EIM

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Patient Case

28-year-old woman

- Abdominal pain for 3 months
- 4 bloody bowel movements/day for 8 weeks
- Stool cultures and parasites (–)
- *C. diff* toxin (–)
- Empiric treatment with metronidazole and ciprofloxacine – no effect
- Peripheral arthropathy with involvement of the small joints (>5, MCP and PIP) for 10 months
- Aphthous stomatitis for 5 years

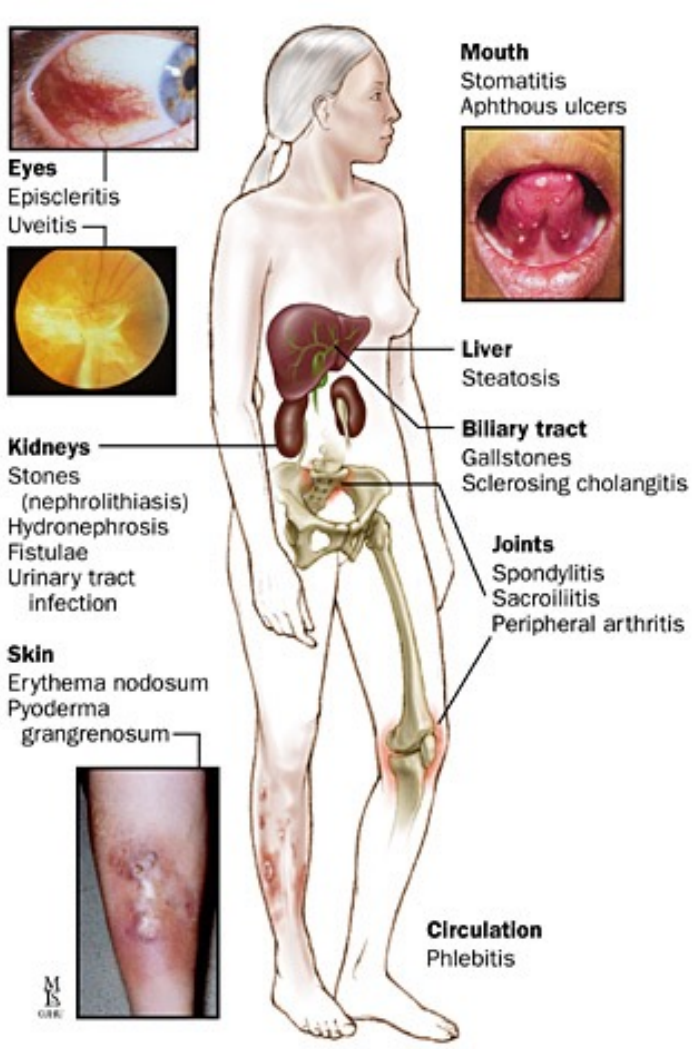
Physical examination

- Slightly tender abdomen
- Ulcers on the lower left leg for 8 months

Lab:

- WBC 8.8G/L
- Hb 11.1g/L
- PLT 386G/L
- Normal LFTs, CRP X3

EIMs vs comorbidities in IBD



System	A. Extraintestinal manifestations [multifocal inflammation]	B. Complications of IBD and its treatment	C. Associated conditions with uncertain mechanism
Joints and bones	Spondyloarthritis	Metabolic bone disease/ osteoporosis—[drug or nutritionally induced]	Non-inflammatory arthralgia
Eye	Uveitis Episcleritis Scleritis	Drug-induced cataracts and other drug-induced and nutritional eye disease [see supplementary Figure 4]	
Oral, aural and nasal	Oral CD Orofacial granulomatosis Metastatic CD		Sensorineural hearing loss
Skin	Erythema nodosum Pyoderma gangrenosum Sweet syndrome Metastatic CD	Drug-induced skin disease [e.g. anti-TNF–induced psoriasis, DILE] Drug-induced skin cancer Drug hypersensitivity	Vitiligo Psoriasis Eczema Epidermolysis bullosa acquisita Cutaneous polyarteritis nodosa Hidradenitis suppurativa
Urogenital	Metastatic CD	Nephrolithiasis Amyloidosis Drug-induced tubulo-interstitial nephritis	
Hepato-pancreato-biliary	PSC	Portal vein thrombosis Hepatic amyloidosis DILI Drug-induced pancreatitis	Autoimmune hepatitis Granulomatous hepatitis Autoimmune pancreatitis
Neurological		Peripheral neuropathy [drug or nutritionally induced] Venous sinus thrombosis Stroke	Central demyelination
Cardiovascular		Ischaemic heart disease Cerebrovascular accident Mesenteric ischaemia	
Pulmonary		Drug-induced lung fibrosis	Inflammatory bronchial and parenchymal lung disease, including asthma, bronchiectasis, and interstitial pneumonias
Coagulopathy		Venous thromboembolism	
Endocrine		Drug-induced Cushing's and Addison syndromes Drug-induced diabetes	Type 1 diabetes Autoimmune thyroid disease
Infection		Infections including systemic and local secondary to immunosuppression; septic complications of IBD or surgery	

Arias Vallejo E. Rev Esp Enferm Apar Dig. 1972 Nov 1;38(5):623
Hedin CRH et al. J Crohns Colitis. 2019 Apr 26;13(5):541-554

Extraintestinal manifestations vs. complications vs. associations

Extraintestinal manifestations
"*inflammation with different location*"

Arthritis, spondylarthropathy
EN, PG
Uveitis
PSC

Extraintestinal complications
"*consequence of inflammation*"

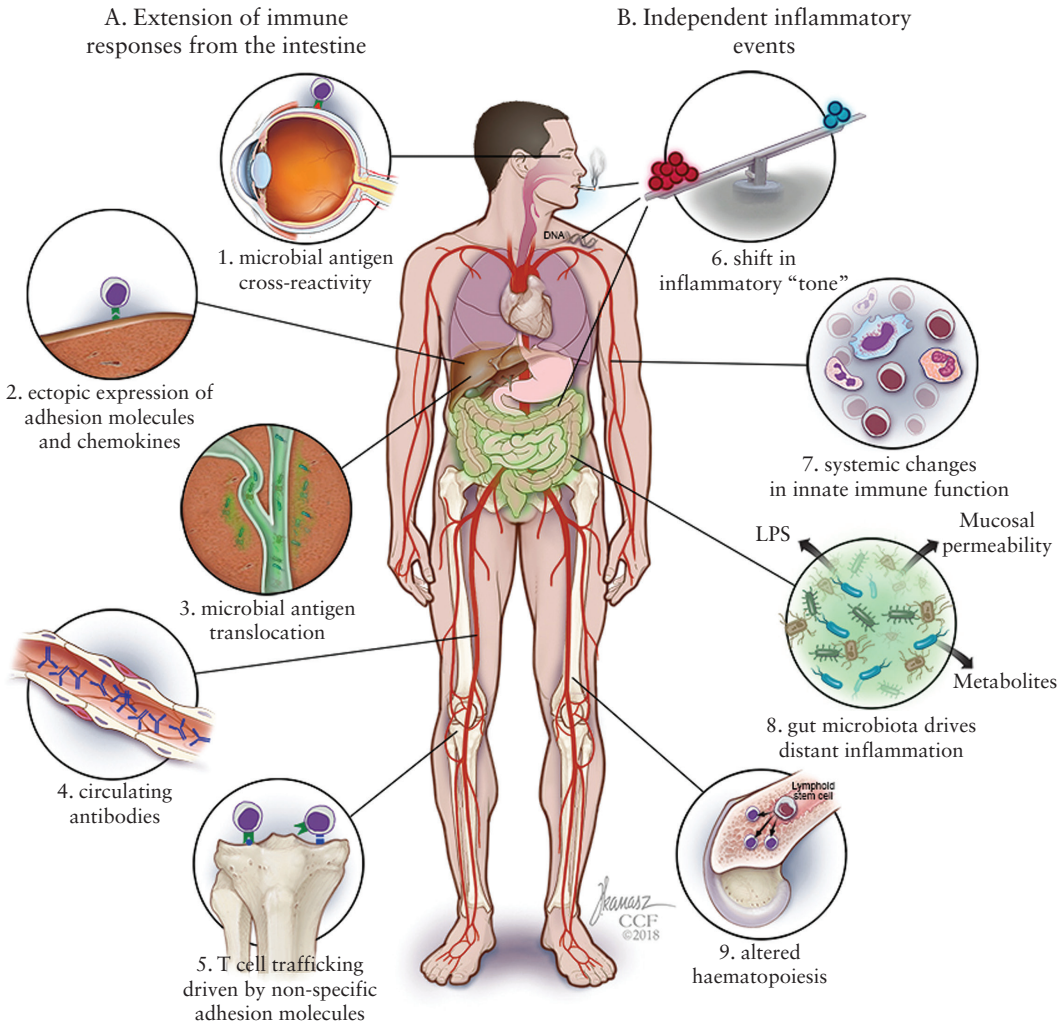
Osteoporosis
Kidney stones
Gallstones
Peripheral neuropathies

