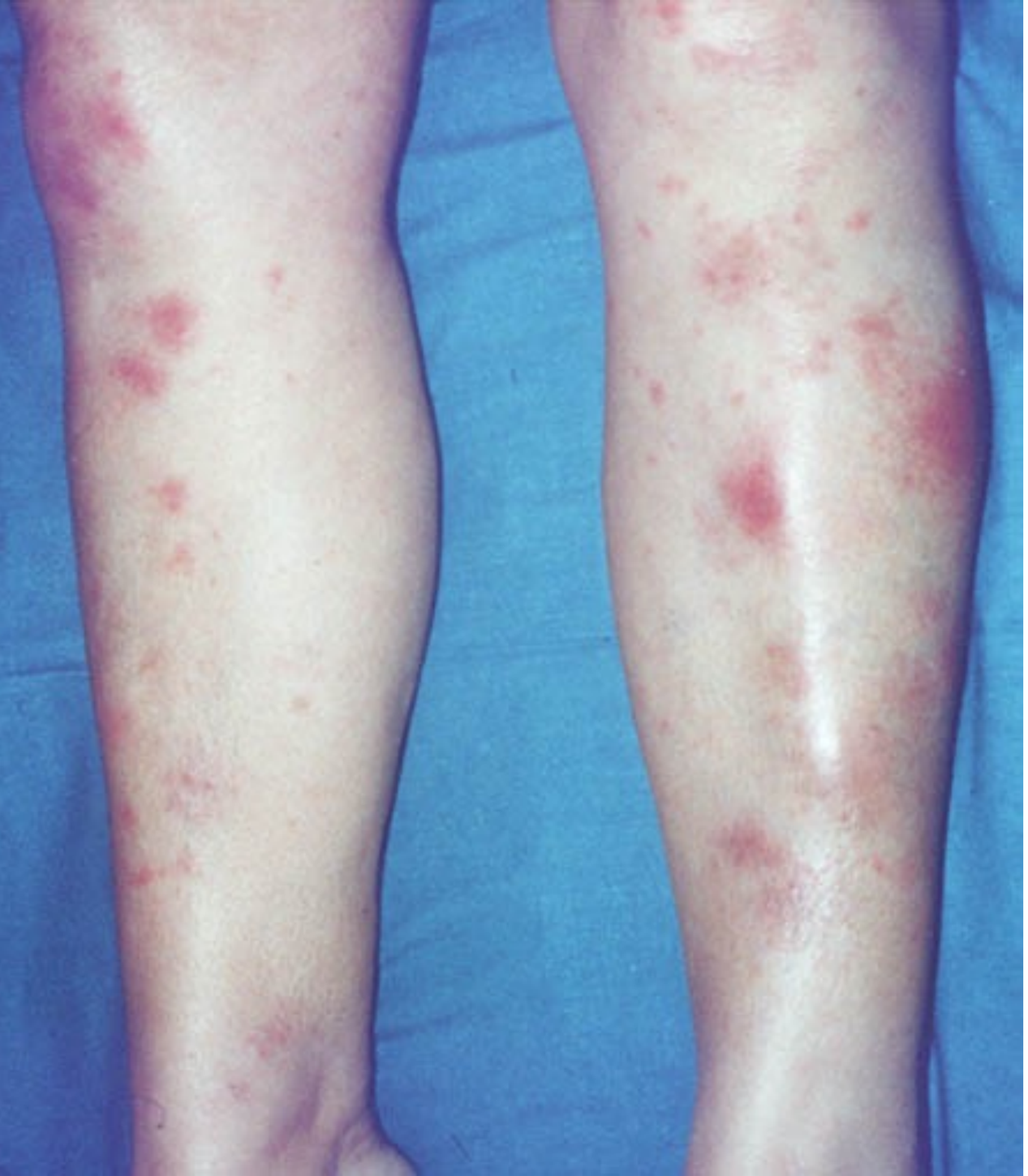

FRIDAY, November 3, 2023

MENTORING in IBD XXIV
THE MASTER CLASS

Dermatological Manifestations of IBD

Melinda Gooderham MSc MD FRCPC

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Photo Requena et al (2002).. *Dermatology Online Journal*, 8(1).
http://dx.doi.org/10.5070/D34829t6rn

Conflicts of interest

Melinda Gooderham has been a speaker, investigator or advisory board member for:

AbbVie, Amgen, Akros, AnaptysBio, Apogee, Arcutis, Arena, Aslan, Bausch Health, Boehringer Ingelheim, BMS, Celgene, Coherus, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, InMagene, Janssen, Kyowa Kirin, LEO Pharma, Medimmune, Moonlake, Nimbus, Novartis, Pfizer, Regeneron, Reistone, Sanofi Genzyme, Sun Pharmaceuticals, Tarsus, Takeda, UCB, Union and Ventyx.

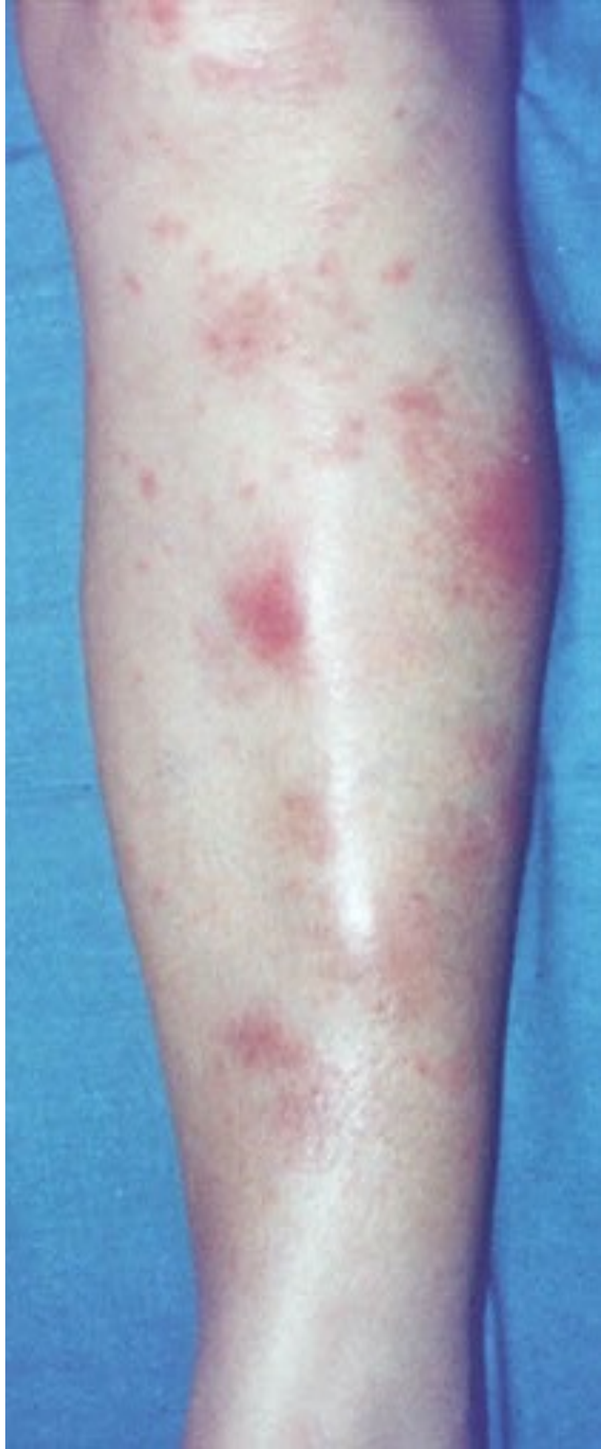

Photo Requena et al (2002).. *Dermatology Online Journal*, 8(1).
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Objectives

01

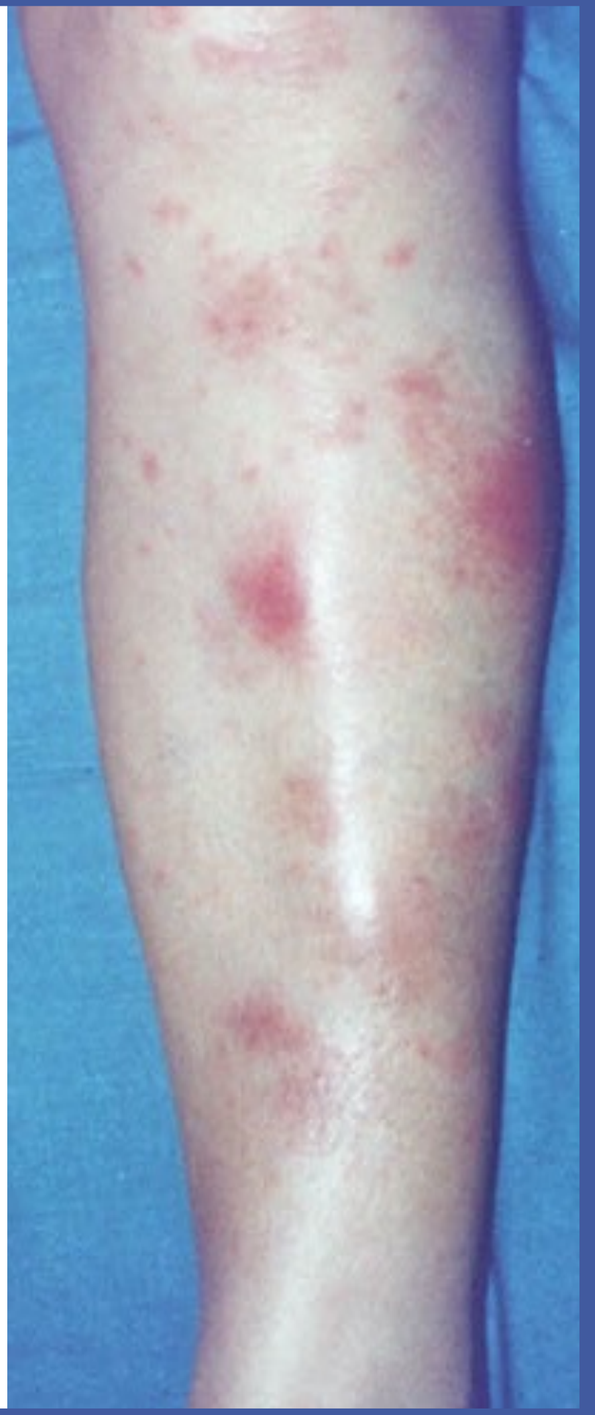
Explore the range of dermatologic manifestations associated with IBD

02

Emphasize the importance of early recognition and interdisciplinary collaboration in patient management

03

Explore treatment options for managing dermatological manifestations in IBD patients



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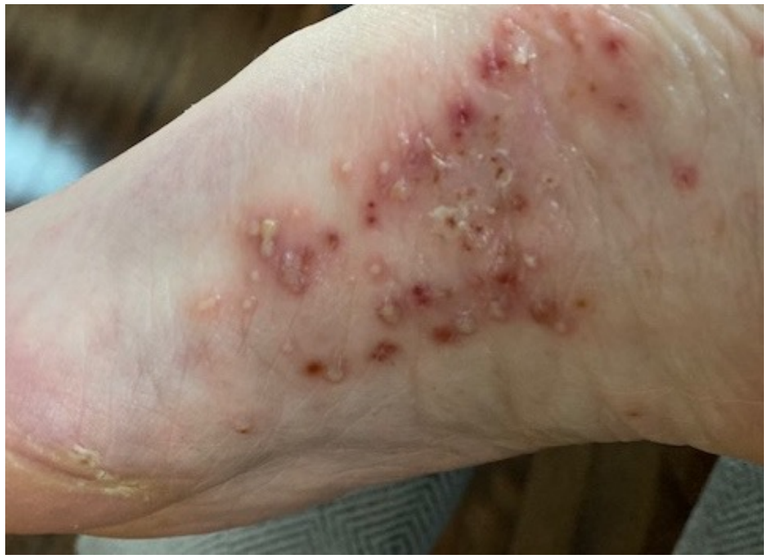
Dermatological Manifestations in IBD

- Estimated **prevalence of 10-15%** of extra-intestinal cutaneous manifestations
- A prospective study in 352 patients found **erythema nodosum** and **pyoderma gangrenosum** were most common (7.4% and 3.2%, respectively)
- With use of biologic agents, particularly **TNF inhibitors**, more **cutaneous manifestations** have been noted (psoriasiform and pustular eruptions)
- **Early identification and management** of these conditions is important to **optimize patient outcomes** for both skin and bowel disease



