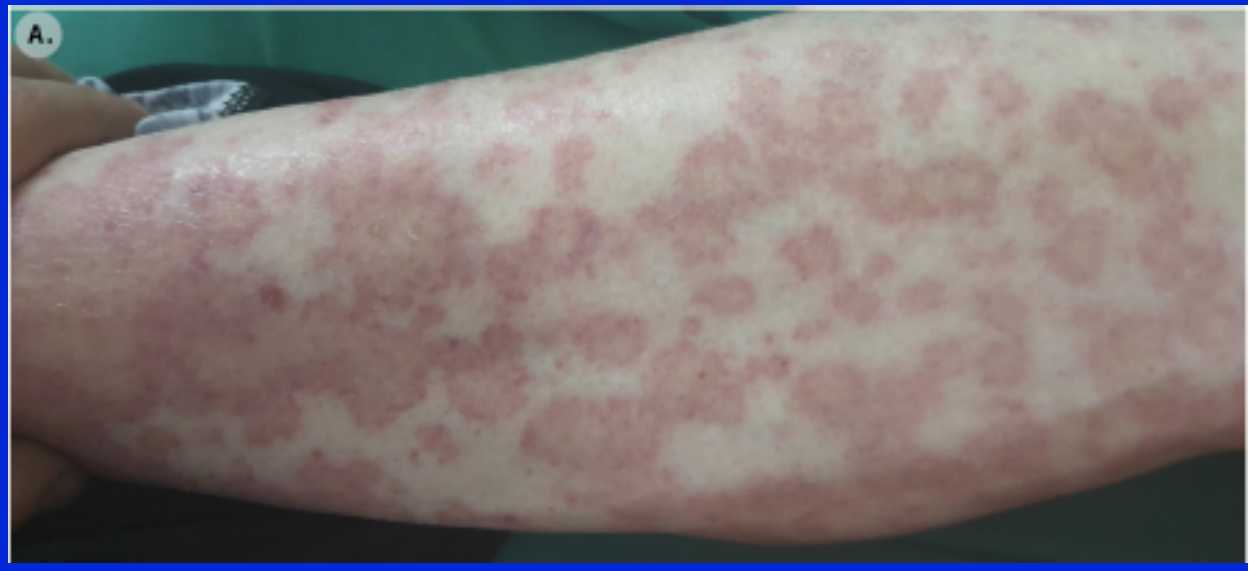
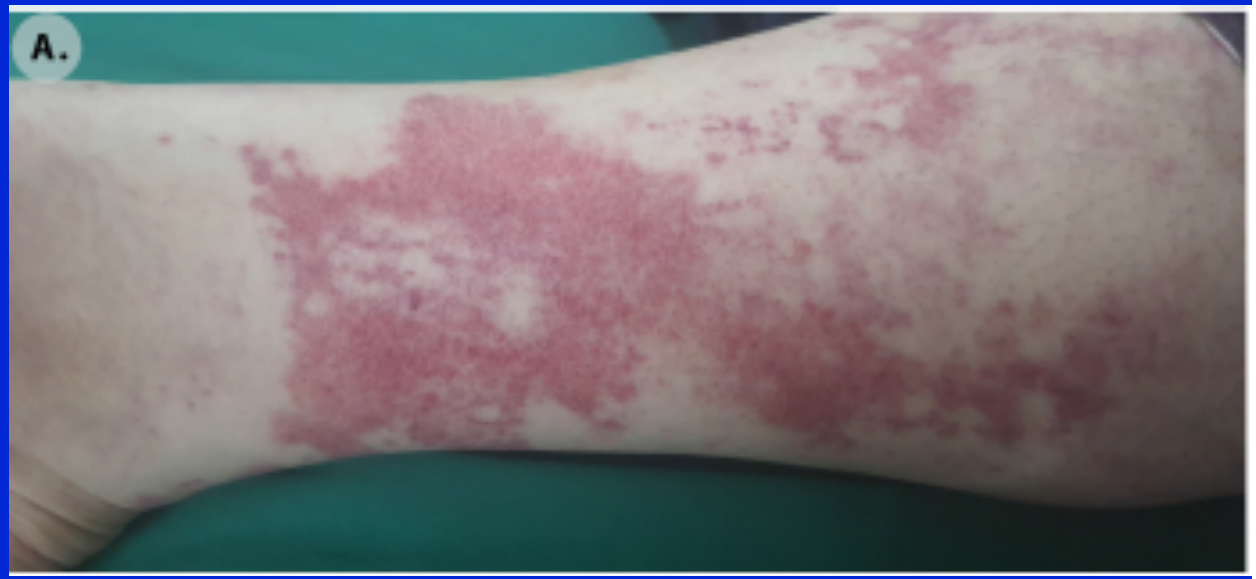


Figure 2. Number of cases and type of new-onset rheumatic autoimmune diseases reported during or after COVID-19. Created with BioRender.com.

Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review







Clinically Suspected Myocarditis Temporally Related to COVID-19 Vaccination in Adolescents and Young Adults: Suspected Myocarditis After COVID-19 Vaccination

Circulation. 2022;

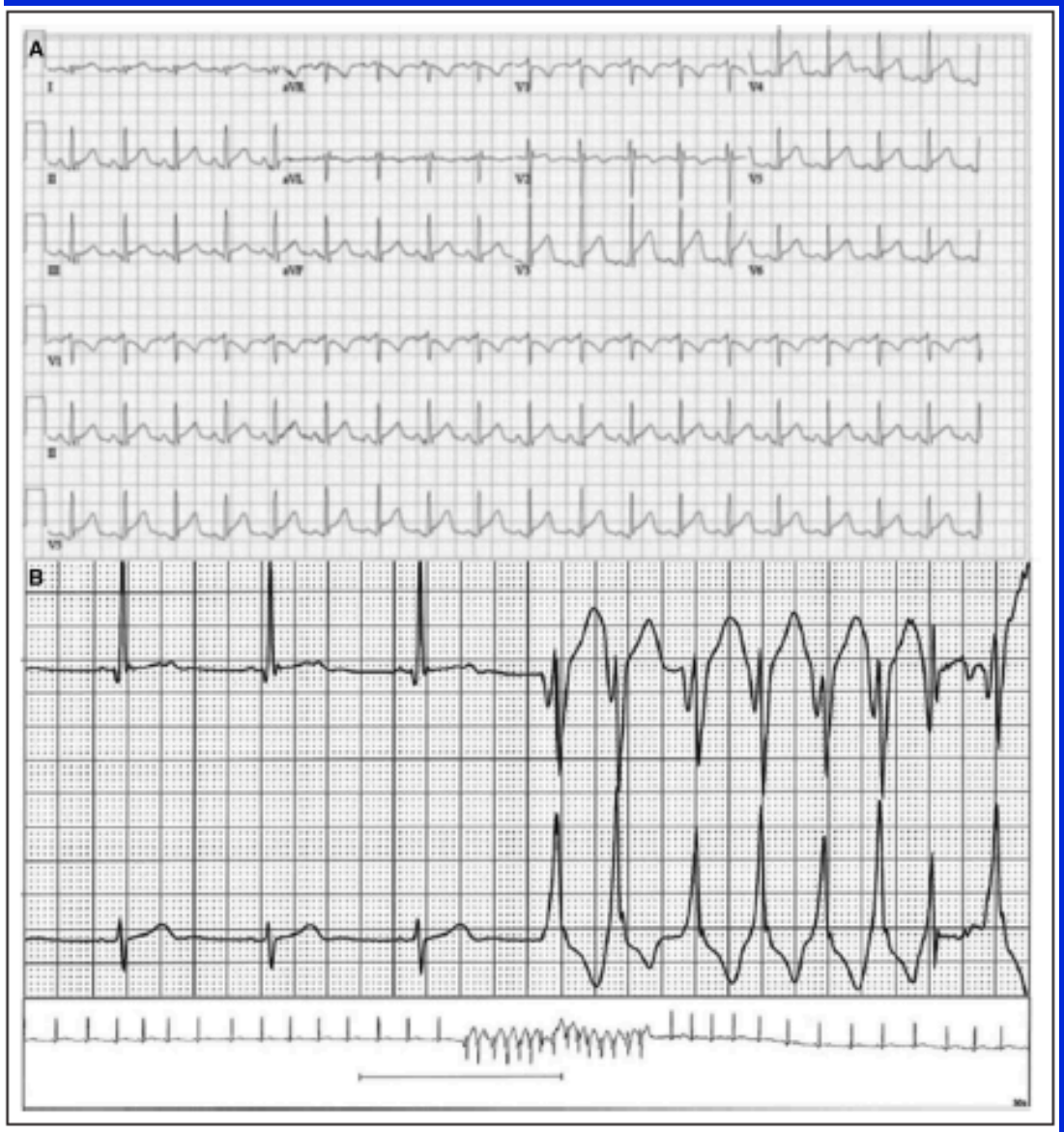
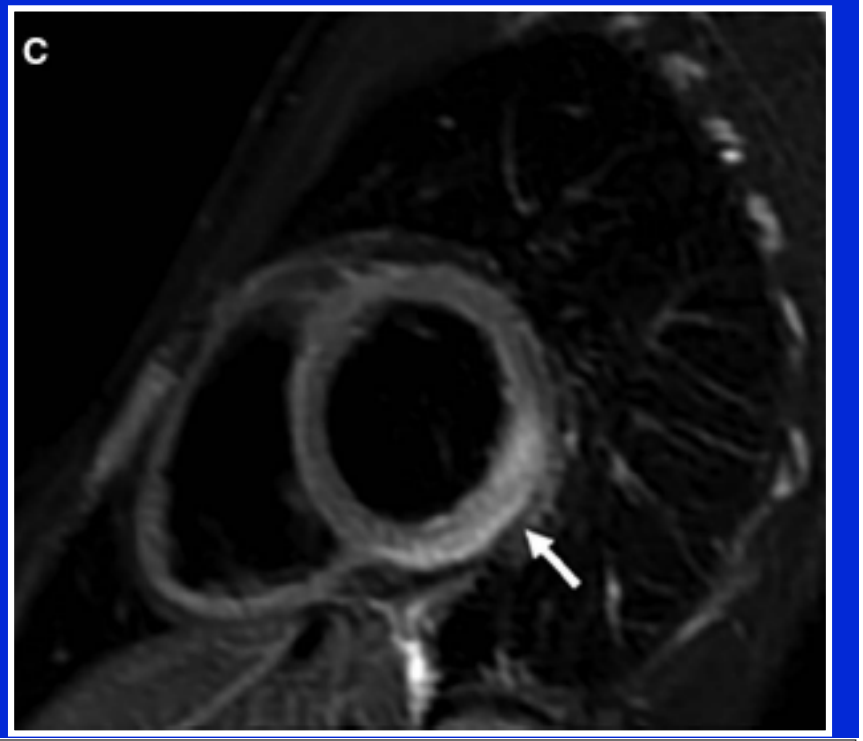


Figure 2. Electrocardiographic abnormalities and rhythm disturbances seen in suspected myocarditis temporally related to vaccination.



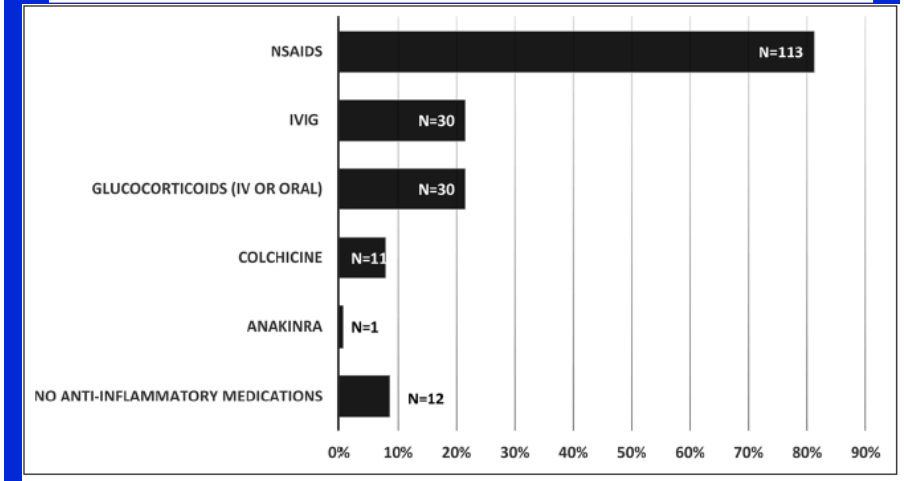
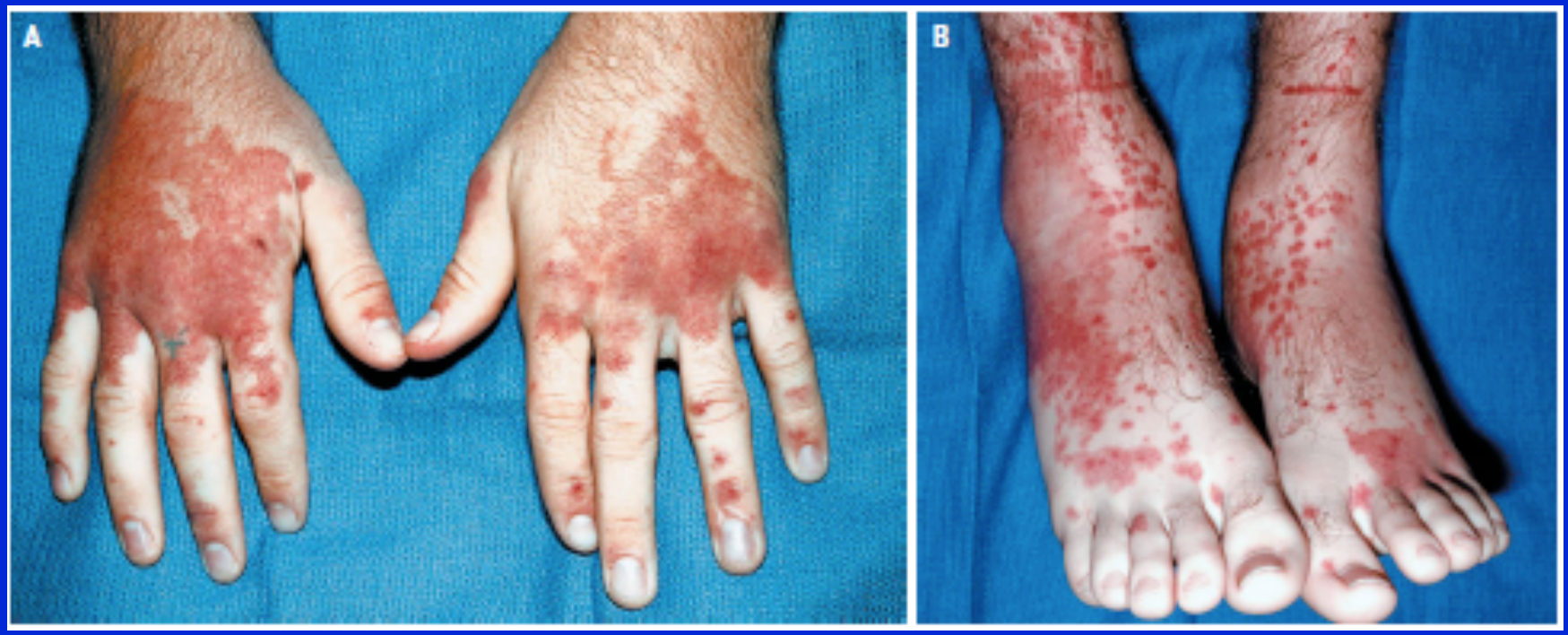


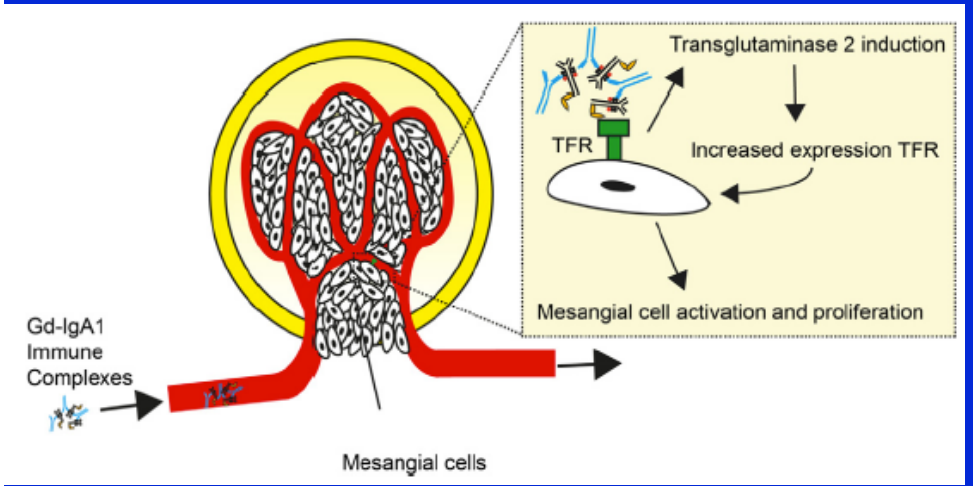
Figure 1. Anti-inflammatory therapies used in the treatment of suspected myocarditis temporally related to the COVID-19 vaccination.

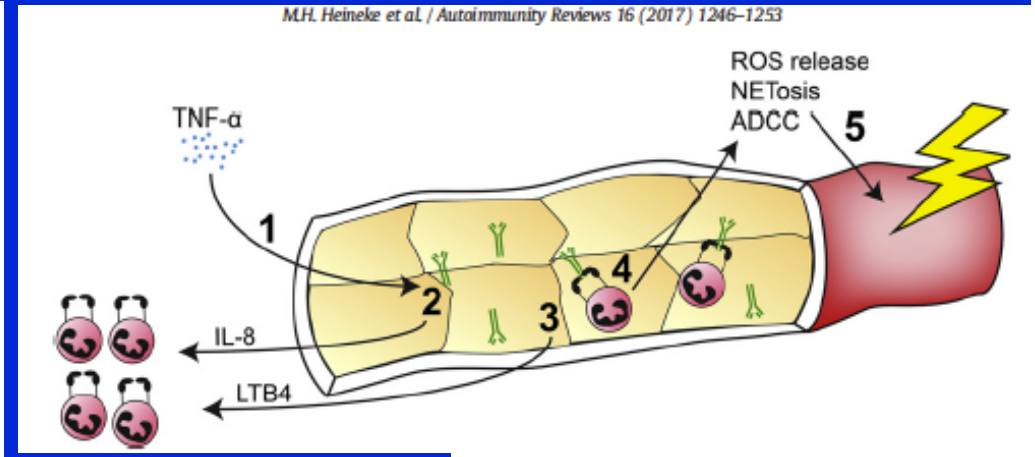
Henoch–Schönlein Purpura

N ENGL J MED 351;3 WWW.NEJM.ORG JULY 15, 2004



New insights in the pathogenesis of immunoglobulin A vasculitis (Henoch-Schönlein purpura)

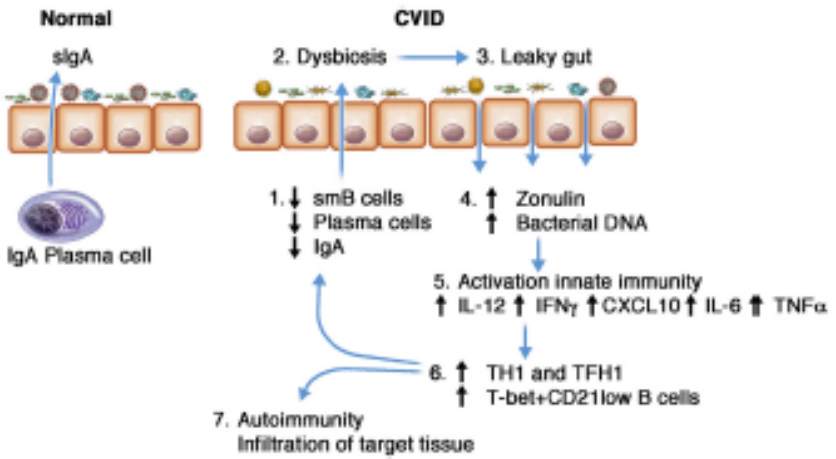




Autoimmunity Reviews 16 (2017) 1246–1253

Immune dysregulation

Pediatric Hyperinflammatory Syndromes



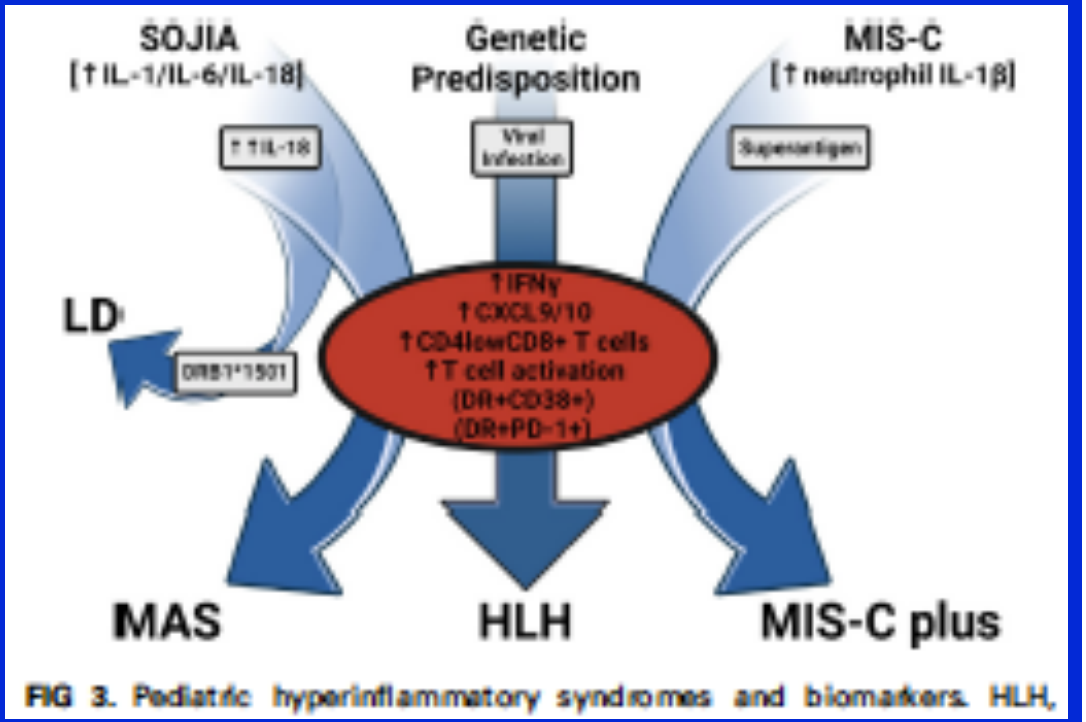
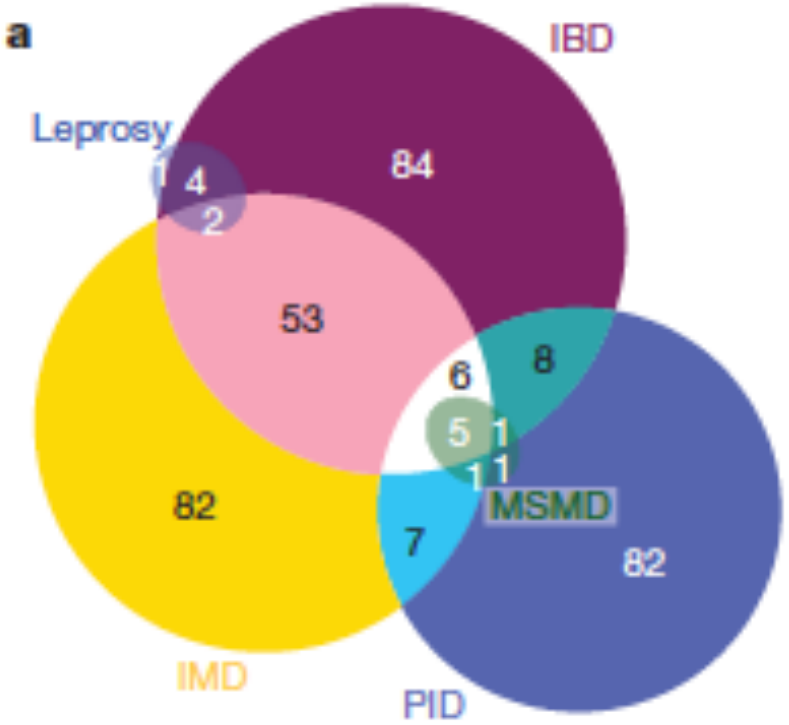


FIG 3. Pediatric hyperinflammatory syndromes and biomarkers. HLH,

SOJA = Systemic onset juvenile idiopathic arthitis (**LD** = interstit. Lung disease)
MIS-C = Multisystemic inflammatory syndrome of children
MAS = Macrophage activation syndrome
HLH = Hemphagocytic lymphocytic histiocytosis

LONG, KLEINER, AND LOONEY

(J Allergy Clin Immunol 2023;



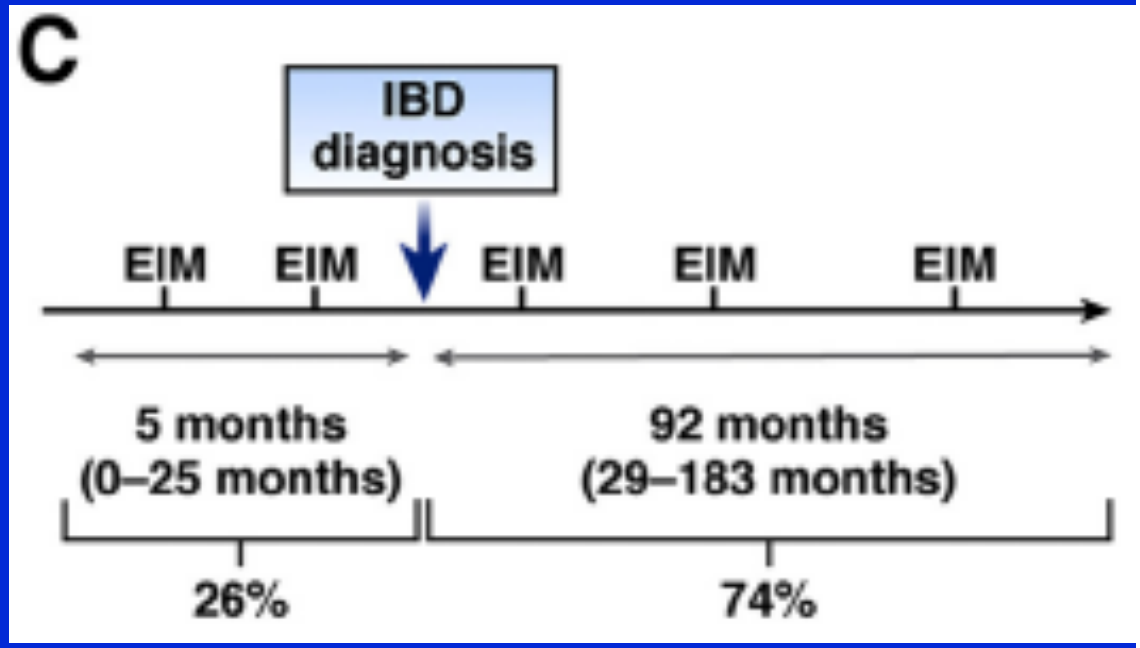
IBD Genetic Loci overlapping with other Immune Mediated Diseases

