Microscopic Colitis – *practical Guide*

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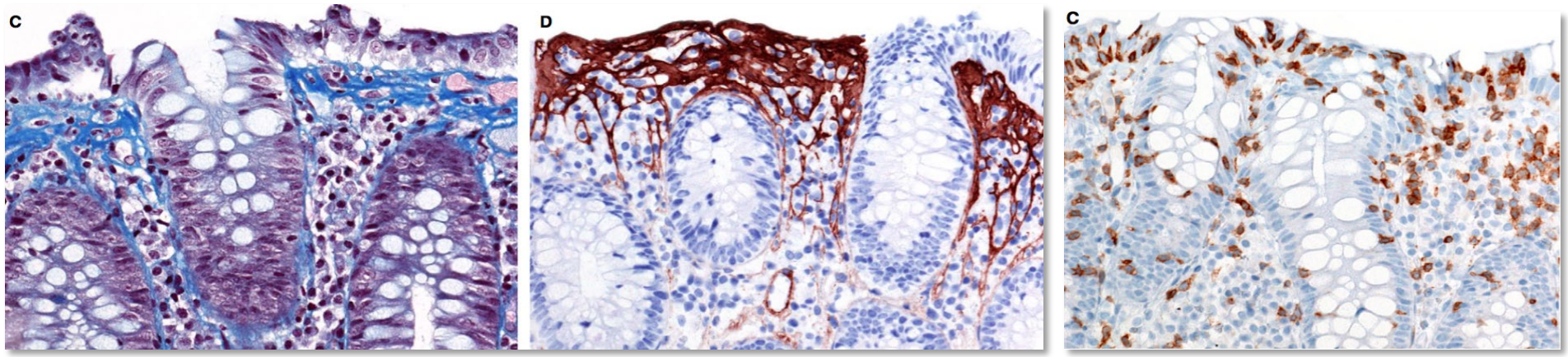
Board Member of the European Microscopic Colitis Group (EMCG)

Microscopic Colitis

What is it ?

How common is it?



Microscopic Colitis – a member of IBD Family

CONSENSUS/GUIDELINES

European consensus on the histopathology of inflammatory bowel disease☆

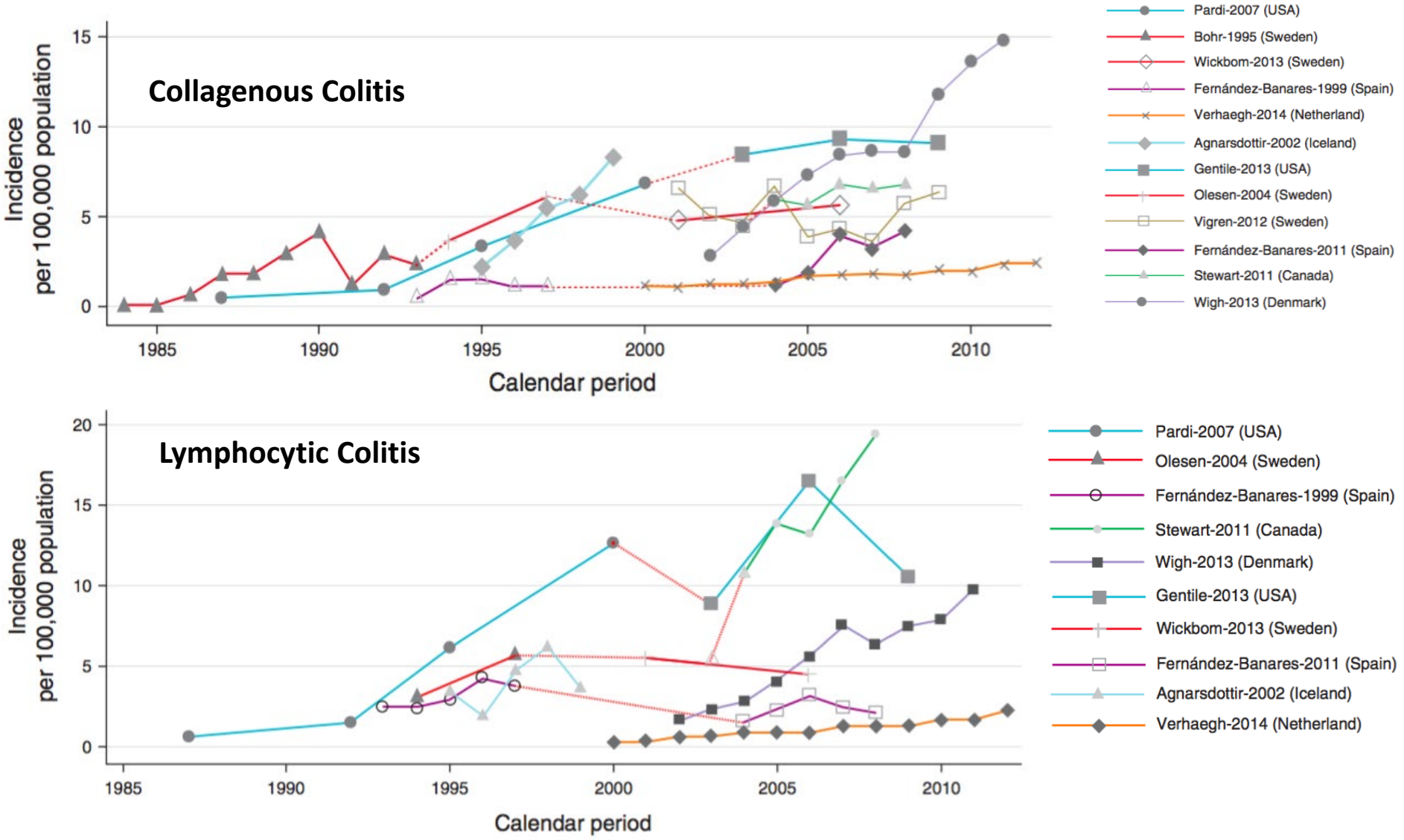
F. Magro[a,*,1], C. Langner[b,1], A. Driessen[c], A. Ensari[d], K. Geboes[e], G.J. Mantzaris[f], V. Villanacci[g], G. Becheanu[h], P. Borralho Nunes[i], G. Cathomas[j], W. Fries[k], A. Jouret-Mourin[l], C. Mescoli[m], G. de Petris[n], C.A. Rubio[o], N.A. Shepherd[p], M. Vieth[q], R. Eliakim[r] on behalf of the European Society of Pathology (ESP) and the European Crohn's and Colitis Organisation (ECCO)[2]

ECCO ESP statement 31

*The term **microscopic colitis** describes a **clinical pathological entity** characterized by **three elements**: (i) a clinical history of **chronic watery (non-bloody) diarrhea**; (ii) a **normal or almost normal endoscopic appearance** of the colon; (iii) a **distinct histologic pattern**. The latter can be either that of **collagenous colitis** or that of **lymphocytic colitis** [EL1]*