Lipson, J. Canadian IBD Today, 2023; Vol 1, Issue 2.; Antonelli et al. J. Clin. Med. 2021, 10, 364. https://doi.org/10.3390/jcm10020364; top photo Depositphotos.com, bottom photo Dr. M Gooderham

Classification of Dermatological Manifestations of IBD

Classification:

Specific manifestations

Associated disorders

Reactive manifestations

Treatment related

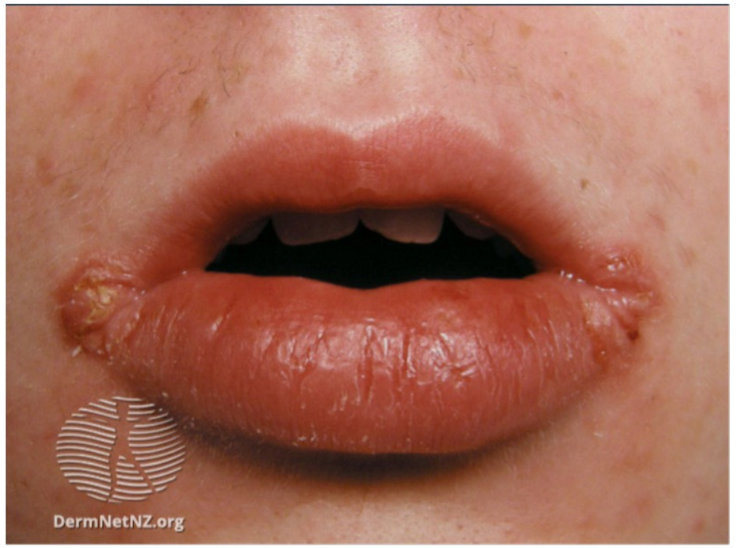
Nutritional malabsorption

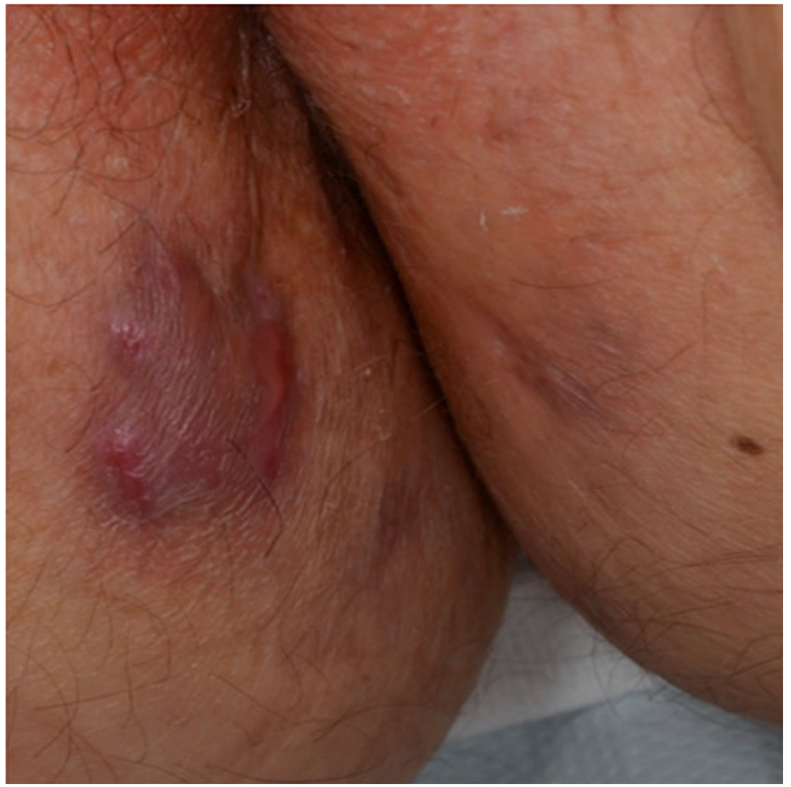
Classification of Dermatological Manifestations of IBD

Classification:	**Specific manifestations**	Associated disorders
Reactive manifestations	Treatment related	Nutritional malabsorption

Classification of Dermatological Manifestations of IBD

Specific Manifestations
Contiguous or continuous Crohn's disease – *fissures, fistulas*
Metastatic Crohn's disease
Granulomatous cheilitis





- Result of intestinal inflammatory process diffusion into the skin and/or external mucosa
- Can be **perianal or orofacial**, can be metastatic, or **non-contiguous**, in nature with non-caseating granulomas distant from the GI tract (seen in CD)

Lipson, J. Canadian IBD Today, 2023; Vol 1, Issue 2.; Antonelli et al. J. Clin. Med. 2021, 10, 364. https://doi.org/10.3390/jcm10020364

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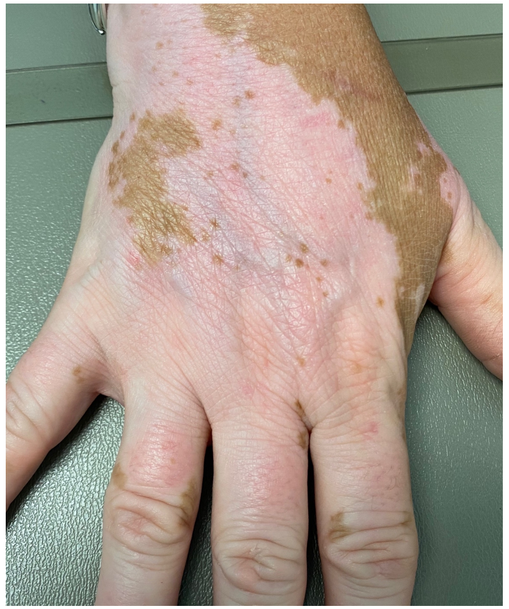
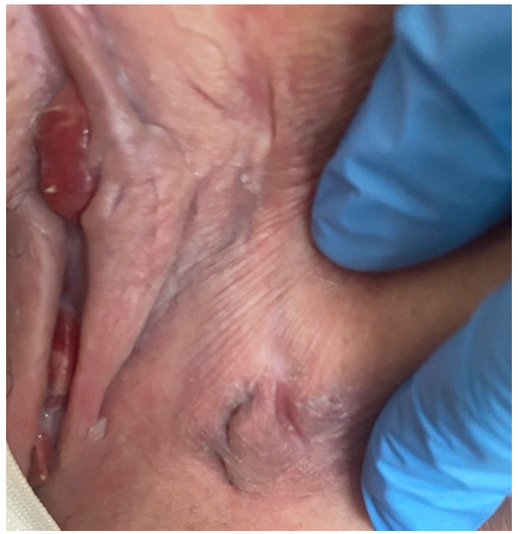
Classification of Dermatological Manifestations of IBD

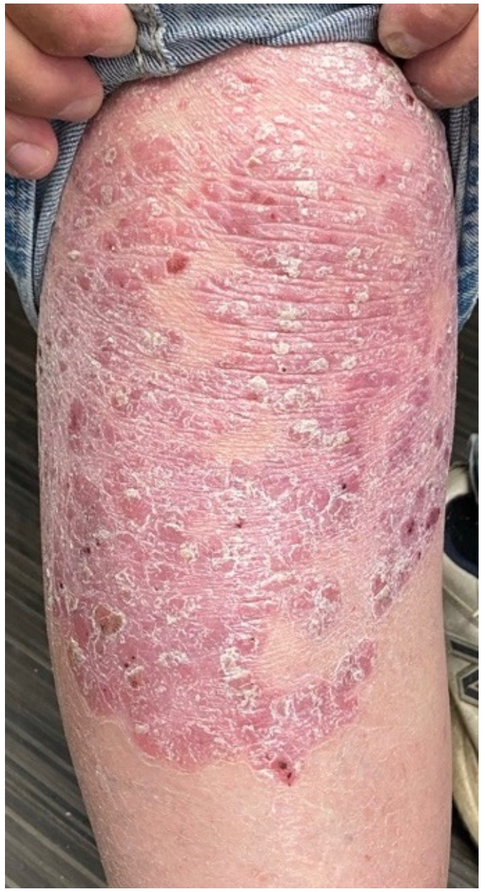
Classification:	Specific manifestations	**Associated disorders**
Reactive manifestations	Treatment related	Nutritional malabsorption

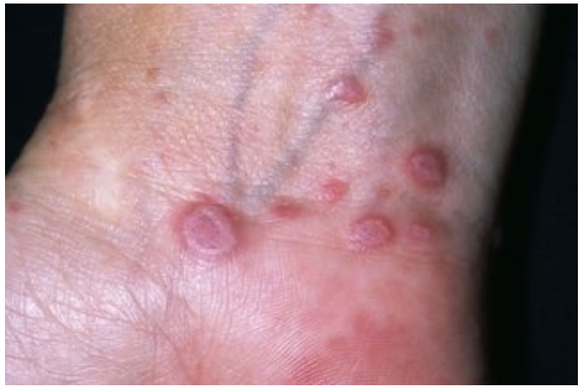
Classification of Dermatological Manifestations of IBD

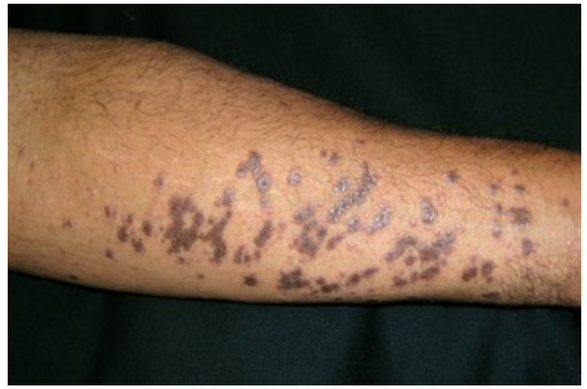
Associated Disorders
Psoriasis
Hidradenitis suppurativa • SAPHO, PAPA syndrome
Epidermolysis bullosa acquisita
Lichen planus
Vitiligo
Linear IgA Dermatosis