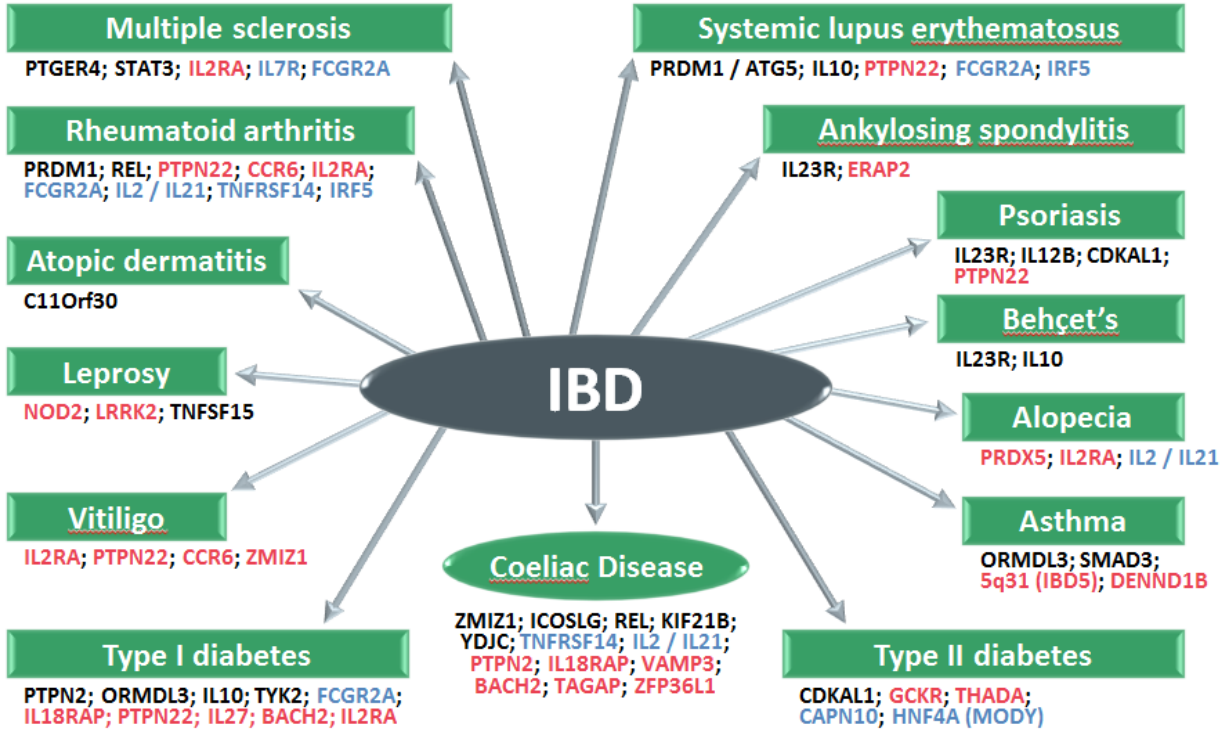
Associated conditions
"*uncertain mechanism*"

Psoriasis
Vitiligo
DMT1
Autoimmune thyroid disorders

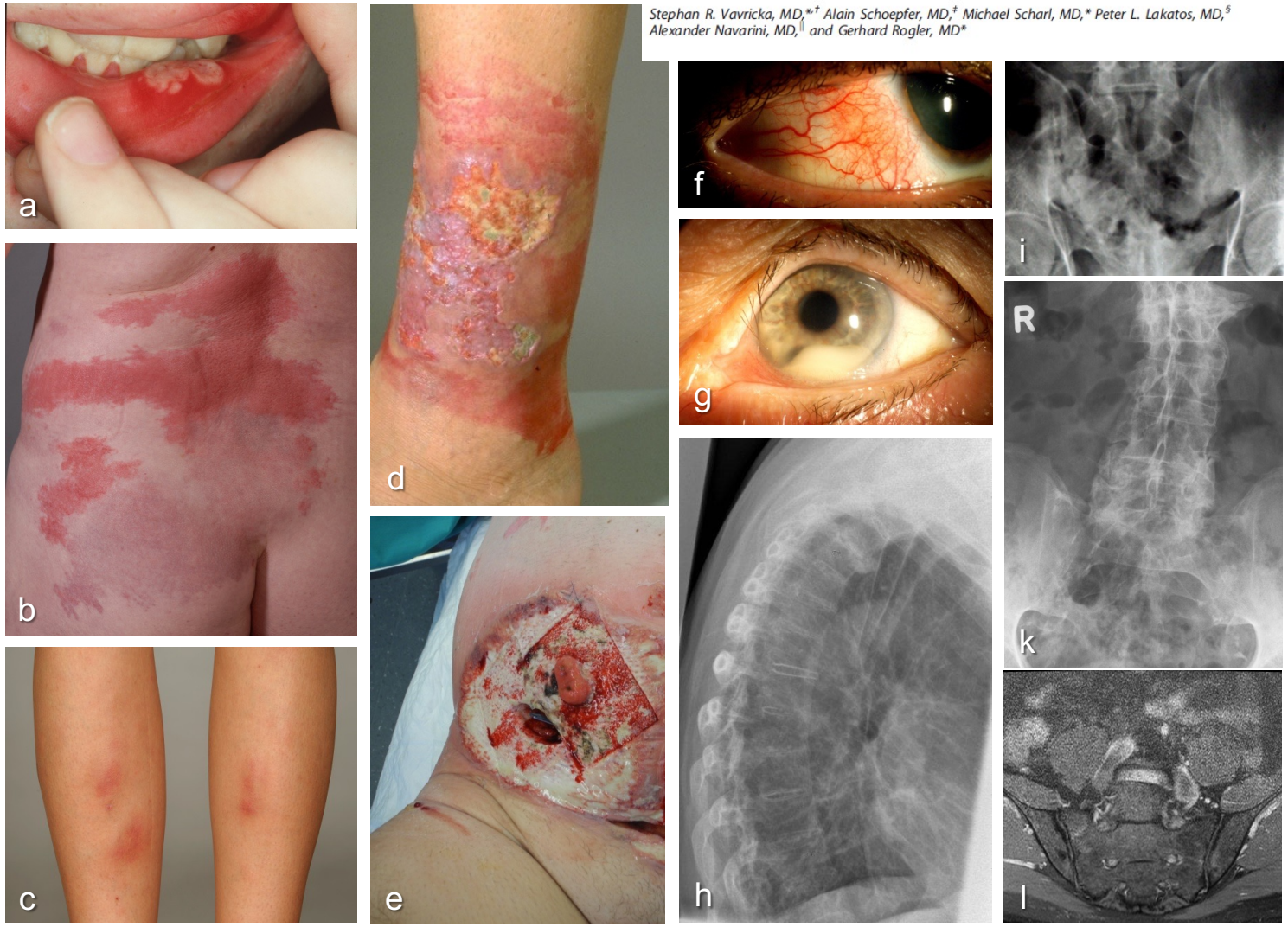
Hedin CRH et al. J Crohns Colitis. 2019 Apr 26;13(5):541-554

Pathomechanisms and genetic background





Hedin CRH et al. J Crohns Colitis. 2019 Apr 26;13(5):541-554
Lees et al. Gut 2011;60:1739–1753



IBD can cause a variety of symptoms, both in the gut and out of the gut

When the disease affects other parts of the body, this is known as an extraintestinal manifestation (EIM)

Between 6–47% of IBD patients are affected by EIMs

50% of IBD patients experience EIMs during disease history

A multidisciplinary approach is often needed

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92

Risk factors in IBD

Patients with CD with active disease were found to suffer significantly more frequently than patients with inactive disease from:

- Peripheral arthritis (45% vs 31%; p=0.016)
- Uveitis (12% vs 5%; p=0.024)
- Aphthous stomatitis (17% vs 9%; p=0.026)