J Crohns & Colitis 2013

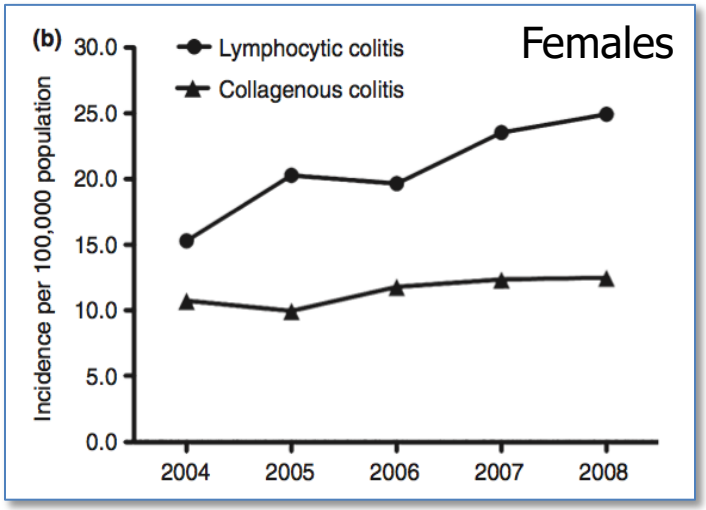
Epidemiology of Microscopic Colitis

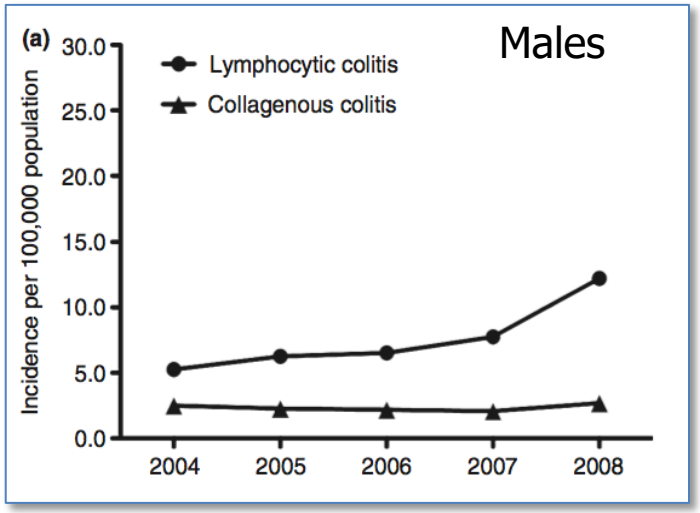


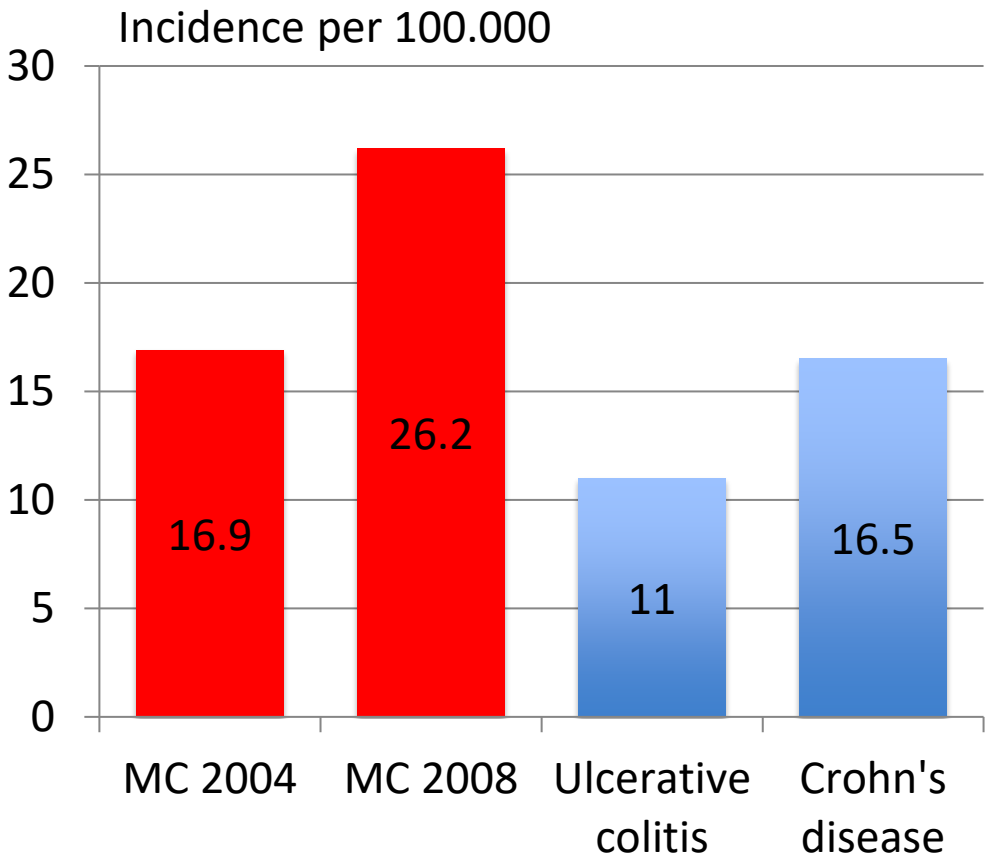
Tong et al, Am J Gastroenterol 2015

Epidemiology of Microscopic Colitis

Population-based Study, Calgary, Canada



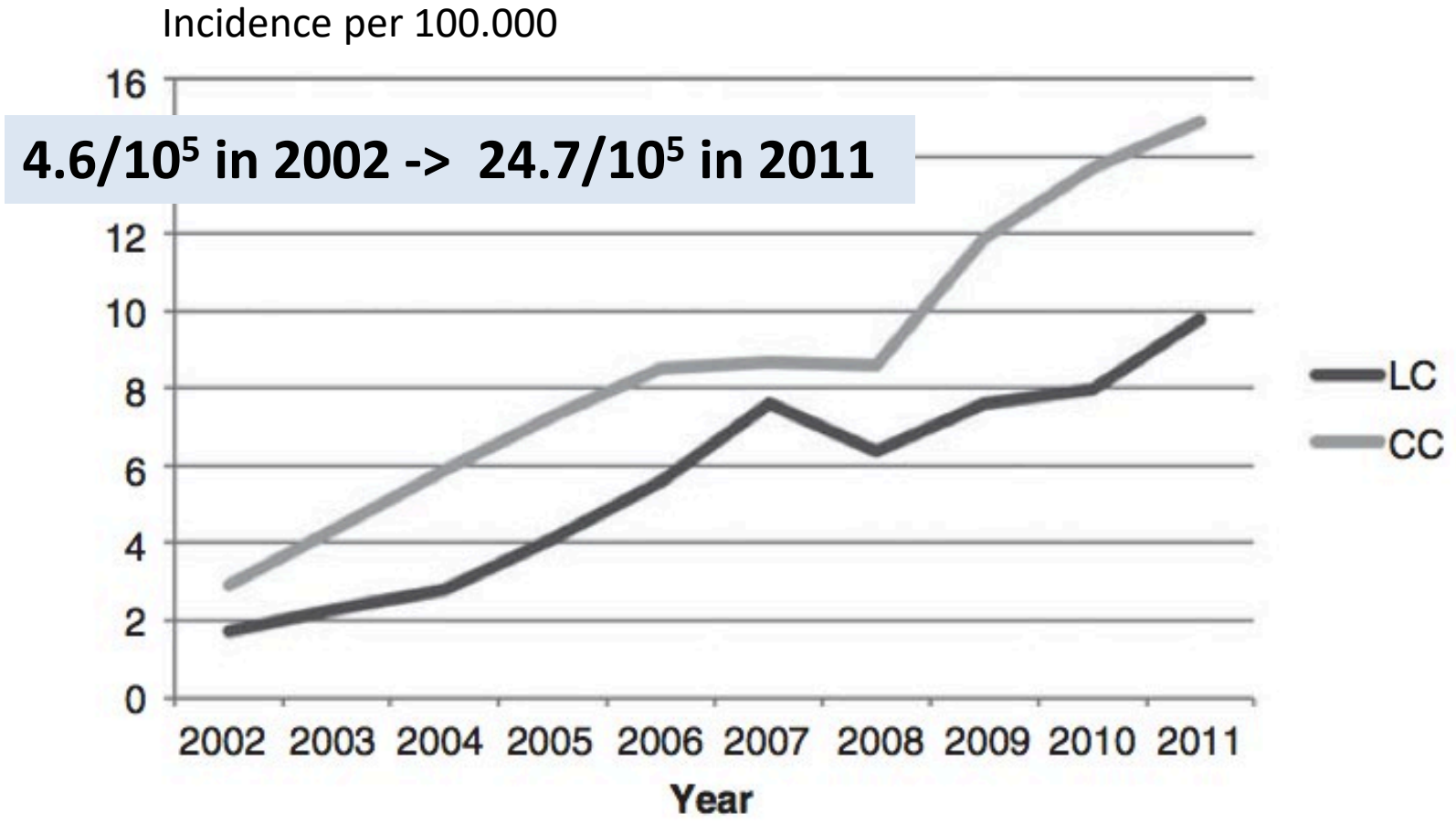




Stewart M et al, Aliment Pharmacol Ther 2011

Epidemiology of Microscopic Colitis

Nation-wide, register-based Cohort Study, Denmark, 2002-2011



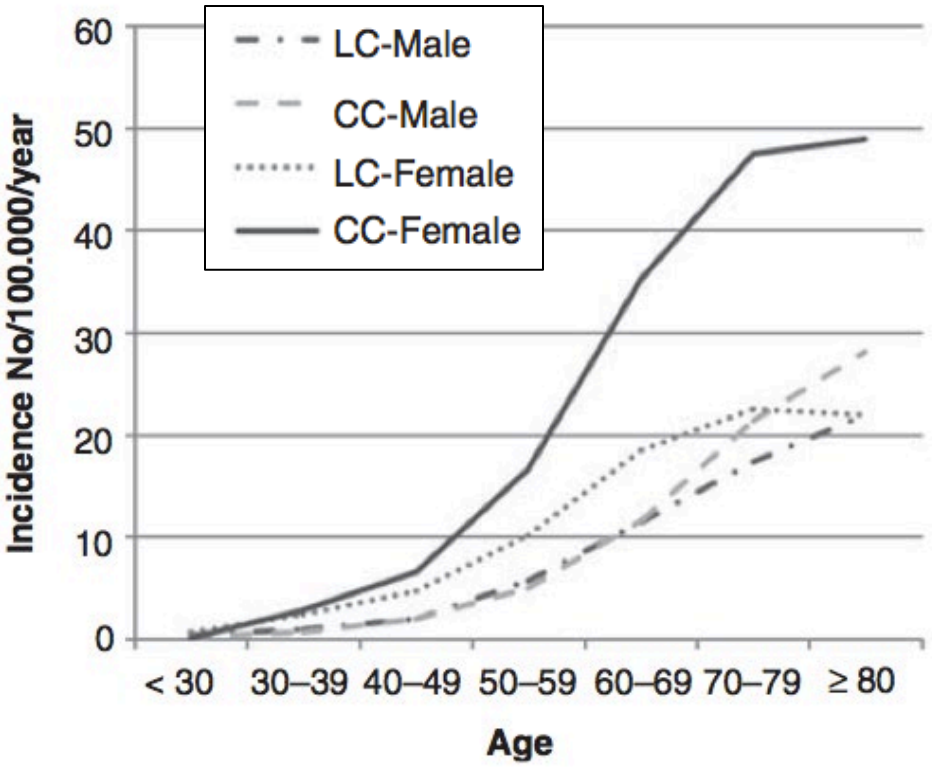
4.6/10^5 in 2002 -> 24.7/10^5 in 2011

Bonderup OK et al, Scand J Gastroenterol 2015