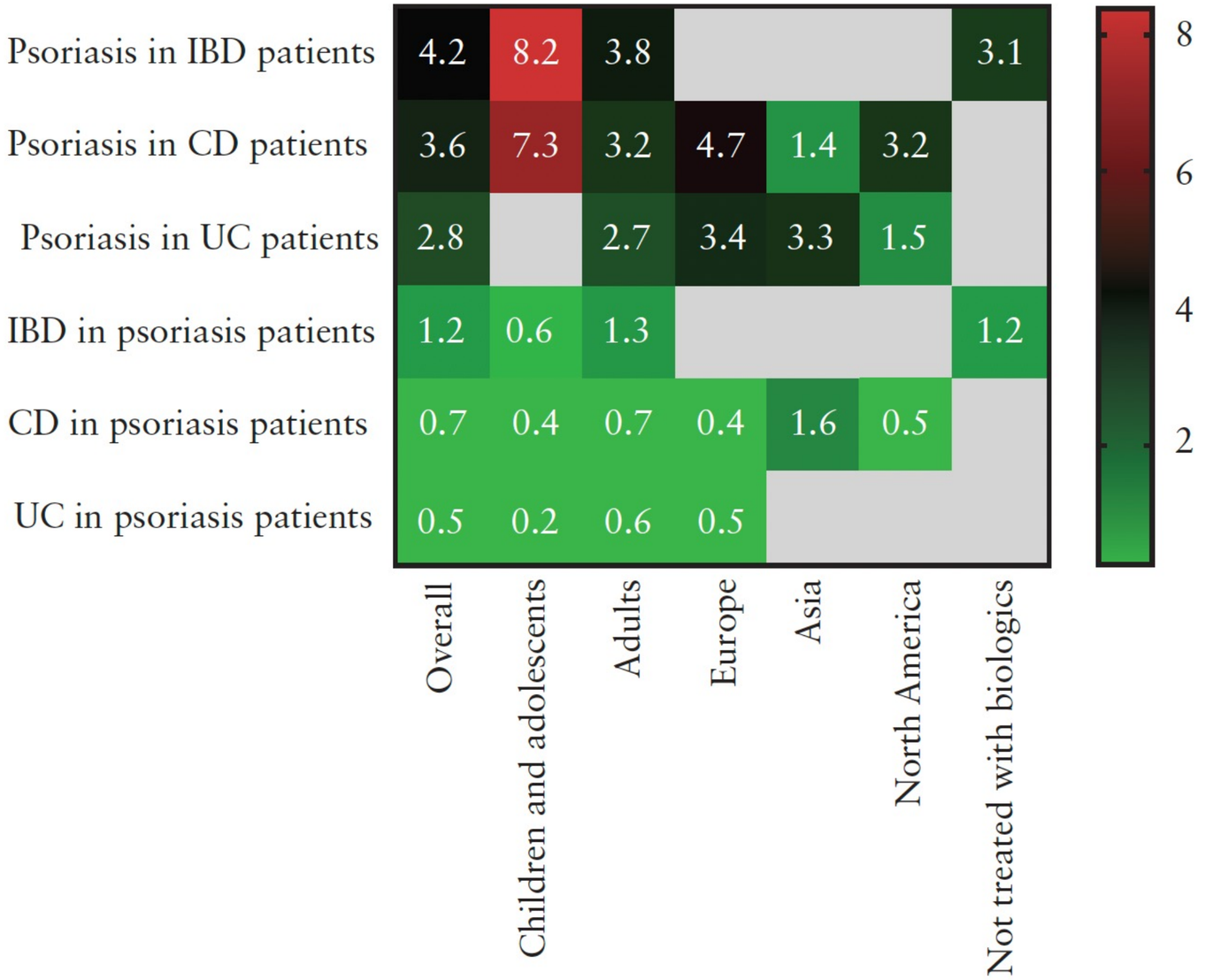




Lipson, J. Canadian IBD Today, 2023; Vol 1, Issue 2; photos: https://www.nhs.uk/conditions/lichen-planus/;vitiligo, HS, psoriasis from Dr. M. Gooderham

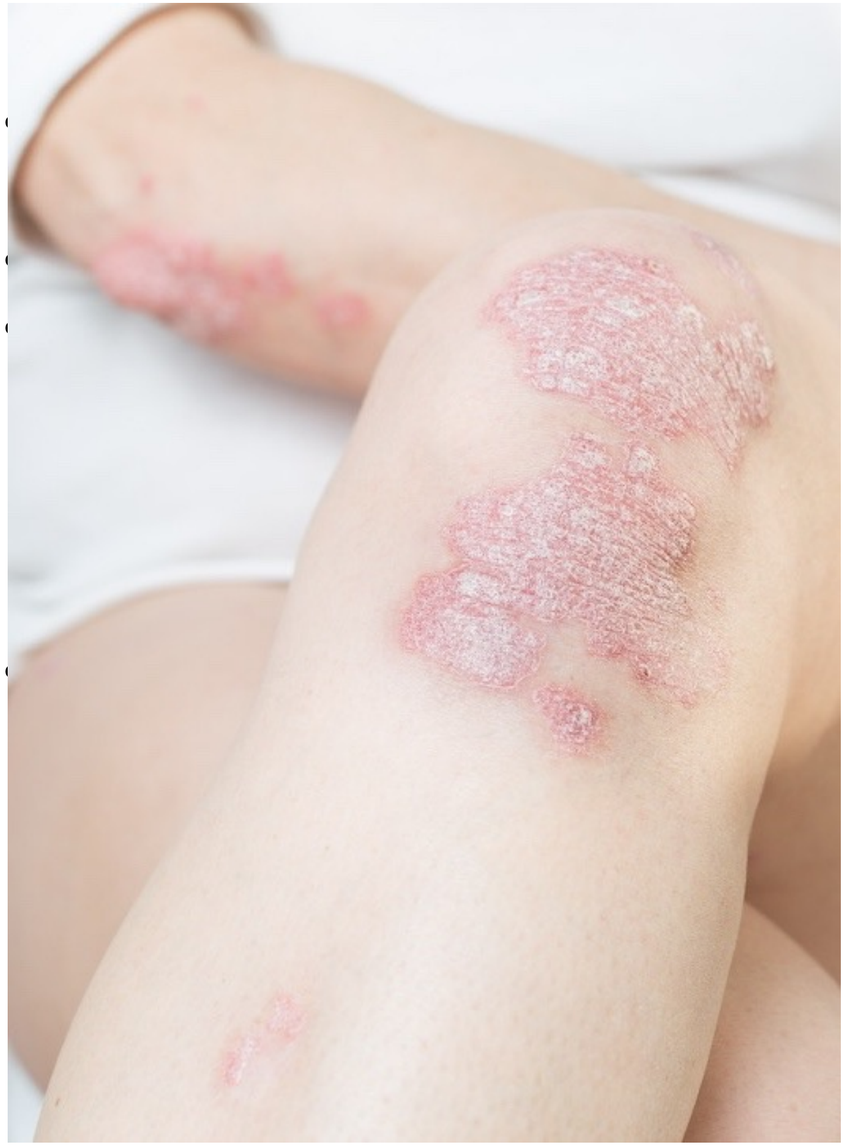
Association of Psoriasis and IBD

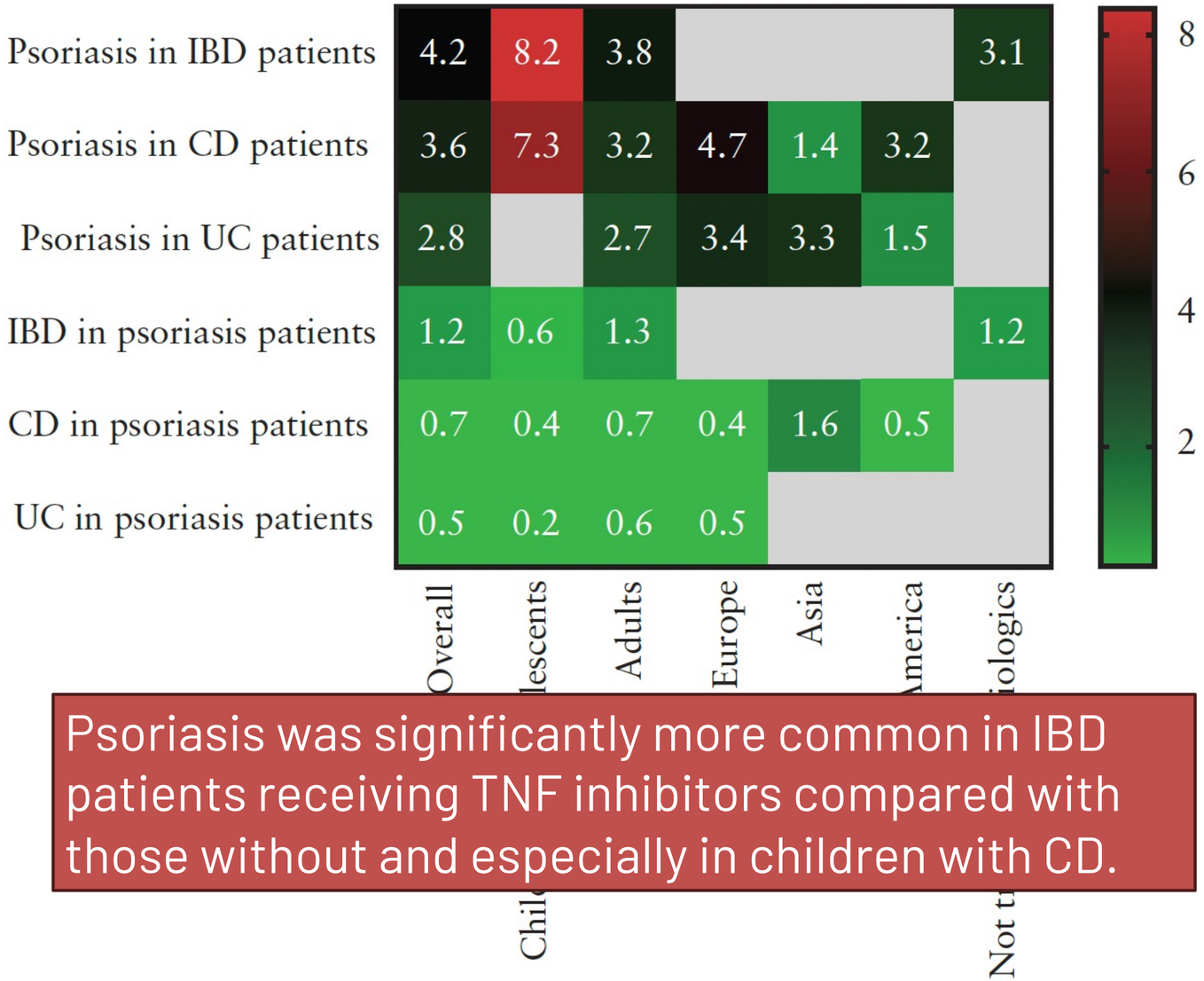
- Systematic review and meta-analysis
- N=93 studies met criteria
- **Prevalence of psoriasis** in **CD and UC** of **3.6%** and **2.8%**, respectively
- Presence of **CD or UC** was significantly associated with **psoriasis, with OR 2.0** [95% CI 1.4–2.9] **and OR 1.5** [95% CI 1.2–2.0], respectively.
- Presence of **psoriasis** was significantly associated with **CD: OR 2.2** [95% CI 1.6–3.1] and with **UC: OR 1.6** [95% CI 1.3–2.0].



Journal of Crohn's and Colitis, 2020, 351–360 doi:10.1093/ecco-jcc/jjz152

Association of Psoriasis and IBD





Psoriasis was significantly more common in IBD patients receiving TNF inhibitors compared with those without and especially in children with CD.

Journal of Crohn's and Colitis, 2020, 351–360 doi:10.1093/ecco-jcc/jjz152; photo Shutterstock.com

Association of Hidradenitis Suppurativa and IBD

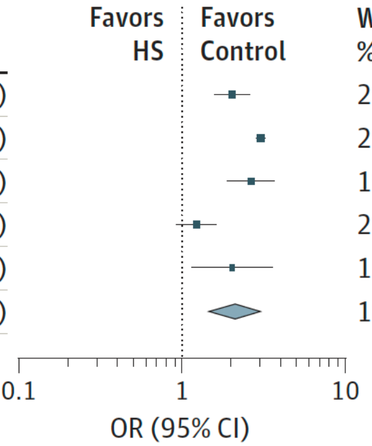
- Systematic review and meta-analysis
- From 397 studies: 5 case-control studies, 2 cross-sectional studies, and 1 cohort study with **N=93 601** unique participants were included
- **HS with Crohn's disease** (**pooled OR, 2.12**; 95%CI, 1.46-3.08) and **ulcerative colitis** (**pooled OR, 1.51**; 95%CI, 1.25-1.82).
- One cohort study found an **increased risk of IBD** in **patients with HS** (**HR, 5.6**; 95%CI NR; P < .002)
- Evidence to date supports an association of HS with IBD

A Crohn disease

Source	Logarithm OR (SE)	Total No. HS Group	Total No. Control Group	IV Randomized OR (95% CI)	Favors HS	Favors Control	Weight, %
Egeberg et al,[34] 2017	0.7135 (0.1274)	7732	4 354 137	2.04 (1.59-2.62)			21.3
Garg et al,[32] 2018	1.1165 (0.0317)	52 340	18 404 260	3.05 (2.87-3.25)			23.3
Ingram et al,[35] 2018	0.9752 (0.1727)	122	187	2.65 (1.89-3.72)			19.7
Lee et al,[26] 2018	0.2035 (0.1442)	28 516	142 580	1.23 (0.92-1.63)			20.7
Shalom et al,[27] 2016	0.7088 (0.2948)	3207	6412	2.03 (1.14-3.62)			15.0
Total		91 917	22 907 576	2.12 (1.46-3.08)			100.0

Heterogeneity: $\tau^2 = 0.15$, $\chi^2_4 = 47.36$ ($P < .001$); $I^2 = 92\%$

Test for overall effect: $z = 3.96$ ($P < .001$)