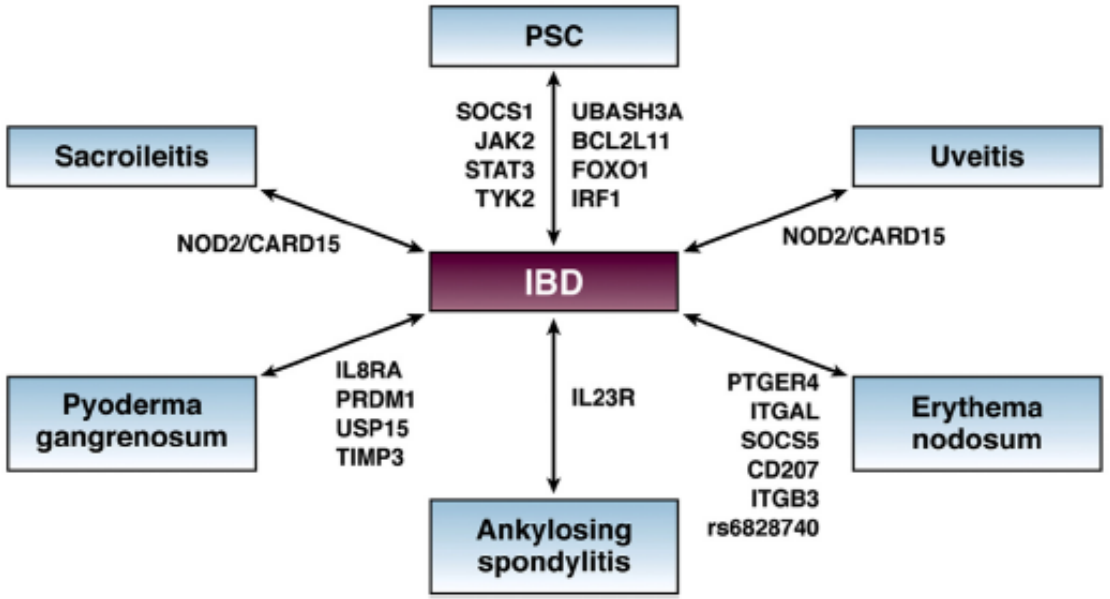
MSMD – Mendelian **S**usceptibility to **M**ycobacterial **D**isease
IMD – **I**mmune **M**ediated **D**iseases
PID – **P**rimary **I**mmune **D**efeciency

Jostins et al., Nature 2012

Extraintestinal Manifestations (EIM) and IBD

Rogler et al., Gastro 2021





Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs

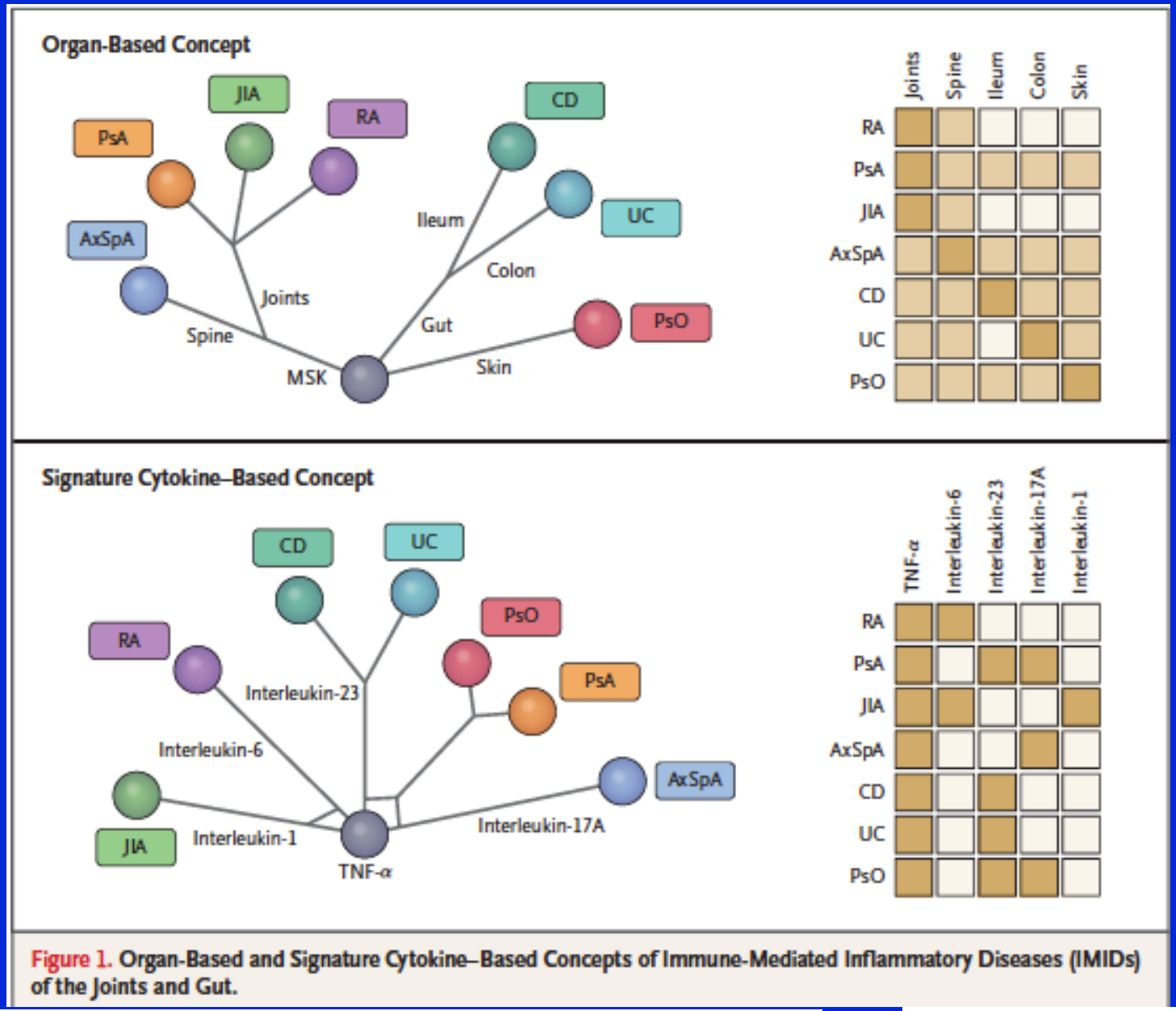


Figure 1. Organ-Based and Signature Cytokine–Based Concepts of Immune-Mediated Inflammatory Diseases (IMIDs) of the Joints and Gut.

Intestinal mucosal barrier function in health and disease

Turner, nature review 2009

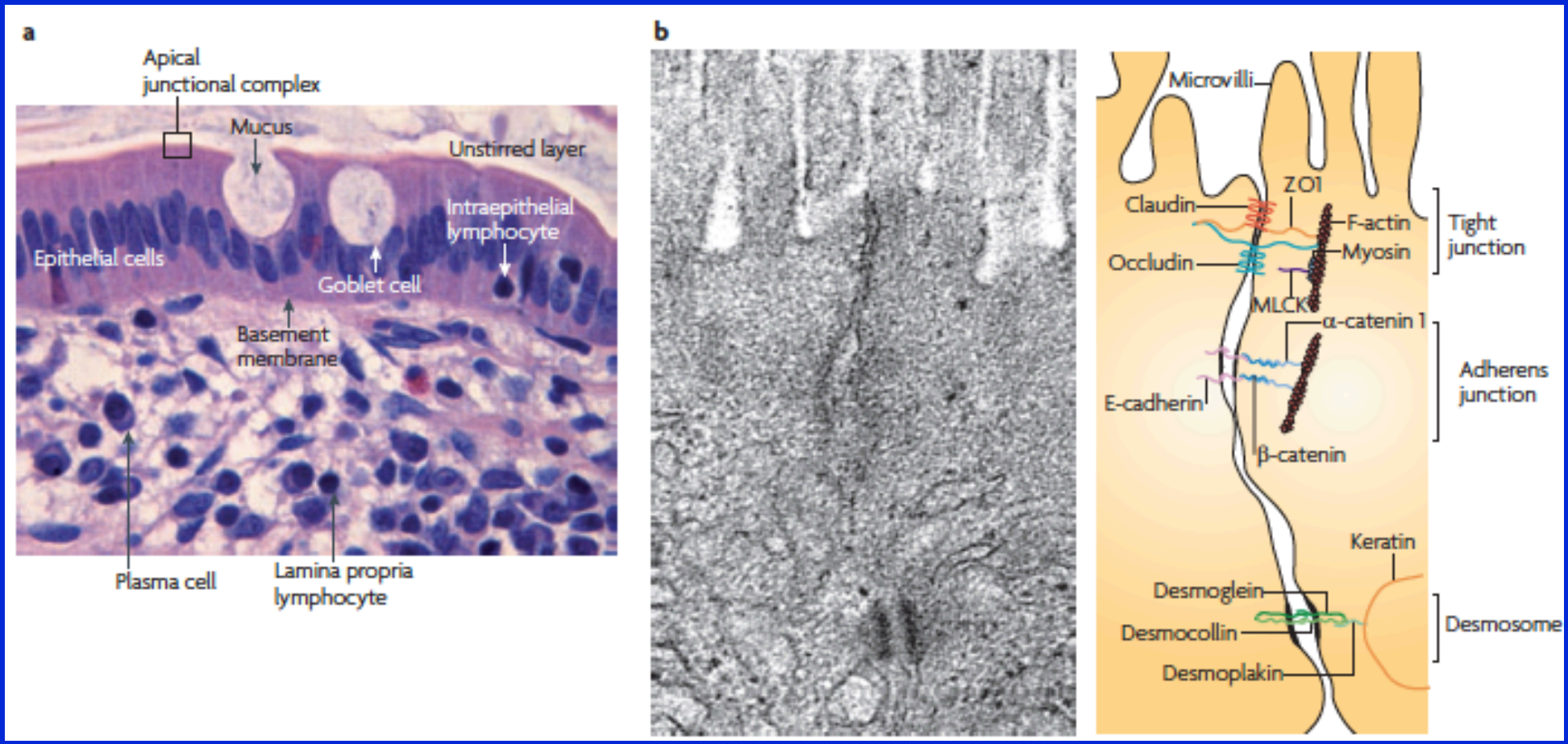
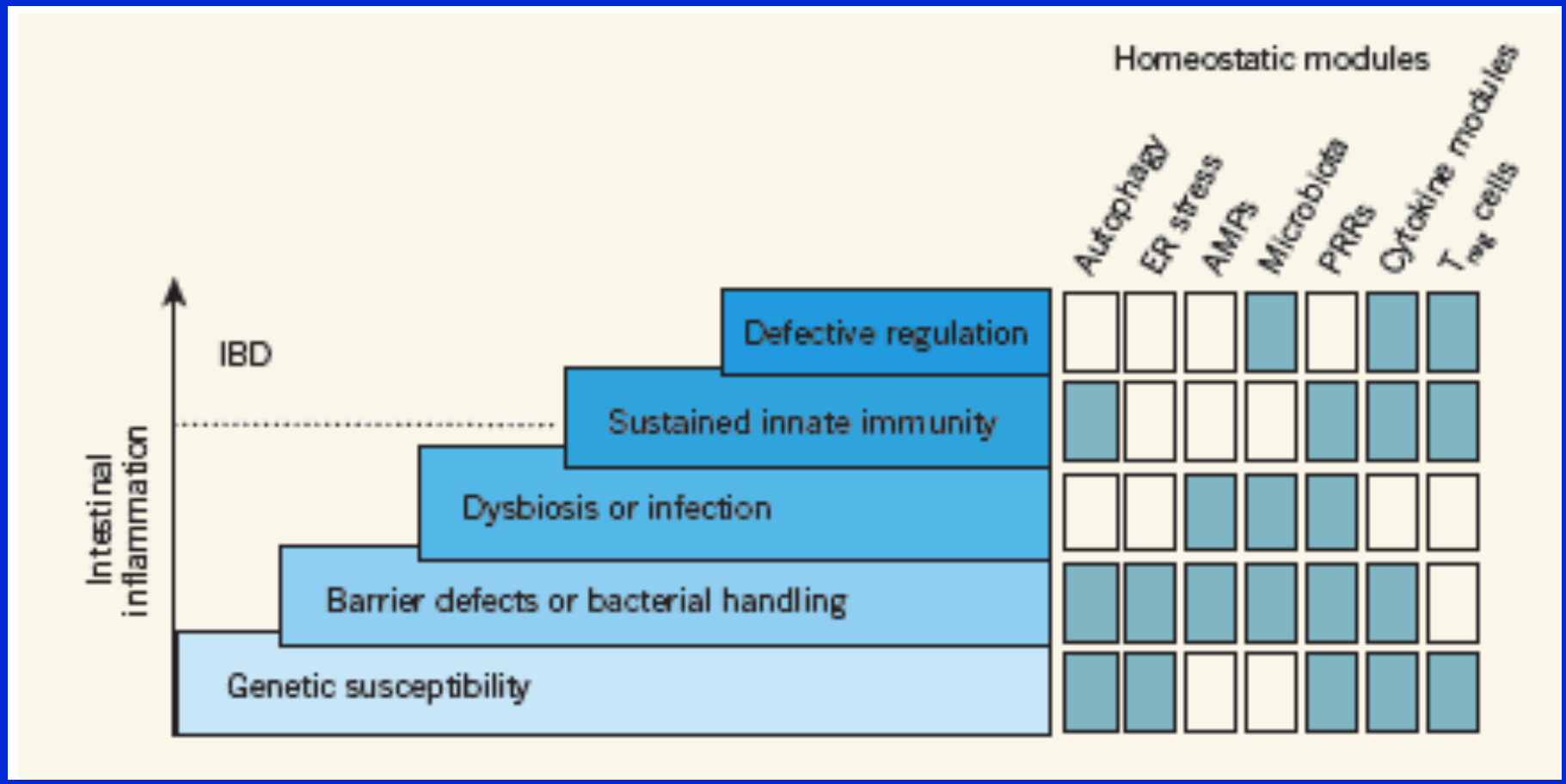


Figure 1 | Anatomy of the mucosal barrier.

Erhöhte Intestinale Permeabilität:

GI Infekte, Mb. Crohn, Zöliakie, NSAR, SIBO (PPI), TNF α, SIRS Sepsis, Obesity,...

Intestinal homeostasis and its breakdown in inflammatory bowel disease



Maloy et al., nature 2011

Intestinal Barrier Dysfunction preceds Clinical IBD by Years

Genetics of Inflammatory Bowel Diseases

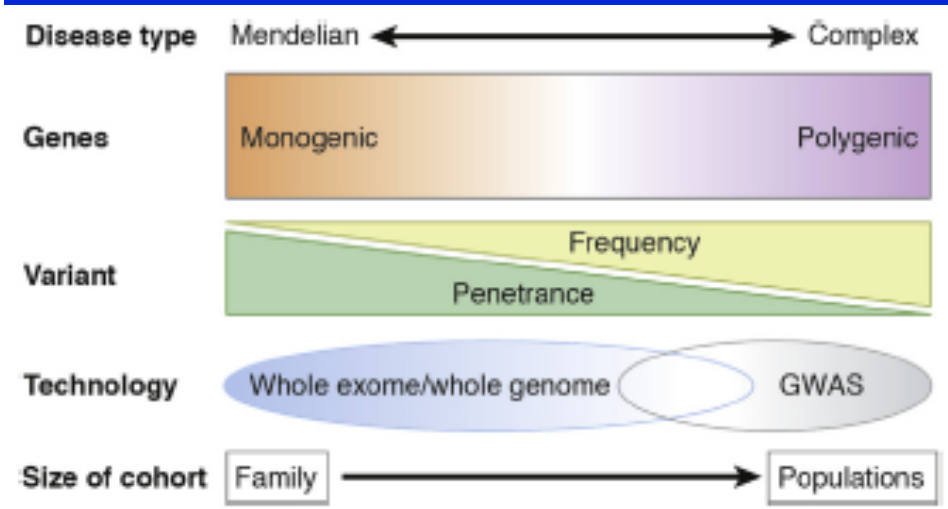


Figure 1. Common and rare genetic variations.

Mc Govern et al., GASTRO 2015

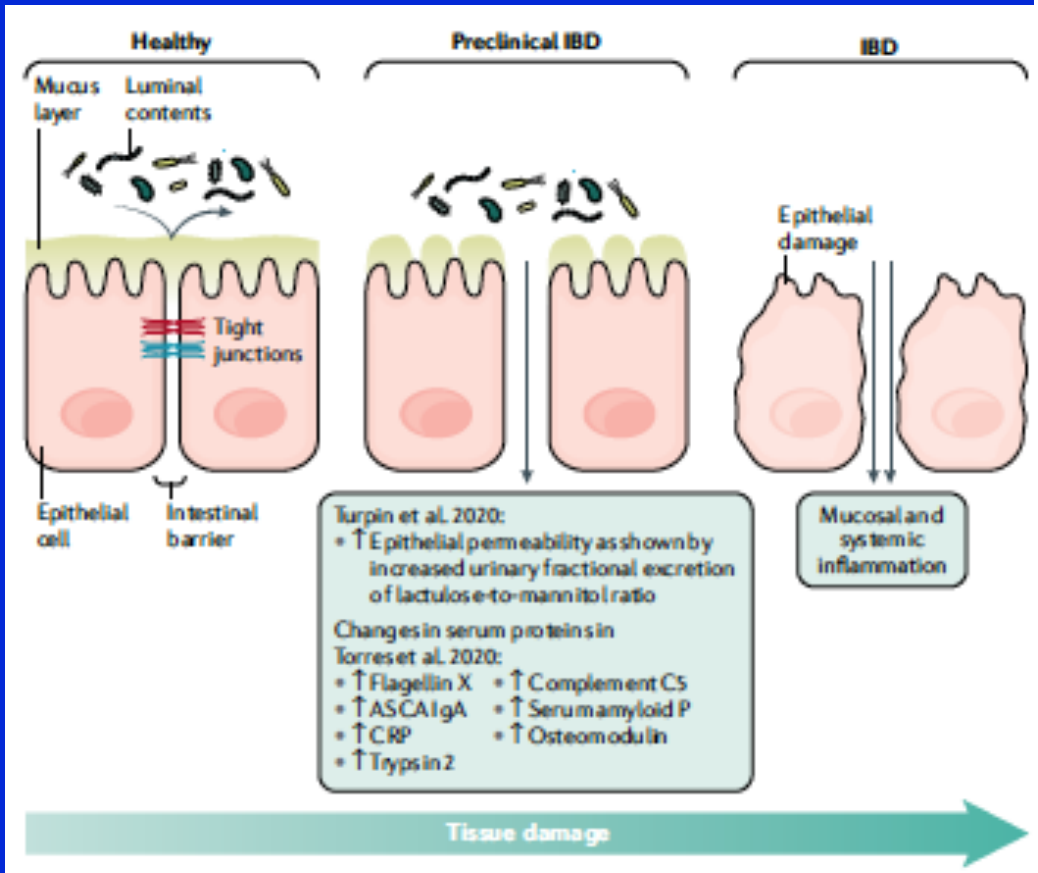
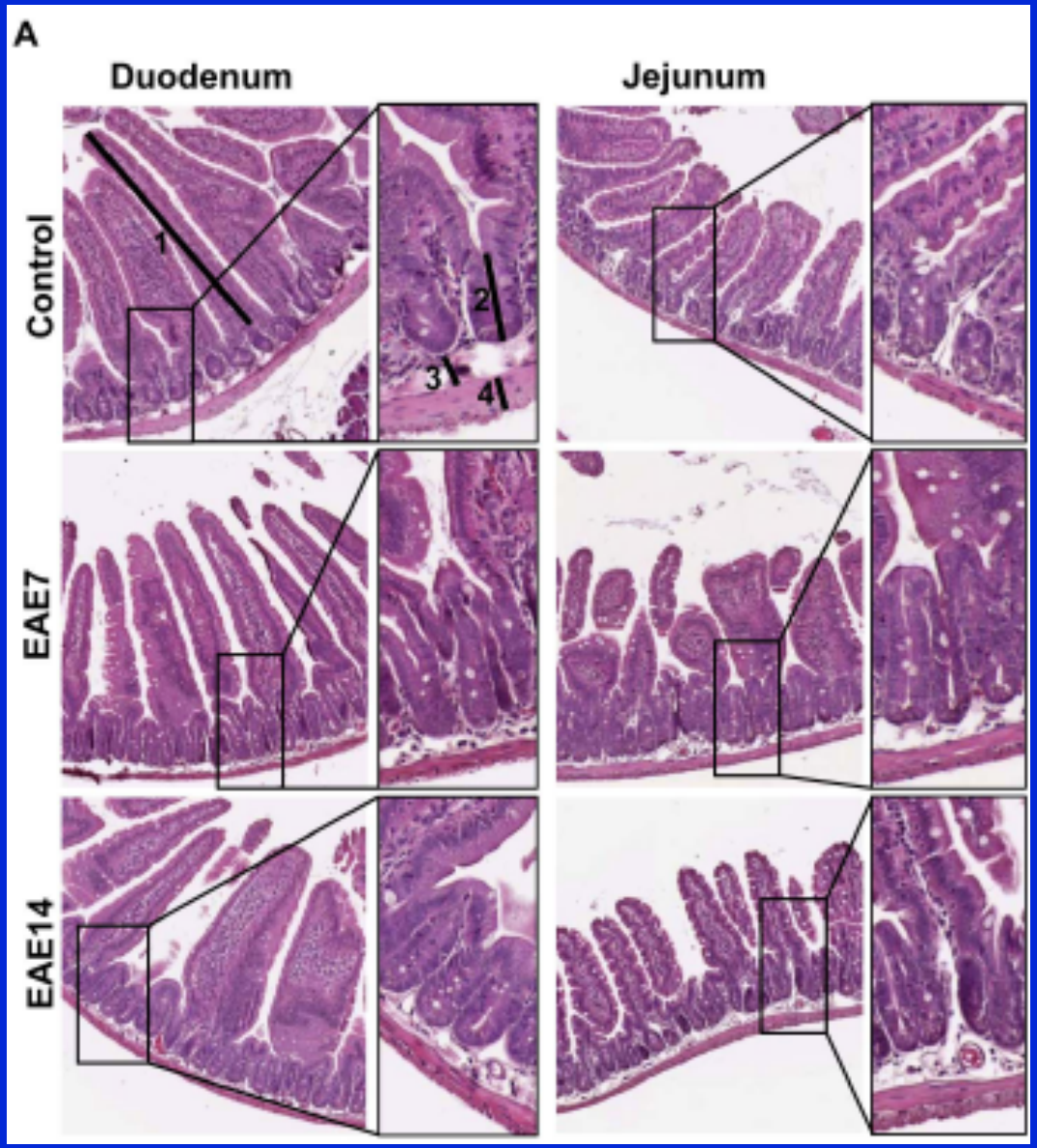


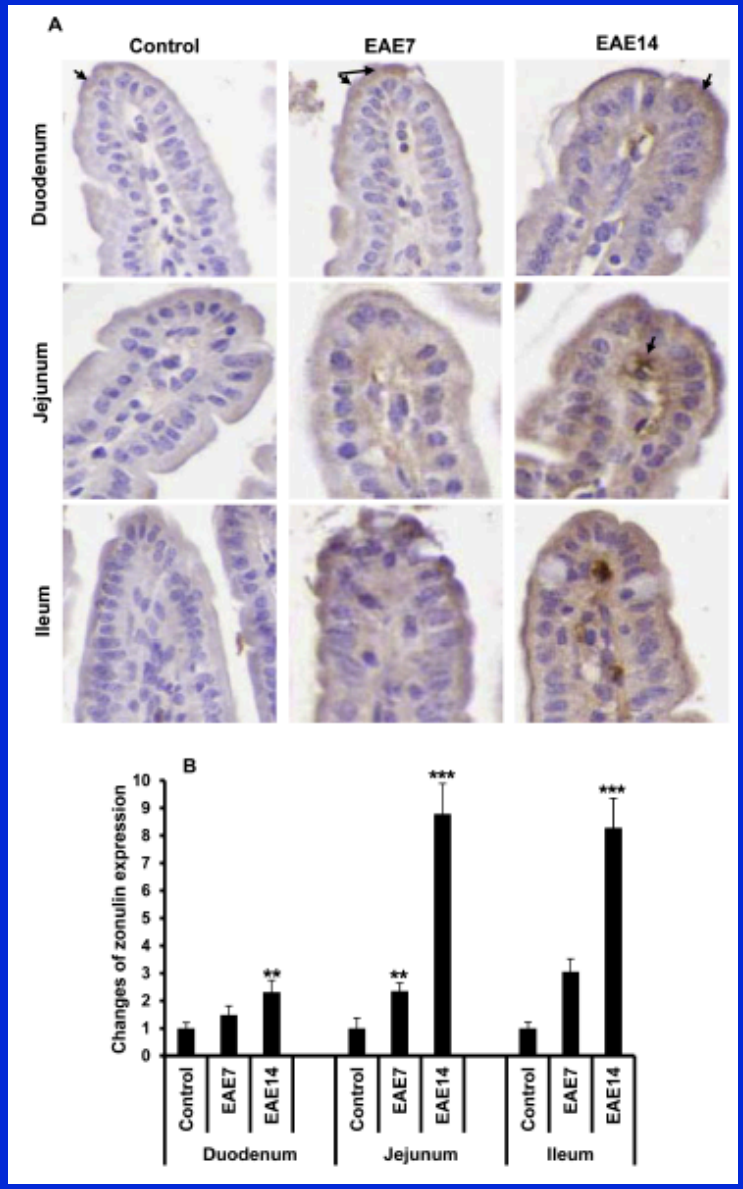
Fig. 1 | **Intestinal barrier dysfunction precedes the development of Crohn's Disease.**

Key studies published in 2020 demonstrate that an impaired intestinal barrier precedes clinical diagnosis of inflammatory bowel disease (IBD) by years. Furthermore, studies identify novel regulators of the intestinal barrier, including intestinal macrophages and diurnal variations of diet–microbiome interactions, which could be future therapeutic strategies for IBD.