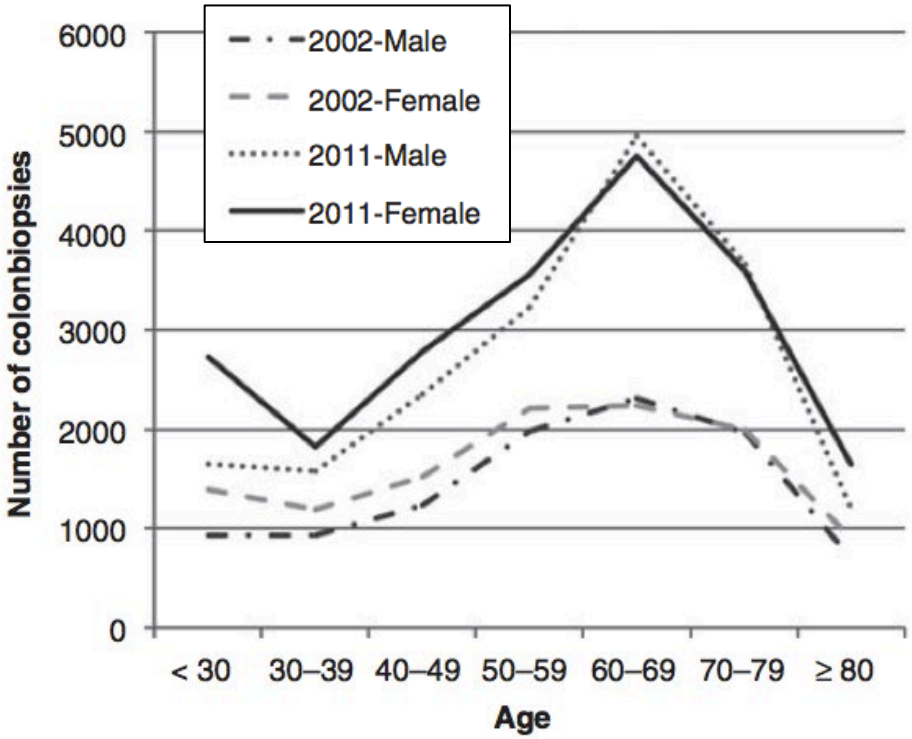
Epidemiology of Microscopic Colitis

Nation-wide, register-based Cohort Study, Denmark, 2002-2011

Age-specific Incidence



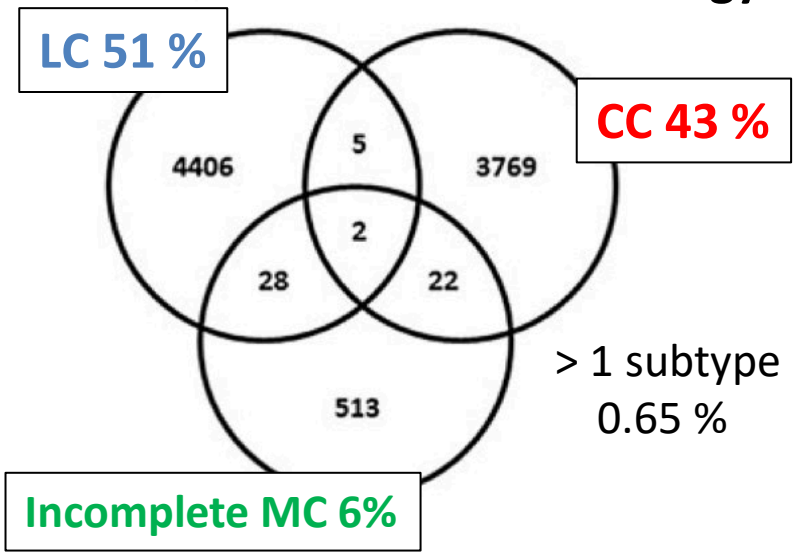
Biopsy Rate



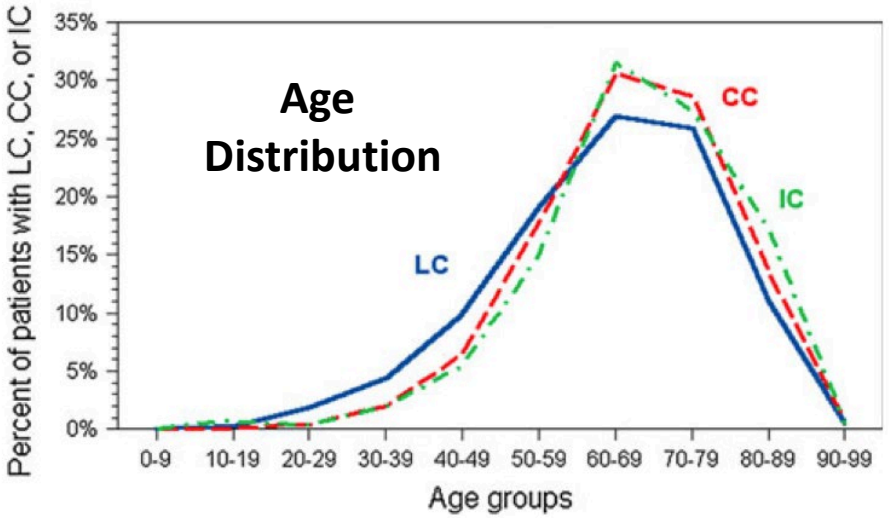
Bonderup OK et al, Scand J Gastroenterol 2015

Epidemiology of Microscopic Colitis

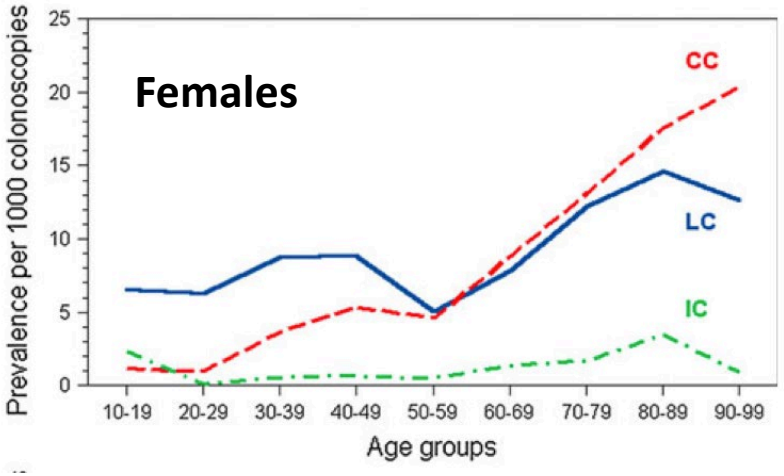
U.S. Pathology Database, 8745 MC cases

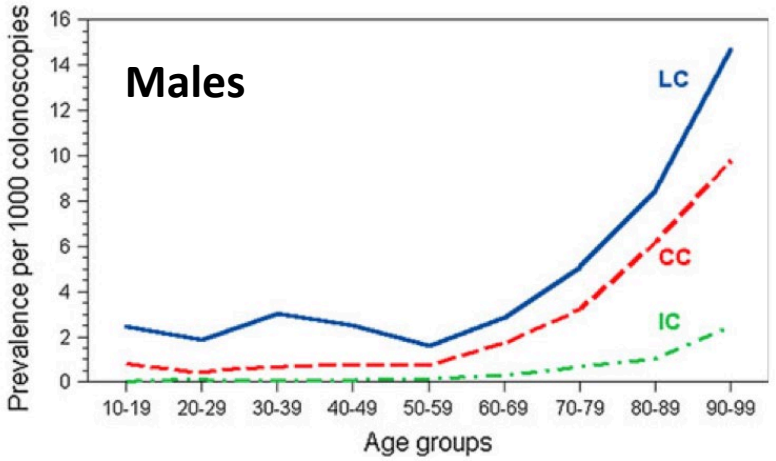


> 1 subtype
0.65 %



Prevalence per 1000 colonoscopies





Sonnenberg A, Genta RM, Dig Dis Sci 2013