Table 2: EIM in CD patients in relation to disease activity

	Inactive CD	Active CD	P value
Activity: frequency	498 (85.9%)	82 (14.1%)	<0.001
EIM frequency	201/498 (40.4%)	48/82 (58.5%)	0.003
EIM type and frequency			
• Arthritis	156/498 (31.3%)	37/82 (45.1%)	0.016
• Uveitis	26/498 (5.2%)	10/82 (12.2%)	0.024
• Pyoderma gangrenosum	7/498 (1.4%)	2/82 (2.4%)	0.317
• Erythema nodosum	34/498 (6.8%)	2/82 (2.4%)	0.212
• Aphthous stomatitis	43/498 (8.6%)	14/82 (17.1%)	0.026
• Ankylosing spondylitis	27/498 (5.4%)	6/82 (7.3%)	0.446
• Primary scleros. cholangitis	2/498 (0.4%)	2/82 (2.4%)	0.098
• Psoriasis	11/498 (2.2%)	0/82	0.378

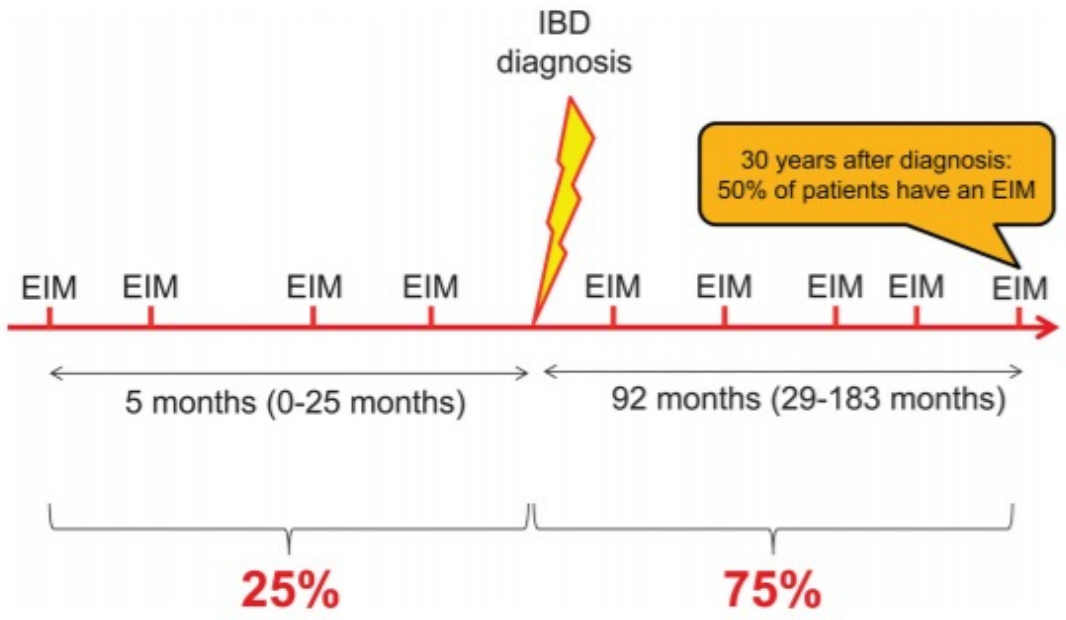
Vavricka SR et al. Am J Gastroenterol. 2011 Jan;106(1):110-9

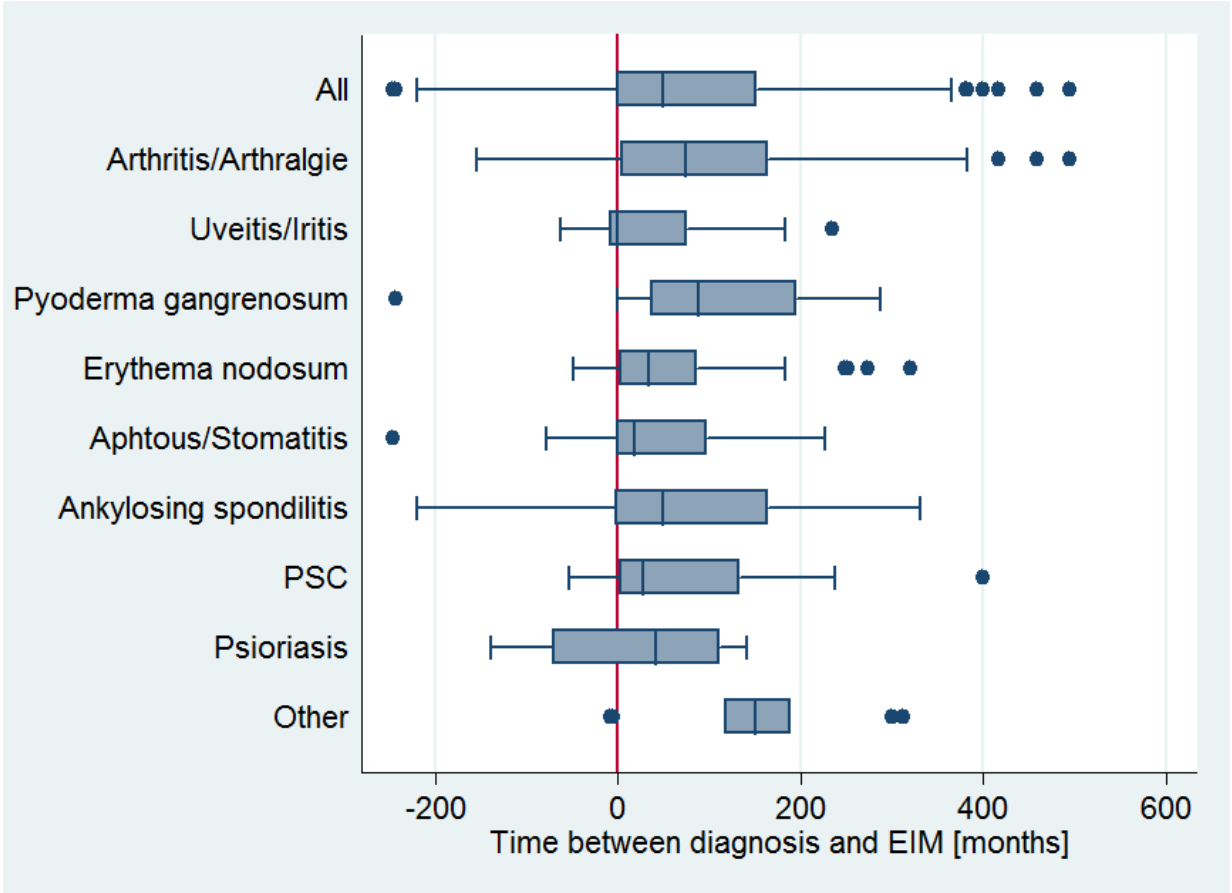
EIMs and IBD activity

Extra-intestinal manifestation	Parallel course of IBD	Separate course of IBD	May or may not parallel disease activity
Axial arthropathy		✓	
Peripheral arthropathy	✓ (pauciarticular)	✓ (polyarticular)	
Erythema nodosum	✓		
Pyoderma gangrenosum			✓
Sweet's syndrome	✓		
Oral aphtous ulcers	✓		
Episcleritis	✓		
Uveitis			✓
Primary sclerosing cholangitis			✓

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92

Chronological appearance of EIMs in IBD patients





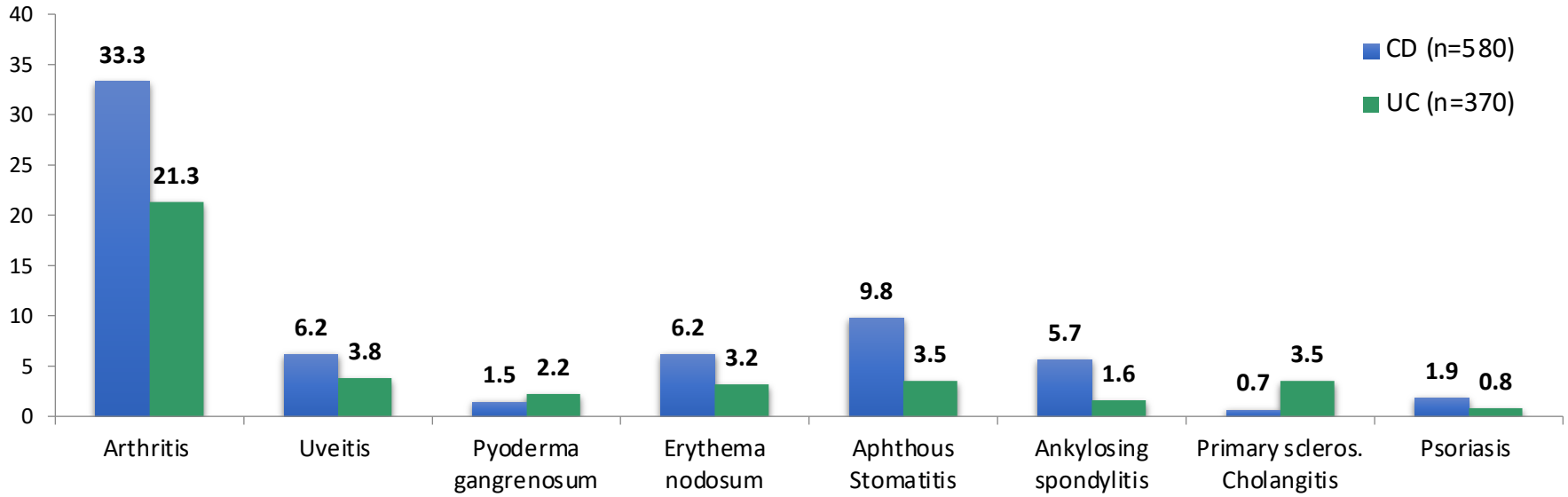
Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92
Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1794-800