S. Mehandru, J.F. Columbel: NATURE REV 2021

Intestinal Barrier Dysfunction Develops at the Onset of Experimental Autoimmune Encephalomyelitis, and Can Be Induced by Adoptive Transfer of Auto-Reactive T Cells





Mehrnaz Nouri[1,2], Anders Bredberg[3,4], Björn Weström[2], Shahram Lavasani[2,3]*

PlosOne 2014

Gut pathobionts as triggers for liver diseases

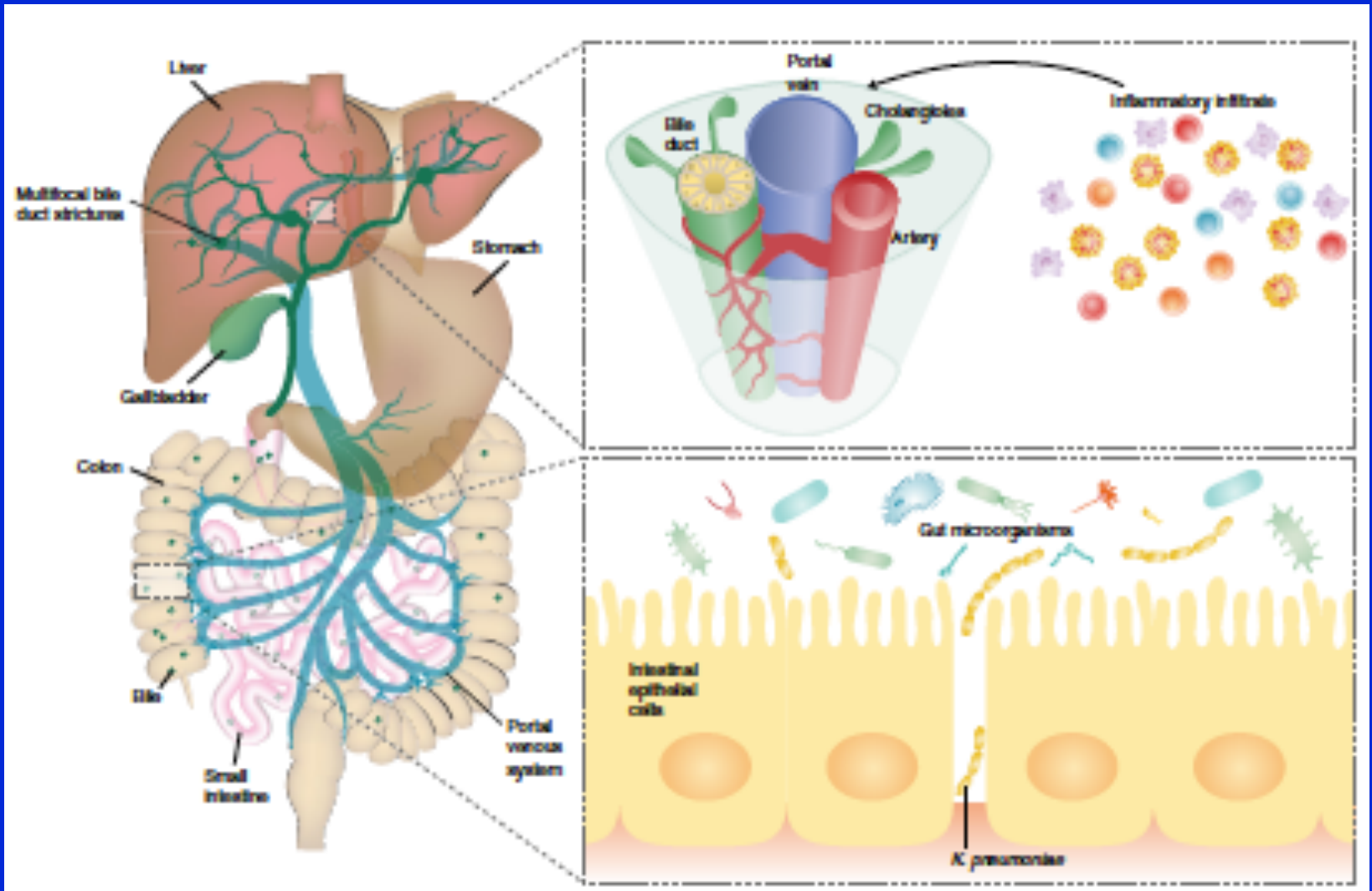
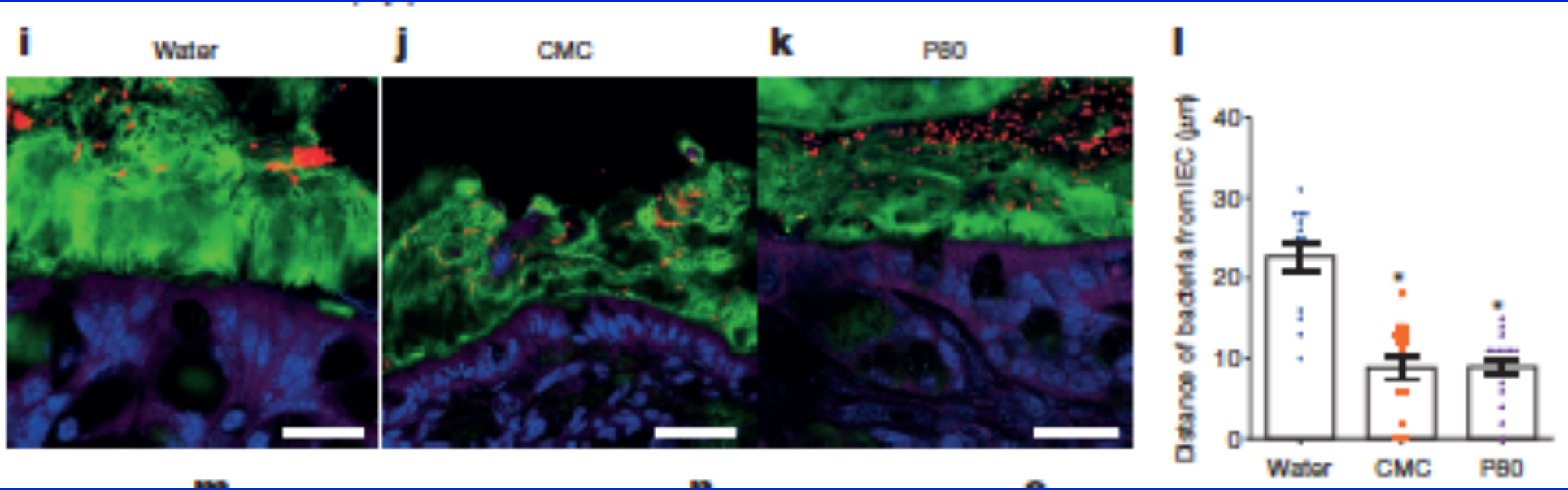


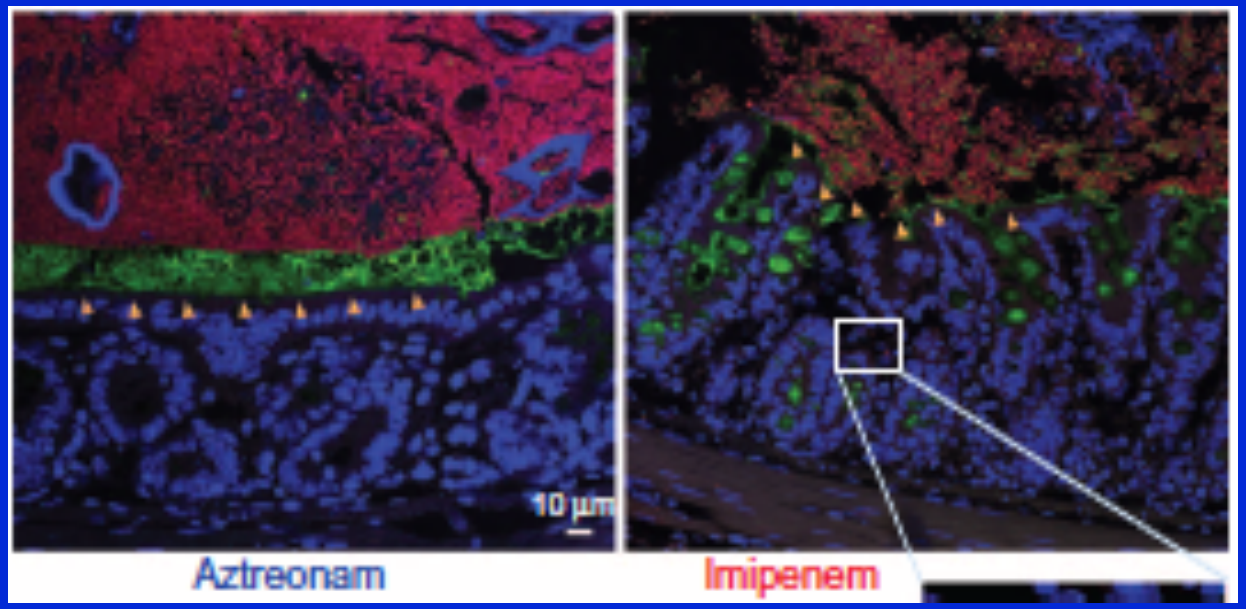
Fig. 1 | **Schematic representation of the gut–liver axis in the pathogenesis of PSC.** Left, PSC is a chronic inflammatory and progressive liver disease, which primarily affects large- and medium-sized bile ducts with strictures and dilatations (bile ducts shown in green) due to inflammatory cells invading the portal system (top right). Nakamoto et al.[1] suggest that pore-forming *K. pneumoniae* increase gut permeability (bottom right) and trigger an inflammatory response in the liver. However, direct bacterial invasion of the liver was not shown. Thus, a causative factor reaching the liver through the portal venous system (shown in blue) remains to be determined.

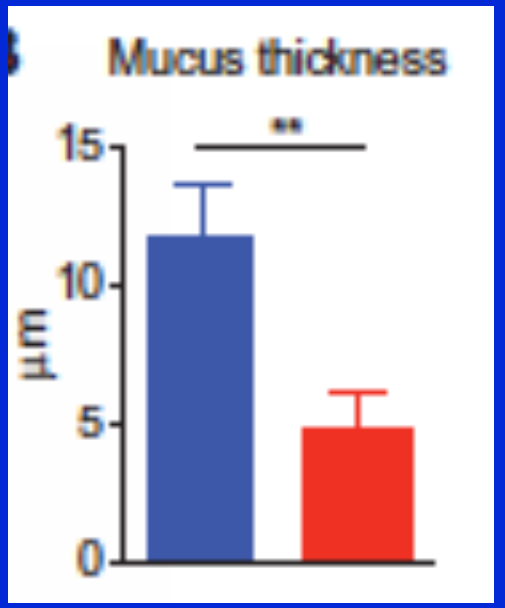
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome



Emulsifiers:
CMC = CarboxyMethyCellulose
P80 = Polsorbate 80

Chassing et al., Nature 2015





Shono et al., Science Translational Medicine 2016

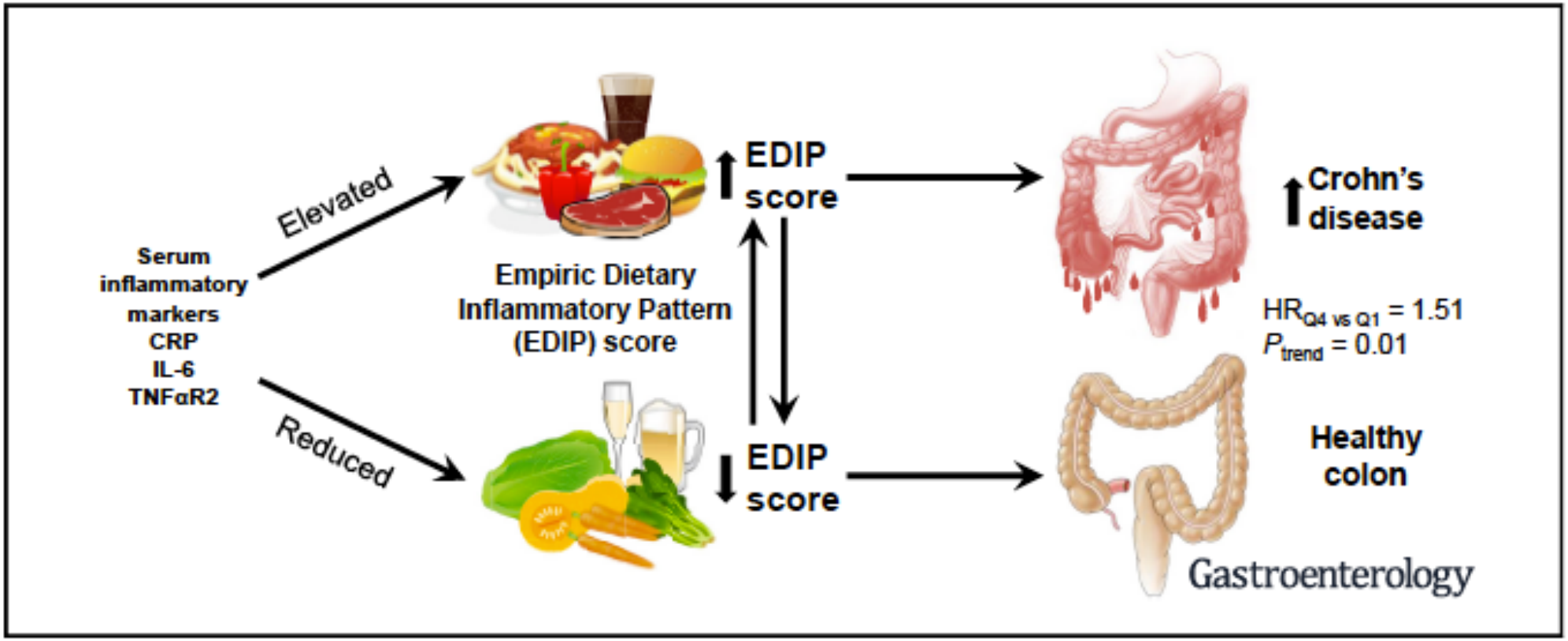
Antibiotic use and inflammatory bowel diseases in childhood

Hviid et al., Gut 2011

	Inflammatory bowel diseases			Crohn's disease		
	Number of cases	RR*	95% CI	Number of cases	RR*	95% CI
Antibiotic use						
No courses	33	1	Reference	11	1	Reference
At least 1 course	84	1.84	(1.08 to 3.15)	39	3.41	(1.45 to 8.02)
Use in last 3 months	26	2.39	(1.36 to 4.19)	14	4.43	(1.88 to 10.44)
Use >3 months previously	58	1.42	(0.79 to 2.53)	25	2.27	(0.88 to 5.84)

Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis

Lo et al., Gastro 2020



the risk of developing UC (P_{trend} = .62). **CONCLUSIONS:** In an analysis of 3 large prospective cohorts, we found dietary patterns with high inflammatory potential to be associated with increased risk of CD but not UC.

Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study

Narula et al., BMJ 2021

Table 3 | Association between total ultra-processed food intake and risk of inflammatory bowel disease. Values are hazard ratios (95% confidence intervals) unless stated otherwise

	Ultra-processed food intake			
	<1 serving/day	1-4 servings/day	≥5 servings/day	P trend
Inflammatory bowel disease				
No of participants	76 415	25 453	11 742	
No (%) of events	199 (0.26)	134 (0.53)	95 (0.81)	
Unadjusted model	1 (ref)	2.20 (1.77 to 2.74)	3.18 (2.49 to 4.07)	<0.001
Minimally adjusted model*	1 (ref)	1.41 (1.11 to 1.79)	1.42 (1.07 to 1.90)	0.01
Fully adjusted model†	1 (ref)	1.67 (1.18 to 2.37)	1.82 (1.22 to 2.72)	0.006
Fully adjusted plus AHEI score model	1 (ref)	1.75 (1.23 to 2.50)	1.92 (1.28 to 2.90)	0.004
Sensitivity analysis using multiple imputation‡	1 (ref)	1.54 (1.21 to 1.84)	1.71 (1.22 to 2.37)	<0.001

CONCLUSIONS

Higher intake of ultra-processed food was positively associated with risk of IBD. Further studies are needed to identify the contributory factors within ultra-processed foods.

Published online: 10 May 2023

Pathogenesis of autoimmune disease

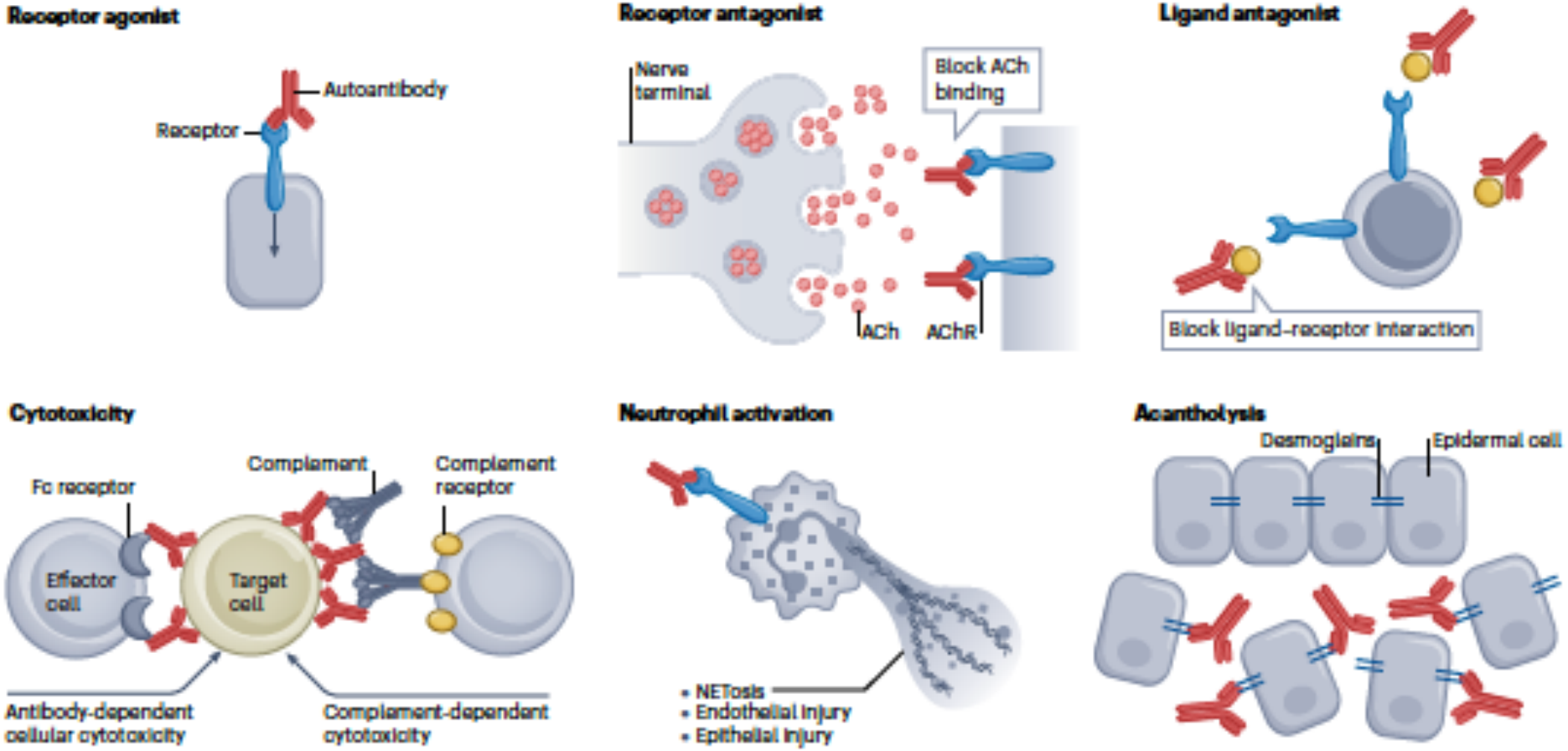
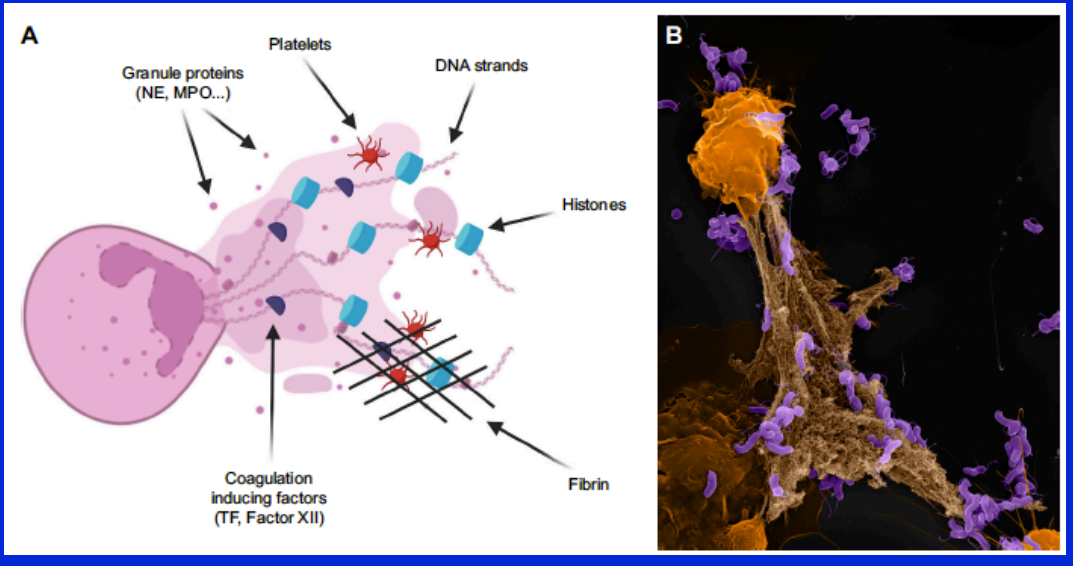


Fig. 2 | The actions of autoantibodies in immunopathology. Autoantibodies can disturb the function of cells or promote their damage or death through diverse mechanisms. These mechanisms include actions as receptor agonists (for example, as occurs in Graves' disease), receptor antagonists (for example, as occurs in myasthenia gravis), ligand antagonists (for example, as occurs in immunodeficiency), cytotoxicity (for example, as occurs in haemolytic anaemia), neutrophil activation (with indirect damage to endothelium and epithelium) and acantholysis (for example, as occurs in pemphigus). ACh, acetylcholine; AChR, acetylcholine receptor; Fc, crystallizable fragment. Adapted from ref. 176, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

NEUTROPHIL EXTRACELLULAR TRAPS IN THE PATHOLOGY OF CANCER AND OTHER INFLAMMATORY DISEASES

HERRE ET AL.



2007: Platelets regulate NET formation (33)

2010: NETs have prothrombotic properties (5)

2012: cancer predispose for NET formation (6)

2020: NETs contribute to the pathophysiology of severe COVID-19 (185)

2009: mitochondrial NET formation described (34)

2010: Viable NET formation described (83)

2013: NETs promote metastasis (213)

2017: circulating host DNases protect from NET-induced thrombosis (143)

2010/2011: PAD4 KO formation (97, 98)

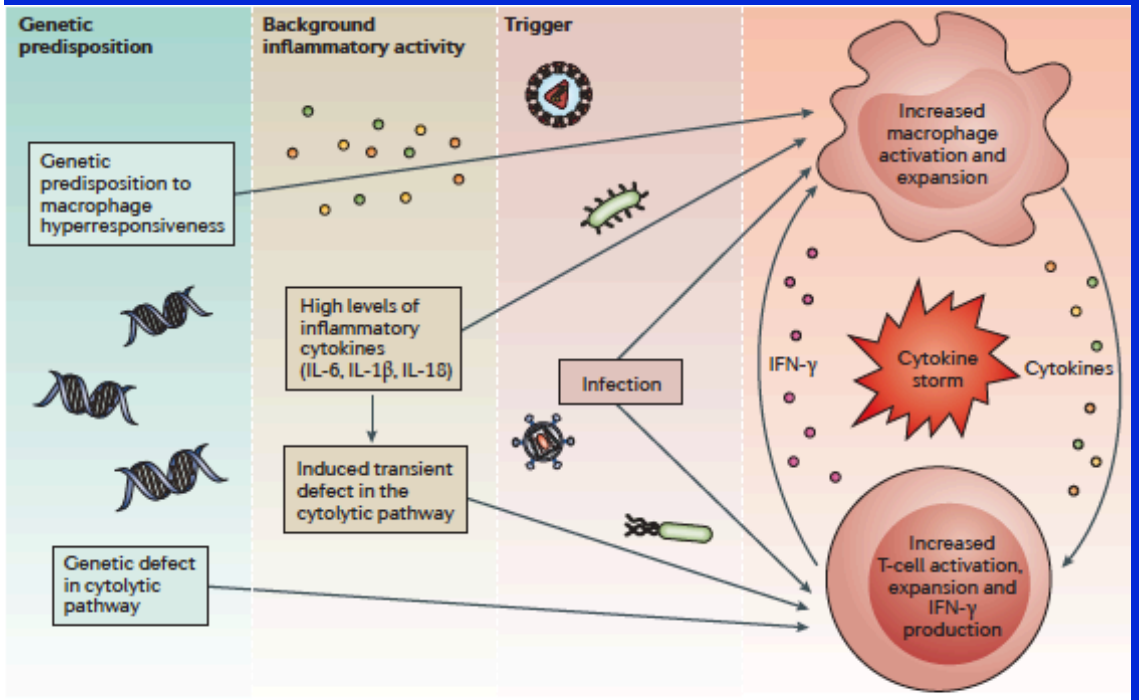
2013: NETs are a source of citrullinated autoantigens and promote inflammation in RA (60)

2015: Intravascular NETs impair peripheral vessel function in cancer (169)

NATURE REVIEWS | RHEUMATOLOGY
MAY 2016

Macrophage activation syndrome in the era of biologic therapy

Grom et al.