Epidemiology of Microscopic Colitis

European guideline on the management of microscopic colitis

EMCG European Microscopic Colitis Group

in association with UNITED EUROPEAN GASTROENTEROLOGY ueg

Metanalyses 2019

Pooled incidence rates

- **MC: 11.4/100,000** person-years (9.2-13.6)
- CC: 4.9 /100,000, LC: 5.0/100.000

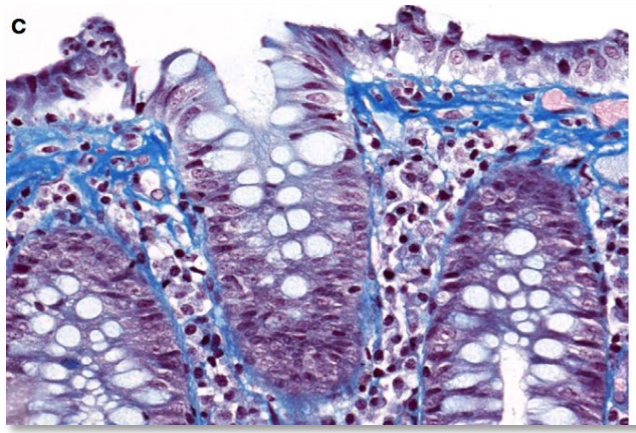
Pooled prevalence rates

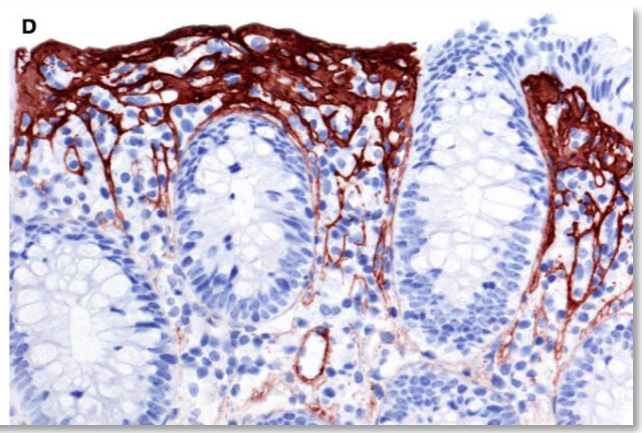
- **MC: 119/100.000** persons (73 to 166)
- CC: 50.1 /100.000, LC: 61.7/100.000

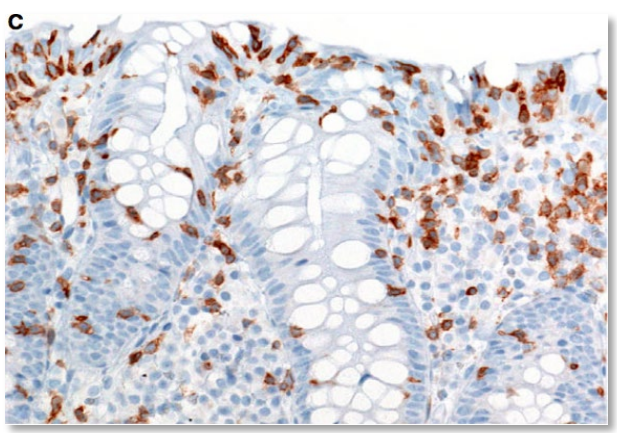
Miehlke S et al. UEG Journal 2020, in preparation