Epidemiology of EIMs

Frequency of EIMs in IBD

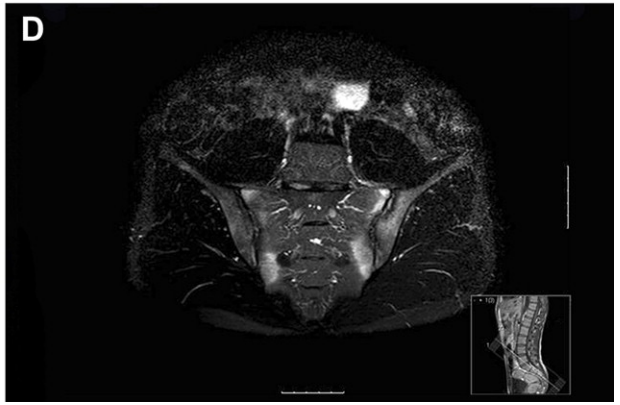
Frequency and Risk Factors for Extraintestinal Manifestations in the Swiss Inflammatory Bowel Disease Cohort

Stephan R. Vavricka, MD[1,6], Lionel Brun[1,6], Pierluigi Ballabeni[2], Valérie Pittet[2], Bettina Mareike Prinz Vavricka, MD[3], Jonas Zeitz, MD[1], Gerhard Rogler, MD[1], Alain M. Schoepfer, MD[4,5] and the Swiss IBD Cohort Study Group[7]



Vavricka SR et al. Am J Gastroenterol. 2011 Jan;106(1):110-9

Rheumatological EIMs



	Pauciarticular (<5 joints)		Polyarticular (≥ 5 joints)		Axial SpA	
	CD	UC	CD	UC	CD	UC
Frequency	10-20%	5-14%	10-20%	5-14%	5-22%	2-6%

Brakenhoff L et al. Gut. 2011;60:1426-35.
Arvikar S et al. Curr Rev Musculoskelet Med. 2011;4:123-131
Bourikos L et al. Inflamm Bowel Dis. 2009;14:1915-1924.
Ardizzone S et al. Dig Liv Dis. 2008;40S:S253-S259
Larsen S et al. Annals of Medicine. 2010;42:97-114.

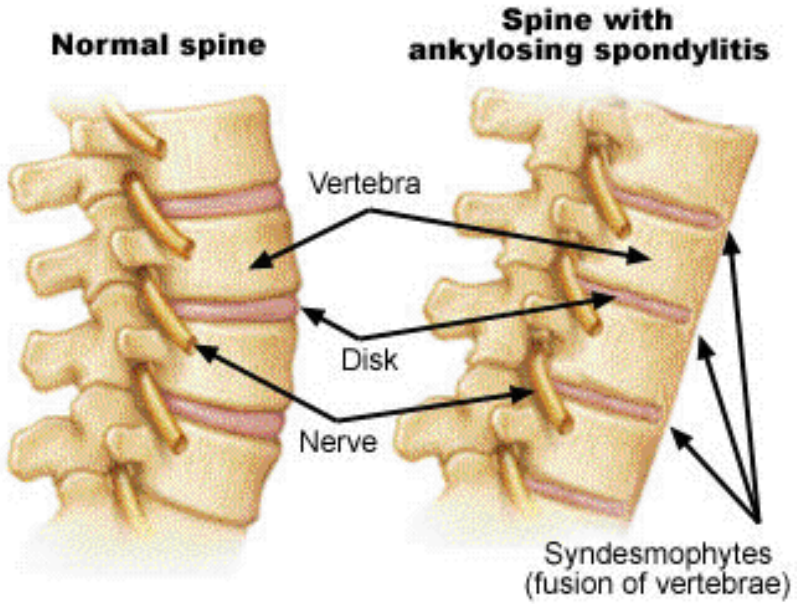
Peripheral arthritis: Type 1 vs. type 2

Type 1 (Pauciarticular)	Type 2 (Polyarticular)
Prevalence in UC, 35%	Prevalence in UC, 24%
Prevalence in CD, 29%	Prevalence in CD, 20%
Less than 5 joints	Five or more joints
Mainly large joints	Mainly small joints
Knee → ankle → wrist → elbow → MCP → hip → shoulder	NCP → knees → PIP → wrist → ankle → ellbow → shoulder
Asymmetric involvement	It can be symmetric or asymmetric, may be erosive
Parallels intestinal disease activity	Clinical course independent of IBD activity
Self-limited episodes that last <10 wk	Persistent inflammation for months or even years
High frequency of other EIM (erythema nodosum and uveiitis)	Associated only with uveitis
Associated with HLA-B27, B35 and DR103	Associated with HLA-B44

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92

Axial spondylarthropathy

- **Axial SpA with IBD**:
  - Onset occurs at any age
  - 1:1 male:female ratio
  - 25-78% of IBD patients with AS are HLA-B27-positive
- **Idiopathic AS**:
  - Onset after age 40 is rare
  - 2.5:1 male: female ratio
  - HLA-B27+ in >90%



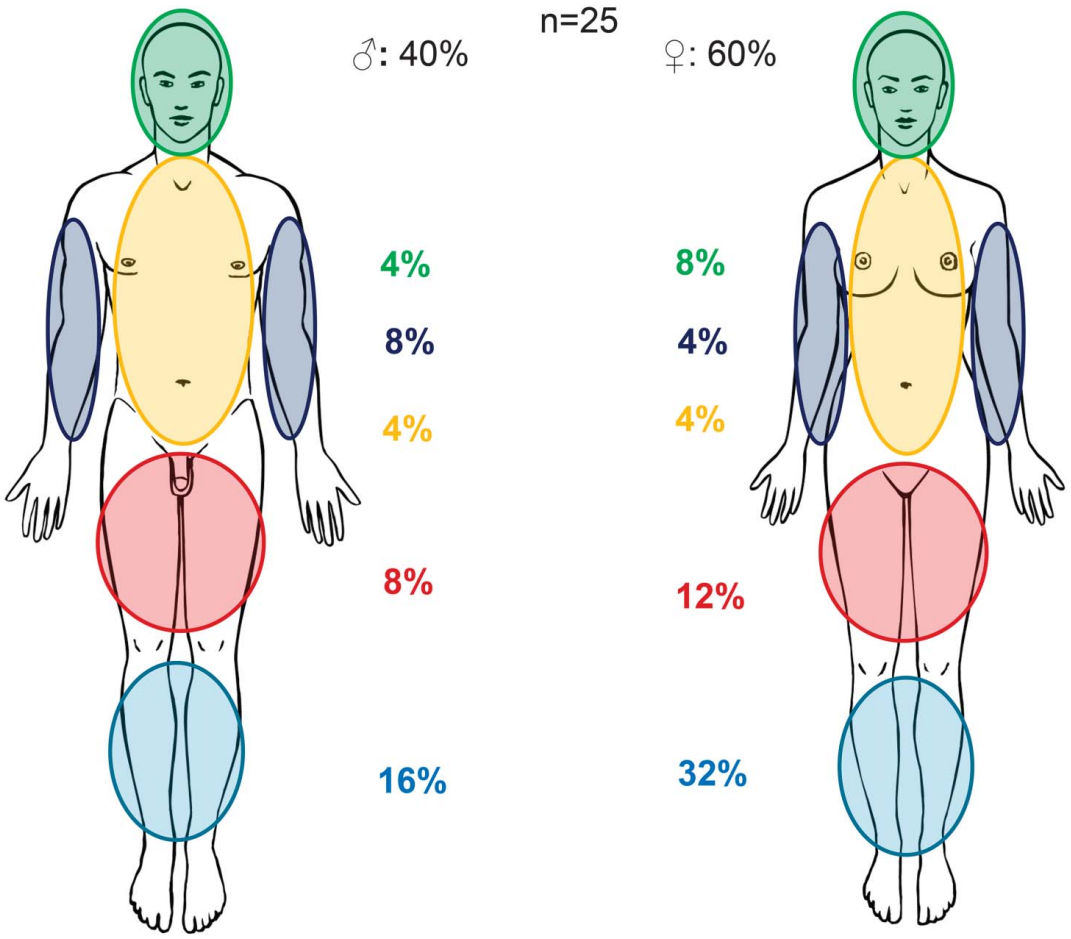
- Partial or total proctocolectomy can induce remission of peripheral arthritis in UC patients, but those surgeries have no effect on axial involvement
- In contrast, colonic resection in CD does not appear to affect the course of arthritis