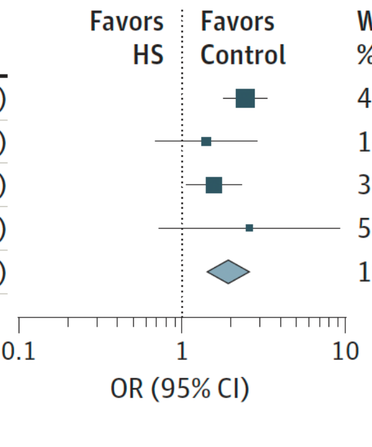


B Ulcerative colitis

Source	Logarithm OR (SE)	Total No. HS Group	Total No. Control Group	IV Randomized OR (95% CI)	Favors HS	Favors Control	Weight, %
Egeberg et al,[34] 2017	0.5604 (0.0999)	7732	4 354 137	1.75 (1.44-2.13)			45.1
Ingram et al,[35] 2018	0.2135 (0.2292)	42	129	1.24 (0.79-1.94)			14.6
Lee et al,[26] 2018	0.281 (0.1258)	28 516	142 580	1.32 (1.04-1.69)			35.1
Shalom et al,[27] 2016	0.5965 (0.4093)	3207	6412	1.82 (0.81-4.05)			5.2
Total		39 497	4 503 258	1.51 (1.25-1.82)			100.0

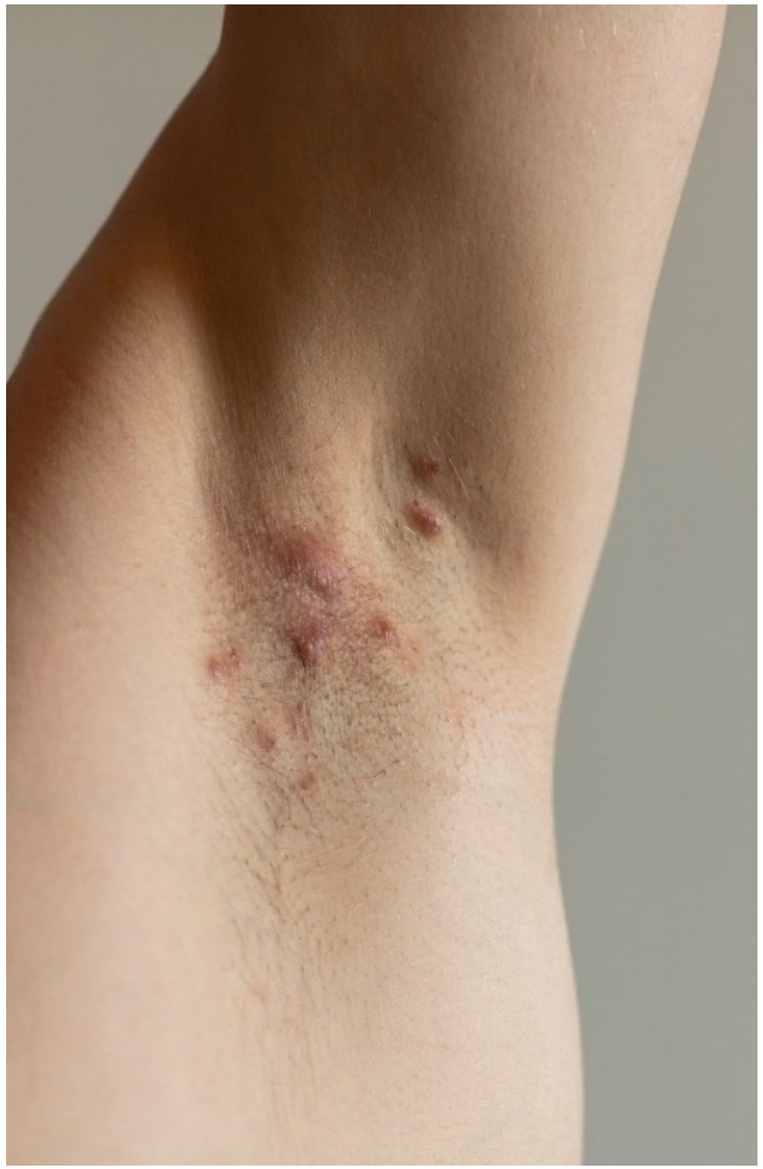
Heterogeneity: $\tau^2 = 0.01$, $\chi^2_3 = 4.16$ ($P = .24$); $I^2 = 28\%$

Test for overall effect: $z = 4.31$ ($P < .001$)



JAMA Dermatol. 2019;155(9):1022-1027. doi:10.1001/jamadermatol.2019.0891

Association of Hidradenitis Suppurativa and IBD



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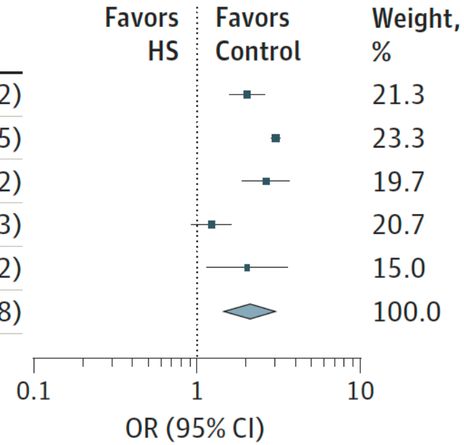

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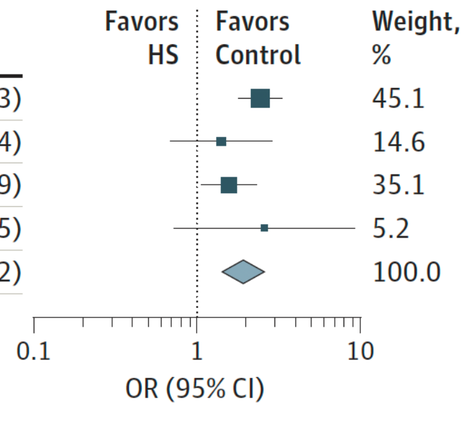

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Classification:

Specific manifestations

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Treatment related

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Classification of Dermatological Manifestations of IBD

Classification:	Specific manifestations	Associated disorders
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Classification of Dermatological Manifestations of IBD

Reactive Manifestations
Erythema nodosum
Pyoderma gangrenosum
Aphthous stomatitis
Neutrophilic dermatosis

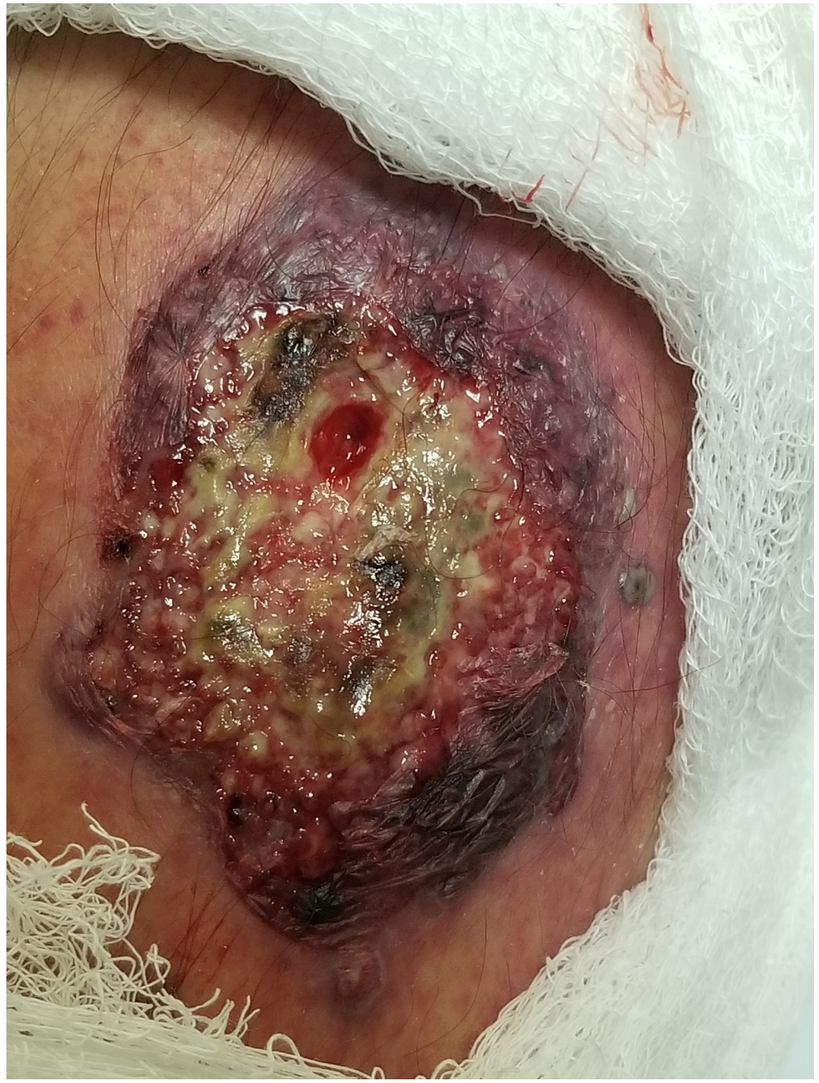
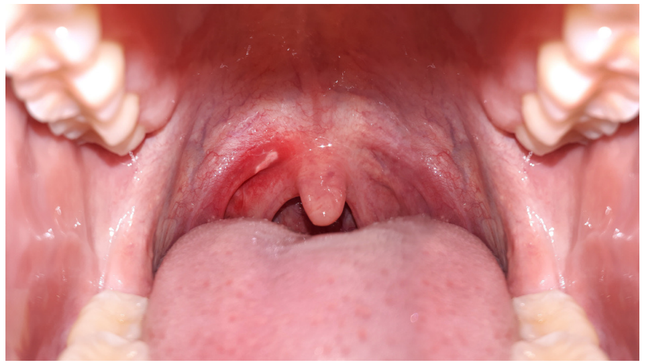
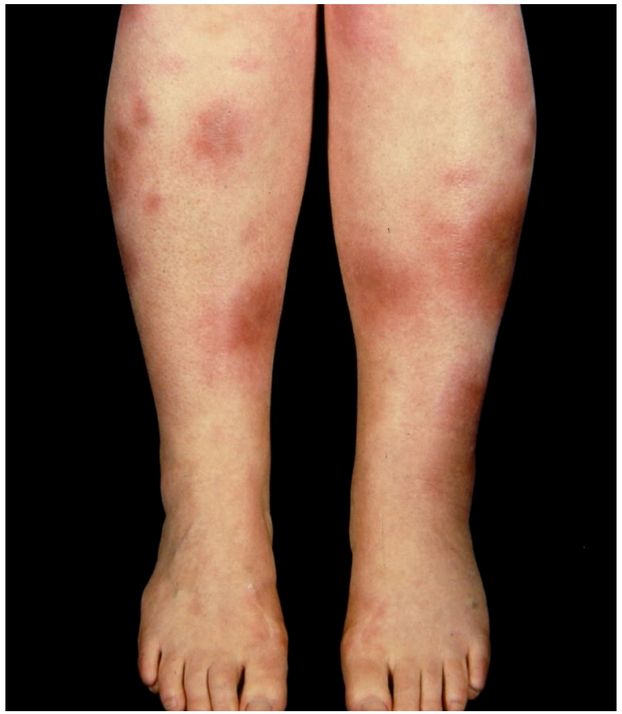


Photo from Depositphotos.com





Lipson, J. Canadian IBD Today, 2023; Vol 1, Issue 2; Hafsi W, Badri T. Erythema Nodosum. [Updated 2022 Nov 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. [Figure, Erythema Nodosum. Source: DermNet] Available from: https://www.ncbi.nlm.nih.gov/books/NBK470369/figure/article-21301.image.f1/;