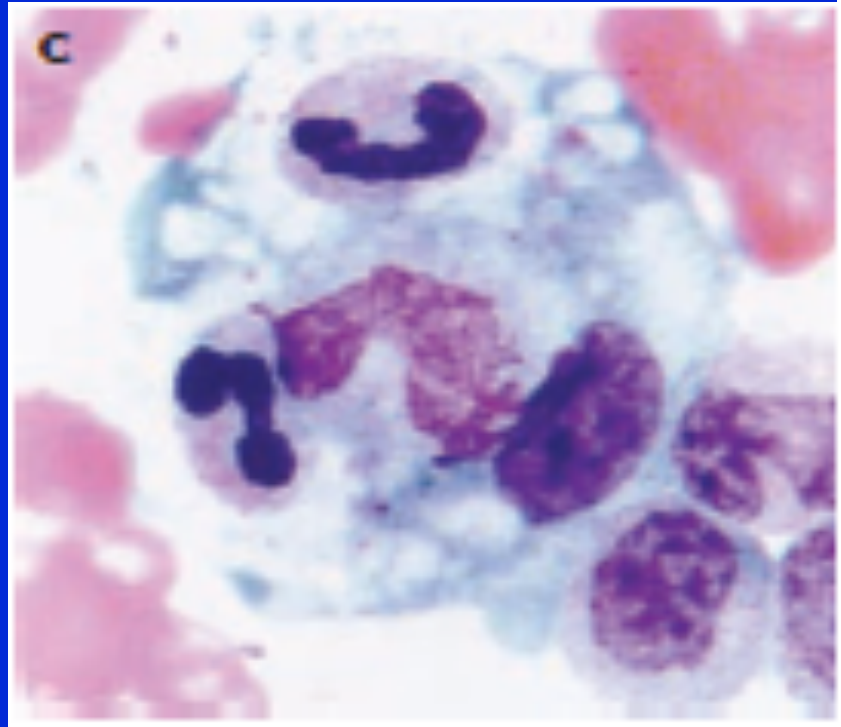


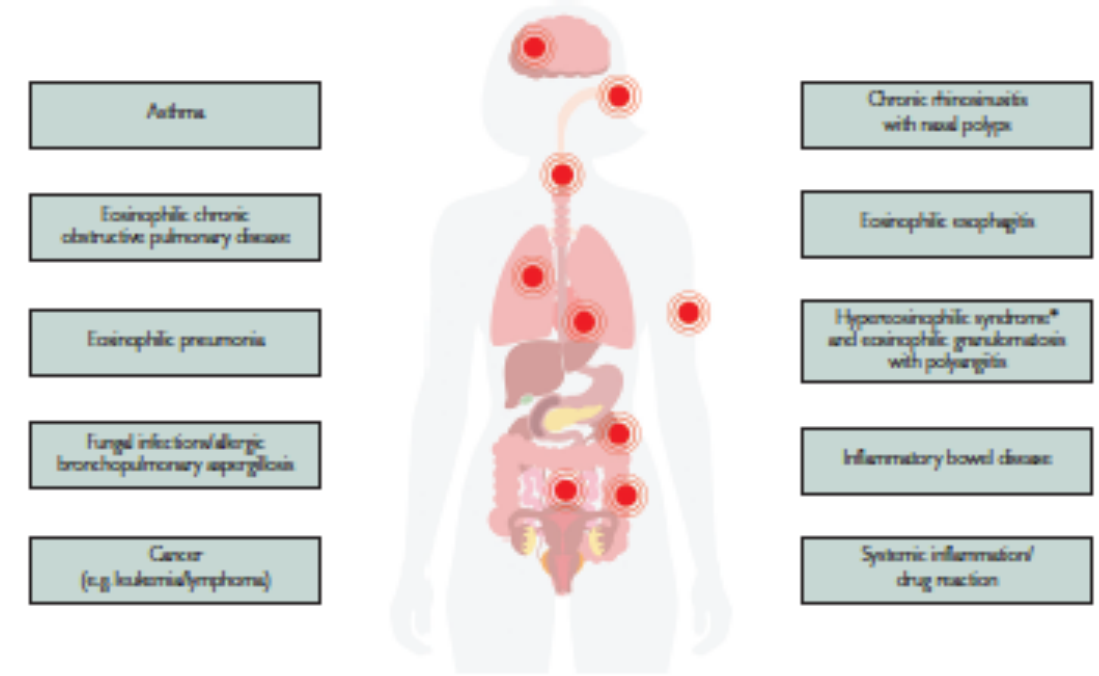
Figure 3 | **Multi-layer model of pathogenic events leading to the development of MAS in the context of rheumatic diseases.** Genetic factors and the inflammatory milieu created by the underlying rheumatic disease act

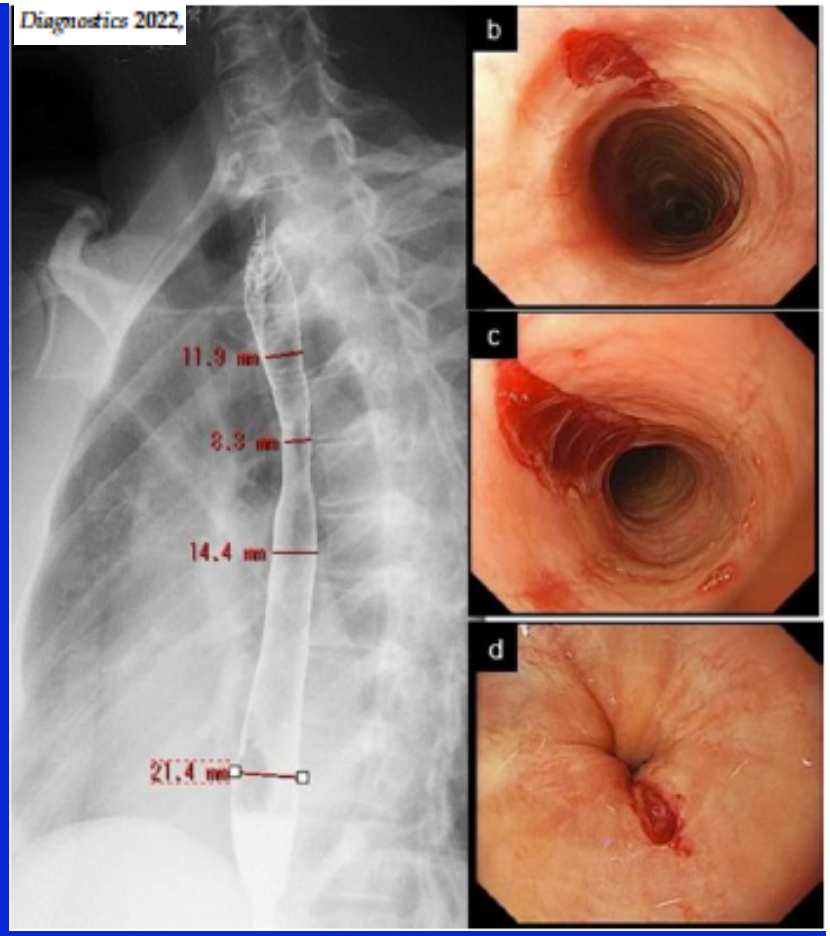
Table 1 | Clinical and laboratory features of sJIA, MAS and HLH

Feature	sJIA	MAS	HLH
Clinical features			
Fever pattern	Quotidian	Unremitting	Unremitting
Rash	Evanescent, maculopapular	Papular, petechial or purpuric	Papular, petechial or purpuric
Hepatomegaly	+	+++	+++
Lymphadenopathy	+	+++	++
Arthritis	+	–	–
Serositis	+	–	–
Encephalopathy	–	++	+++

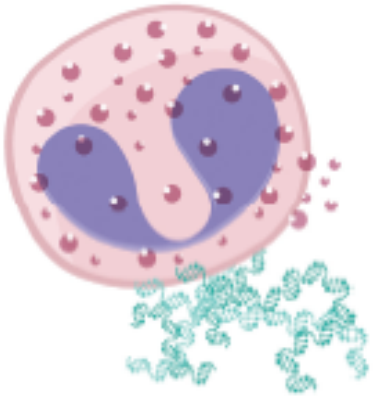
Eosinophils in Health and Disease: A State-of-the-Art Review

MAYO CLINIC



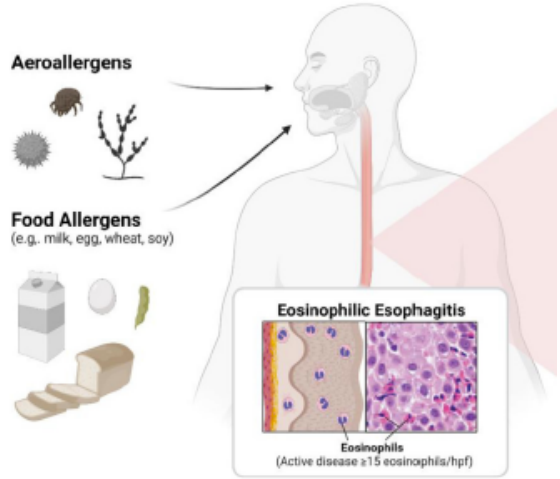


Mayo Clin Proc. ■ October 2021;



	Helminth toxicity	Antibacterial	Antiviral	Immune system	Epithelial activation and remodeling factor expression
EPX	✓	—	—	—	✓
MBP	✓	✓	—	Neutrophil, mast cell and basophil activation	✓
ECP	✓	✓	✓	—	—
EDN	—	—	✓	Dendritic cell recruitment and activation	—
CLC/gal-10	—	—	—	Th2 activation	—
EET	—	✓	—	—	—

Ann Allergy Asthma Immunol 130(2023)



Mastocytosis and Mast Cell Activation Disorders: Clearing the Air *Int. J. Mol. Sci.* 2021,

Mast cell activation syndromes

GENETIC FACTORS

Mast cell

Allergen (foods, drugs etc)
Cross-linkage of high affinity IgE receptor

Mastocytosis
Mast cell activation disorder

Mediator generation

Increased vascular permeability (endothelial barrier disruption)
Vasodilatation
Fluid extravasation
Inflammatory cell recruitment and activation

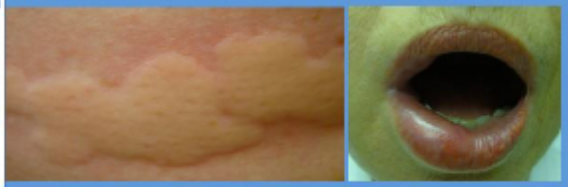
Hypovolemia/hypotension/shock
Urticaria and angioedema
Wheezing and respiratory distress
Vomiting/diarrhea/gastrointestinal distress

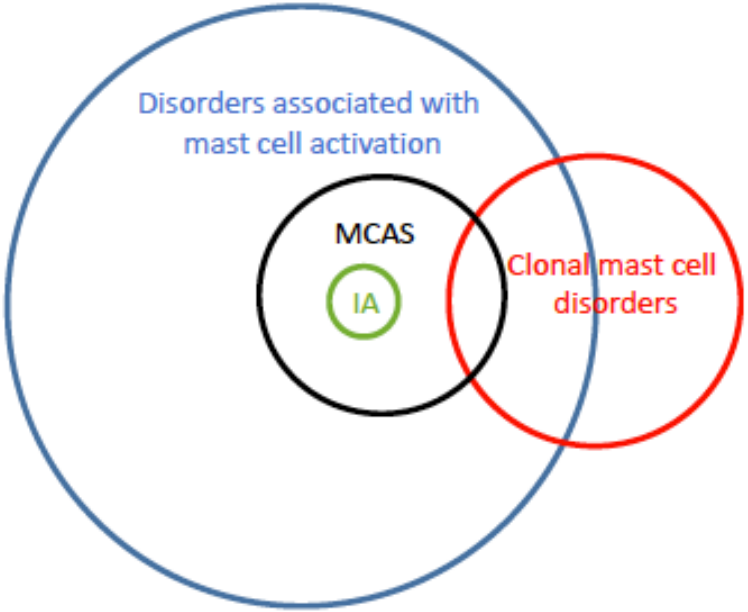
ANAPHYLAXIS

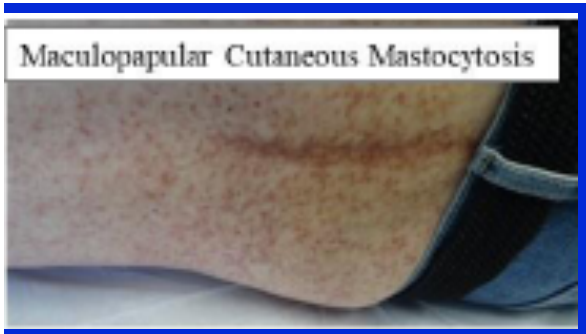
MAST CELL SIGNALING

- Activation of mast cell signaling
- FcεRI activates ITAMs/Lyn, followed by Syc which phosphorylates other targets
- This activates phospholipase Cγ (PLCγ) which then catalyzes PIP2 (phosphatidyl inositol 4,5-bisphophate) hydrolysis to form DAG (diacyl glycerol) and IP_3 (inositol triphosphate).
- IP_3 promotes intracellular calcium release that triggers degranulation.

Inset







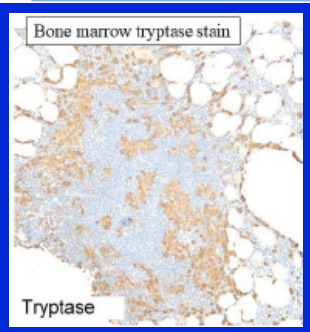
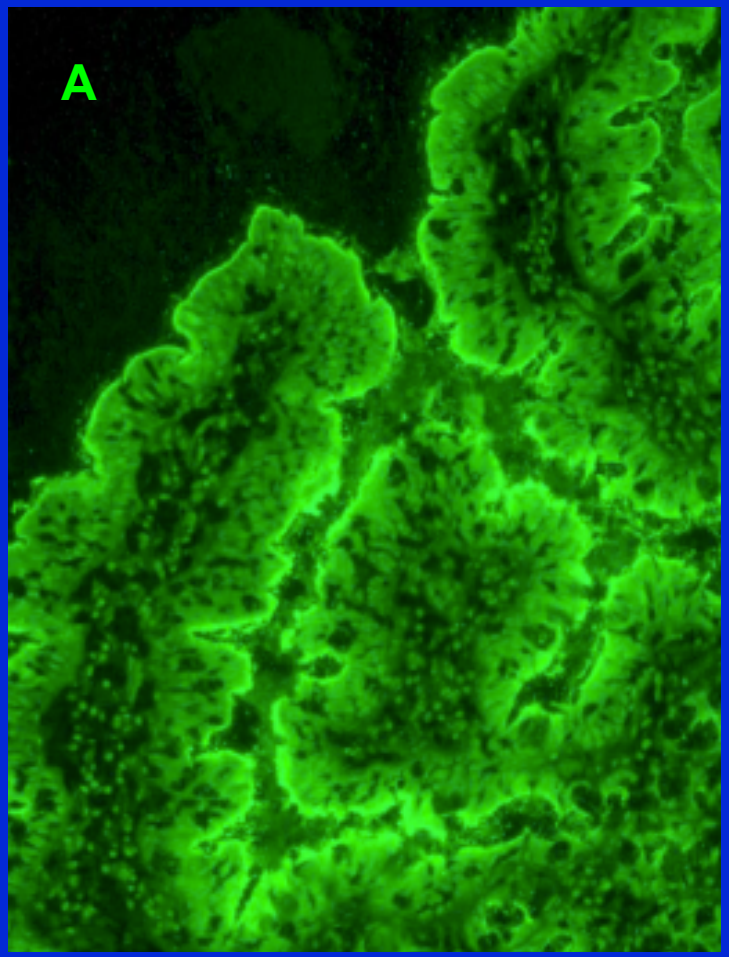


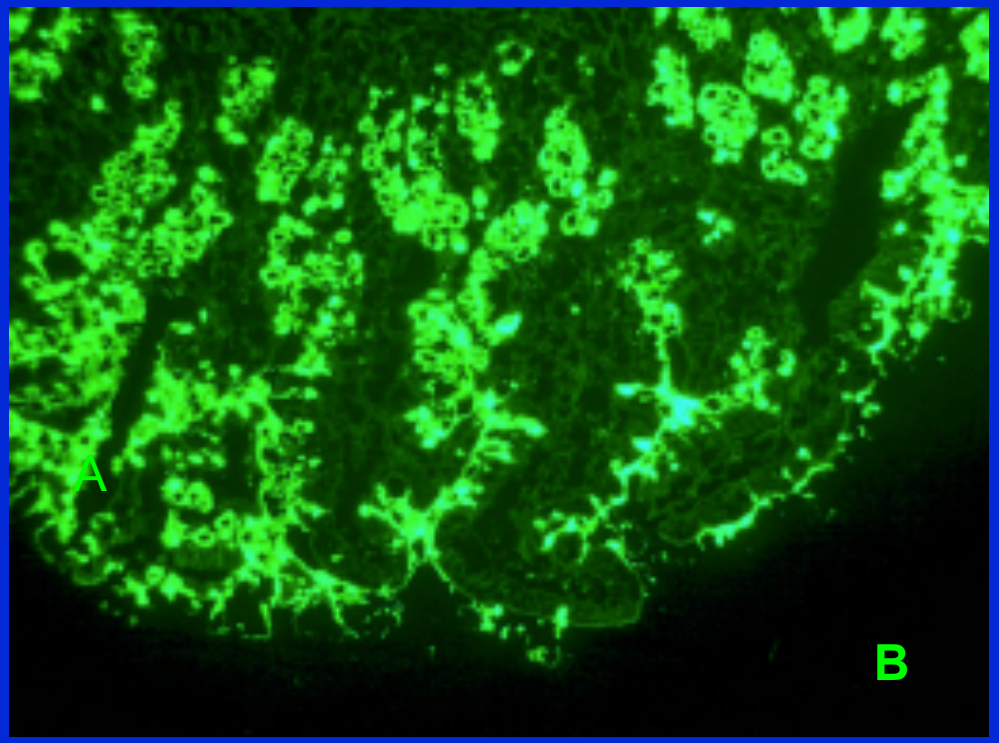
TABLE I. Proposed criteria for mast cell activation syndrome (all 3 must be present)

1. Episodic multisystem symptoms consistent with mast cell activation
2. Appropriate response to medications targeting mast cell activation
3. Documented increase in validated markers of mast cell activation systemically (ie, either in serum or urine) during a symptomatic period compared with the patient's baseline values*

J ALLERGY CLIN IMMUNOL
AUGUST 2017

Adult Autoimmune Enteropathy: Mayo Clinic Rochester Experience





Immunfluoreszenz Färbung
A: Enterozyten AK
B: Becherzellen AK

Akram et al.

Clin Gastroenterol Hepatol. 2007 November

Autoimmune enteropathies

Virchows Arch (2018)

Sarah E. Umetsu[1] · Ian Brown[2] · Cord Langner[3] · Gregory Y. Lauwers[4]

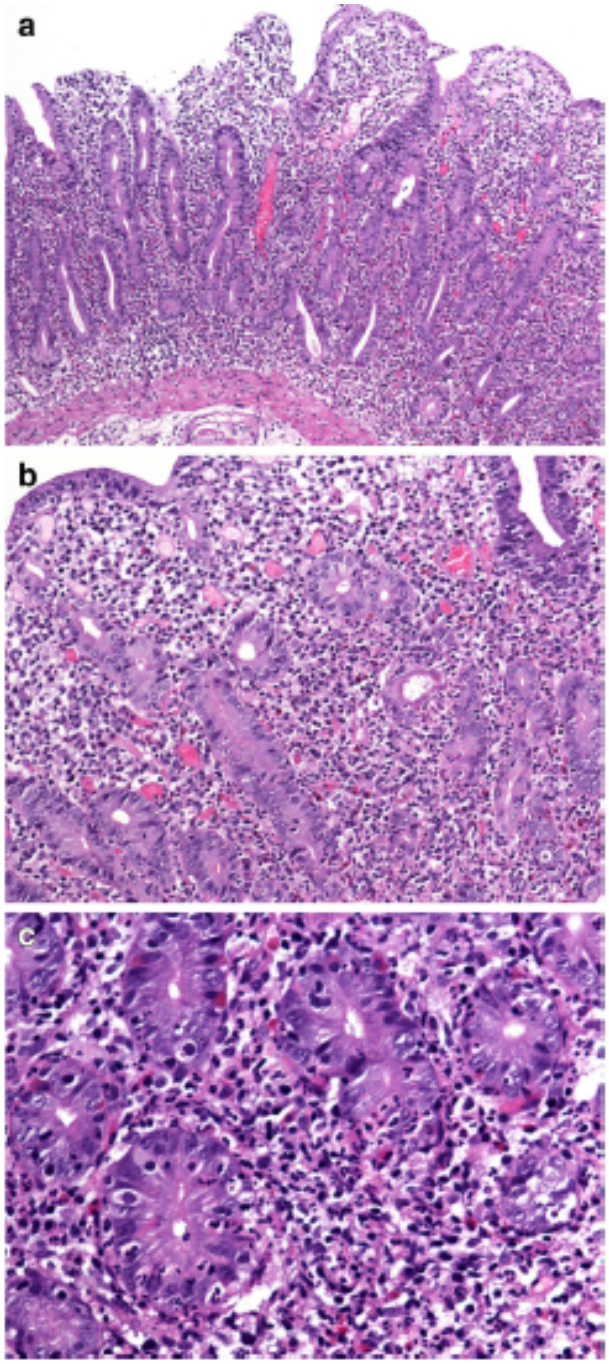


Fig. 1 Active chronic enteritis pattern. a Low power view of a duodenal biopsy showing villous blunting, expansion of the lamina propria by a mixed inflammatory infiltrate, and prominent cryptitis. b and c Higher power views showing prominent neutrophilic infiltrate and focal epithelial apoptosis

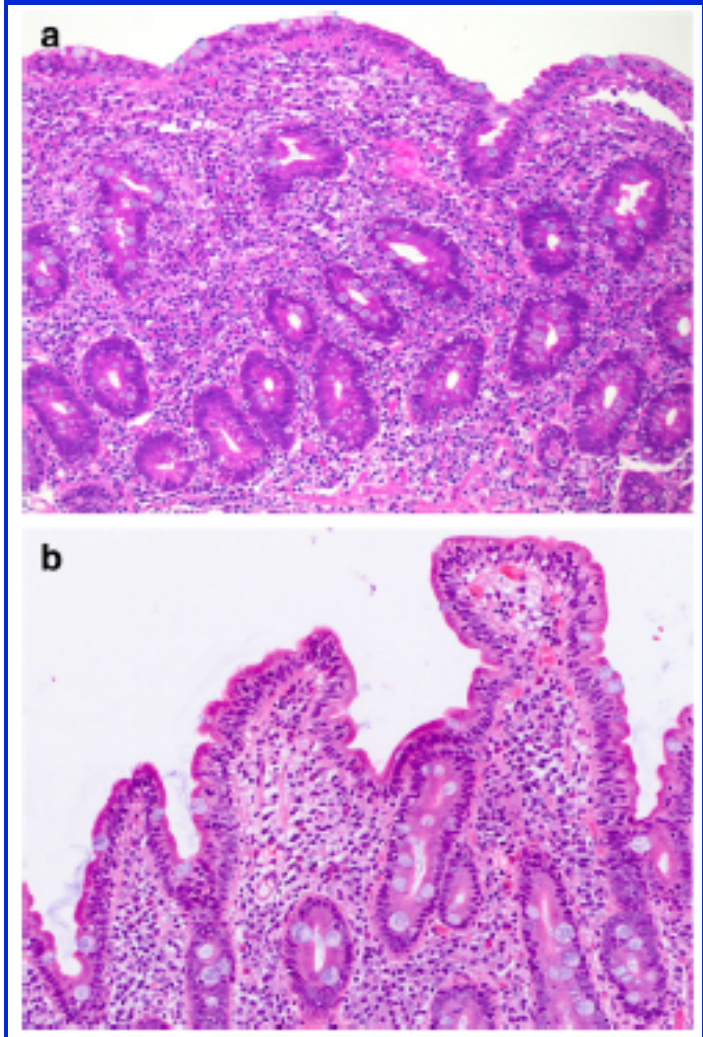


Fig. 2 Celiac disease-like pattern. a Low power view of a duodenal biopsy showing villous blunting and increased intraepithelial lymphocytes. b Higher power view of a different duodenal biopsy with intraepithelial lymphocytes

- Primary AIE (pediatric)
- Syndromic AIE (pediatric)

- Primary (sporadic) AIE of adults
- Secondary (iatrogenic driven) AIE of adults
- Paraneoplastic AIE

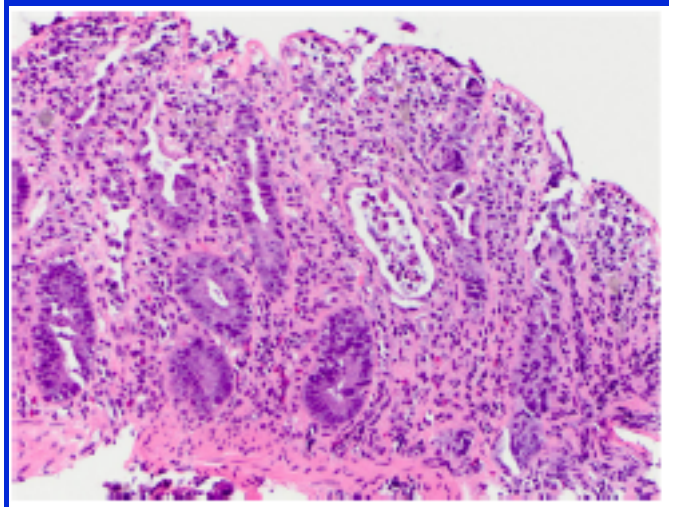


Fig. 3 Graft-versus-host disease-like pattern. Duodenal biopsy showing villous blunting and atrophic glands, some containing luminal debris

A Review of Autoimmune Enteropathy and Its Associated Syndromes

Digestive Diseases and Sciences (2020)

Autoimmune enteropathy type	Histopathological features
Celiac-like	Villous blunting, increased intraepithelial lymphocytes
Chronic active duodenitis	Villous blunting, inflammatory infiltrates in the lamina propria, neutrophilic cryptitis
Graft-vs-host-like	Villous blunting, epithelial cell apoptosis
Mixed/no predominant	Villous blunting, inflammatory infiltrates in the lamina propria

Table 3 Therapies for autoimmune enteropathy and associated syndromes

Therapy	Response rate (%) [reference number]
Systemic corticosteroids	26–60 [3, 5]
Open-capsule budesonide	85 [72]
Calcineurin inhibitors (tacrolimus and cyclosporine)	75 [22]
Sirolimus	67 [22]
Azathioprine	36 [22]
Mycophenolate mofetil	Anecdotal reports of efficacy [22]
Methotrexate	Anecdotal reports of efficacy [22]
Anti-tumor necrosis factor	50 [22]
Abatacept (for CTLA-4 deficiency)	Anecdotal reports of efficacy [77, 78]
Stem cell transplantation	82 [5]
Parenteral nutrition*	Varies based on series [5]

Diagnosis and Management of Microscopic Colitis

Table 1. Drugs implicated as causing microscopic colitis

Drug (class)	Likelihood
Acarbose	High
Aspirin	High
Proton pump inhibitors	High
NSAIDs	High
H2 receptor antagonists	High
SSRIs	High
Ticlopidine	High
Carbamazepine	Intermediate
Flutamide	Intermediate
Lisinopril	Intermediate
Levodopa/benserazide	Intermediate
Statins	Intermediate

NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor. Likelihood refers to the strength of data.
Adapted from Beaugerie and Pardi (92).

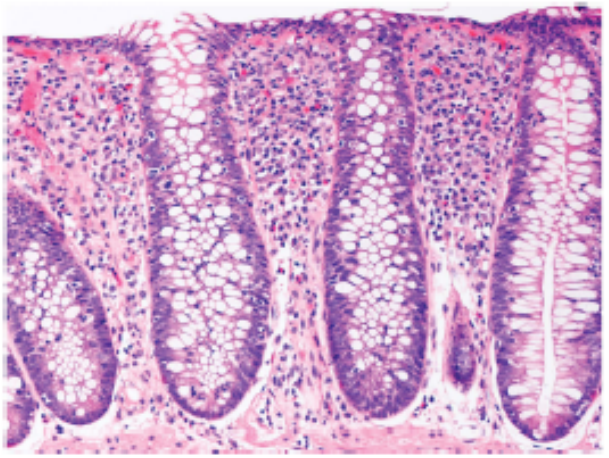


Figure 1. Lymphocytic colitis, with intraepithelial lymphocytosis, surface epithelial damage, and mixed inflammatory infiltrate in the lamina propria. Hematoxylin eosin stain, ×100 magnification. Courtesy of Thomas C. Smyrk, MD, Department of Pathology, Mayo Clinic Rochester, Rochester, MN.

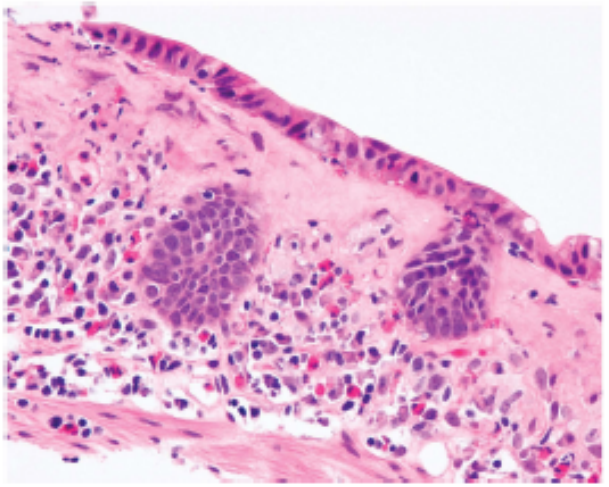


Figure 2. Collagenous colitis, with a thickened subepithelial collagen band, less prominent lymphocytosis, and surface epithelial damage. Hematoxylin eosin stain, ×100 magnification. Courtesy of Thomas C. Smyrk, MD, Department of Pathology, Mayo Clinic Rochester, Rochester, MN.