Bourikas L, et al. Inflamm Bowel Dis. 2009;14:1915-1924.
Brakenhoff L, et al. Gut. 2011;60:1426-35.
Larsen S, et al. Annals of Medicine. 2010;42:97-114.

Cutaneous EIMs

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92

Pyoderma gangrenosum



Clinical characteristics

- Necrotic ulcers developing in days, usually sterile

Location:

- PG: Mostly legs but also peristomal
- Pyodermatitis/Pyostomatitis vegetans: inguinal-axillar / oral

Occurrence:

- 5–12% in UC, 1–2% in CD

Timing:

- PG does not mirror IBD activity

Gender:

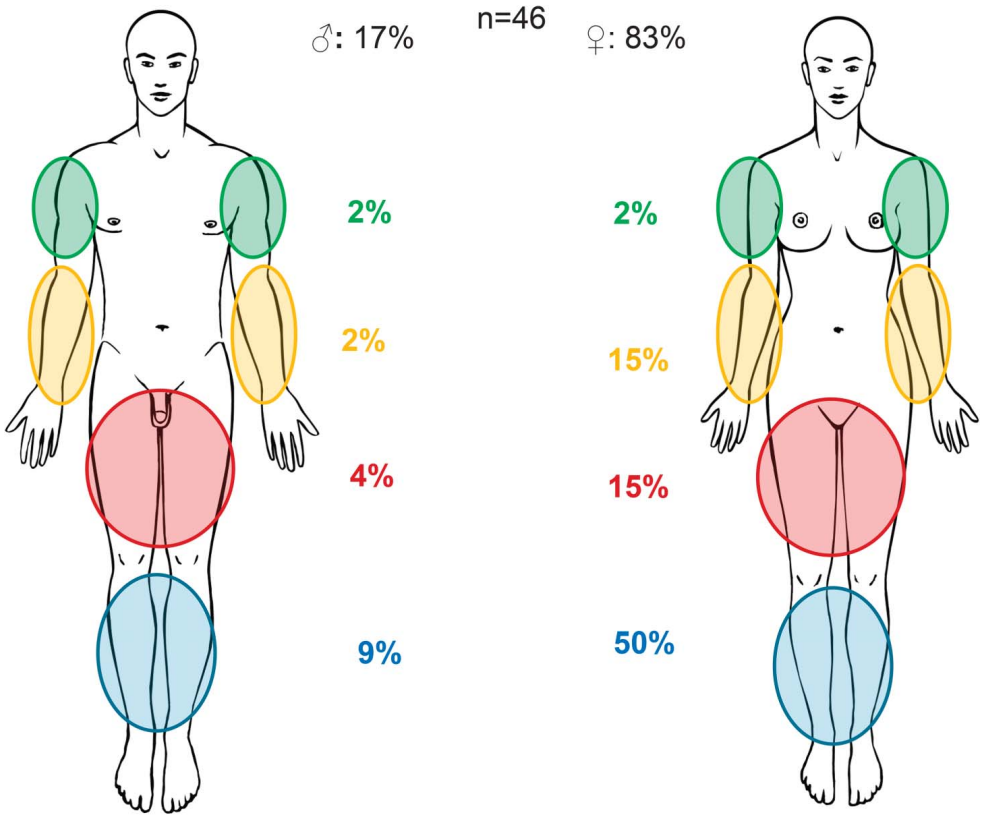
- F > M

Associated diseases:

- UC/CD 20-30%
- Arthritis 20%
- Hemato-oncological 15–25%
- Monoclonal gammopathy 15%
- Idiopathic 30–50%

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92
Greuter T et al. Clin Rev Allergy Immunol. 2017 Dec;53(3):413-427

Erythema nodosum



Clinical characteristics

- Red elevated nodules
- Painful

Location:

- Lower limb

Occurrence:

- 3–10% in UC, 6–15%in CD

Timing:

- EN parallels IBD activity

Gender:

- F > M

Associated diseases:

- Infections (Streptococcus, Yersinia, TBC)
- Malignancies (Hodgkin, Non-Hodgkin)
- IBD
- Behçet's disease
- Sarcoidosis
- Drugs (sulfonamides, oral contraceptives)
- Pregnancy

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92
Greuter T et al. Clin Rev Allergy Immunol. 2017 Dec;53(3):413-427

Aphthous stomatitis

Clinical charateristics:

- Shallow whitish-yellow ulcers with erythematous halo

Location:

- Mostly lower lips and buccal mucosa

Occurrence:

- 4% in UC, 10% in CD

Gender:

- F > M

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92
Greuter T et al. Clin Rev Allergy Immunol. 2017 Dec;53(3):413-427

Psoriasis

Clinical characteristics:

- Sharply demarcated erythematous plaques

Location:

- Elbows, knees, scalp, trunk

Occurrence:

- 7–11% in IBD, 5.7% in UC, 11.2% in CD

Genetics:

- Overlap with CD

Risk:

- Increased risk for other autoimmune pathologies if psoriasis and IBD

Vavricka S et al. Inflamm Bowel Dis. 2015 Aug;21(8):1982-92
Greuter T et al. Clin Rev Allergy Immunol. 2017 Dec;53(3):413-427

Patient Case

42-year old journalist with CD,
4 weeks after starting anti-TNF

Is it psoriasis?

Anti-TNF induced skin lesions

Clinical characteristics

- Psoriasiform vs eczematiform

Location:

- Hands, feet, trunk (rather flexures than extensors)

Occurrence:

- Up to 5–10%

Timing:

- Months to years during anti-TNF
- No association with intestinal disease activity

Treatment:

- Topical steroids, MTX, stop anti-TNF, switch to another IBD treatment, ustekinumab

Greuter T et al. Clin Rev Allergy Immunol. 2017 Dec;53(3):413-427

Ocular EIMs

Scleritis

2–17%

CD > UC

Episcleritis

2–18%

UC > CD

Anterior uveitis

2–29%

UC > CD

F > M

1st Pattern: Localization of Inflammation	Most Frequent Diagnosis	Likelihood, %	2nd Pattern: Laterality	Likelihood, %
Anterior	Ankylosing spondylitis	9.5	Alternating	27.7
			Unilateral	9.0
			Bilateral	6.6
	Herpes	8.5	Unilateral	12.4
			Bilateral	2.1
	Juvenile idiopathic arthritis	6.8	Bilateral	11.8
			Unilateral	4.3
	Undifferentiated SpA	3.9	Unilateral	3.9
			Bilateral	3.8
	Sarcoidosis	3.3	Bilateral	5.2
			Unilateral	2.2
	Inflammatory bowel disease	2.0	Bilateral	3.5
			Unilateral	1.2

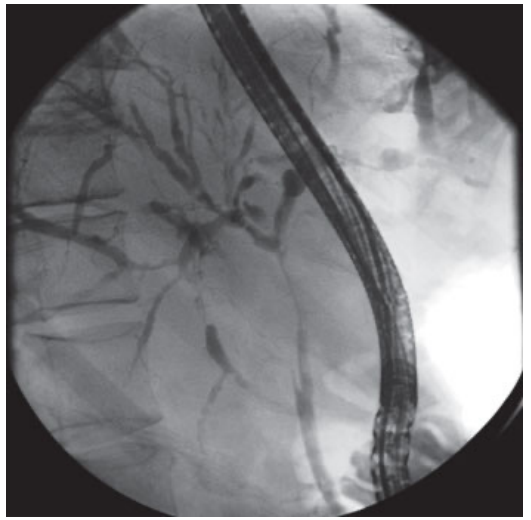
Roithfuss K et al. World J Gastroenterol. 2006;12(30):4819-4831
Ardizzone S et al. Dig Liver Dis. 2008:40S:S253-250.
Scherer J. Drugs of Today. 2009;45(3):227-41
Larsen S et al. Annals of Medicine. 2010;42:97-114.
Levine J et al. Gastroenterol Hepatol. 2011;7(4):235-41.
Jakob E et al. J Rheumatol. 2009;36:127-136
http://www.hopkinsmedicine.org/wilmer/conditions/scleritis.html
http://images.rheumatology.org/viewphoto.php?albumId=75692&imageId=2862497; Anterior Uveitis Image: http://www.lookfordiagnosis.com/mesh_info.php?term=Uveitis%2C+Anterior&lang=1