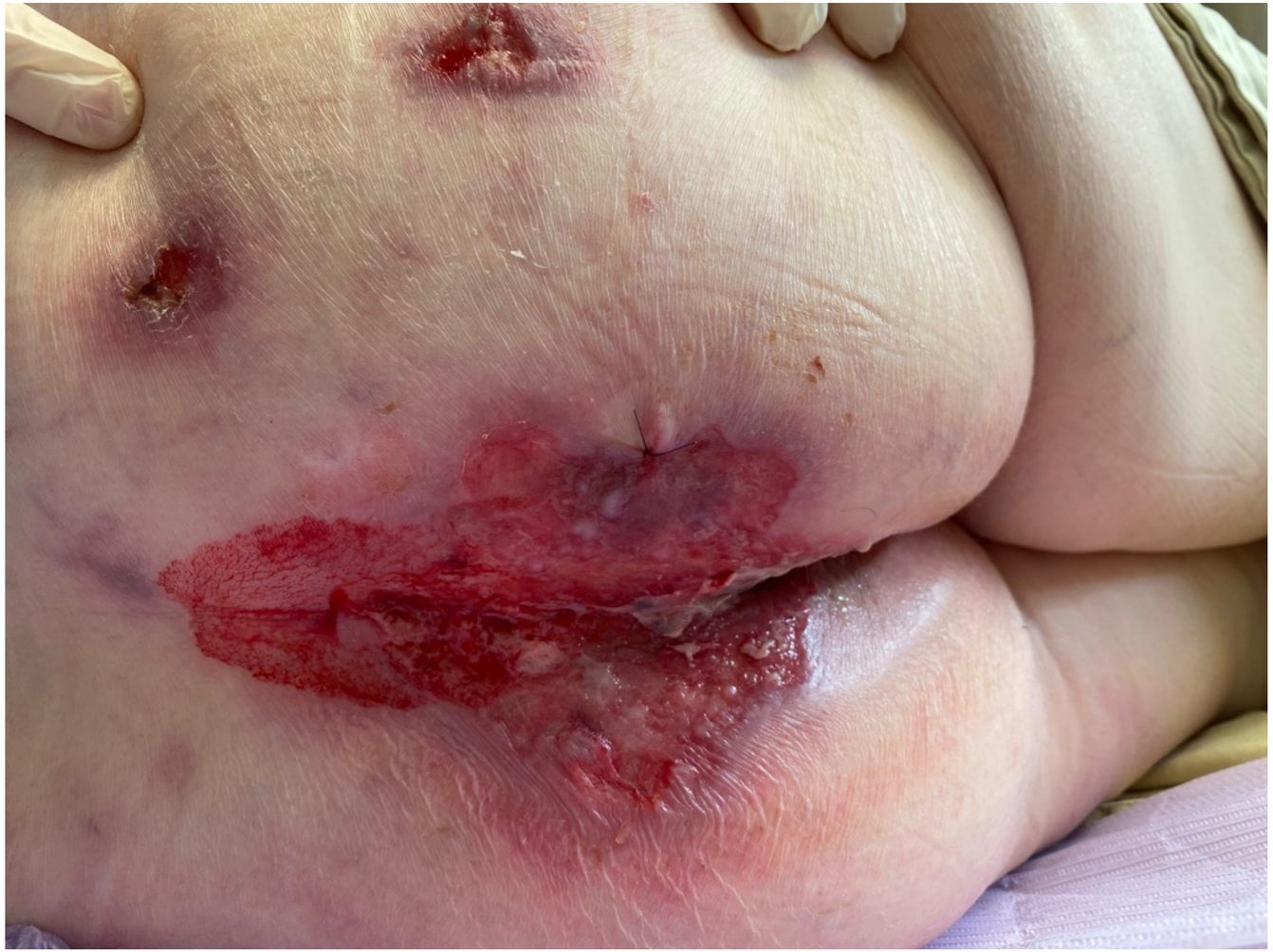
Association of EN and PG with IBD

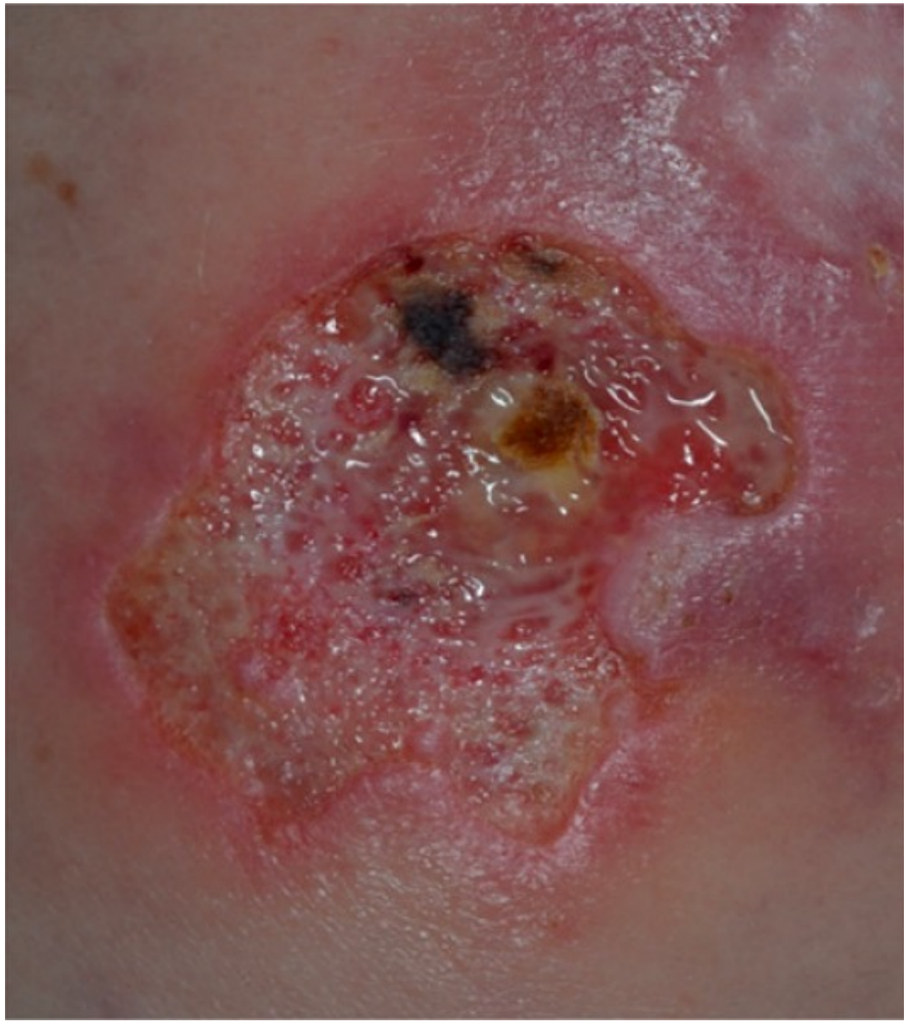
- Cohort study from the Improve Care Now network (ICN) database
- cohort study evaluated **32,497 patients ages ≤ 21 years**
- overall incidence of **EN was 1.57%** (95% CI: 1.43% to 1.71%) and **PG was 0.90%** (95% CI: 0.80% to 1.00%) and **both EN and PG was 0.30%** (95% CI: 0.25% to 0.37%).
- Multivariable logistic regression models confirmed association of **Physicians Global Assessment, uveitis, arthritis, and corticosteroids** with **both EN and PG**.
- Rate of biologics were less in EN compared to controls (49.5% vs 54%, p=0.03), and not associated with PG

Factor	EN		PG	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender	1.34 (1.07, 1.67)	0.0101	-	-
Age at visit	0.89 (0.87, 0.92)	<.0001	0.92 (0.88, 0.96)	<.0001
Diagnosis at Visit Crohn's Disease Ulcerative Colitis Indeterminate Colitis	 1.00 0.29 (0.22, 0.40) 0.24 (0.12, 0.46)	 <.0001 <.0001	 - -	 - -
PGA	2.37 (2.06, 2.73)	<.0001	1.87 (1.50, 2.33)	<.0001
Colectomy	-	-	2.93 (1.29, 6.65)	0.0103
Ileostomy or Colostomy	-	-	8.39 (4.35, 16.20)	<.0001
Unsatisfactory Nutrition or Growth	1.47 (1.13, 1.92)	0.0044	-	-
Uveitis	70.87 (40.98, 122.54)	<.0001	85.14 (44.64, 162.41)	<.0001
Arthritis	5.92 (4.20, 8.33)	<.0001	8.48 (5.32, 13.52)	<.0001
Albumin Result	-	-	0.69 (0.50, 0.95)	0.0247
Corticosteroids	2.83 (2.17, 3.68)	<.0001	1.81 (1.16, 2.82)	0.0089
Immunomodulators	1.32 (1.05, 1.66)	0.0168	-	-
Biologics	0.77 (0.62, 0.96)	0.0219	-	-

Inflammatory Bowel Diseases, Volume 29, Issue Supplement_1, February 2023, Pages S60–S61,

Reactive Manifestations: Pyoderma gangrenosum





Photos (left) Dr. M. Gooderham and (right) Antonelli *et al*. J. Clin. Med. 2021, 10, 364

Association of Pyoderma Gangrenosum and IBD

- Systematic review and meta-analysis
- **14 studies** were included in addition to **1057 IBD patients and 26 PG cases** from the Louisville cohort
- **PG incidence** ranged from **0.4 to 2.6%**
- PG was associated with **female gender** (RR = 1.328, 95% CI 1.161–1.520), **Crohn's disease** (RR = 1.193, 95% CI 1.001–1.422), **erythema nodosum** (RR = 9.281, 95% CI 6.081–14.164), and **ocular EIM** (RR = 4.55, 95% CI 3.04–6.81).

Louisville IBD Cohort

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	(95% CI)	*p* value
Age	1	0.98–1.03	0.97			
Age at diagnosis	1.01	0.98–1.04	0.54			
Disease duration	0.99	0.96–1.04	0.82			
Female Gender	**3.06**	**1.1–8.23**	**0.03**	0.49	0.18–1.38	0.18
Ethnicity Caucasian	> 999.99	0–infinity	0.97			
Family history of IBD	1.49	0.66–3.38	0.34			
IBD subtype-CD	**4.73**	**1.4–15.95**	**0.01**	2.64	0.75–9.34	0.13
Smoking—yes	1.63	0.73–3.66	0.24			
EIM						
Any organ system	1.37	0.61–3.1	0.45			
Joint	0.98	0.44–2.19	0.96			
Cutaneous	3.15	0.88–11.29	0.08			
Ocular	**2.83**	**1.19–6.75**	**0.02**	**2.77**	**1.09–7.07**	**0.03**
Stoma						
Any	13.08	5.2–32.931	< 0.001			
Temporary	1.85	0.61–5.60	0.28			
Permanent	**9.6**	**3.6–25.58**	**< 0.001**	**6.77**	**2.27–20.22**	**< 0.001**