Microscopic Colitis

Risk factors







Studies on MC and Drug Exposure

1°Author, Year	Country	Study design	Setting	Diseases assessed	Control group	Drugs investigated
Riddell, 1992	Canada	Case-control, retrospective	Single-center	CC n=31	IBS, diverticulosis	NSAID
Keszthelyi, 2010	Netherlands	Case-control, retrospective	Multi-center	CC, LC n=95	General population	PPI, NSAID
Fernandez-B. 2007	Spain	Case-control, prospective	Single-center	CC, LC n=78	Functional diarrhea, Outpatient surgery unit	NSAID, SSRI, ß-blockers, statins, bisphophonates
Fernandez-B. 2013	Spain	Case-control, prospective	Multi-center	CC, LC n=190	Outpatient surgery unit	lansoprazole, aspirin, ß-blockers, sertraline, omeprazole, antidiabetics
Thorn, 2013	Sweden	CC vs. LC, prospective	Multi-center	CC, LC n=272	General Population, Uppsala region	PPI
Bonderup, 2014	Denmark	Case-control, retrospective	Nation-wide	CC, LC n=5751	General population	PPI, NSAID, statins, SSRI
Macaigne, 2014	France	Case-control, prospective	Multi-center	CC, LC n=128	IBS-D	Any new drug (<3 months)
Guagnozzi, 2015	Spain	Case-control, prospective	Single-center	CC, LC n=46	Chronic diarrhea, normal colonic biopsy	Topiramate, NSAID
Masclee , 2015	Netherlands	Case-control, retrospective	Nation-wide	CC, LC n=162	General population normal colonic biopsy	PPI, NSAID, aspirin, SSRI, ß-blockers, ACE inhibitors
Verhaegh, 2016	UK	Case-control, retrospective	Nation-wide	CC, LC, MCi n=1211	General population	PPI, NSAID, statins, SSRI, H2-RA
Bonderup, 2018	Denmark	Case-control, retrospective	Nation-wide	CC, LC n=10.652	General population	PPI, NSAID

adapted from Lucendo A, Drugs R D 2017

High risk of drug-induced microscopic colitis with concomitant use of NSAIDs and proton pump inhibitors

retrospective study, **1211 MC**, British Clinical Research Datalink, 1992-2013

	Cases		Controls		Adjusted†
	n	%	*n*	%	OR (95% CI)
NSAID use alone					
Never	124	10.2	492	8.1	1.00
Past use	500	41.3	2497	41.3	0.91 (0.80–1.06)
Recent use	50	4.1	189	3.1	1.31 (0.93–1.86)
Current use	44	3.6	177	2.9	1.29 (0.90–1.86)
PPI use alone					
Never	292	24.1	2173	36.0	1.00
Past use	88	7.3	375	6.2	1.15 (0.89–1.48)
Recent use	128	10.6	288	4.8	2.73 (2.15–3.46)**
Current use	210	17.3	519	8.6	2.41 (1.98–2.92)**
Concomitant NSAID and PPI use					
Never	184	15.2	1772	29.3	1.00
Past use	216	17.8	800	13.2	1.42 (1.19–1.69)**
Recent use	44	3.6	40	0.7	5.40 (3.46–8.42)**
Current use	49	4.1	74	1.2	3.61 (2.46–5.29)**

Verhaegh B et al, Aliment Pharmacol Ther 2016

Significant association between the use of different proton pump inhibitors and microscopic colitis: a nationwide Danish case-control study

retrospective, **10.652 MC** cases, 2004-2013, registry-based

PPI	Numbers exposed		Crude OR (95% CI)	Adjusted OR (95% CI)
	Cases	Controls		
Collagenous colitis				
Never users	2040	40 533	1.00 (Ref)	1.00 (Ref)
Current users	2470	6088	9.17 (8.52-9.88)	6.98 (6.45-7.55)
Recent users	904	3225	5.95 (5.39-6.57)	5.16 (4.66-5.72)
Past users	836	9996	1.75 (1.60-1.92)	1.52 (1.39-1.67)
Lymphocytic colitis				
Never users	1980	28760	1.00 (Ref)	1.00 (Ref)
Current users	1267	3791	5.24 (4.80-5.72)	3.95 (3.60-4.33)
Recent users	413	2102	2.82 (2.49-3.20)	2.31 (2.03-2.64)
Past users	742	6886	1.59 (1.45-1.75)	1.35 (1.23-1.49)

Bonderup O et al, Aliment Pharmacol Ther 2018

Significant association between the use of different proton pump inhibitors and microscopic colitis: a nationwide Danish case-control study

retrospective, **10.652 MC** cases, 2004-2013, registry-based

Collagenous colitis

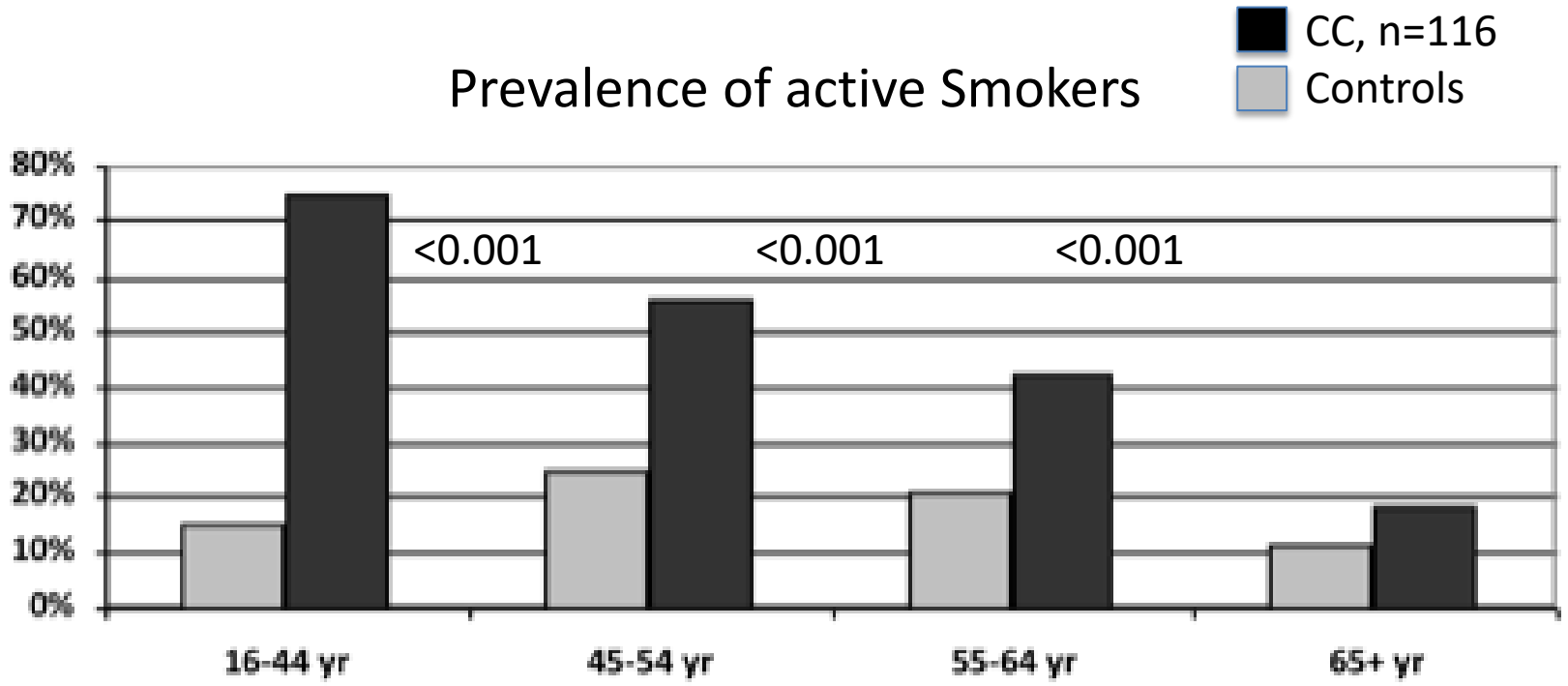
	Numbers exposed			
	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Collagenous colitis				
Neither PPI nor NSAIDs	3157	48 037	1.00 (ref)	1.00 (ref)
PPI but not NSAIDs	1751	4856	6.00 (5.59-6.44)	4.78 (4.43-5.15)
NSAIDs but not PPI	623	5717	1.72 (1.56-1.89)	1.60 (1.45-1.76)
Both PPI and NSAIDs	719	1232	9.26 (8.26-10.36)	7.45 (6.63-8.38)