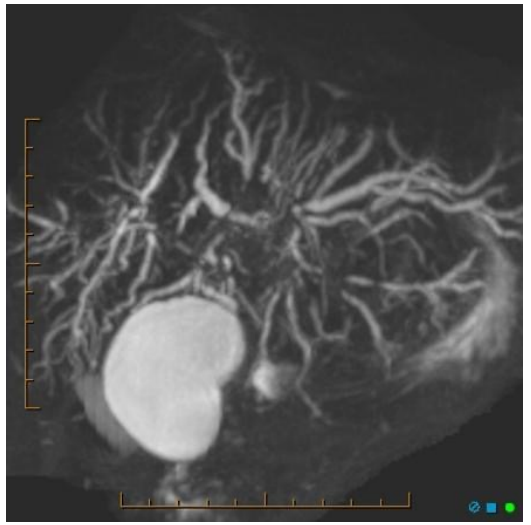
Hepatobiliary EIMs

- Auto-immune liver disease:
  - **Primary sclerosing cholangitis (PSC)**
  - Auto-immune hepatitis
  - Primary biliary cholangitis
- Steatosis
- Cholelithiasis
- (IBD medication related liver function abnormalities)

PSC

- UC > CD
- M > F
- Major risk factor for: Cholangiocarcinoma (10–15%), colon cancer
- Diagnosis with MRI (MRCP) – ERCP
- **CAVE dominant strictures**
- 5% in UC and 3%–4% in CD
- 90% of PSC patients have IBD
- Elevated serum alkaline phosphatase found in 5% of UC patients (85% of whom had PSC on ERCP in a Swedish study)
- More common in men with pancolitis
- Common symptoms include pruritus and lethargy but 40%–50% are asymptomatic at time of diagnosis (at mean age 40–45)

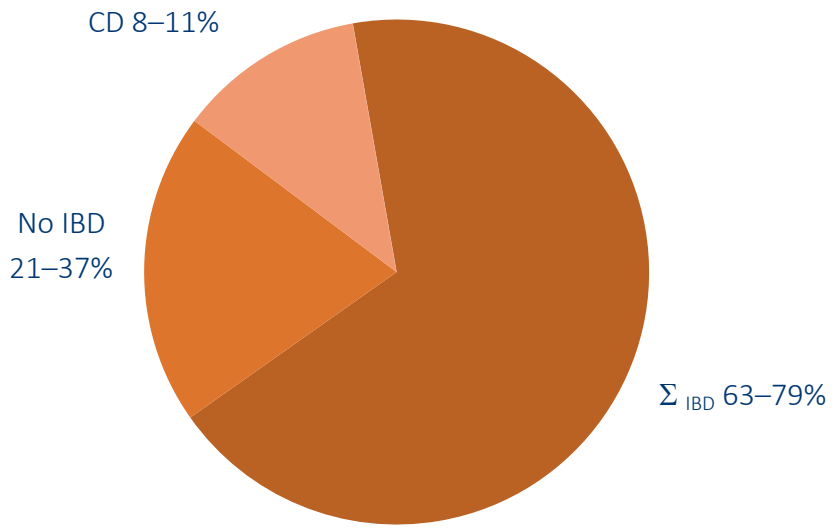




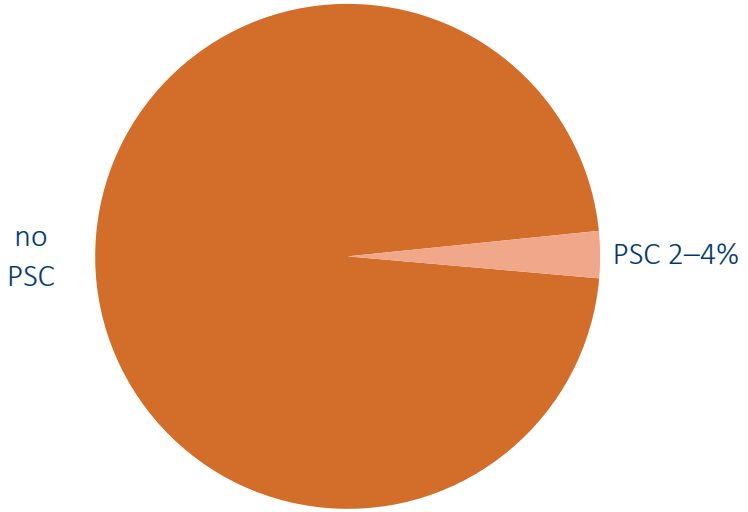
Olsson R et al. Gastroenterology. 1991;100(5 Pt 1):1319-1323.
Saich R, Chapman R. World J Gastroenterol. 2008;14:331-337.

PSC is frequently associated with IBD

PSC patients

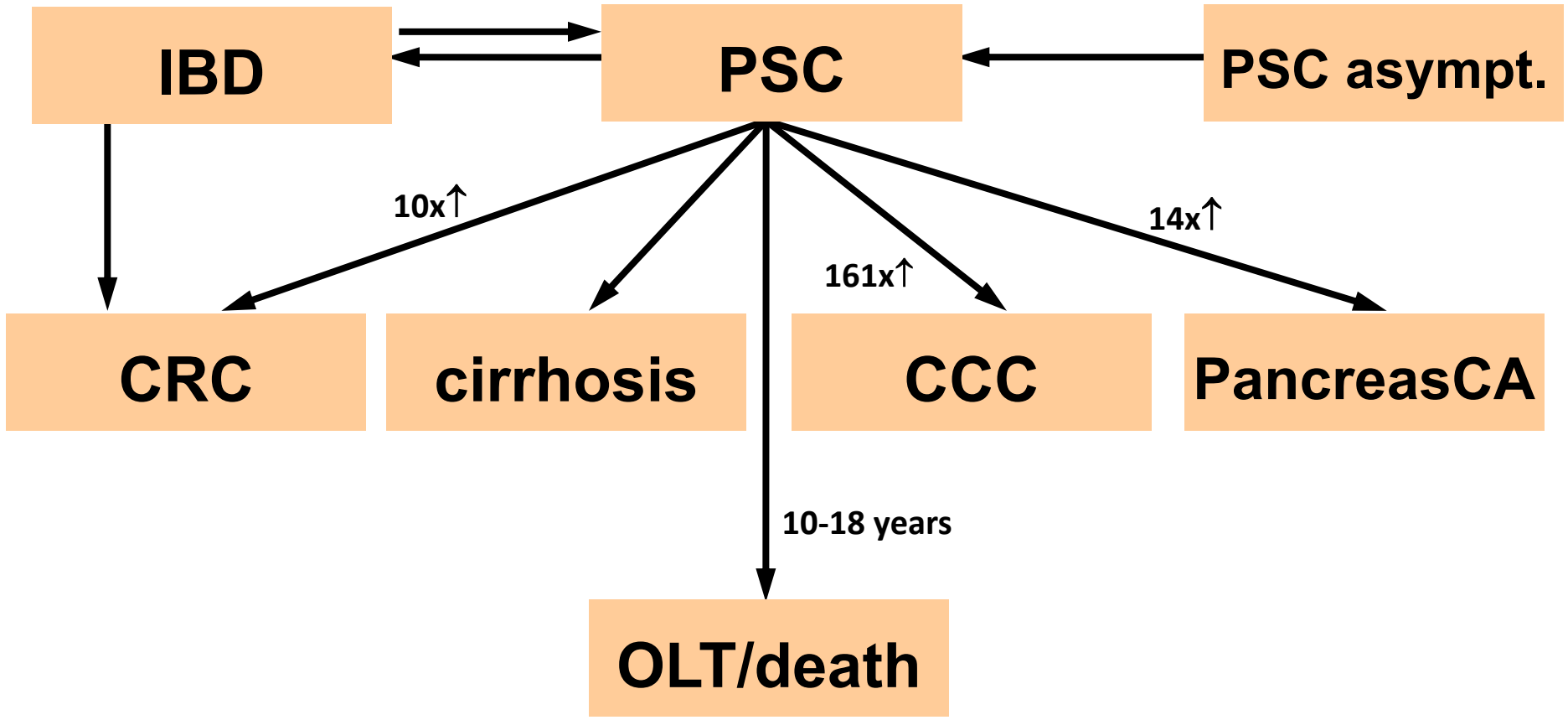


IBD patients



Tischendorf J. Am J Gastroenterol. 2007;102:107
Bergquist A. Scand J Gastroenterol. 2007;42:88
LaRusso N. Hepatology. 2006;44:746