Bold values indicate statistical significance

Digestive Diseases and Sciences (2020) 65:2675–2685

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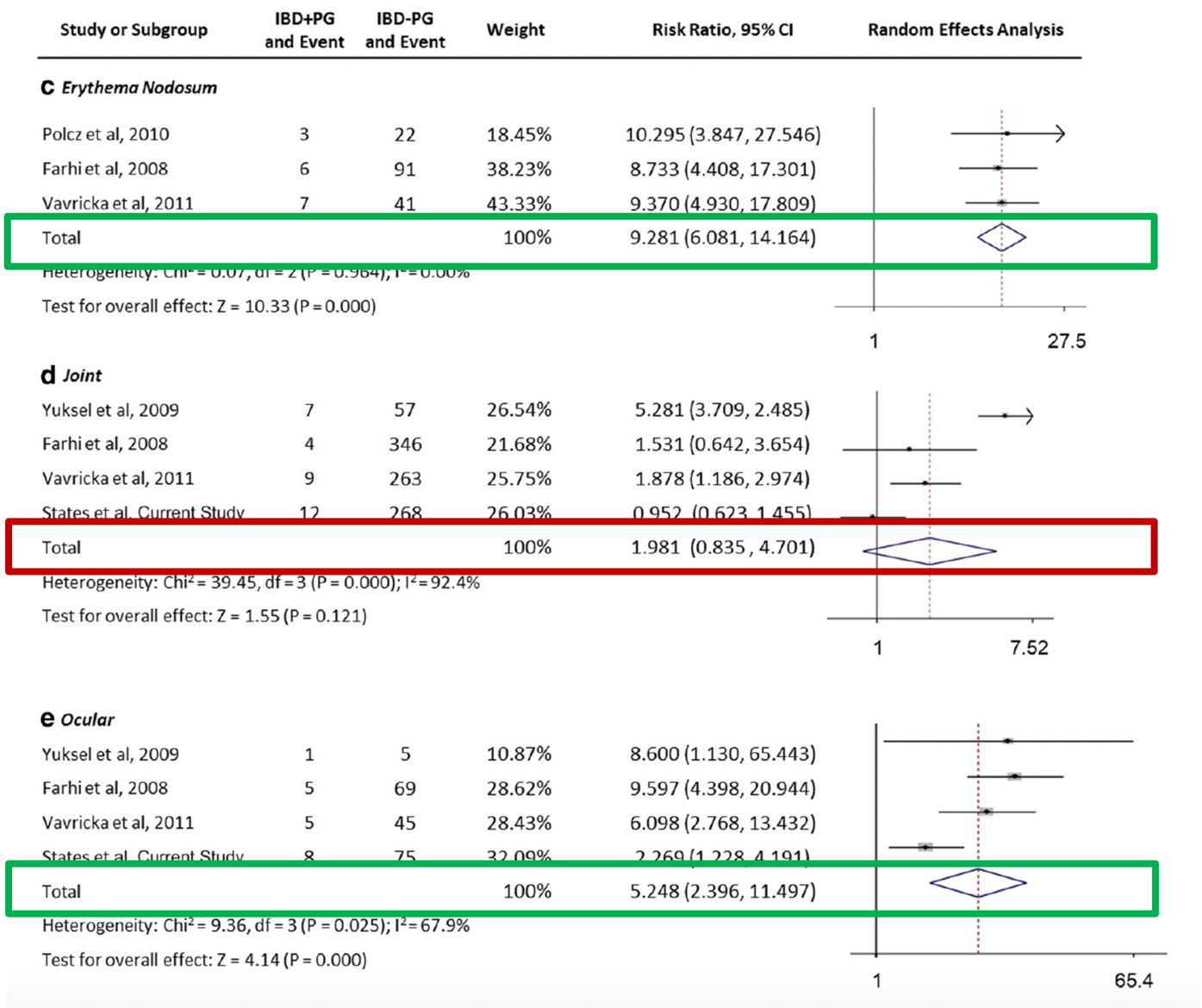
- **PG incidence** ranged from **0.4 to 2.6%**
- PG was associated with **female gender** (RR = 1.328, 95% CI 1.161–1.520), **Crohn's disease** (RR = 1.193, 95% CI 1.001–1.422), **erythema nodosum** (RR = 9.281, 95% CI 6.081–14.164), and **ocular EIM** (RR = 4.55, 95% CI 3.04–6.81).



Digestive Diseases and Sciences (2020) 65:2675–2685

Classification of Dermatological Manifestations of IBD

Classification:

Specific manifestations

Associated disorders

Reactive manifestations

Treatment related

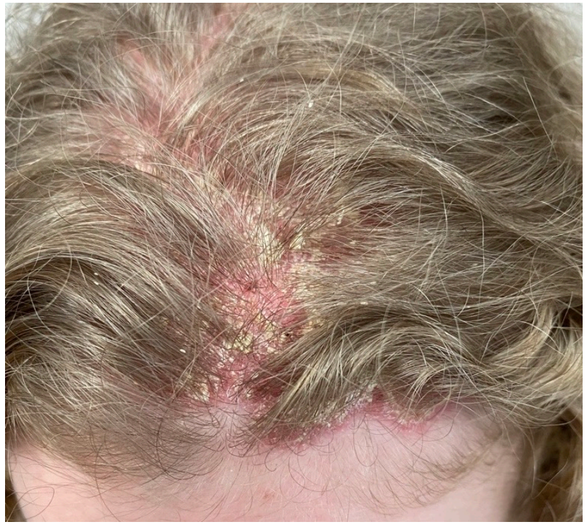
Nutritional malabsorption

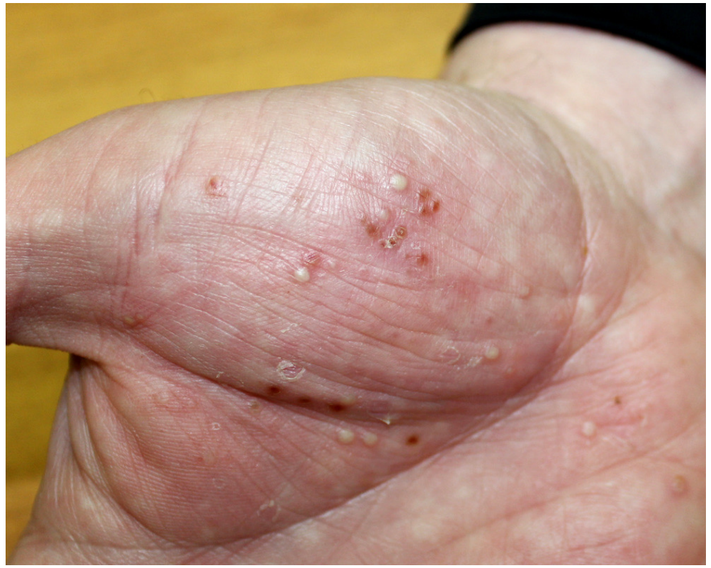
Classification of Dermatological Manifestations of IBD

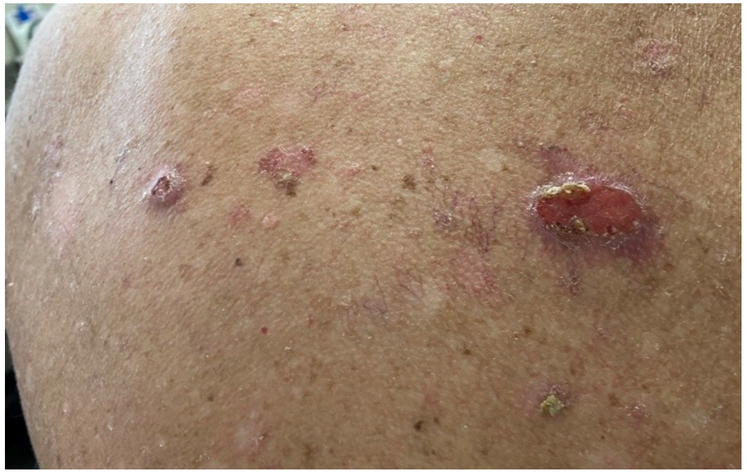
Classification:	Specific manifestations	Associated disorders
Reactive manifestations	**Treatment related**	Nutritional malabsorption

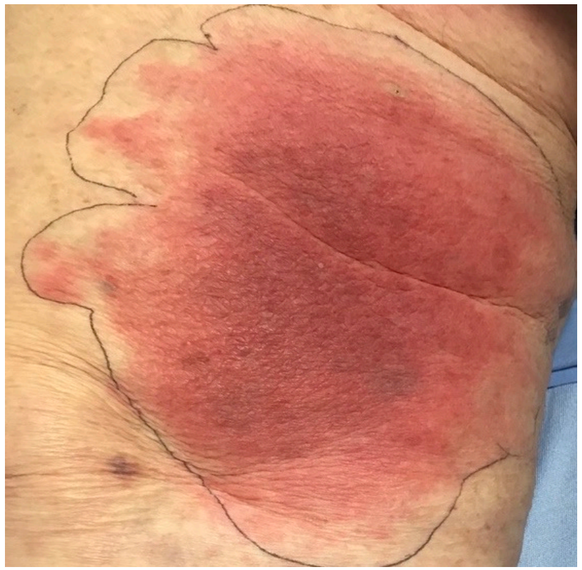
Classification of Dermatological Manifestations of IBD

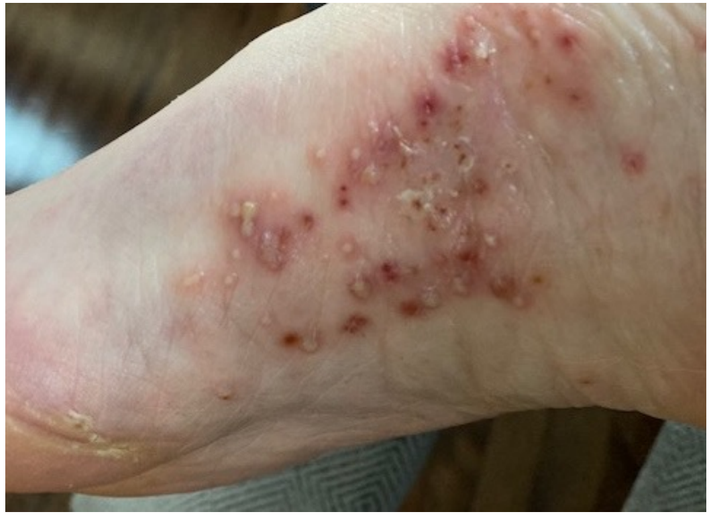
Treatment related
TNF-induced psoriasiform eruption
TNF-induced palmoplantar pustulosis
Injection site reaction
Cutaneous malignancies







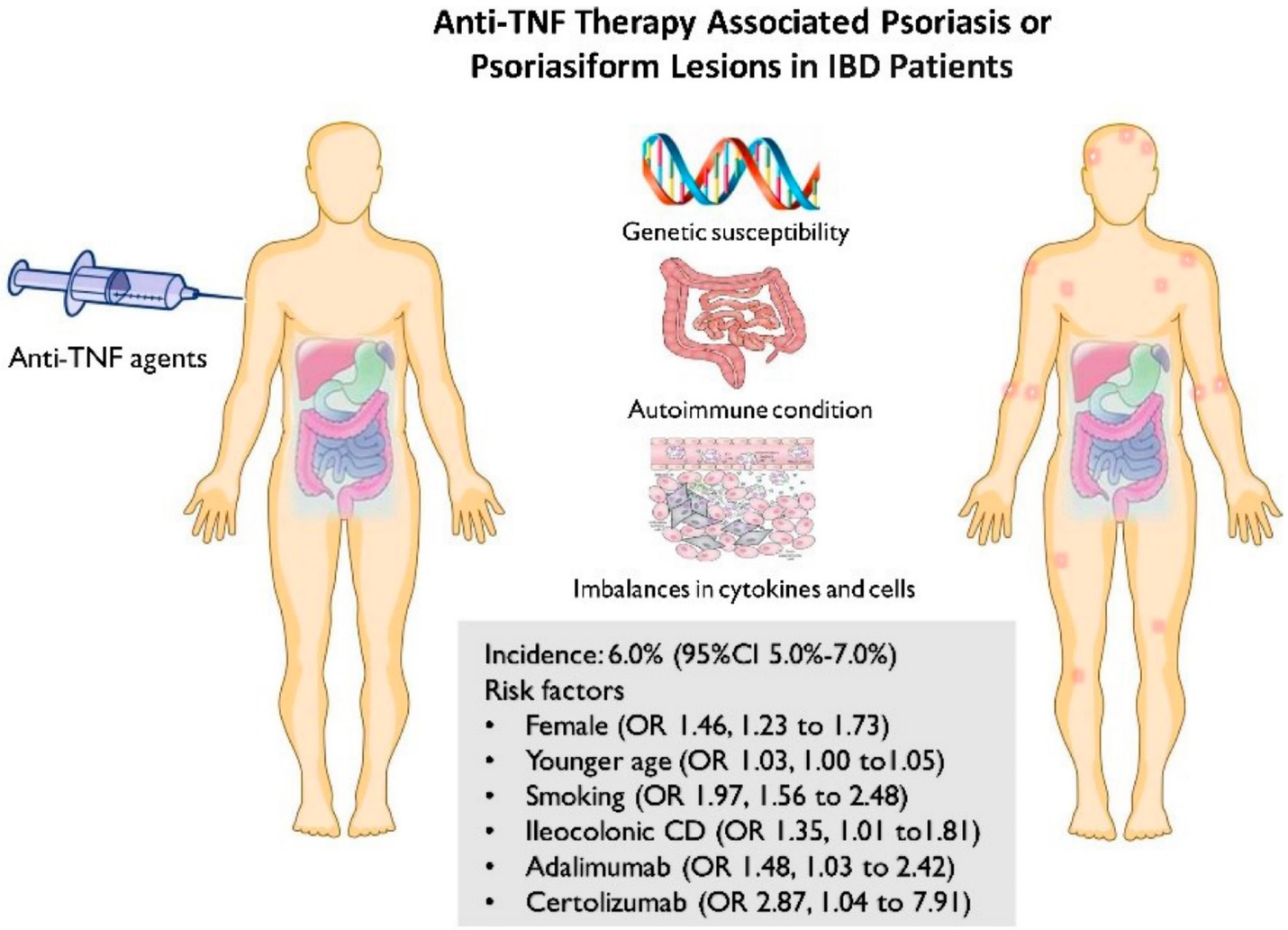




Lipson, J. Canadian IBD Today, 2023; Vol 1, Issue 2; photos: Dr. M. Gooderham, Depositphoto.com