Microscopic colitis: pathophysiology and clinical management

Stephan Miehlke, Bas Verhaegh, Gian Eugenio Tontini, Ahmed Madisch, Cord Langner, Andreas Münch

Lancet Gastroenterol Hepatol
2019; 4: 305–14

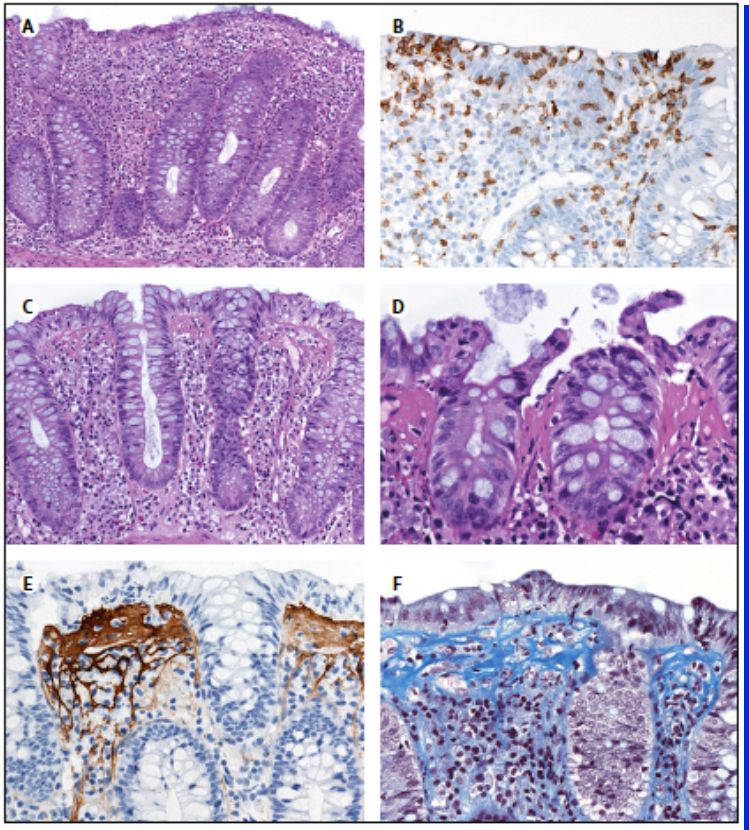


Figure 3: Key histological features of microscopic colitis

	Lymphocytic colitis	Incomplete lymphocytic colitis	Collagenous colitis	Incomplete collagenous colitis
Mononuclear inflammation in the lamina propria	Moderately increased	Slightly increased	Moderately increased	Slightly increased
Number of intraepithelial lymphocytes	>20/100 cells	>10 to ≤20/100 cells	Normal or slightly increased	Normal or slightly increased
Thickness of subepithelial collagen band	Normal or slightly increased	Normal or slightly increased	>10 µm	>5 to ≤10 µm

Table: Key histological features of lymphocytic and collagenous colitis, including incomplete forms

Microscopic colitis: pathophysiology and clinical management

Lancet Gastroenterol Hepatol
2019; 4: 305–14

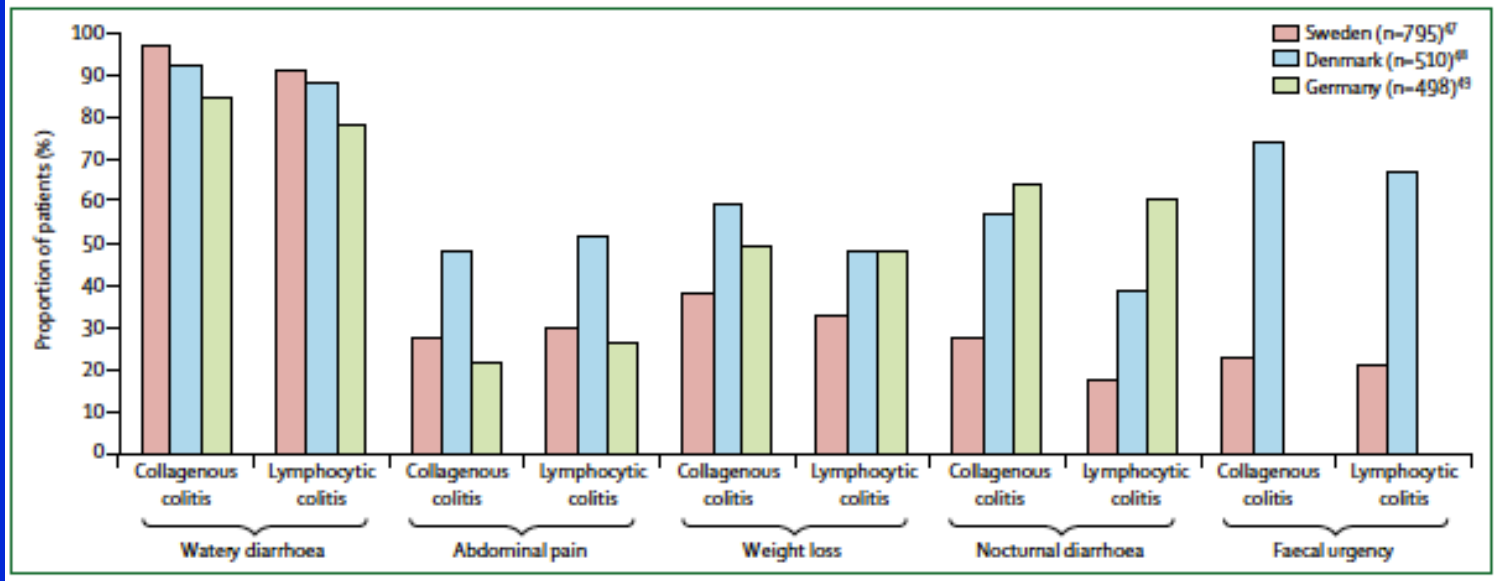


Figure 2: Symptom burden of microscopic colitis

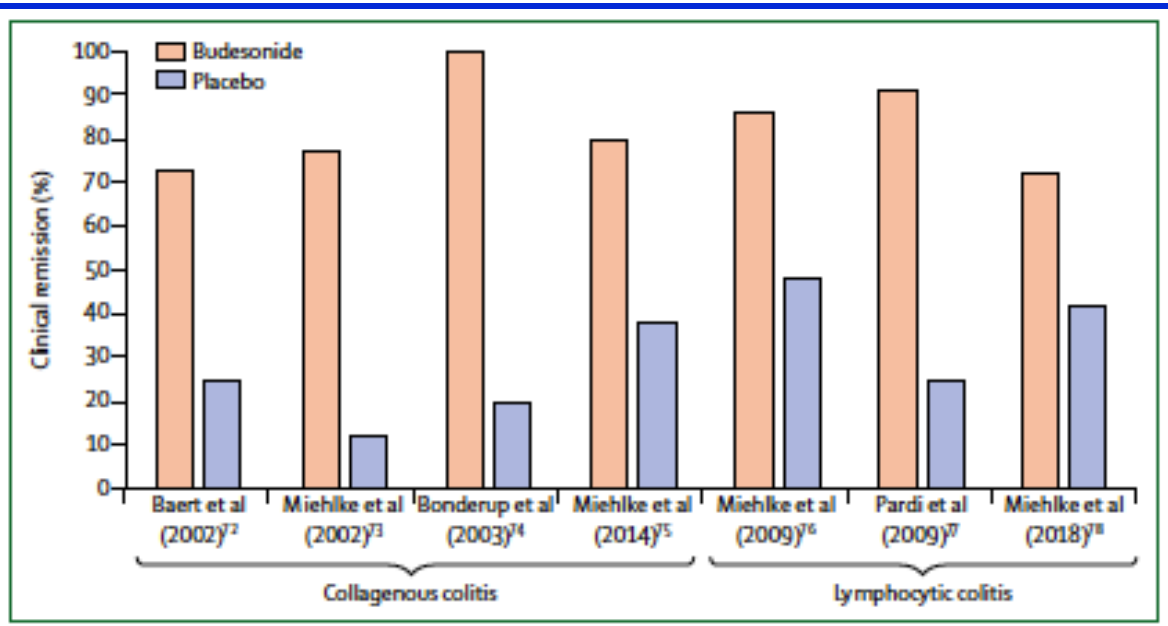


Figure 4: Randomised placebo-controlled trials of budesonide to induce remission in microscopic colitis

Microscopic colitis: pathophysiology and clinical management

Lancet Gastroenterol Hepatol
2019; 4: 305–14

Stephan Miehlke, Bas Verhaegh, Gian Eugenio Tontini, Ahmed Madisch, Cord Langner, Andreas Münch

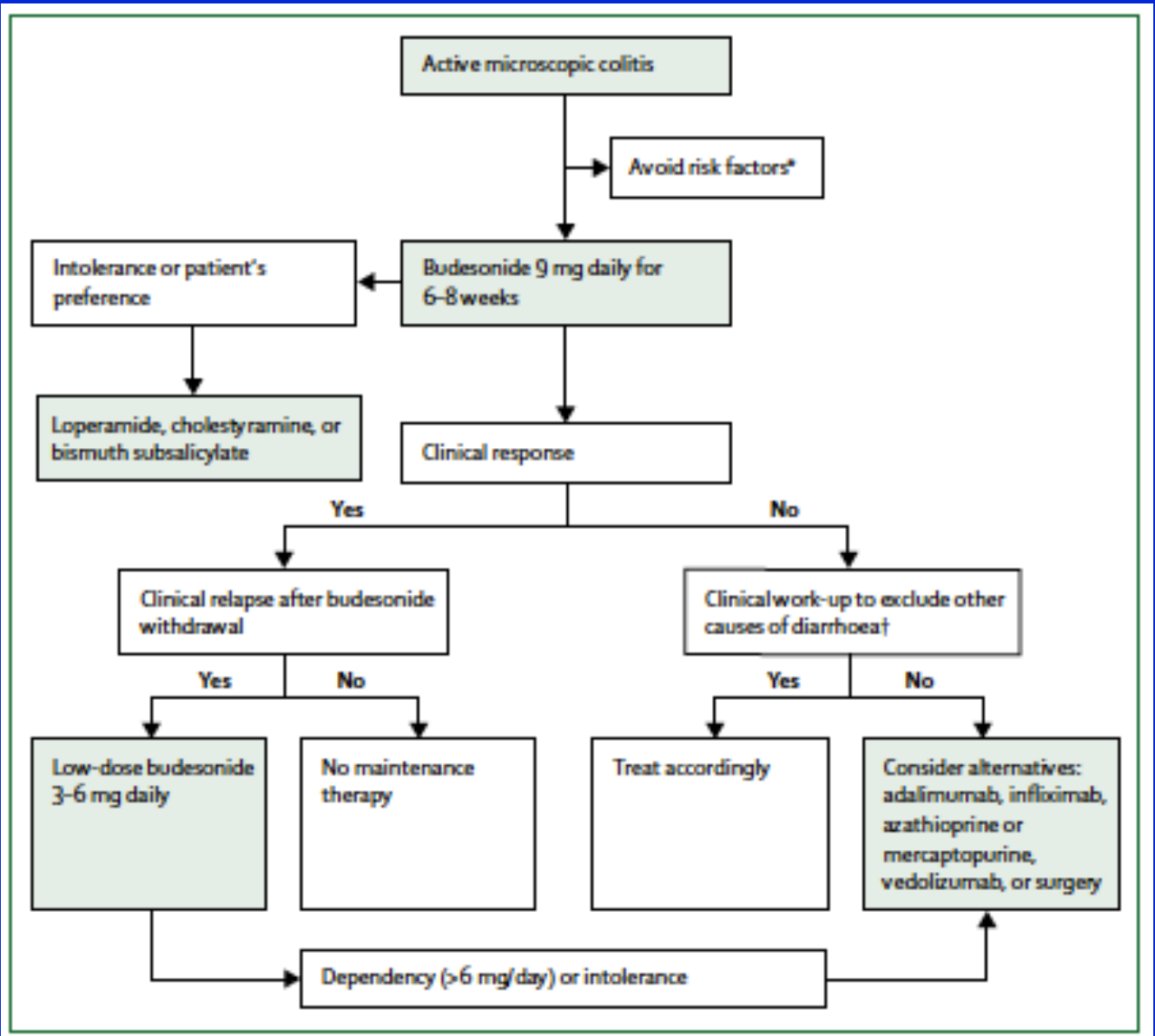
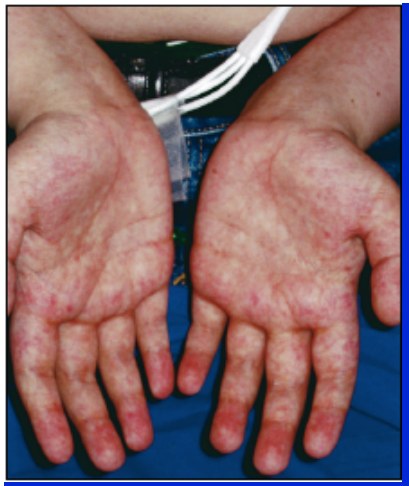


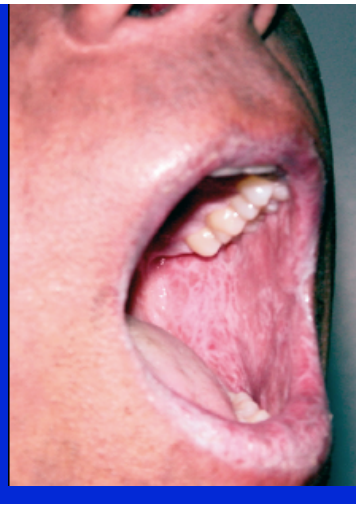
Figure 5: **Proposed algorithm for the therapeutic management of microscopic colitis**



Gut microbiota injury in allogeneic haematopoietic stem cell transplantation

NATURE REVIEWS | CANCER
VOLUME 18 | MAY 2018 | 283

*Yusuke Shono[1,2] and Marcel R. M. van den Brink[1,3,4]**



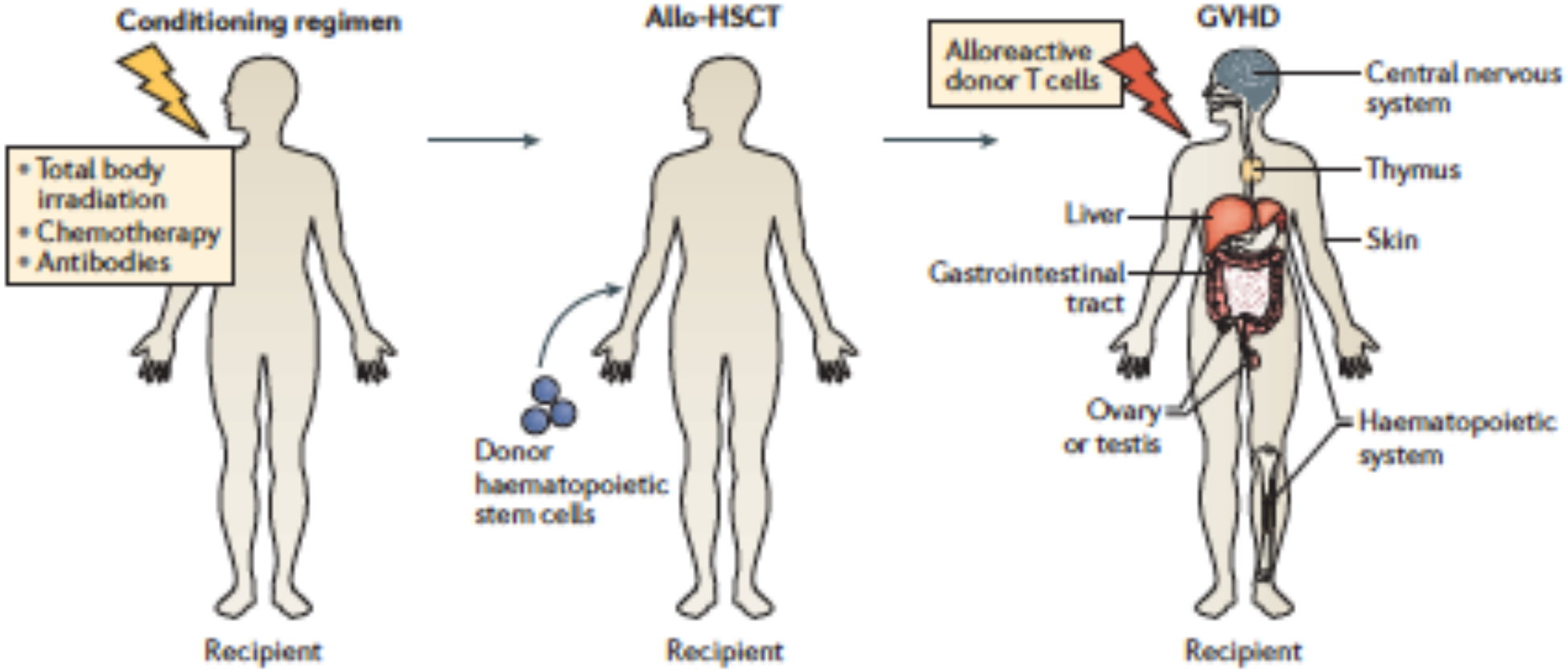


Figure 1 | **Allo-HSCT and GVHD.** Patients undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT)

Gut microbiota injury in allogeneic haematopoietic stem cell transplantation

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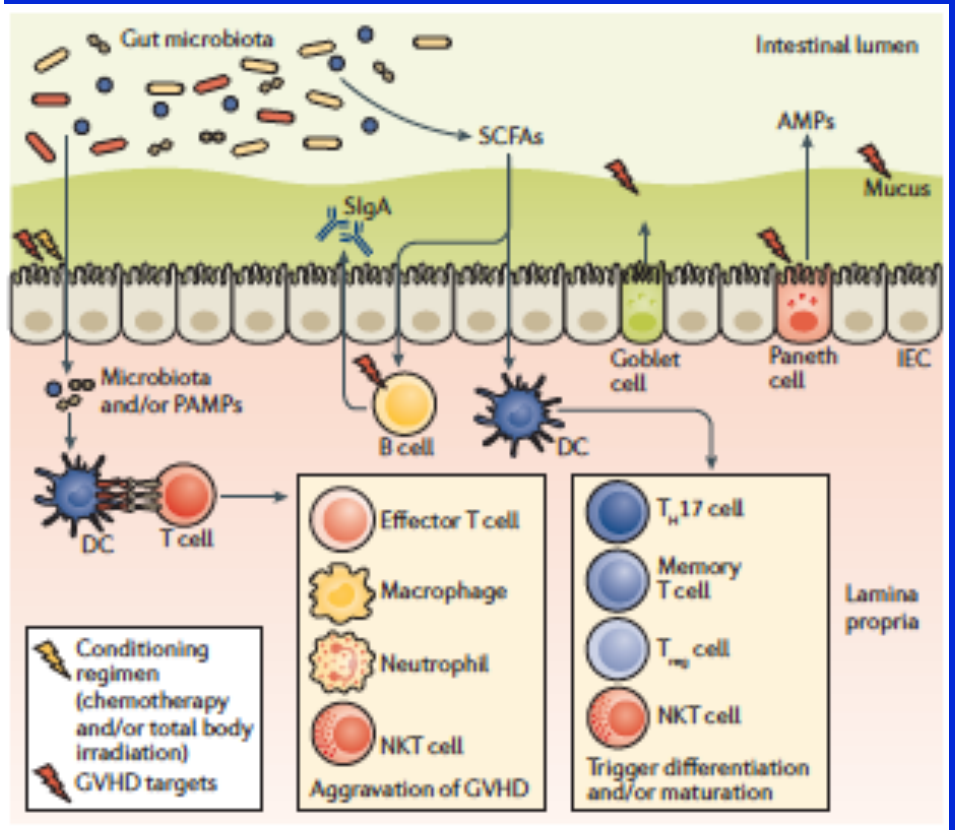


Figure 4 | **The interplay between gut microbiota and host physiology and immunity.**

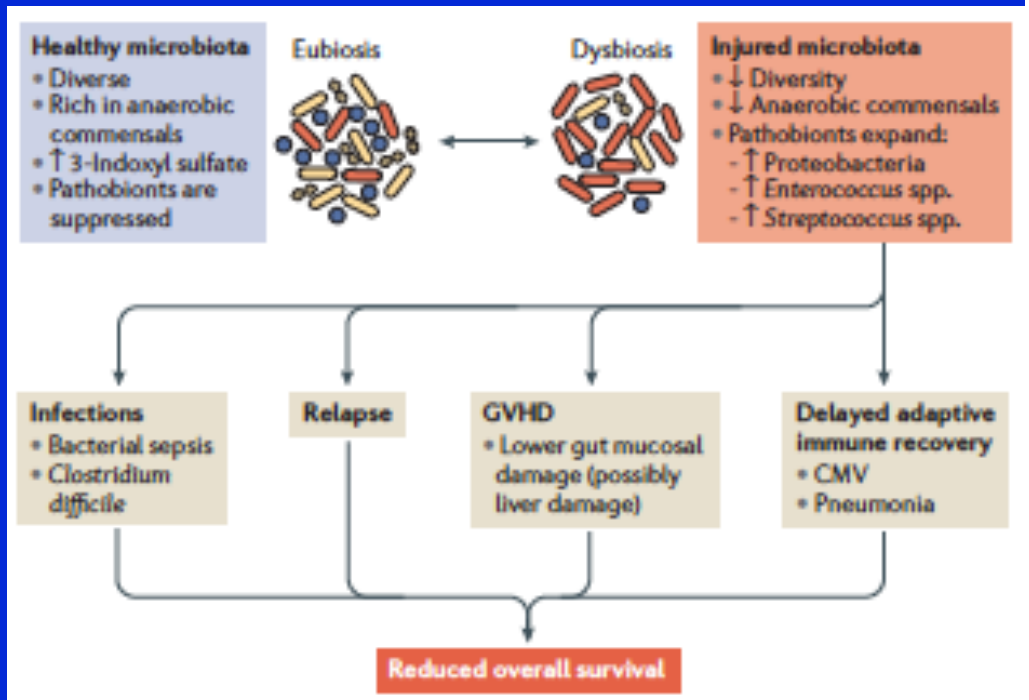
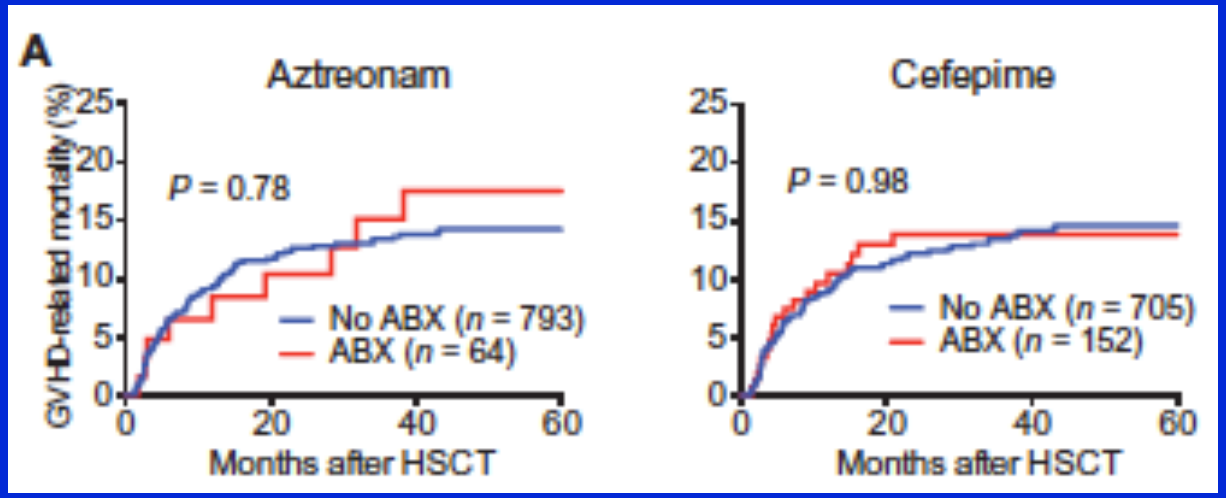
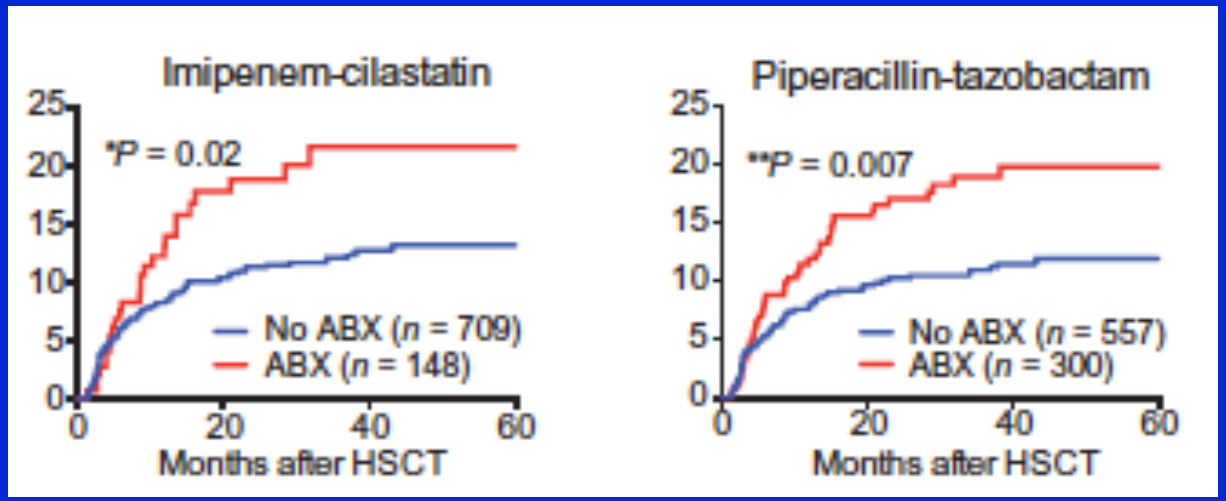


Figure 5 | **Microbiota injury and complications after allo-HSCT.** The top panels

Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice



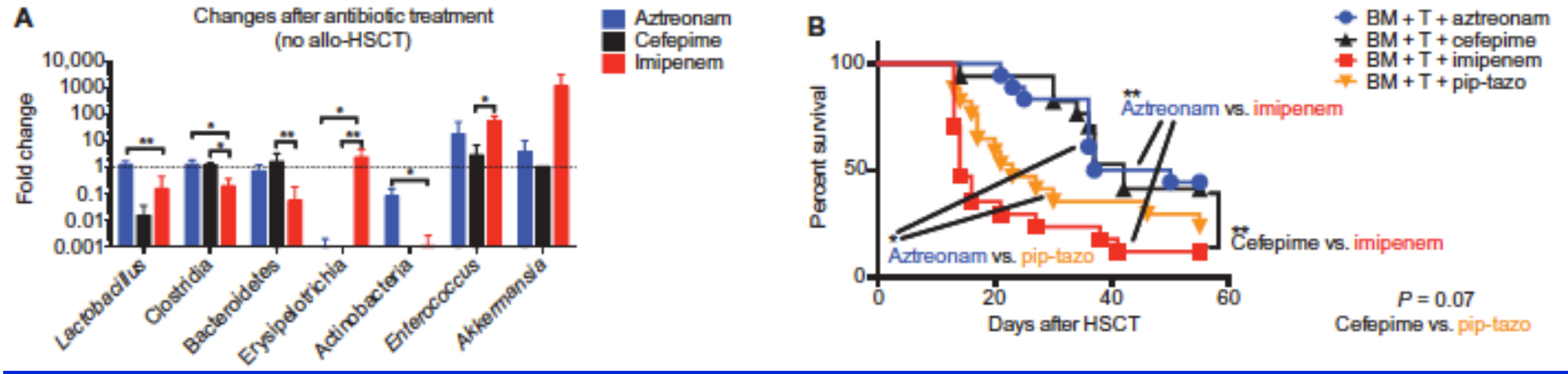
GVHD-related mortality %



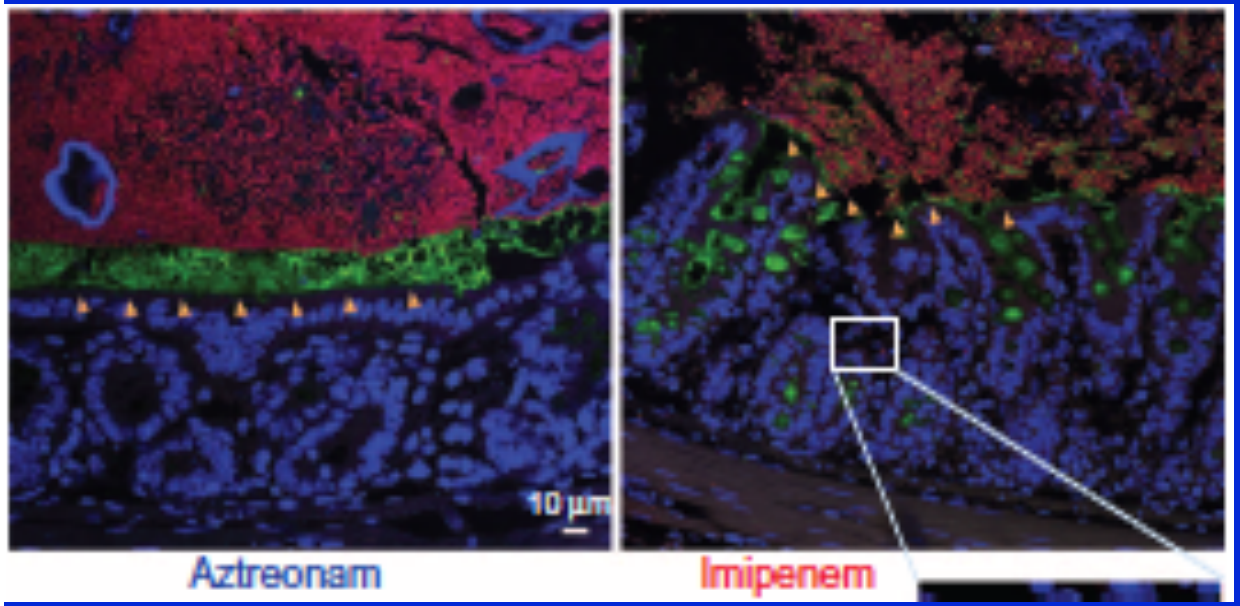
Shono et al., Science Translational Medicine 2016