PSC: Risk for progression and cancer



Sokol H. World J Gastroenterol. 2008;14(22):3497-503
Bergquist A. J Hepatology.2002;36:321

Anemia

Multi-factorial

- Iron deficiency anaemia (IDA)
- Anaemia of chronic disease (ACD)
- Mixed type
- Other: Vit. B12, Folic acid, medication

Epidemiology

- 6–74%
- Higher prevalence among hospitalized and newly diagnosed patients

Causes of anemia and influence on red blood cell morphology and reticulocyte count

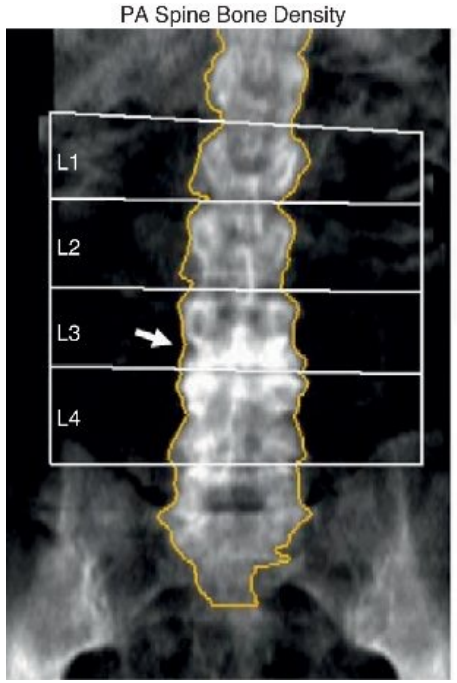
Morphology	Reticulocyte count	Examples of causes of anemia
Macrocytic anemia (MCV >100 fl)	Normal/low	Vitamin B12 or folate deficiency
		Drug induced (azathioprin, sulfasalazin, methotrexate)
		Myelodysplatic syndrome
	Elevated	Hemolysis
		Myelodysplastic syndrome with hemolysis
Normocytic anemia (MCV between 80 and 100 fl)	Normal/low	Early iron deficiency anemia
		Anemia of chronic disease
		Aplastic anemia
		Renal anemia
		Acute hemorrhage
	Elevated	Hemolysis
Microcytic anemia (MCV <80 fl)	Normal/low	Iron deficiency anemia
		Anemia of chronic disease (mostly normocytic)
		Hereditary anemia
	Elevated	Hemoglobinpathies (e.g. thalassemia)

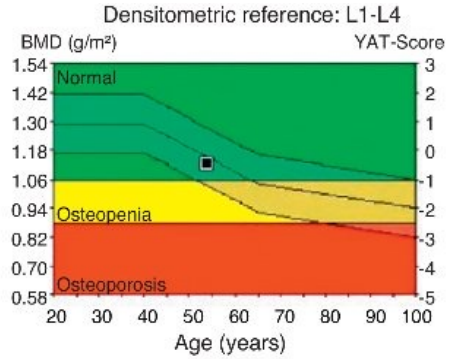
MCV = mean corpuscular volume

Niepel D et al. Therap Adv Gastroenterol. 2018; 11: 1756284818769074

Osteoporosis

- Low bone mass (osteopenia) – osteoporosis (20-50%)
- Risk factors : chronic inflammation, steroid use, malabsorption due extensive inflammation or resections, smoking, deficiencies, low physical activity
- Diagnosis: Bone mineral density scan (Dexa)



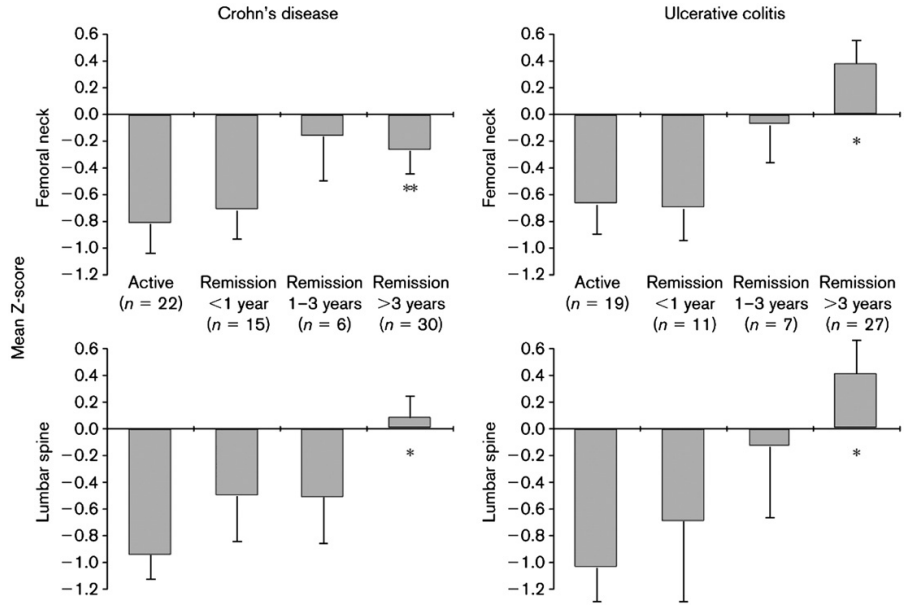


Region	BMD [1] (g/m²)	Young adult [2] (%)	T-score	Adj. to age [3] (%)	Z-score
L1	0.883	78	-2.1	80	-1.8
L2	0.991	83	-1.7	85	-1.5
L3	1.326	111	1.1	113	1.3
L4	1.217	101	0.1	104	0.4
L1-L4	1.122	95	-0.5	97	-0.3
L2-L4	1.184	99	-0.1	101	0.1

Table 1 Bone density in patients with inflammatory bowel disease

Normal bmd $T>-1$	Osteopenia $T<-1>-2,5$	Osteoporosis $T<-2,5$	Author
Crohn's disease			
42%	23%	35%	von Tirpitz et al. (1999)[3]
8%	55%	7%	Ardizzone et al. (2000)[4]
37%	50%	13%	Siffledeen et al. (2004)[5]
Ulcerative colitis			
15%	67%	18%	Ardizzone et al. (2000)[4]