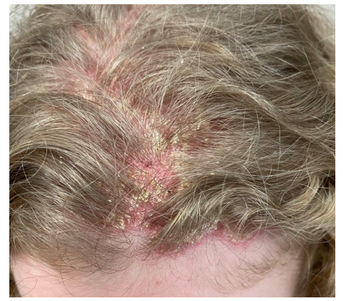
Anti-TNF therapy associated psoriasis or psoriasiform dermatitis in IBD patients

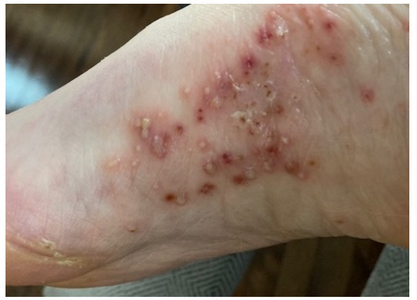
- Systematic review and meta-analysis
- **30 articles** comprising **24,547 IBD patients** treated by anti-TNF were included
- **overall pooled incidence** of **psoriasis** and/or **psoriasiform** lesions following anti-TNF therapy was **6.0%** (5.0–7.0%; I^2 = 93.9%)
- **6.9%** (5.1–8.7%; I^2 = 92.4%) **for psoriasiform** lesions and **4.6%** (3.6–5.6%; I^2 = 93.9%) **for psoriasis**.
- Female, younger age, smoker, ileocolonic Crohn's disease, and the types of anti-TNF were significantly associated with risk

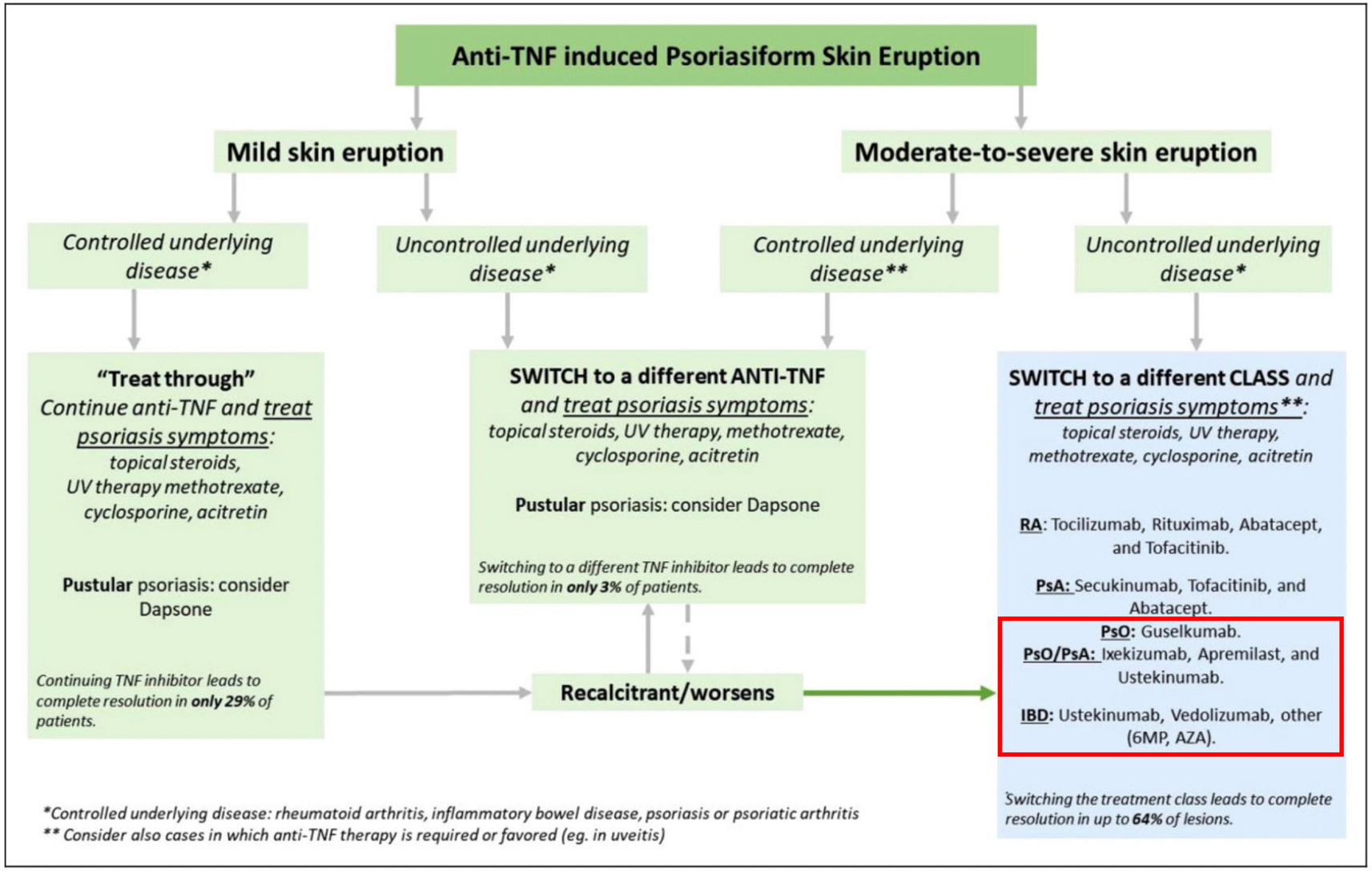


Xie W, et al (2022) Front. Immunol. 13:847160. doi: 10.3389/fimmu.2022.847160

MANAGING ANTI-TNF **INDUCED ERUPTION:**







** **Risankizumab and upadacitinib** were not available when this paper was published

Li et al. Journal of Psoriasis and Psoriatic Arthritis 4, 70–80.. doi:10.1177/2475530318810851; photos M. Gooderham

Paradoxical Psoriasiform Eruptions in Children Receiving TNFα Inhibitors

103 Patients with TNFi-induced psoriasiform eruptions

65 Patients continued initial TNFi

65 Psoriasiform treatment and response, %			
Treatment	Resolved or improved	No improvement	Not documented
Topicals alone	43 (66)	1 (2)	5 (8)
Methotrexate	12 (18)	0	0
Systemic steroids	1 (2)	1 (2)	0
Phototherapy + acitretin	1 (2)	0	0
Phototherapy	1 (2)	0	0

12 Patients discontinued initial TNFi and did not start second-line TNFi

12 Psoriasiform treatment and response, %			
Treatment	Resolved or improved	No improvement	Not documented
Topicals alone	2 (17)	2 (17)	1 (8)
Methotrexate	2 (17)	2 (17)	0
Azathioprine	1 (8)	0	0
Ustekinumab	2 (17)	0	0

26 Patients switched to second-line TNFi

26 Psoriasiform treatment and response, %			
Treatment	Resolved or improved	No improvement	Not documented
Topicals alone	14 (54)	1 (4)	1 (4)
Methotrexate	5 (19)	1 (4)	0
Systemic steroids	2 (8)	0	0
Phototherapy + systemic steroids	1 (4)	0	0
Phototherapy + methotrexate	1 (4)	0	0

18 Patients continued second-line TNFi without recurrent psoriasiform eruption

8 Patients developed a second TNFi-induced psoriasiform eruption

31%

2 Patients continued second-line TNFi

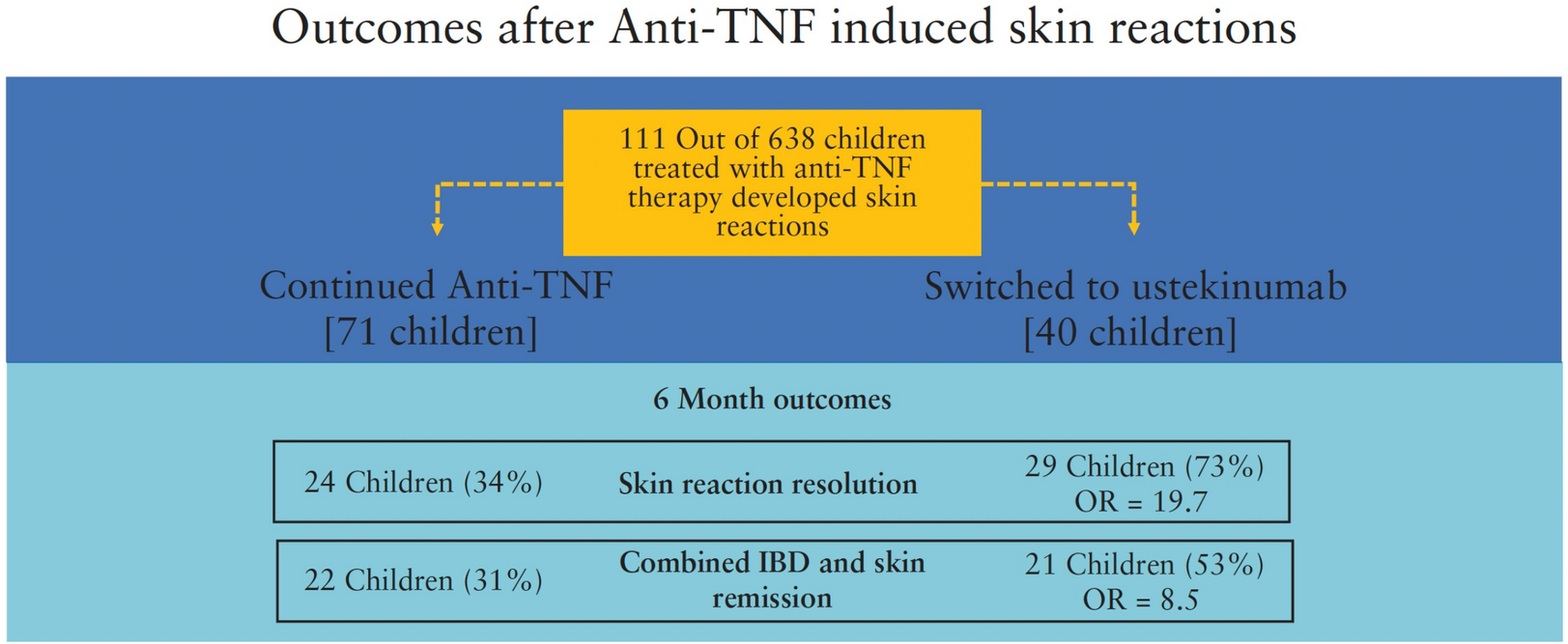
6 Patients discontinued second-line TNFi and did not start another biologic

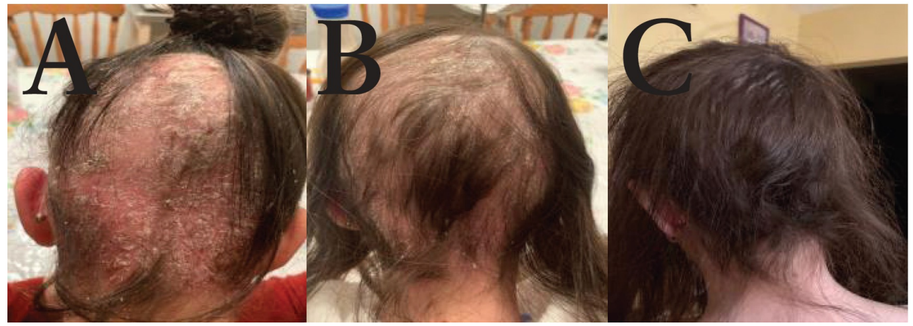
- Multi-centre retrospective chart review from **2000 – 2016** in pediatric patients
- N=103 identified; 65% treated with infliximab, 34% with adalimumab, and 1% with certolizumab pegol
- **IBD was the most common indication in 91%**
- **Scalp involvement most common 63%**

Eickstaedt J. *et al.* JAMA Dermatology. 2023;159(6):637

Outcomes of Children with Inflammatory Bowel Disease who Develop Anti-tumour Necrosis Factor-induced Skin Reactions