Lymphocytic colitis

	Numbers exposed			
	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Lymphocytic colitis				
Neither PPI nor NSAIDs	2714	33 998	1.00 (ref)	1.00 (ref)
PPI but not NSAIDs	1006	3059	4.29 (3.94-4.68)	3.34 (3.05-3.66)
NSAIDs but not PPI	421	3750	1.41 (1.26-1.57)	1.28 (1.14-1.43)
Both PPI and NSAIDs	261	732	4.88 (4.15-5.75)	3.54 (2.98-4.20)

Bonderup O et al, Aliment Pharmacol Ther 2018

Smoking is a Risk Factor for MC



CC diagnosis 14 years earlier smokers than in non-smokers ($p<0.003$)

All CC smokers started smoking before CC diagnosis (median 17 years)

Vigren et al , Scand J Gastroenterol 2011

Smoking is Associated with an Increased Risk of Microscopic Colitis: Results From Two Large Prospective Cohort Studies of US Women

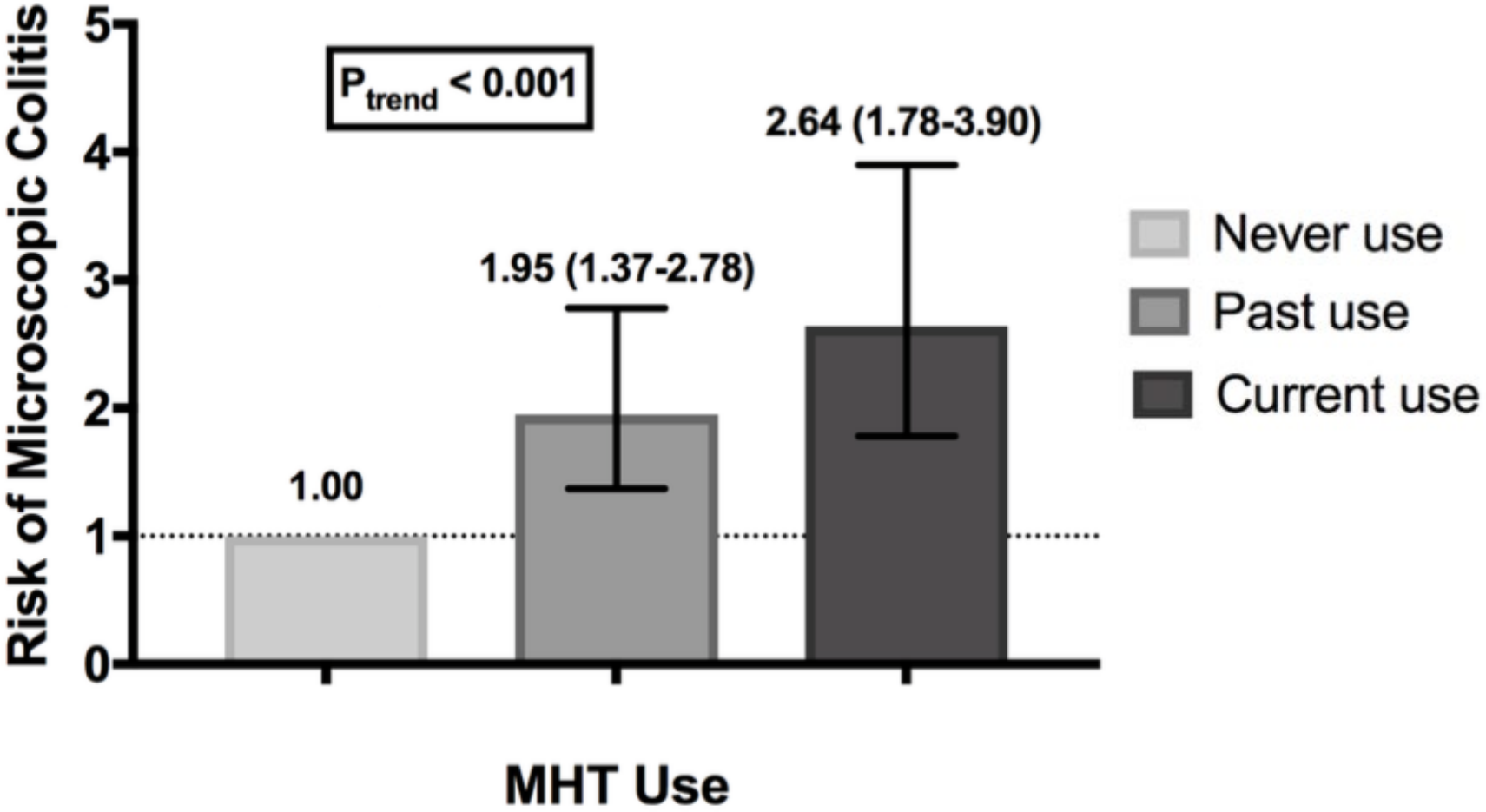
166 incident MC

	No. of case	Age-adjusted hazard ratio [95% CI]	Multivariable-adjusted hazard ratio [95% CI][1]
Smoking status			
Never	61	[reference]	[reference]
Past	78	1.56 [1.11, 2.19]	1.54 [1.09, 2.17]
Current	27	2.59 [1.64, 4.10]	2.52 [1.59, 4.00]
p trend		<0.0001	<0.0001
Pack-years of smoking			
Never	61	[reference]	[reference]
≤ 10 years	35	1.56 [1.03, 2.37]	1.53 [1.00, 2.32]
10.1–20 years	17	1.28 [0.75, 2.20]	1.27 [0.74, 2.18]
20.1–30 years	19	2.28 [1.36, 3.84]	2.23 [1.32, 3.75]
30.1–50 years	24	2.32 [1.43, 3.75]	2.31 [1.42, 3.75]
> 50 years	10	1.79 [0.90, 3.55]	1.79 [0.90, 3.56]
p trend[2]		0.0042	0.0013
Years since smoking discontinuation			
Current smokers	27	[reference]	[reference]
0–5 years	11	0.94 [0.47–1.90]	0.97 [0.47–1.95]
>5 years	67	0.57 [0.36–0.89]	0.57 [0.36–0.91]
Never smokers	61	0.39 [0.24–0.61]	0.40 [0.24–0.63]
p trend[3]		0.012	0.017