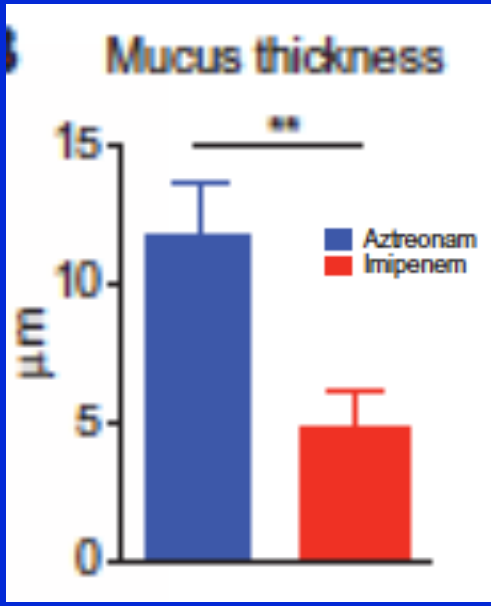
mice

Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice



mucin staining





Shono et al., Science Translational Medicine 2016

Acute graft-versus-host disease of the gut: considerations for the gastroenterologist

Steven Naymagon[1], Leonard Naymagon[2], Serre-Yu Wong[1], Huaibin Mabel Ko[1,3], Anne Renteria[2], John Levine[2], Jean-Frederic Colombel[1] and James Ferrara[2]

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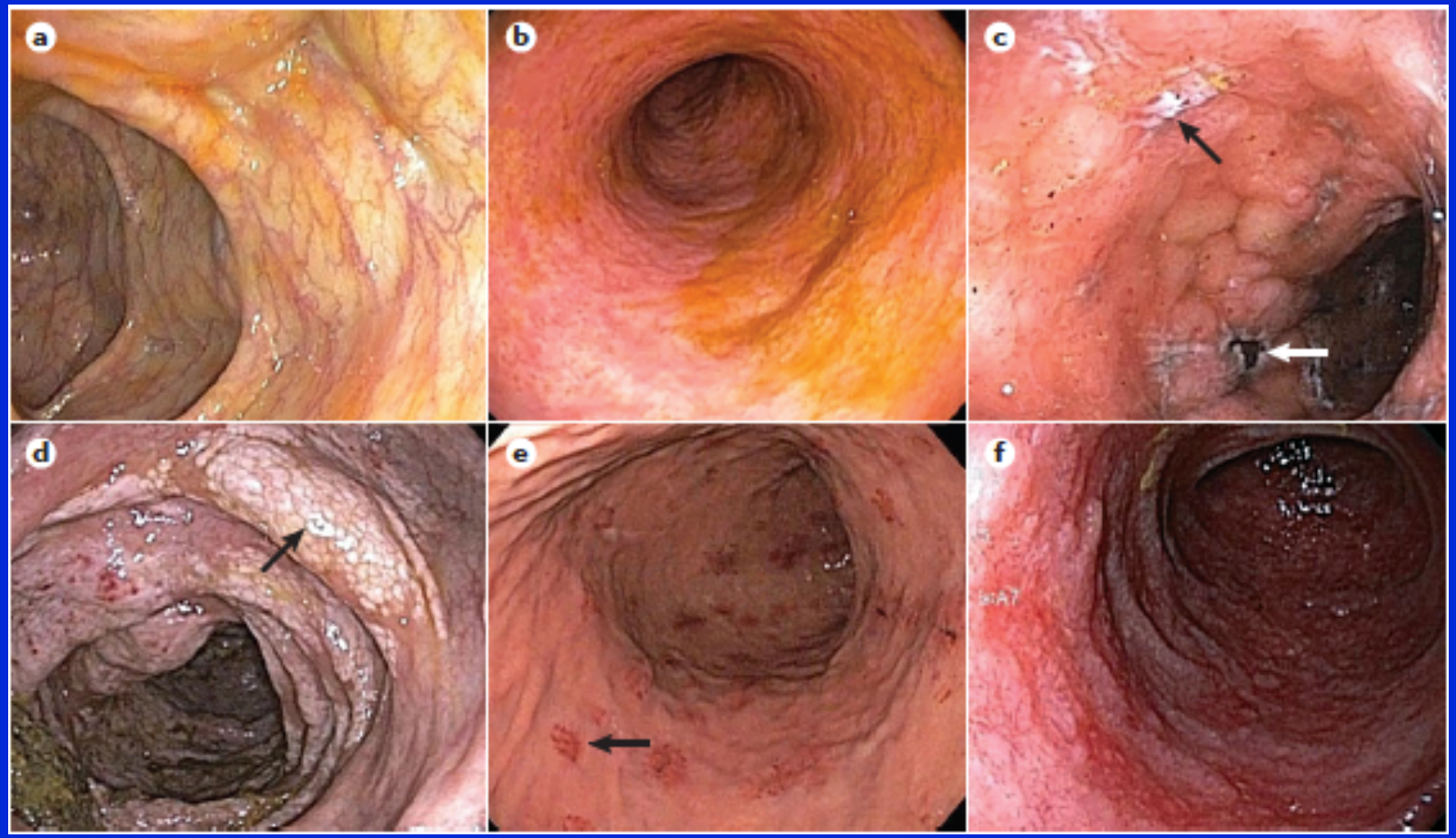

Table 1 | Grading endoscopic severity in gastrointestinal acute GVHD

Grade	Freiburg Classification for endoscopic findings[64]
1	Normal mucosa or the absence of higher-grade findings
2	Spotted erythema or initial aphthous lesion
3	Aphthous lesions or focal erosions
4	Confluent defects, ulcerations and/or complete denudation of the mucosa

Acute graft-versus-host disease of the gut: considerations for the gastroenterologist

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY
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Table 2 | Grading histological severity in gastrointestinal acute GVHD

Grade	Histological classification
1	Isolated apoptotic epithelial cells without crypt loss
2	Crypt necrosis, withering and individual crypt loss
3	Contiguous areas of multiple crypt loss
4	Extensive crypt dropout with denudation of the epithelium

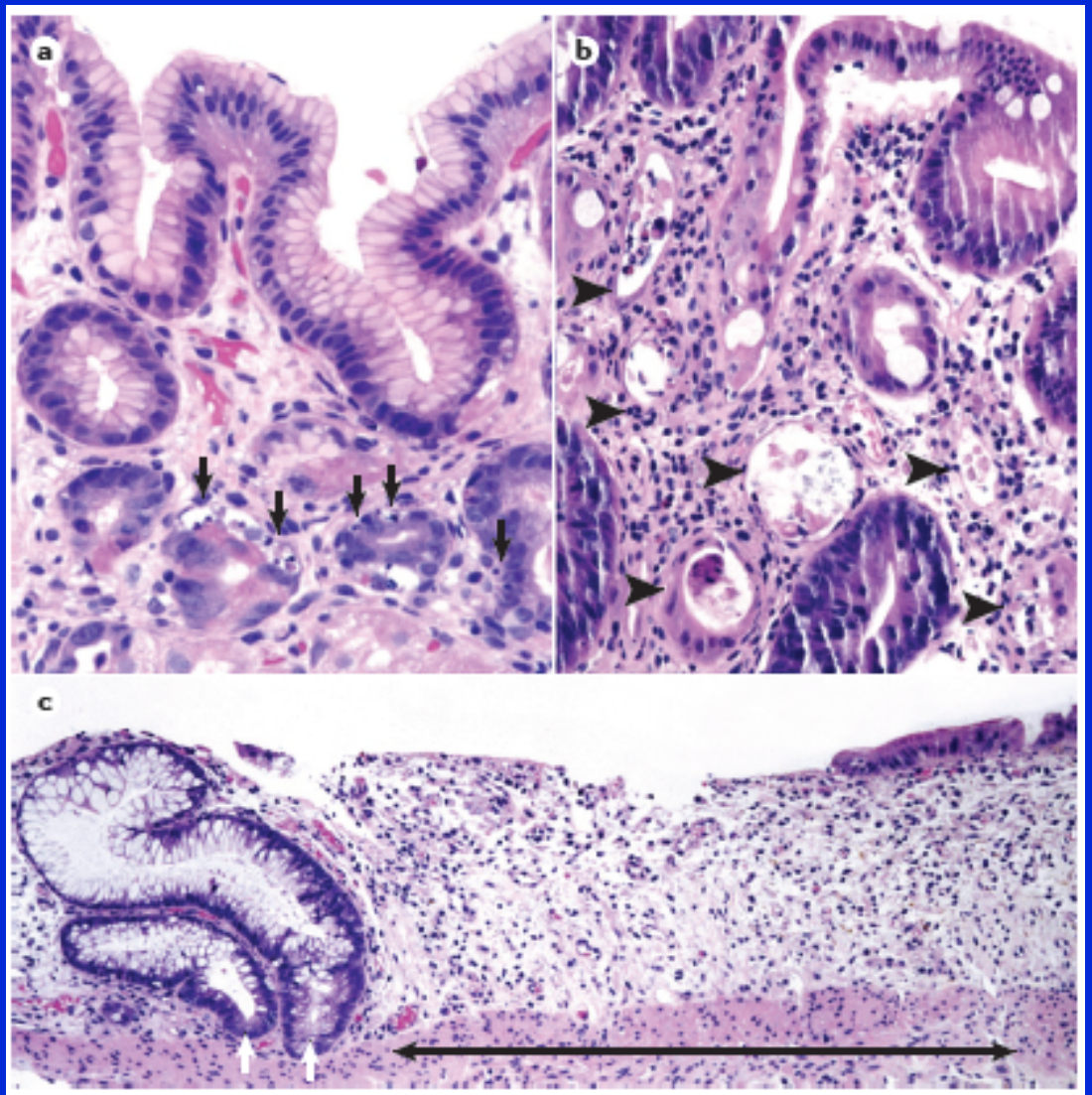


Figure 3 | Histopathological findings in GVHD of the gastrointestinal tract.

Acute graft-versus-host disease of the gut: considerations for the gastroenterologist

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY VOLUME 14 | DECEMBER 2017 | 711

Clinical stage of acute GVHD

Stage	Target organ			
	Skin (active erythema only)	Liver (serum total bilirubin)	Upper gastrointestinal	Lower gastrointestinal (stool output)
0	No active (erythematous) rash	<2 mg/dL (<34.21 µmol/L)	No or intermittent nausea, vomiting or anorexia	• Adult: <500 mL per day • Child: <10 mL/kg per day
1	Maculopapular rash, <25% BSA	2–3 mg/dL (34.21–51.31 µmol/L)	Persistent nausea, vomiting or anorexia	• Adult: 500–999 mL per day • Child: 10–19.9 mL/kg per day
2	Maculopapular rash, 25–50% BSA	3.1–6 mg/dL (53.02–102.62 µmol/L)	–	• Adult: 1,000–1,500 mL per day • Child: 20–30 mL/kg per day
3	Maculopapular rash, >50% BSA	6.1–15 mg/dL (104.33–256.56 µmol/L)	–	• Adult: >1,500 mL per day • Child: >30 mL/kg per day
4	Generalized erythroderma (>50% BSA), plus bullous formation and desquamation (>5% BSA)	>15 mg/dL (>256.56 µmol/L)	–	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of volume)

Acute graft-versus-host disease of the gut: considerations for the gastroenterologist

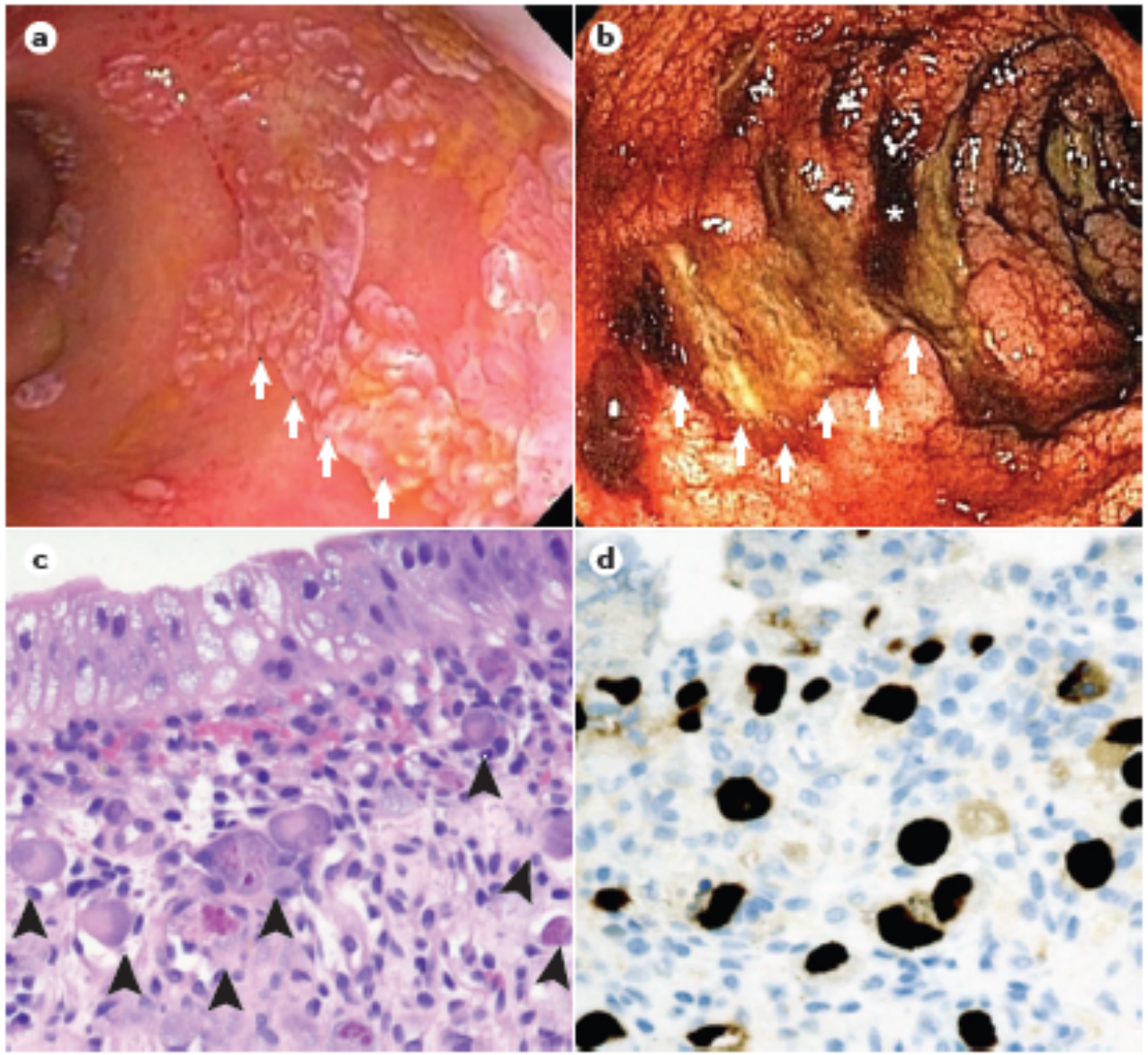
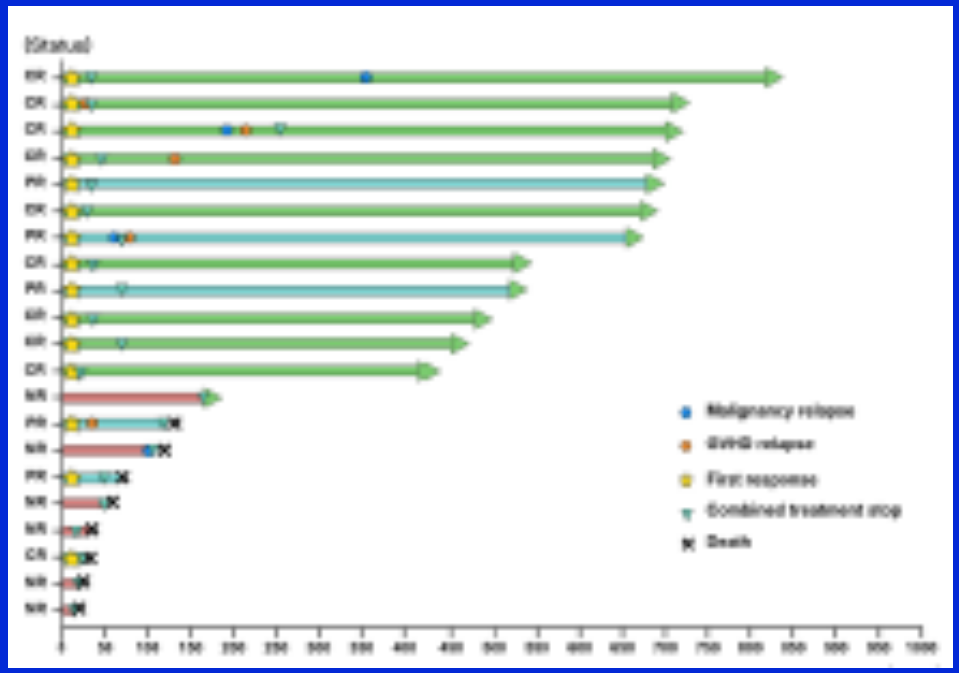
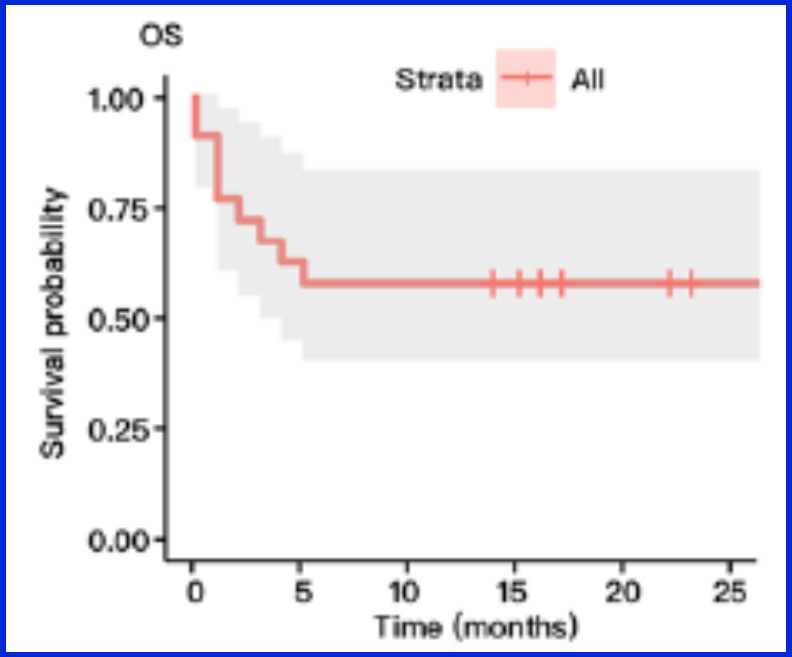


Figure 4 | Gastrointestinal cytomegalovirus infection following HSCT. Endoscopic

Fecal microbiota transplantation combined with ruxolitinib as a salvage treatment for intestinal steroid-refractory acute GVHD

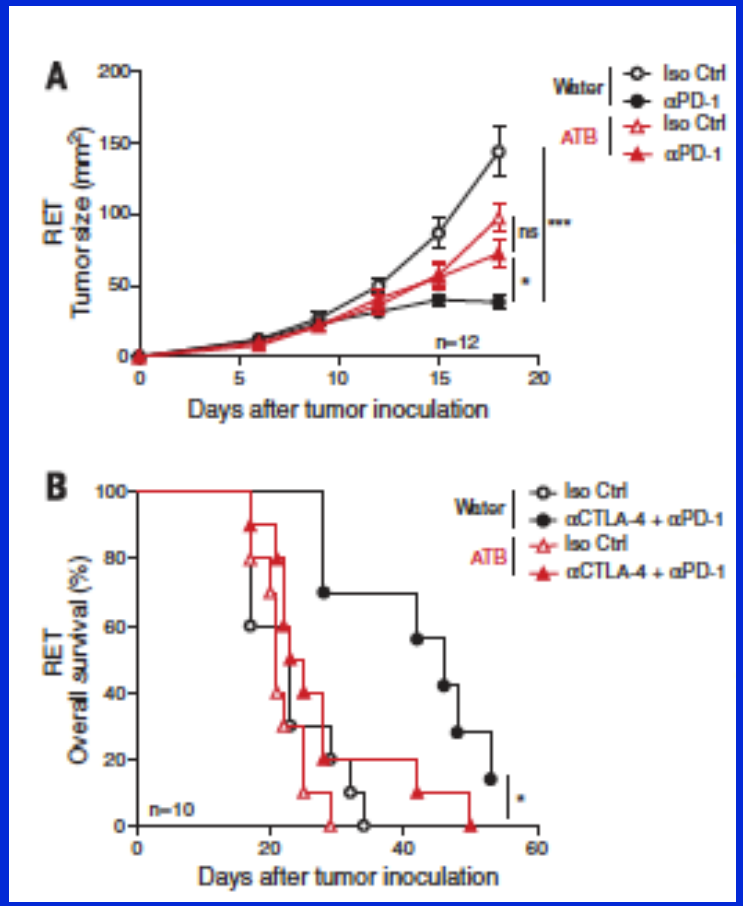
Liu et al.
Experimental Hematology & Oncology (2022)

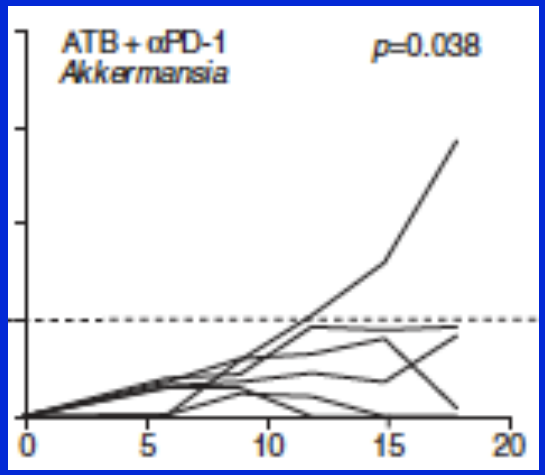


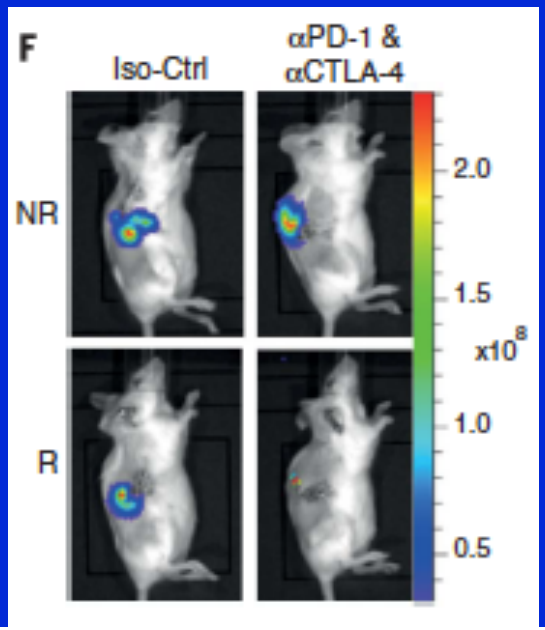


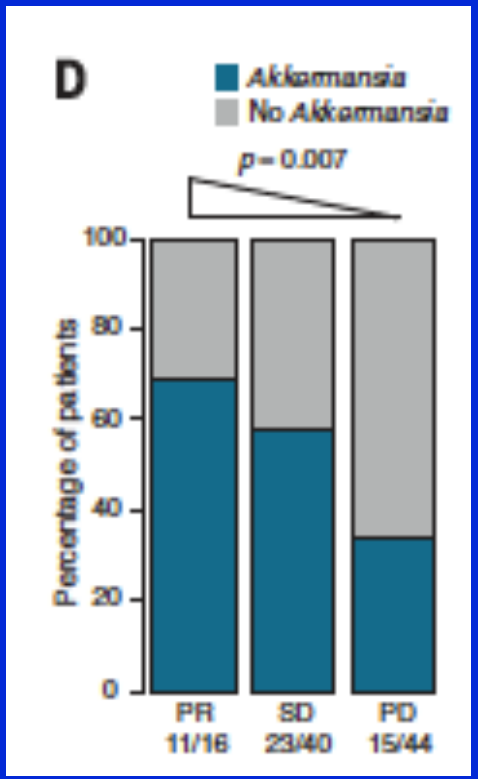
Acute graft-versus-host disease (aGVHD), especially intestinal aGVHD, is one of the most severe complications after allogeneic hematopoietic stem cell transplantation (HSCT). Fecal microbiota transplantation (FMT) has been applied to the treatment of intestinal steroid-refractory aGVHD (SR-aGVHD). Ruxolitinib is the first drug recommended for SR-aGVHD. Here, we reported the outcome data from 21 patients who had received the combined treatment of FMT with ruxolitinib as a salvage treatment in intestinal SR-aGVHD after HSCT. The overall response rate on day 28 was 71.4% (95% CI 50.4–92.5%), including 10 patients with complete responses. The durable overall response at day 56 in responders was 80%. GVHD relapse rate was 33.3% in responders. The levels of inflammatory cytokines as well as T cells and NK cells activation declined. The diversity of the intestinal microbiota was improved in responders. Viral reactivations and severe cytopenia were the major adverse events (61.9% and 81% respectively). The estimated 6-month overall survival was 57.1% (95% CI: 35.9–78.3%), while event-free survival was 52.4% (95% CI: 21.7%-64.1%). Collectively, FMT with ruxolitinib could be an effective treatment for intestinal SR-aGVHD after HSCT.

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors









Routy et al., Sciene 2018

N Engl J Med 2018;378

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

Michael A. Postow, M.D., Robert Sidlow, M.D., and Matthew D. Hellmann, M.D.