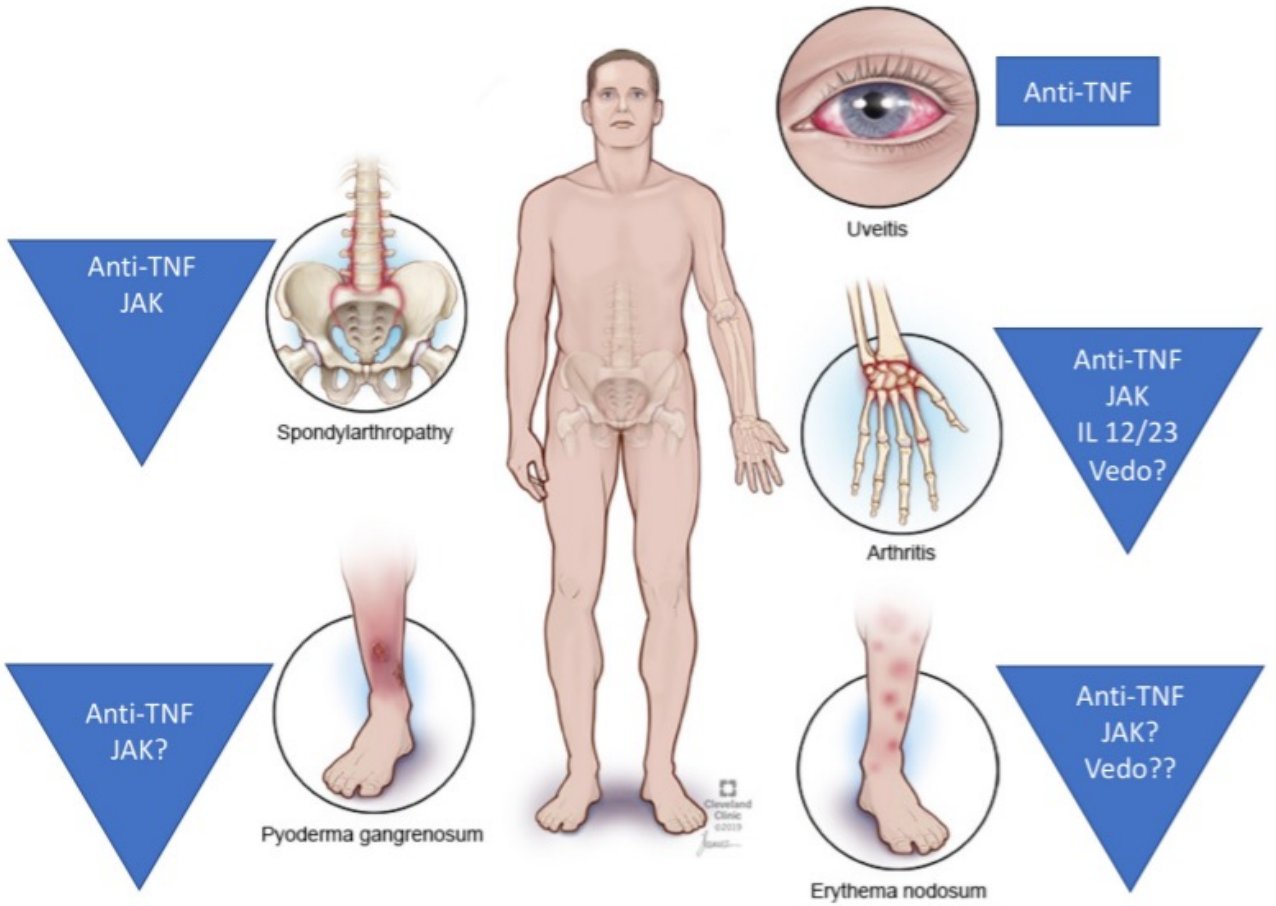
Proportion of patients with normal bone mineral density (bmd), osteopenia $T<1$and >-2.5 and osteoporosis in %.



Reinshagen M. J Crohns Colitis. 2008 Sep;2(3):202-7.

Therapy: from conventional treatment to future options

	Conventional treatment
Axial SpA	Short-term NSAIDs (COX2)
Peripheral arthritis	Short-term NSAIDs, (COX2), Sulfasalazine MTX
Uveitis Episcleritis	Steroids, immune-suppressants
EN	Steroids
PG	Systemic steroids, CNI (local or systemic)



Rule number 1: always treat intestinal disease activity first

Greuter T et al. Gut. 2021 Apr;70(4):796-802

IBD MATTERS

Treatment options

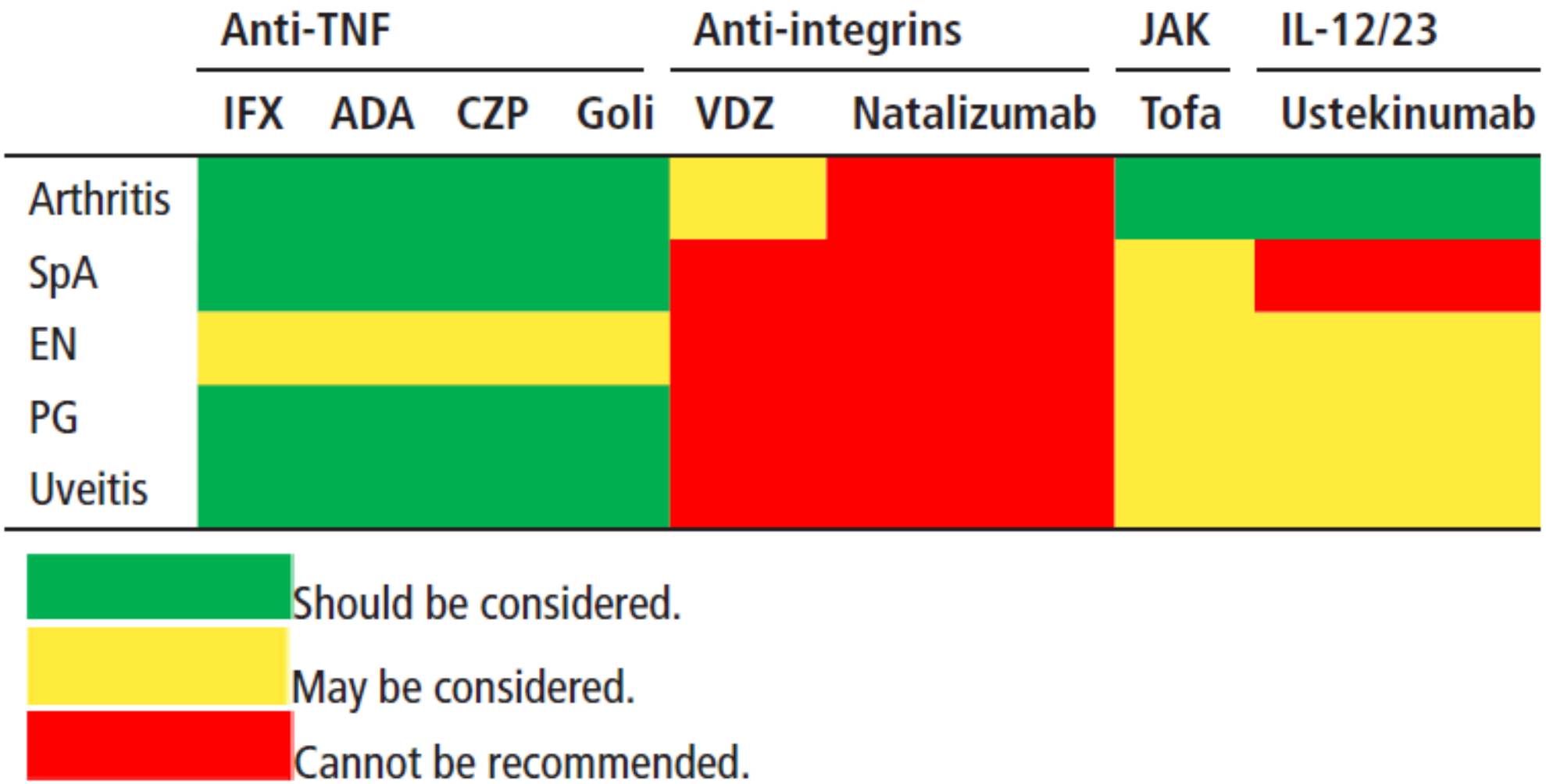
Table 1 Synopsis over current and emerging treatment options for different types of EIM

	Conventional treatment	Anti-TNF	Anti-integrins	JAK inhibitors	Anti-IL-12/23	Comments
Axial SpA	Short-term NSAIDs (COX-2)	Early use, particularly in refractory cases	No clinical data available	Efficacious in SpA, not approved yet	Efficacious in phase II trials, phase III trials early terminated	
Peripheral arthritis	Short-term NSAIDs, (COX-2), sulfasalazine MTX	For resistant cases	Response in up to 50%, but also paradoxical arthritis possible	Approved for rheumatoid arthritis	Approved for psoriatic arthritis	Main goal: treatment of underlying IBD
Uveitis episcleritis	Steroids, immunosuppressants	Very efficacious, but small sample size	No data available	Successful use in two patients	Successful use in one patient	
EN	Steroids	Consider in severe or refractory cases	Resolution or partial response, but only case reports/series absence of MAdCAM1 expression in the skin	Approved for psoriatic arthritis, STAT3 expression in skin biopsies of patients with EN	Approved for psoriasis, high improvement rates based on a single case series	Main goal: treatment of underlying IBD
PG	Systemic steroids, CNI (local or systemic)	Consider early use	No resolution with VDZ (case report), absence of MAdCAM1 expression in the skin	Approved for psoriatic arthritis, resolution of PG in three patients	Approved for psoriasis, high improvement rates based on a single case series	

CNI, calcineurin inhibitor; EIM, extraintestinal manifestation; EN, erythema nodosum; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PG, pyoderma gangrenosum; SpA, axial spondyloarthropathy; TNF, tumour necrosis factor; VDZ, vedolizumab.

Greuter T et al. Gut. 2021 Apr;70(4):796-802

Which biologic agent for which EIM?



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Herzlichen Dank für die
Aufmerksamkeit