Burke KE et al, J Crohn' Colitis 2018

Identification of Menopausal and Reproductive Risk Factors for Microscopic Colitis – Results From the Nurses' Health Study

NHS + NHSII, 227.766 women, 1988-2015, 275 incident MC cases



MHT: Menopausal Hormone Therapy

Burke KE et al, Gastroenterology 2018

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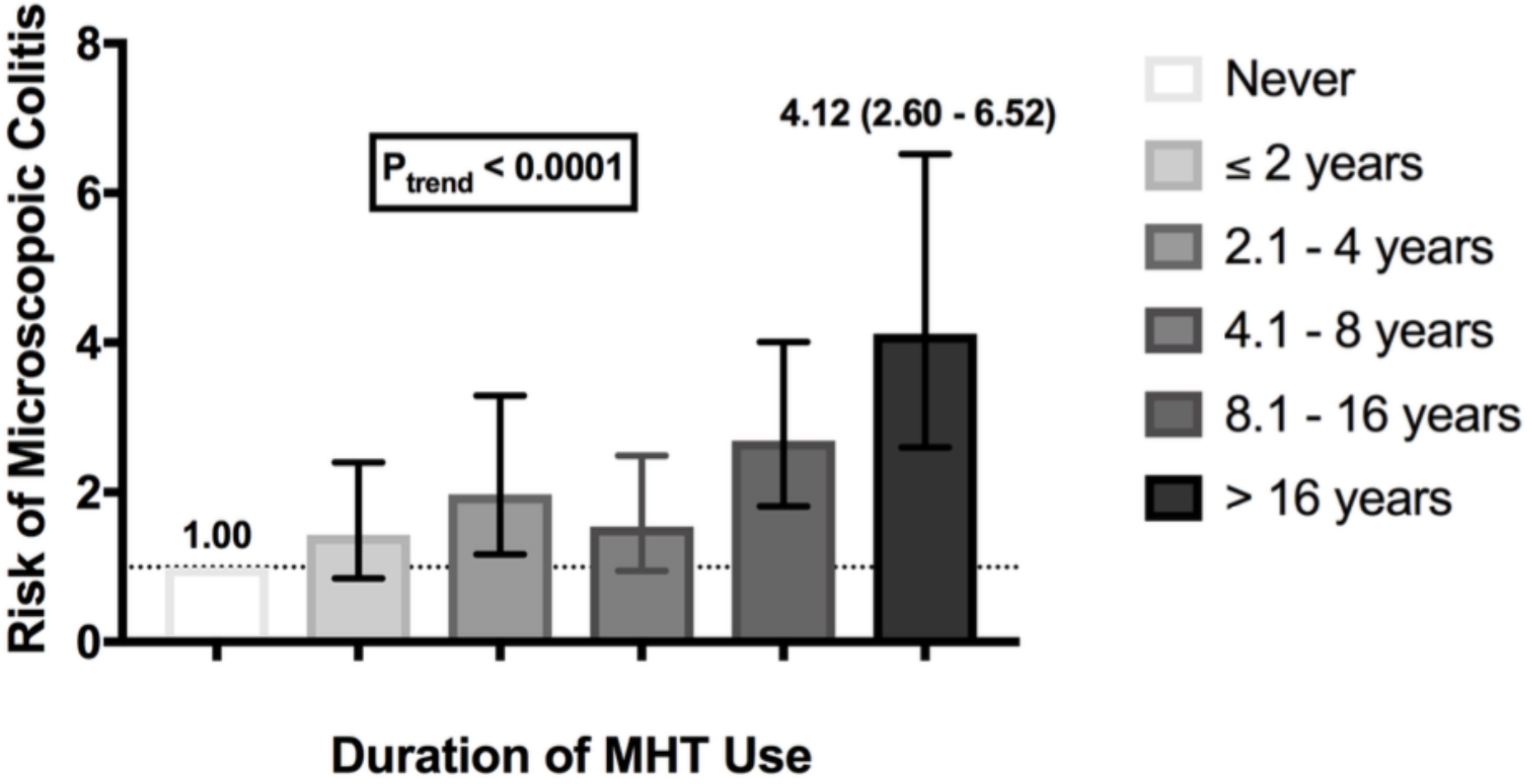

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Burke KE et al, Gastroenterology 2018

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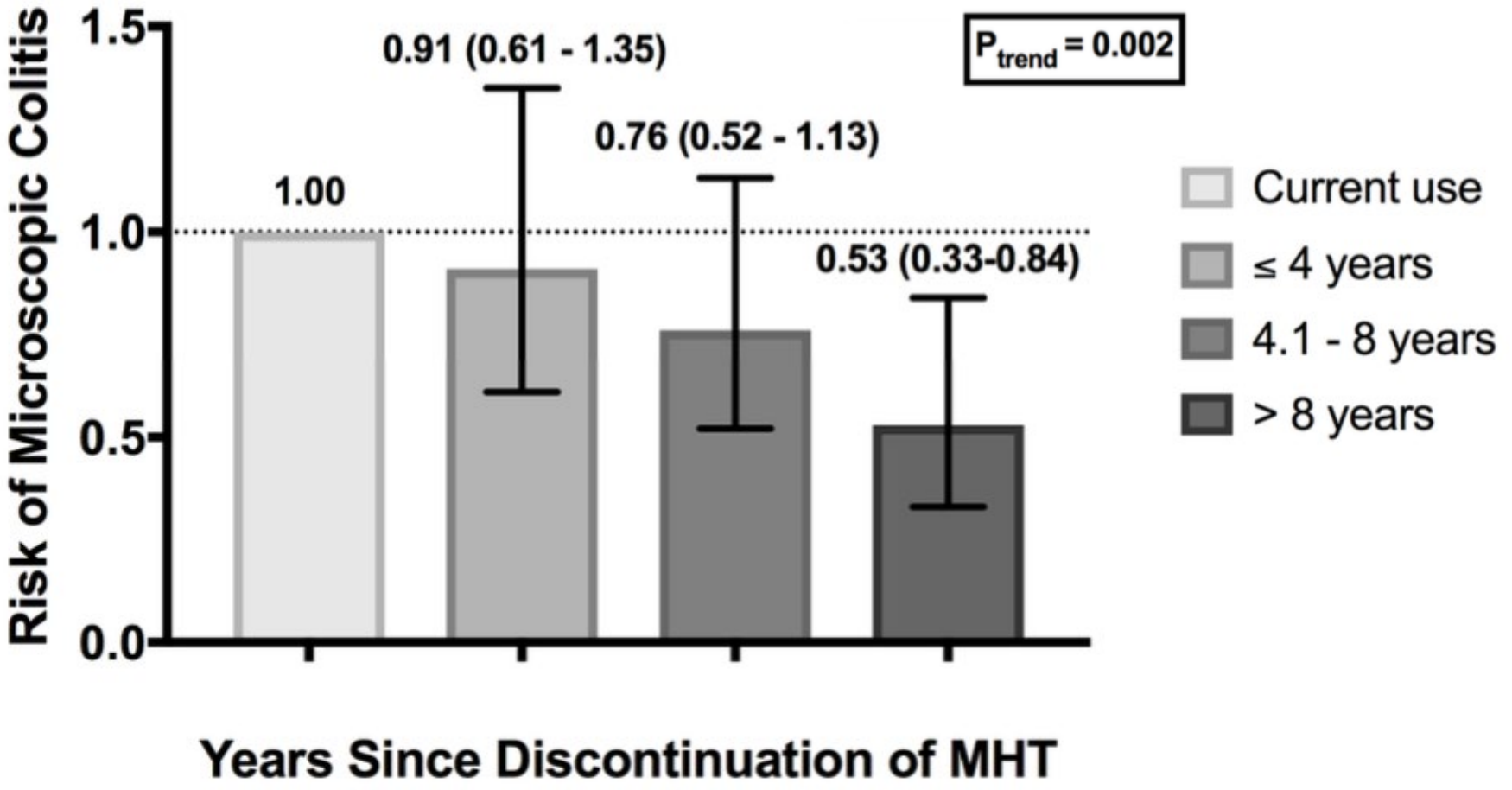
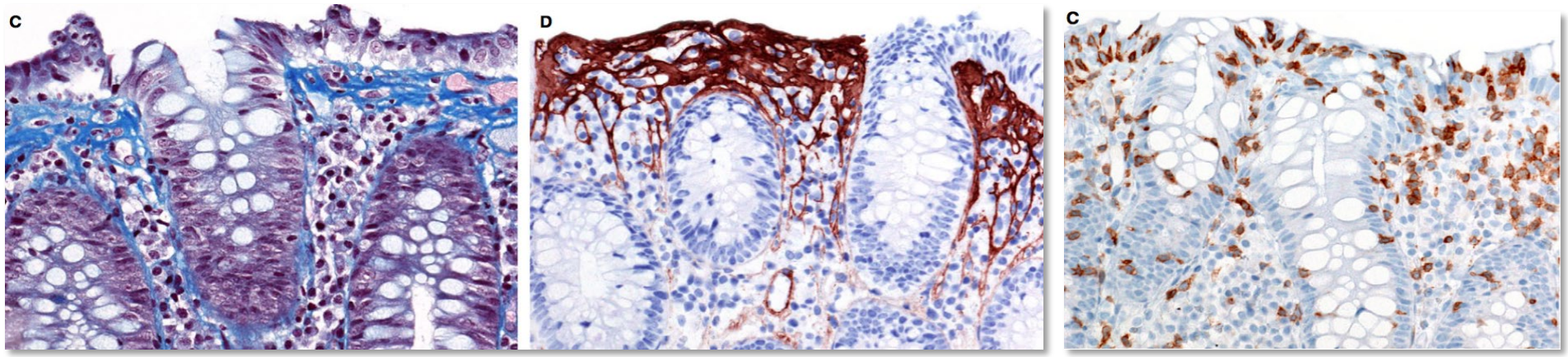