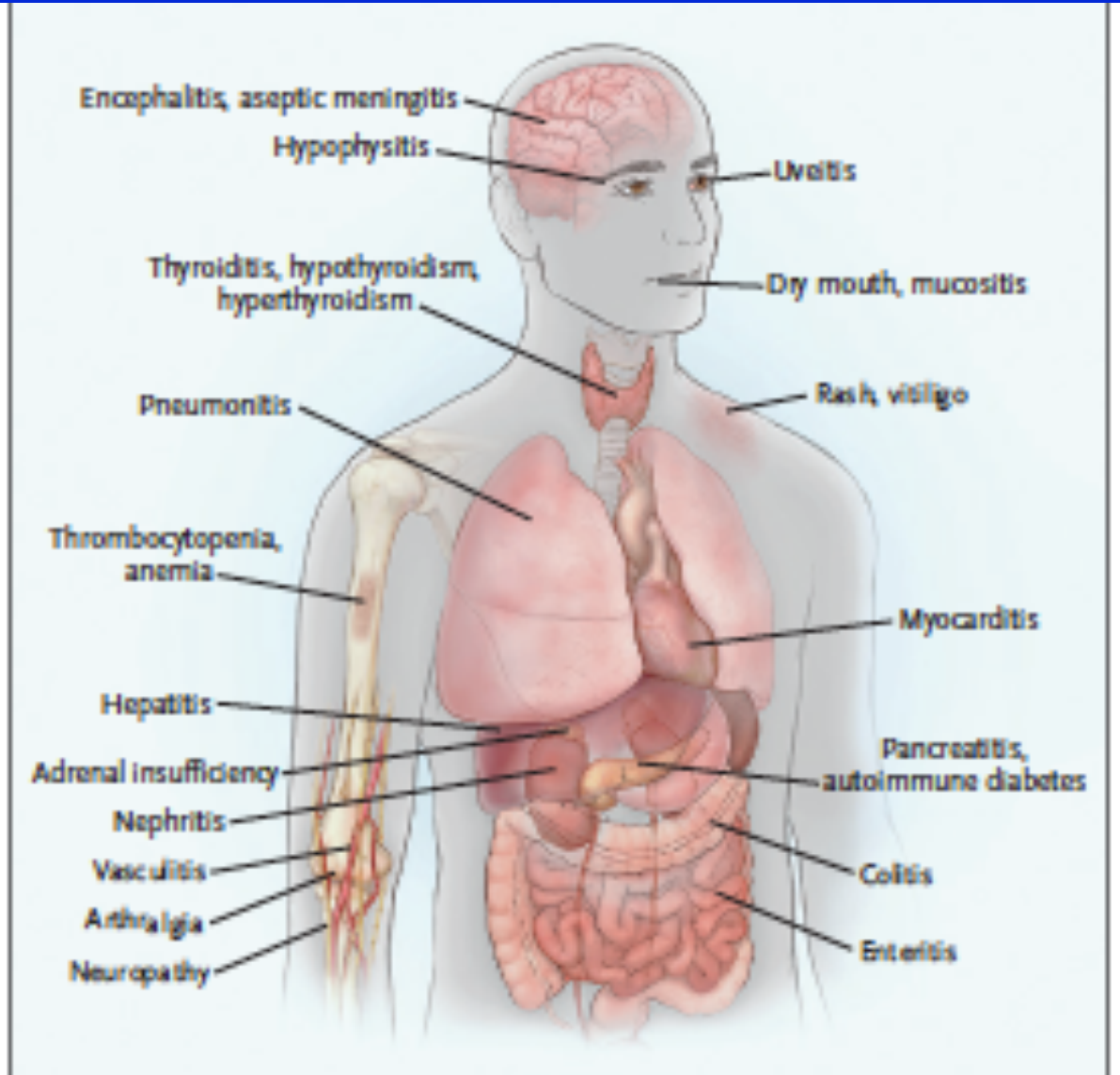


Figure 1. Organs Affected by Immune Checkpoint Blockade.

Immune-related adverse events of checkpoint inhibitors

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(2020) 6:38

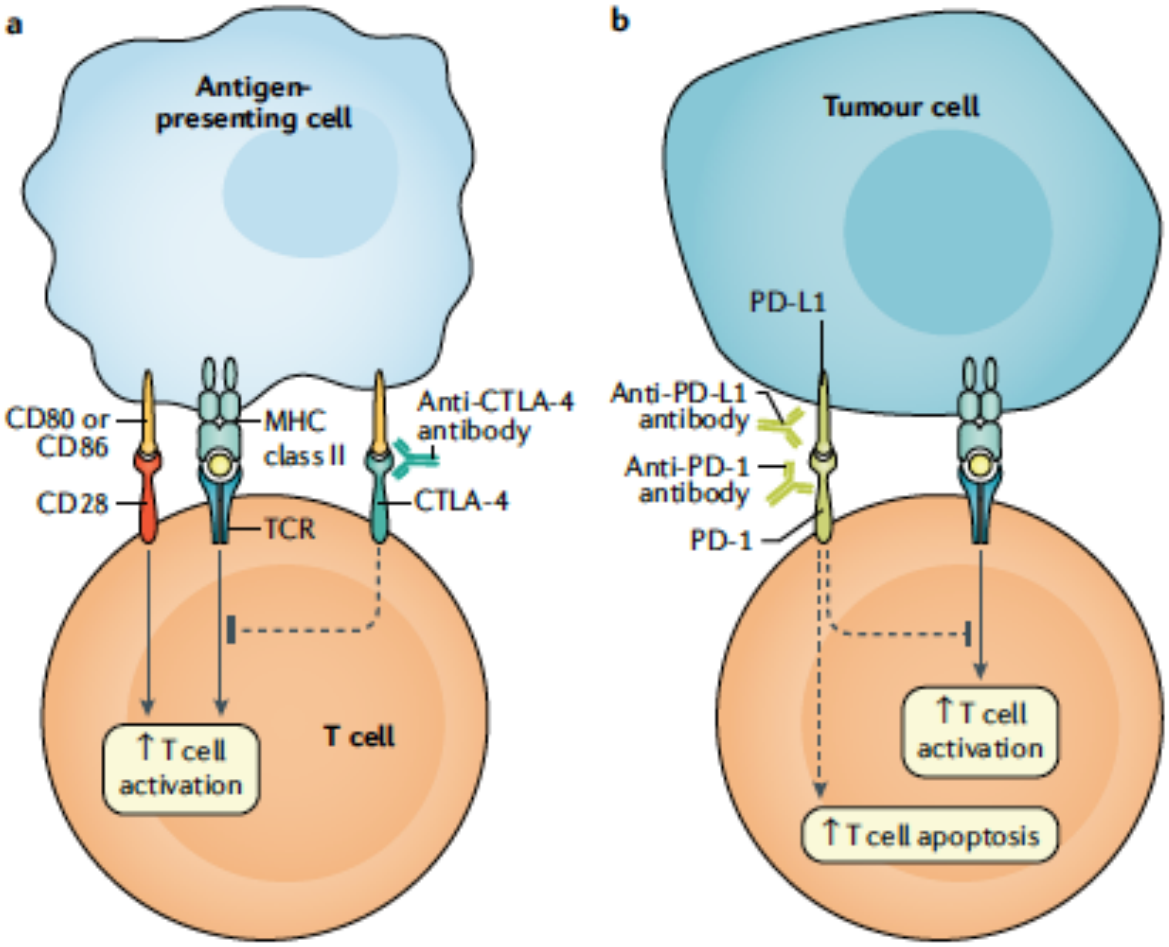

Fig. 1 | **Mechanism of immune checkpoints and immune checkpoint inhibitors.**

Manuel Ramos-Casals[1,2,3]✉, Julie R. Brahmer[4], Margaret K. Callahan[5,6,7], Alejandra Flores-Chávez[2], Niamh Keegan[5], Munther A. Khamashta[8], Olivier Lambotte[9,10], Xavier Mariette[11], Aleix Prat[12,13] and Maria E. Suárez-Almazor[14]

Immune-related adverse events of checkpoint inhibitors

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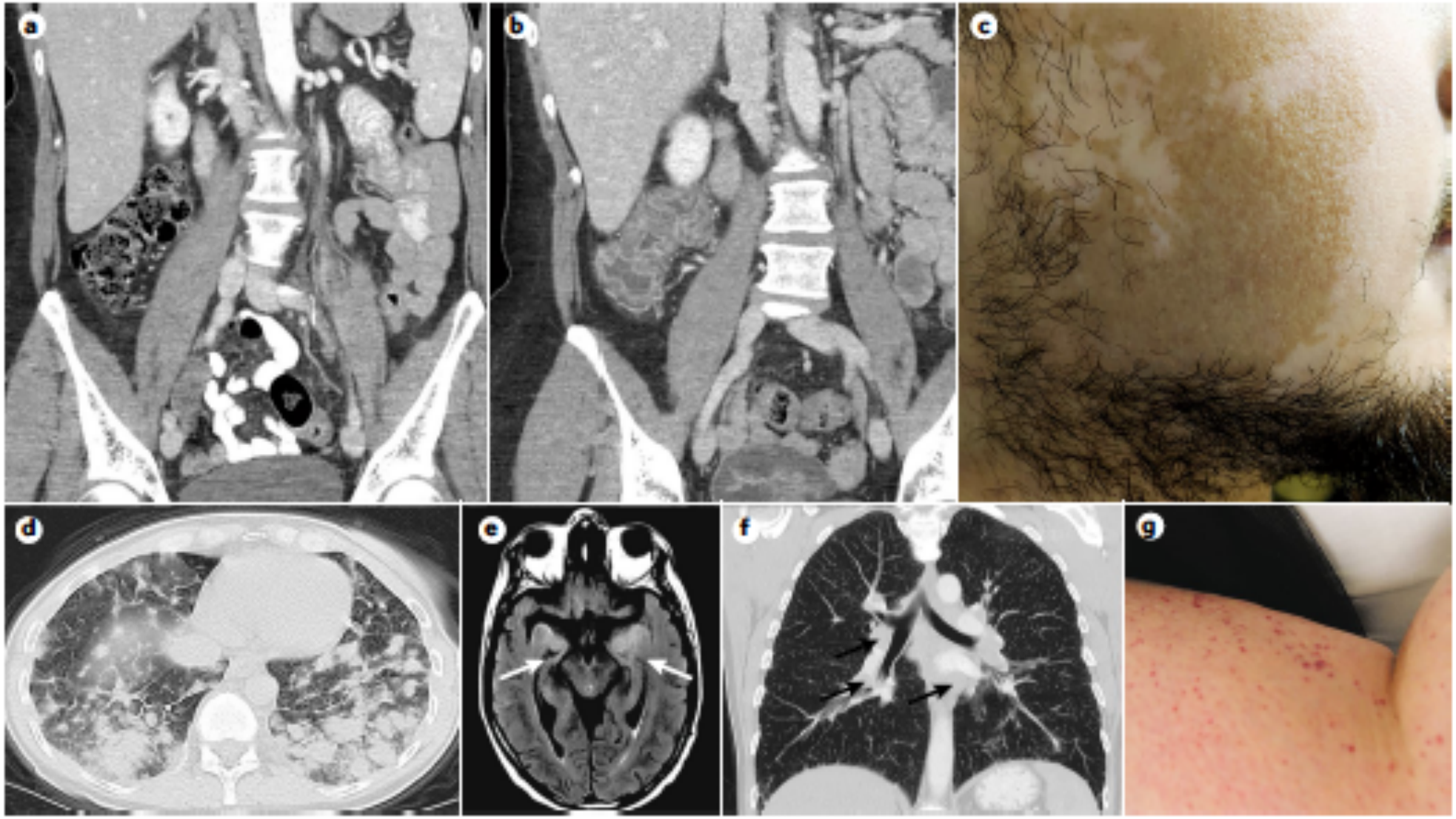

Fig. 3 | **Radiological and/or photographical appearance of immune-related adverse events. a** | CT image of immune

Immune-related adverse events of checkpoint inhibitors

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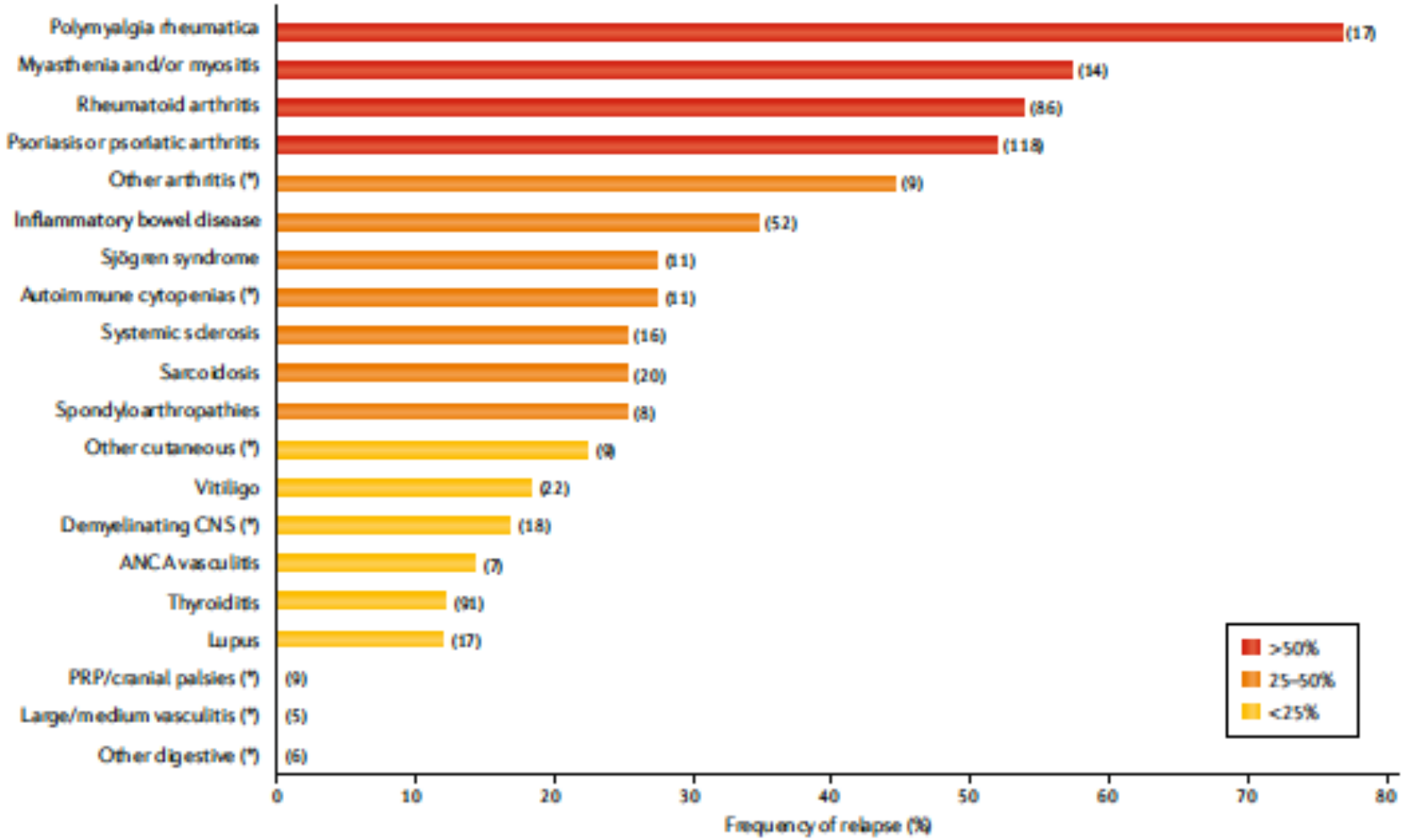

Fig. 4 | **Rate of reactivation/flare of pre-existing autoimmune diseases after immune checkpoint inhibitor therapy.**

Immune-related adverse events of checkpoint inhibitors

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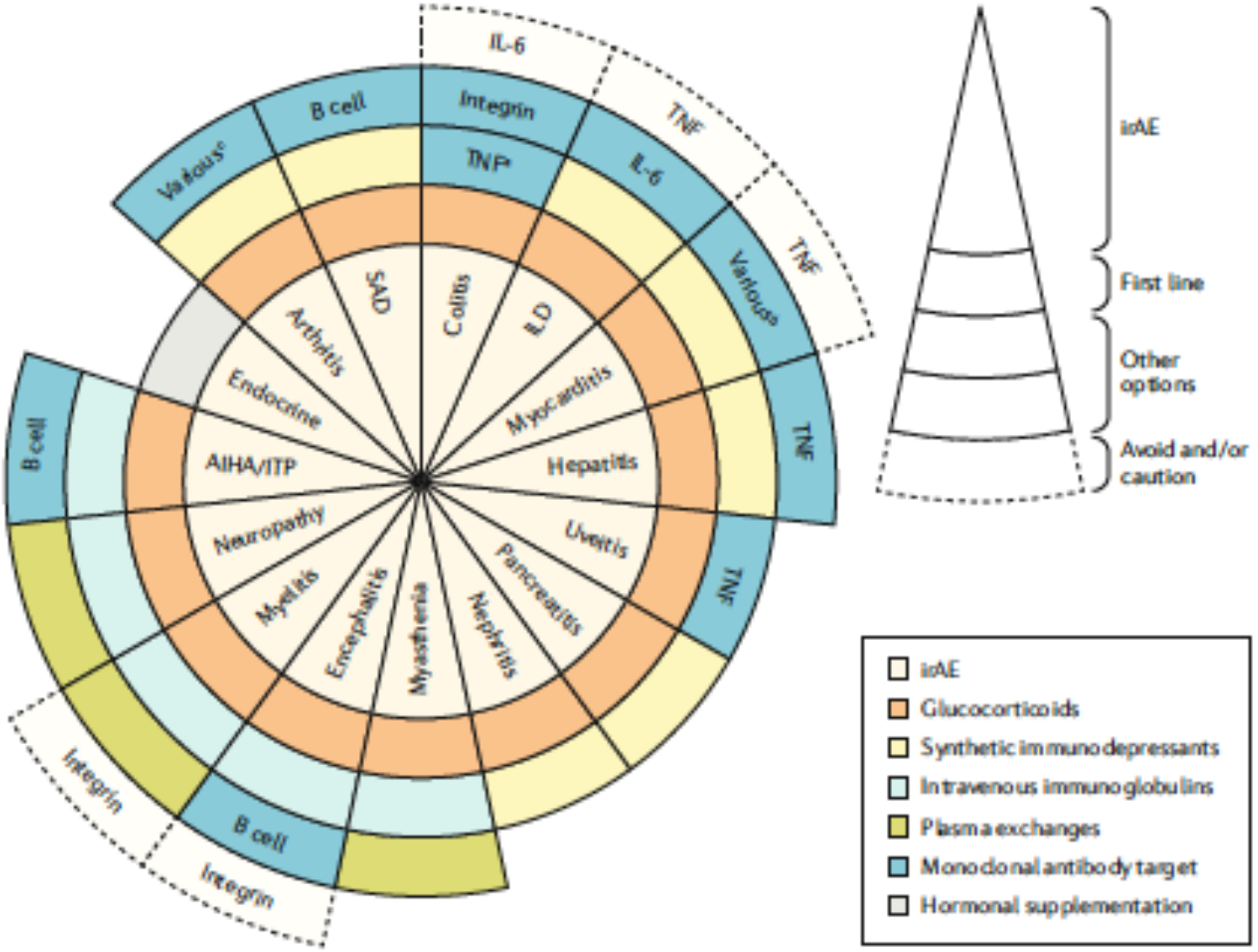


Fig. 5 | **Suggested therapeutic algorithm for the organ-by-organ management of irAEs.** When a systemic therapy is

Checkpoint Inhibitor–Induced Colitis

Emanuelle Bellaguarda, MD[1] and Stephen Hanauer, MD[1]

Am J Gastroenterol 2020;115:202–210.

Table 1. ICIs and current FDA-approved indications

	ICIs	Indications
Anti–CTLA-4	Ipilimumab	Advanced melanoma
Anti–PD-1	Nivolumab and pembrolizumab	Melanoma, metastatic NSCLC, head and neck squamous cancers, urothelial carcinoma, gastric adenocarcinoma, mismatch repair–deficient solid tumors, and classic Hodgkin lymphoma
	Nivolumab	Hepatocellular carcinoma and renal cell carcinoma
	Cemiplimab	Cutaneous squamous cell carcinoma
Anti–PD-L1	Atezolizumab	Urothelial cancers, NSCLC, and triple-negative breast cancer
	Durvalumab	Urothelial cancers and stage III NSCLC
	Avelumab	Merkel cell carcinoma, urothelial carcinoma, and renal cell carcinoma

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; NSCLC, non–small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Checkpoint Inhibitor–Induced Colitis

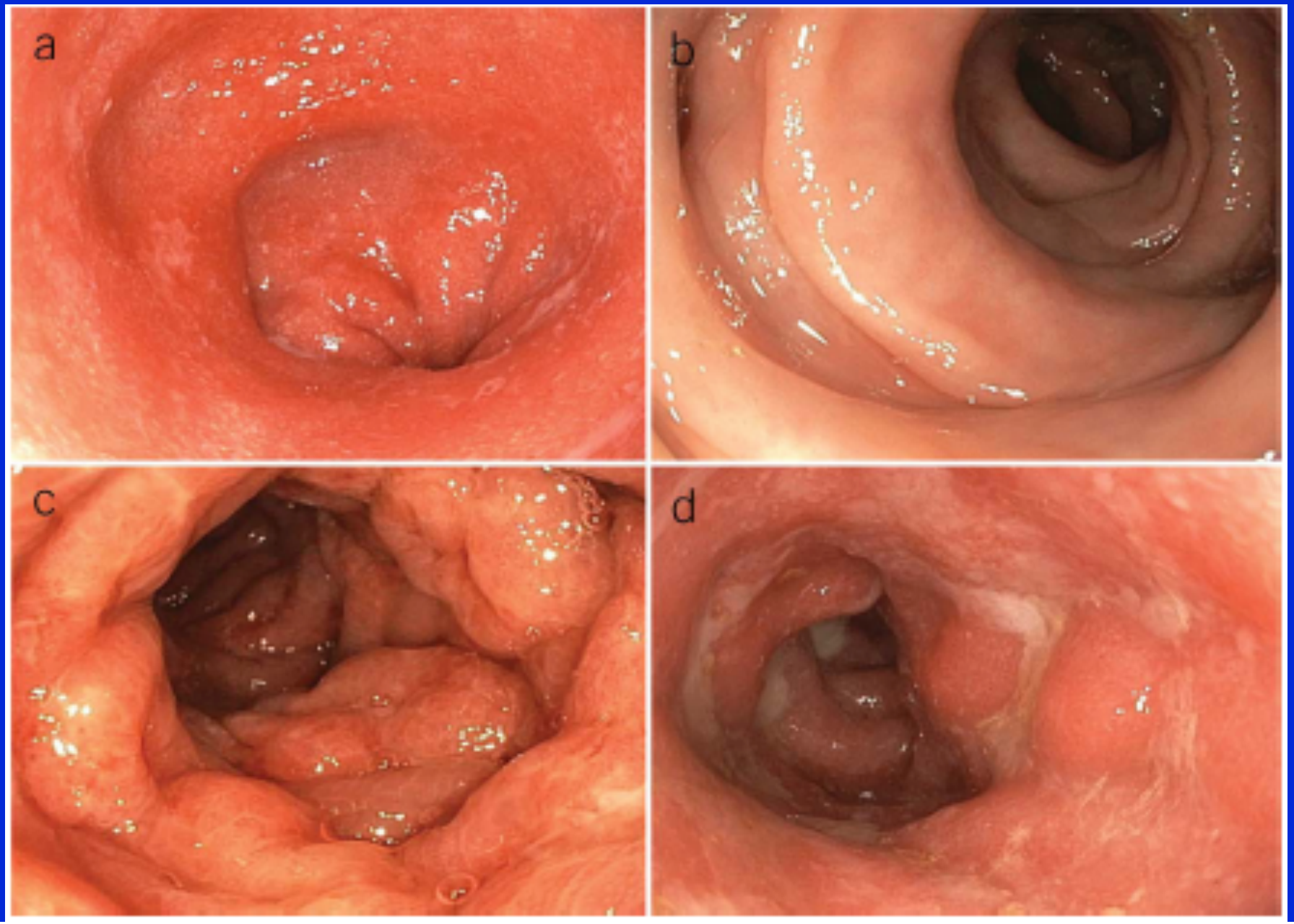
Am J Gastroenterol 2020;115:202–210.

Table 2. Common terminology criteria for adverse events (12)

Grade	Diarrhea	Colitis
1	Increase of <4 stools/d over baseline	Asymptomatic
2	Increase of >4–6 stools/d	Abdominal pain, mucous, and blood in the stools
3	Increase of ≥7 stools/d, incontinence, and limiting self-care activity of daily living	Severe pain, fever, peritoneal signs, and ileus
4	Life-threatening consequences (hemodynamic collapse)	Life-threatening consequences (perforation, ischemia, necrosis, bleeding, and toxic megacolon)
5	Death	Death

Checkpoint Inhibitor–Induced Colitis

Am J Gastroenterol 2020;115:202–210.



Checkpoint Inhibitor–Induced Colitis

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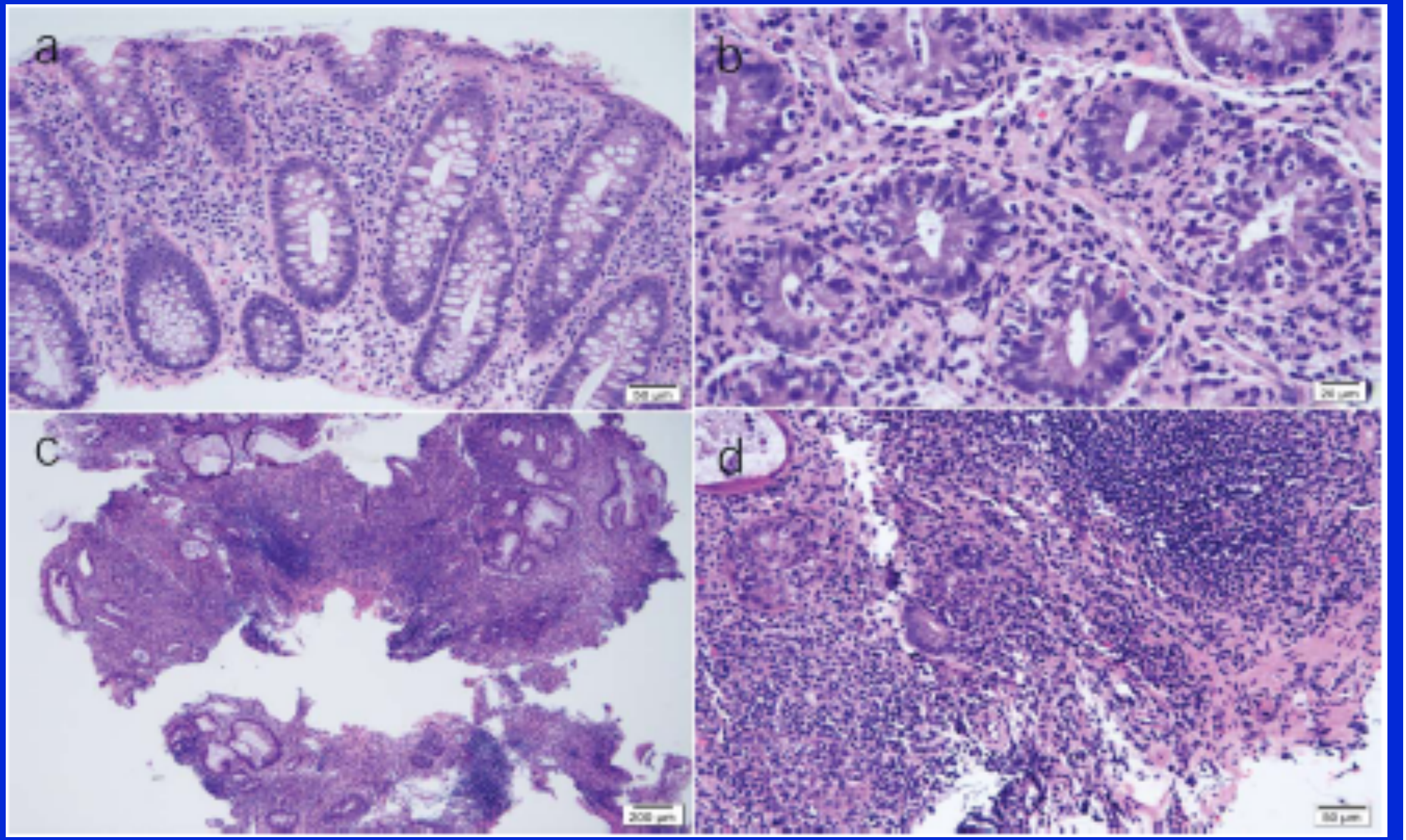


Am J Gastroenterol 2020;115:202–210.