- Chart review of pediatric IBD with TNF skin reactions
- N=111/638 [**17%**] children **had a skin reaction**
- N=85, [21%] IFX; N=26, [11%] ADA
- N=80 [**72%**] had a **psoriasiform eruption**, N=25 [**23%**] **infections**, and N=4 [**4%**] **alopecia areata**
- 64% continued anti-TNF and 36% switched to UST
- Children who switched to UST were more likely to have improved outcomes



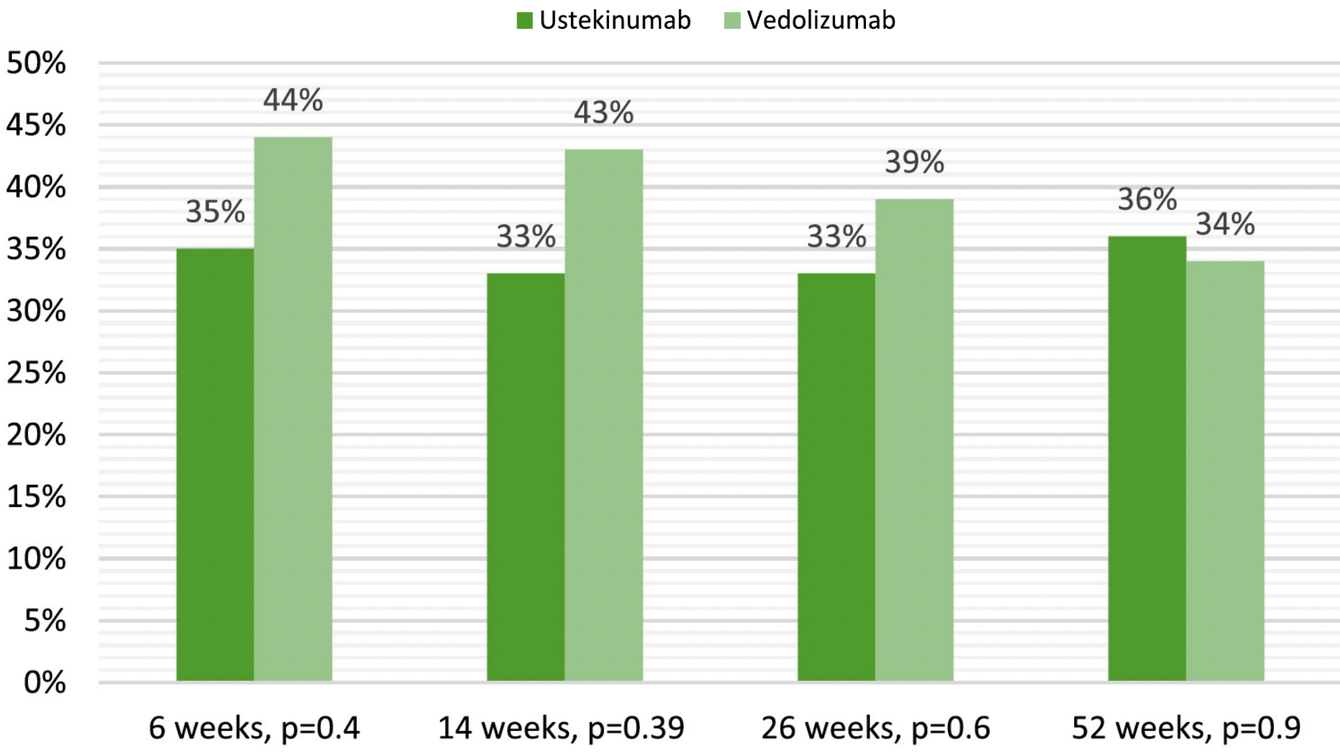


Journal of Crohn's and Colitis, 2022, **16**, 1420–1427

Ustekinumab and vedolizumab for EIMs in IBD- a retrospective study

- Retrospective review Sheba Medical Centre, 2015-2021
- **111 patients** were included: N=53 (48%) were treated with ustekinumab; 88% (N=99) had CD
- Most common EIM was **arthralgia** (n-95/111, 84%)
- Clinical response of EIM at week 52 in 36% of patients treated with ustekinumab (n-18/50) and 34% of patients (n-19/54) treated with vedolizumab, with **no statistically significant difference** (p = 0.9)

		Ustekinumab	Vedolizumab	*P* value
	Male	21 (40%)	29 (49%)	0.2
	Female	32 (60%)	29 (50%)	
		28 ± 13	33 ± 18	0.1
		39 ± 15	43 ± 19	0.2
		7 (13%)	8 (13.5%)	0.9
		10 (19%)	11 (19%)	0.3
		51 (96%)	36 (63%)	0.000
IBD	Crohn's disease	52 (98%)	46 (79%)	0.02
	Ulcerative colitis	1 (21%)	12 (20%)	
	Small bowel	30 (58%)	27 (59%)	0.9
	Colon	3 (6%)	5 (11%)	0.6
	Small bowel and colonic disease	19 (36%)	14 (30%)	0.6
	Inflammatory	21 (40%)	25 (53%)	0.2
	Stricturing	12 (23%)	13 (28%)	0.7
	Penetrating	19 (37%)	8 (19%)	0.09
	Proctitis	1 (100%)	0	
	Left sided	0	1 (8%)	
	Pancolitis	0	11 (92%)	
		4 (8%)	2 (4%)	0.3
EIM	Arthralgia	50 (94%)	56 (96.5%)	0.6
	Arthritis	10 (20%)	11 (19%)	0.4
	Back pain	9 (17%)	5 (8%)	0.3
	Sacroiliitis	2 (4%)	1 (2%)	0.5
	Apthous Stomatitis	1 (2%)	1 (2%)	0.9
	Erythema Nodosum	2 (4%)	3 (5%)	0.7
	Uveitis/Iritis	4 (8%)	2 (4%)	0.3
	Pyoderma	3 (5%)	1 (2%)	0.3



Clinical response of the intestinal disease VEDO vs. UST at different timepoints.

Digestive and Liver Disease 55 (2023) 223–229

Classification of Dermatological Manifestations of IBD

Classification:

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Treatment related

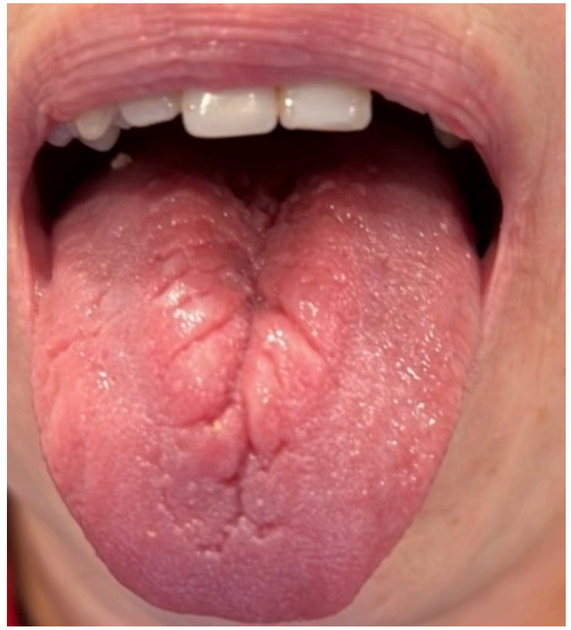
Nutritional malabsorption

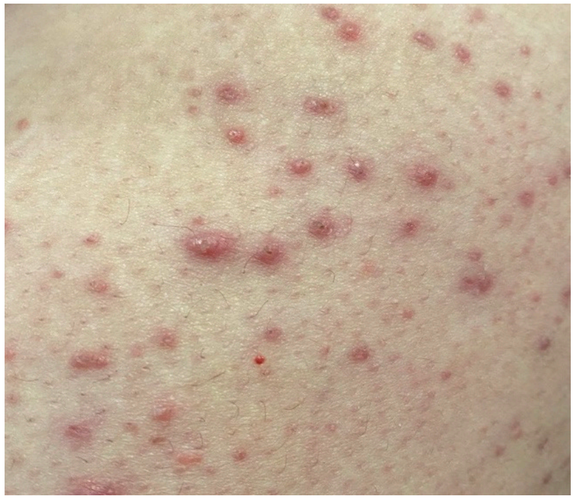
Classification of Dermatological Manifestations of IBD

Classification:	Specific manifestations	Associated disorders
Reactive manifestations	Treatment related	**Nutritional malabsorption**

Nutritional malabsorption

Deficient Nutrients	Disease	Cutaneous Manifestation
Vitamin B		Stomatitis, glossitis, angular cheilitis
Niacin (B3)	Pellagra	Photosensitivity, sunburn-like rash, Perigenital inflammation, glossitis
Zinc	Acrodermatitis Enteropathica	Acral and periorificial dermatitis, alopecia, glossitis, nail dystrophy
Vitamin C	Scurvy	Bruising, corkscrew hairs, follicular papules, splinter hemorrhages, bleeding gums
Vitamin A	Phrynoderma	Hyperkeratotic papules on thighs, arms
Vitamin K		Purpura





Photos M. Gooderham

Conclusions

01

Reviewed the various dermatological manifestations of IBD including specific and reactive manifestations, associated disorders and treatment related

02

Adverse effects of TNF inhibitors were reviewed with psoriasiform eruptions most common and often requiring a treatment switch

03

Highlighted the importance of newer targeted therapies and collaboration between specialties to improve patient outcomes

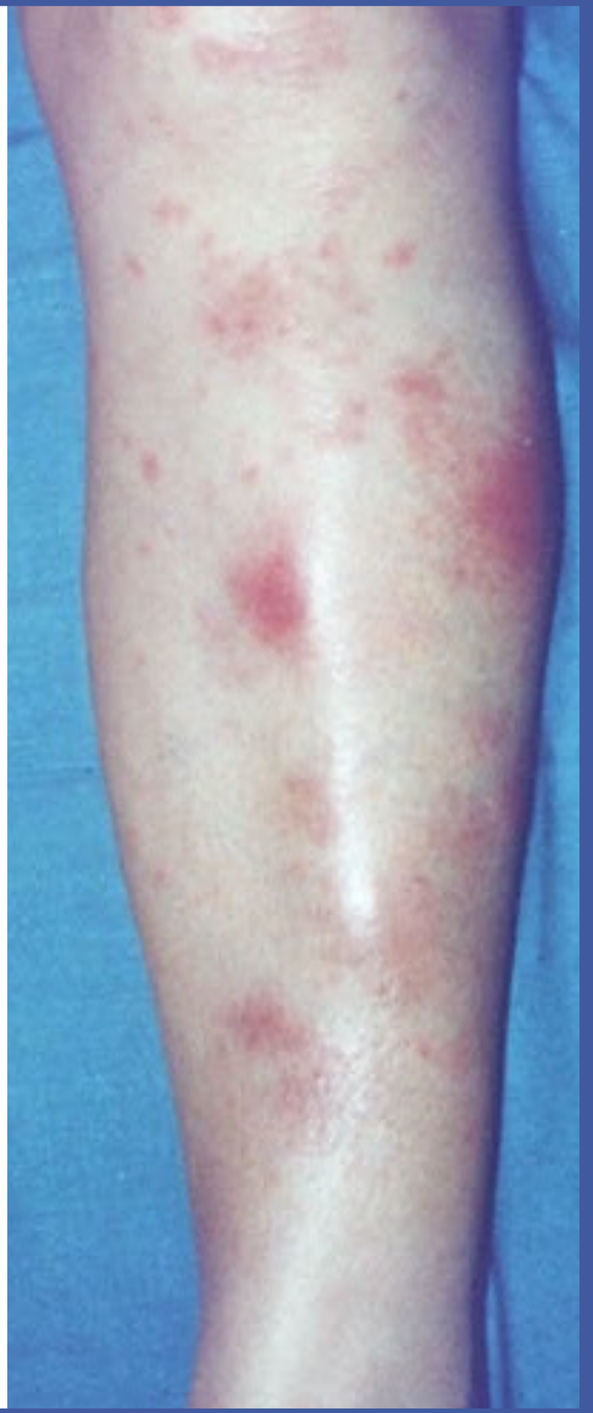


Photo Requena et al (2002).. *Dermatology Online Journal*, 8(1). http://dx.doi.org/10.5070/D34829t6rn