Histological findings

Microscopically, IMC can present as acute colitis, chronic colitis, acute on chronic colitis, or microscopic colitis. The most common histological features are an acute inflammatory infiltrate characterized by marked lamina propria infiltration of neutrophils, lymphocytes, plasma cells, and eosinophils. Foci of neutrophilic cryptitis, crypt abscesses, crypt epithelial cell apoptosis, glandular destruction, and erosions are also evident (29,35,53). Granulomas in association with ruptured crypts have also been reported (62). Diffuse rather than patchy inflammation is seen in 75% of cases (35). Chronic inflammation (basal lymphoplasmacytosis and crypt architectural distortion) with submucosal infiltration has been observed at the initial presentation in nearly half of patients (52,63,64). The presence of acute on chronic inflammation tended to have persistent histological inflammation on follow-up colonoscopy (52). Microscopic colitis (lymphocytic colitis and collagenous colitis) has been reported in approximately 12% of cases with increased lymphocyte and plasma cell infiltrates in the lamina propria and significantly increased intraepithelial lymphocyte infiltrates, particularly in the surface epithelia (29,30,65,66) (Figure 2).

Checkpoint Inhibitor–Induced Colitis

Am J Gastroenterol 2020;115:202–210.

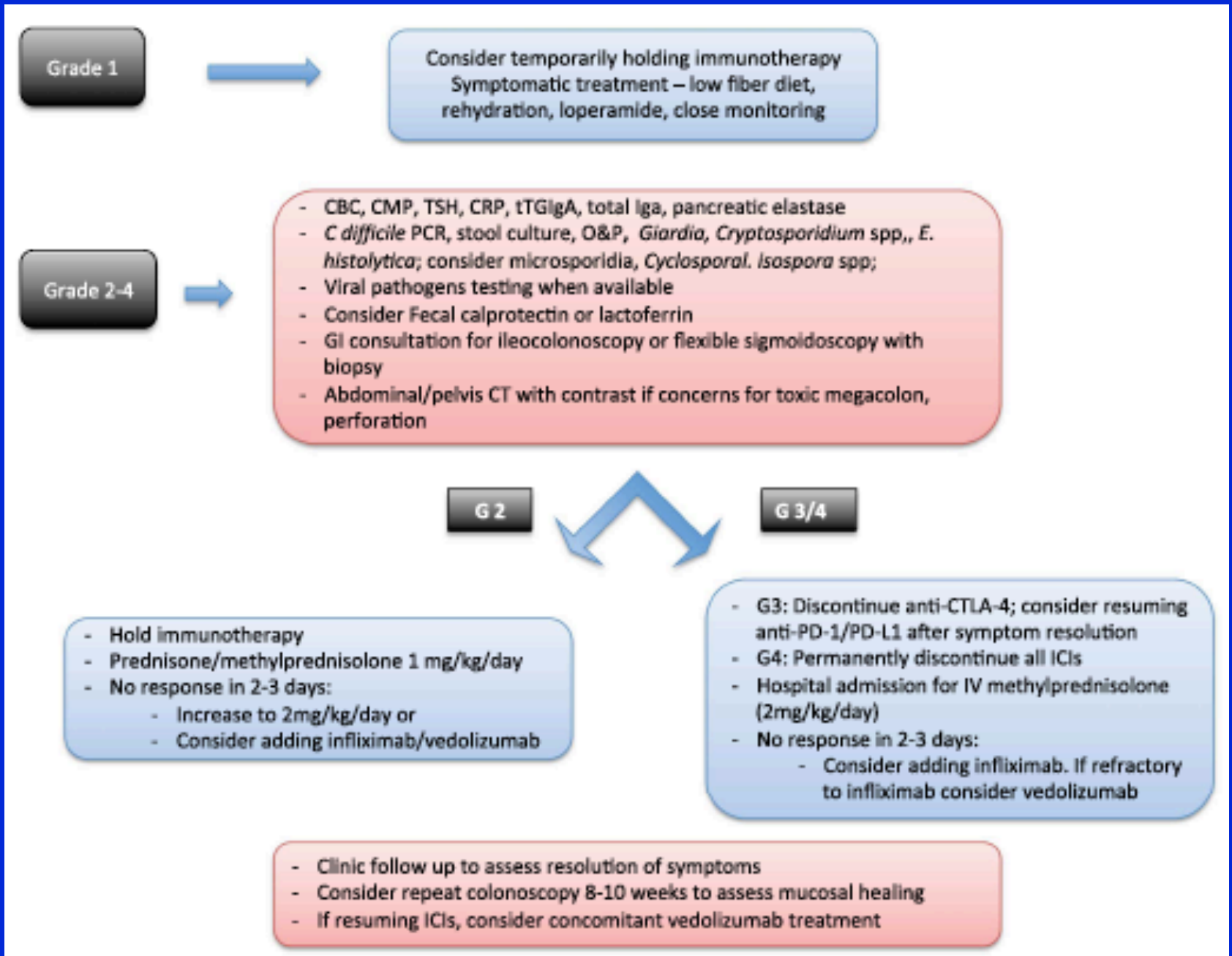


Figure 3. Management of diarrhea/IMC due to ICIs. CBC, complete blood count; CMP, complete metabolic panel; CRP, C-reactive protein; ICI, immune checkpoint inhibitor; IMC, immune-mediated colitis; O & P, ova and parasite; TSH, thyroid function test; tTG IgA, tissue transglutaminase immunoglobulin A.

Immune Checkpoint Inhibitor–Mediated Diarrhea and Colitis: A Clinical Review

Gong et al., JCO 2020

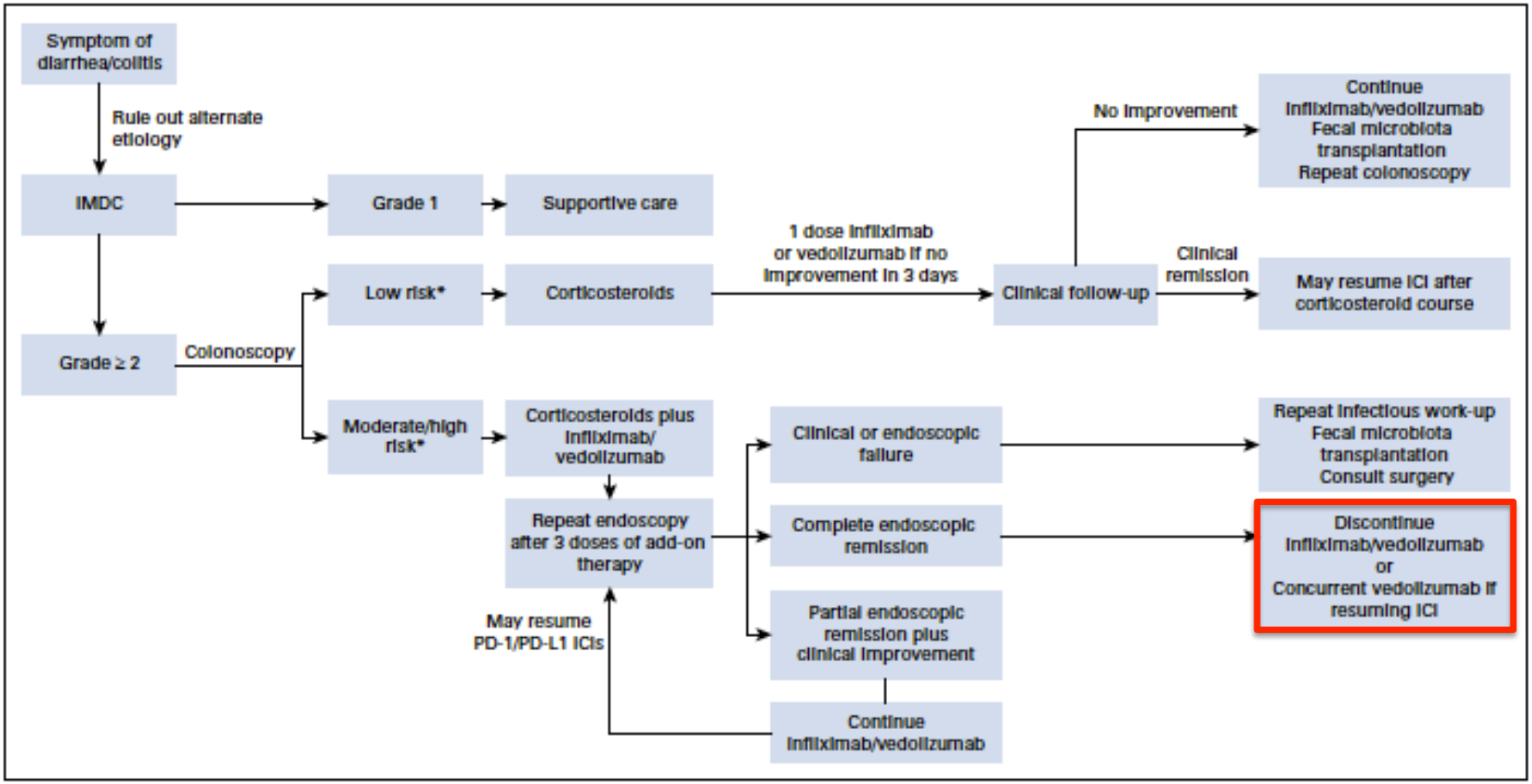
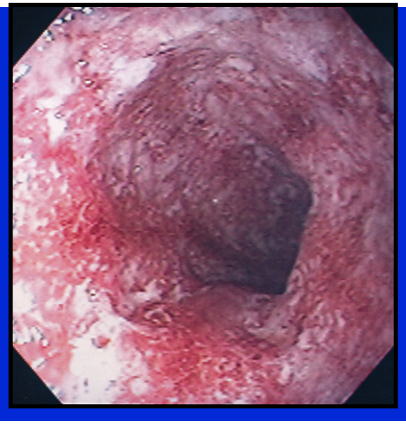


FIG 1. Management algorithm of immune-mediated diarrhea and colitis (IMDC). (*) Low-risk endoscopic features include normal endoscopic and histologic findings. Moderate-risk endoscopic features include normal colon appearance, with pathology showing inflammation; small ulcer < 1 cm, shallow ulcer < 2 mm, and/or number of ulcers < 3; inflammation limited to the left colon only; and nonulcer inflammation. High-risk endoscopic features include large ulcer ≥ 1 cm, deep ulcer ≥ 2 mm, and/or number of ulcers ≥ 3 and extensive inflammation beyond left colon. ICI, immune checkpoint inhibitor; PD-1/PD-L1, programmed cell death 1/programmed cell death-ligand 1.

Ulcerative colitis



Montreal[22]		
Extent*	E1	Ulcerative proctitis
	E2	Left-sided UC (distal to splenic flexure)
	E3	Extensive (proximal to splenic flexure)

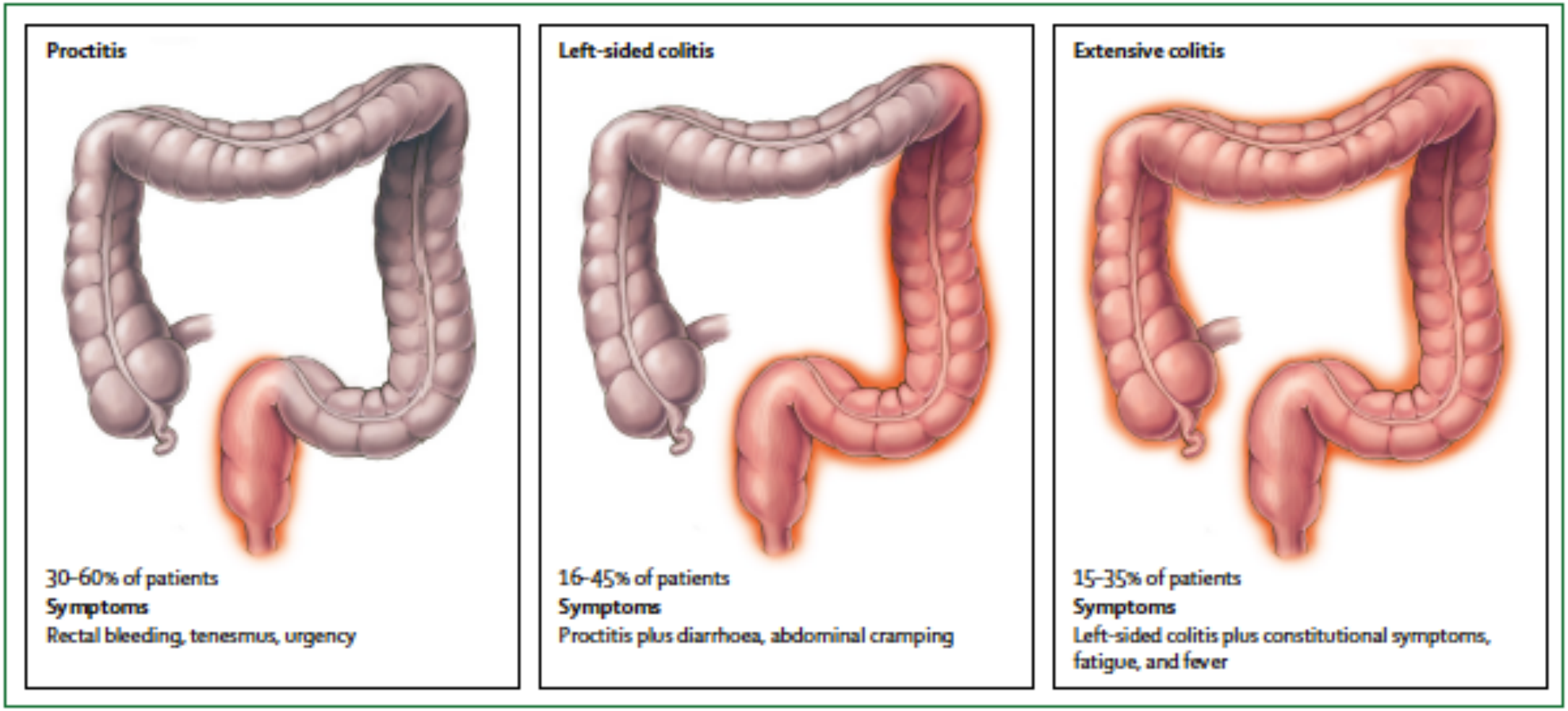


Figure 3: Ulcerative colitis phenotypes by Montreal Classification[21]

Initiales Assessment- Toxisches Megakolon 5% SCU

Panel 1: **Diagnostic criteria for toxic megacolon**

Radiographic evidence of colonic distension
At least three of the following:
Fever >38°C (101·5°F)
Heart rate >120/min
Neutrophilic leucocytosis >10·5×10⁹/L
Anaemia
In addition to the above, at least one of the following:
Dehydration
Altered consciousness
Electrolyte disturbances
Hypotension

JALAN`S CRITERIA

Sheth et al., Lancet 1998;
Gan et al., AJG 2003;
Panes et al., ECCO Imaging Consensus JCC 2013;

mid colon transversum dilatation **> 5,5cm**

Inoue et al., Internal Medicine 2012

Table 1. Causes and Associations With Toxic Megacolon

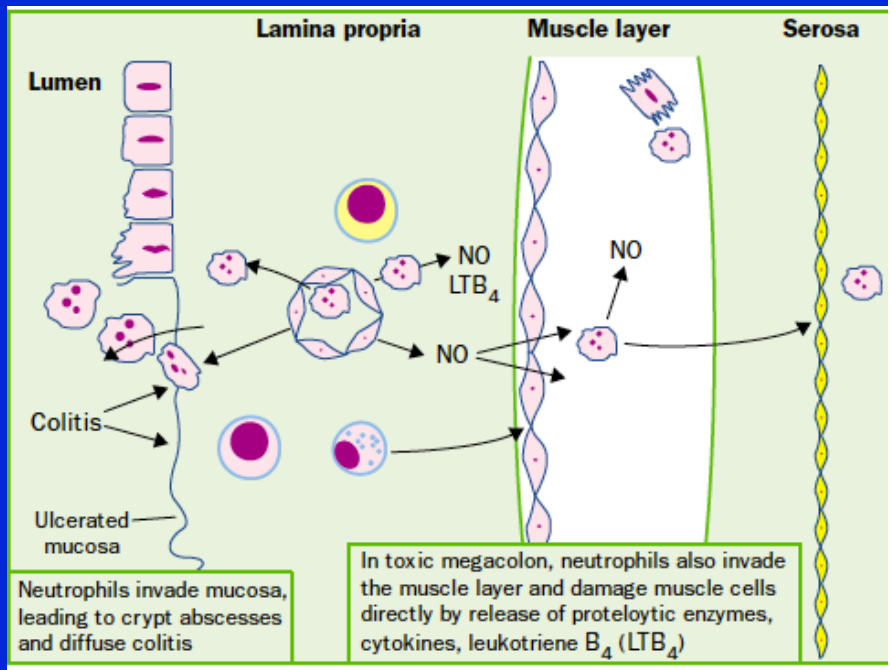
Inflammatory
- Ulcerative colitis
- Crohn's disease

Infectious
- *Clostridium difficile*
- Salmonella, Shigella, Yersinia, Camplyobacter
- Cryptosporidium
- Entameba
- Cytomegalovirus

Ischemia

Malignancy
- Kaposi's sarcoma

Potential triggers and exacerbating factors
- Hypokalemia, hypomagnesemia
- Barium enema
- Discontinuation of steroids
- Narcotics
- Anticholinergics
- Chemotherapy
- Colonoscopy



Pathogenesis of toxic megacolon

Crohn's disease

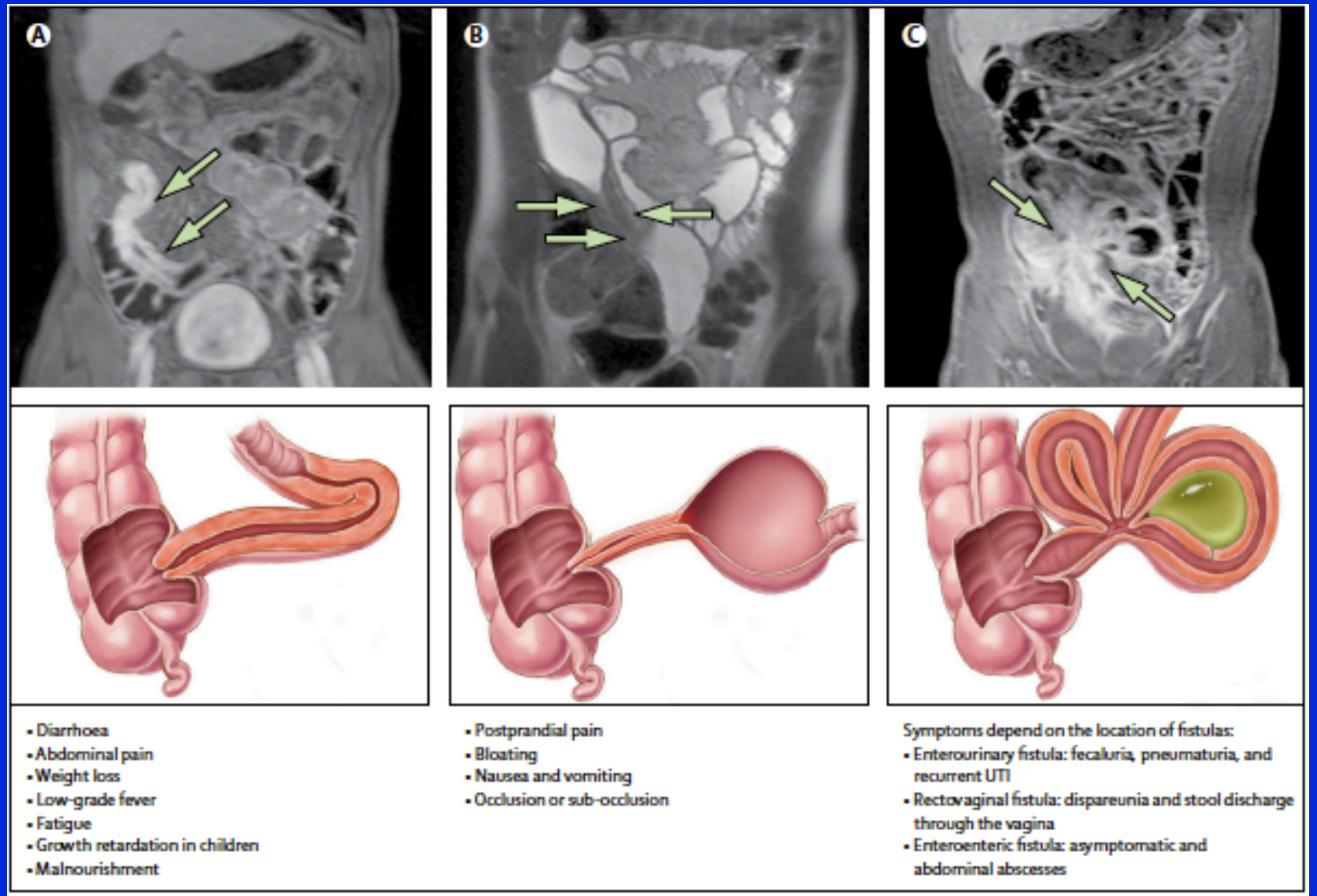
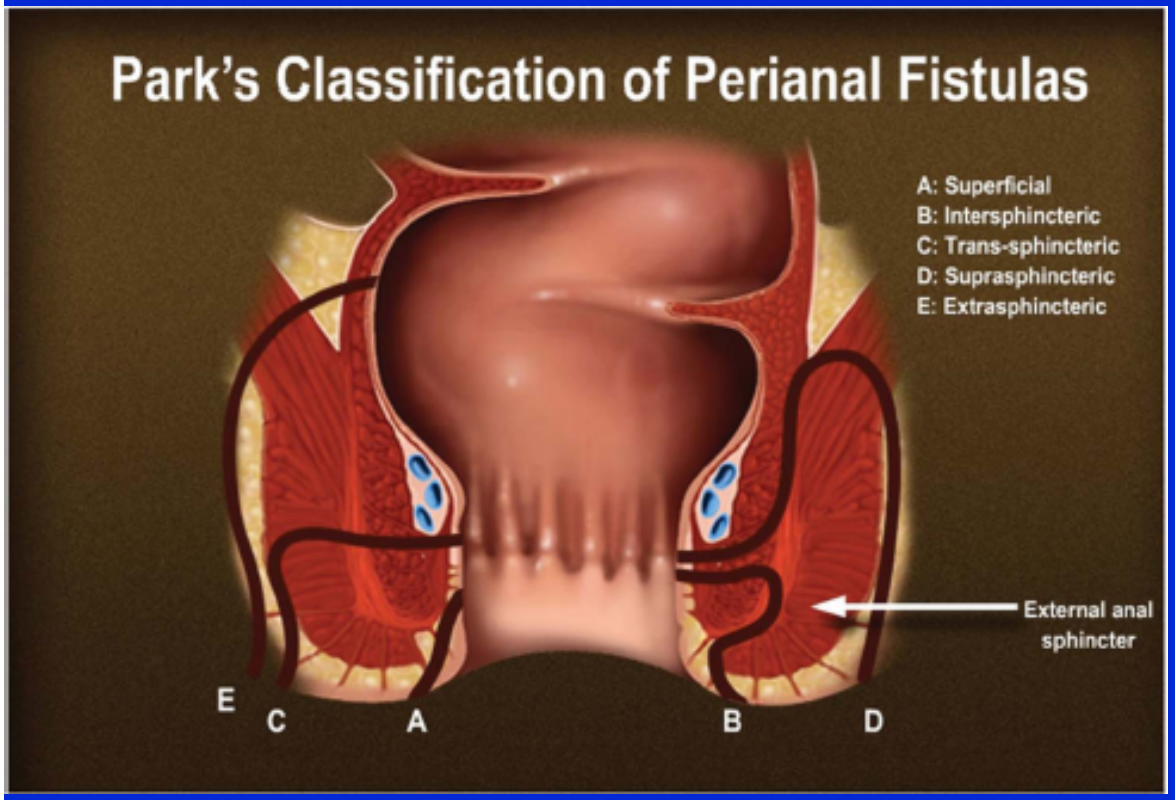
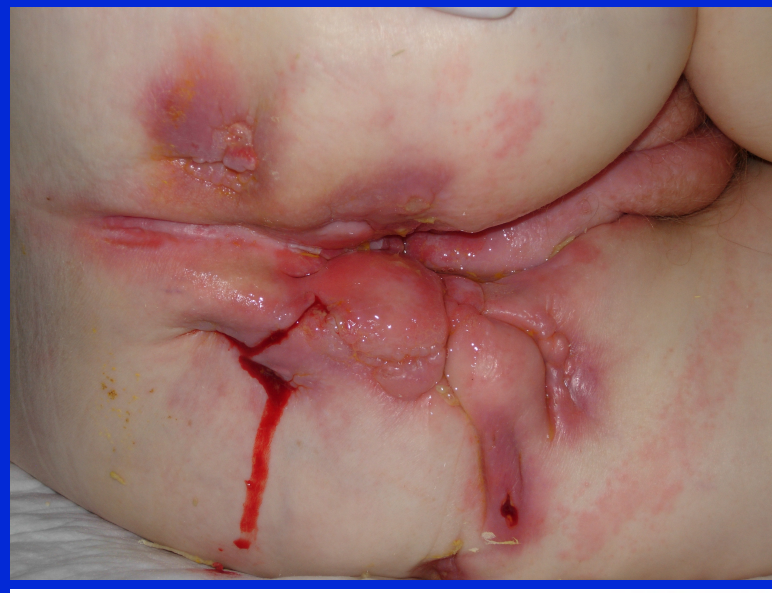


Figure 2: Behaviour of CD as per Montreal classification represented in MRE and illustrated with typical symptoms

Guidelines for the Multidisciplinary Management of Crohn's Perianal Fistulas: Summary Statement





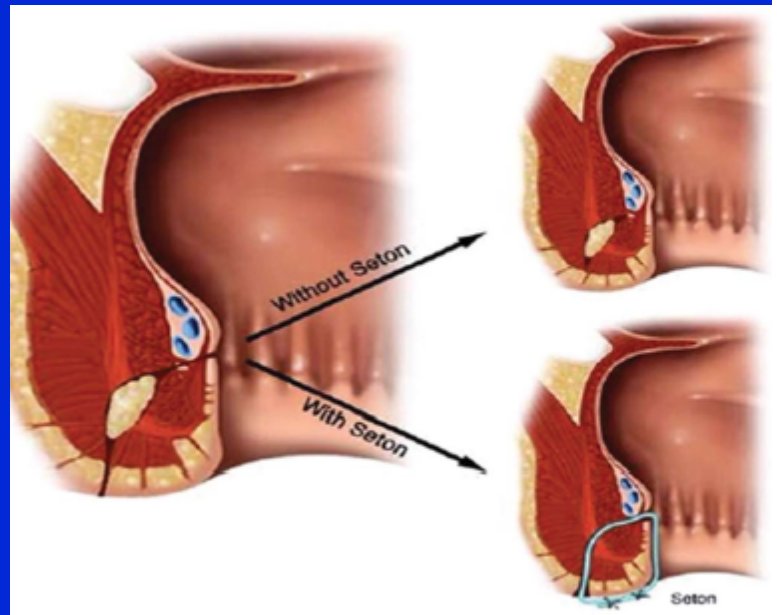


FIGURE 6. How setons prevent premature fistula closure.

SCHWARTZ et al., IBD 2015

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