MHT: Menopausal Hormone Therapy

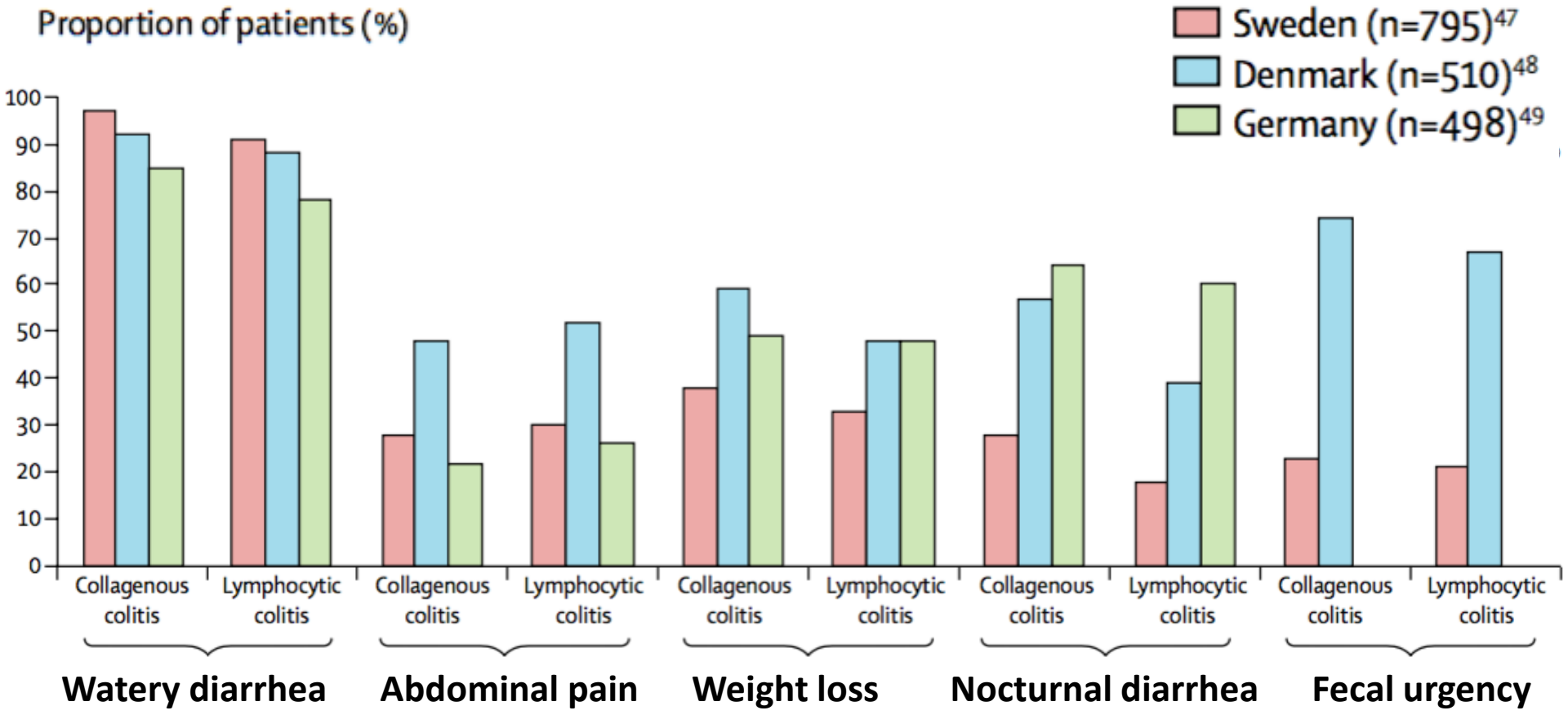
Burke KE et al, Gastroenterology 2018

Microscopic Colitis

Symptoms (burden of disease)
Quality of life
Assessment of disease activity



Symptom Burden in Microscopic Colitis



Mellander MR et al, *Scand J Gastroenterol* 2016
Bjornbak C et al, *Aliment Pharmacol Ther* 2011
Madisch A et al, *Z Gastroenterol* 2014

Miehlke S et al.
Lancet Gastroenterol Hepatol 2019

Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case–control study

Collagenous colitis (n=115)

	CC, *n* = 115 (%)	Matched controls, *n* = 263 (%)	OR	95% CI
Diarrhoea last week	43 (39%)	26 (10%)	5.7	3.3–10.0 ***
Constipation	16 (14%)	26 (10%)	1.4	0.7–2.8
Abdominal pain	56 (50%)	51 (20%)	4.0	2.5–6.5***
Fatigue	67 (58%)	99 (38%)	2.2	1.4–3.5**
Arthralgia	67 (59%)	95 (37%)	2.5	1.6–3.9***
Myalgia	60 (53%)	92 (36%)	2.0	1.3–3.1**
Faecal incontinence	43 (39%)	23 (9%)	6.2	3.5–11.1***
Nocturnal defecation	17 (16%)	7 (3%)	6.3	2.5–15.7***

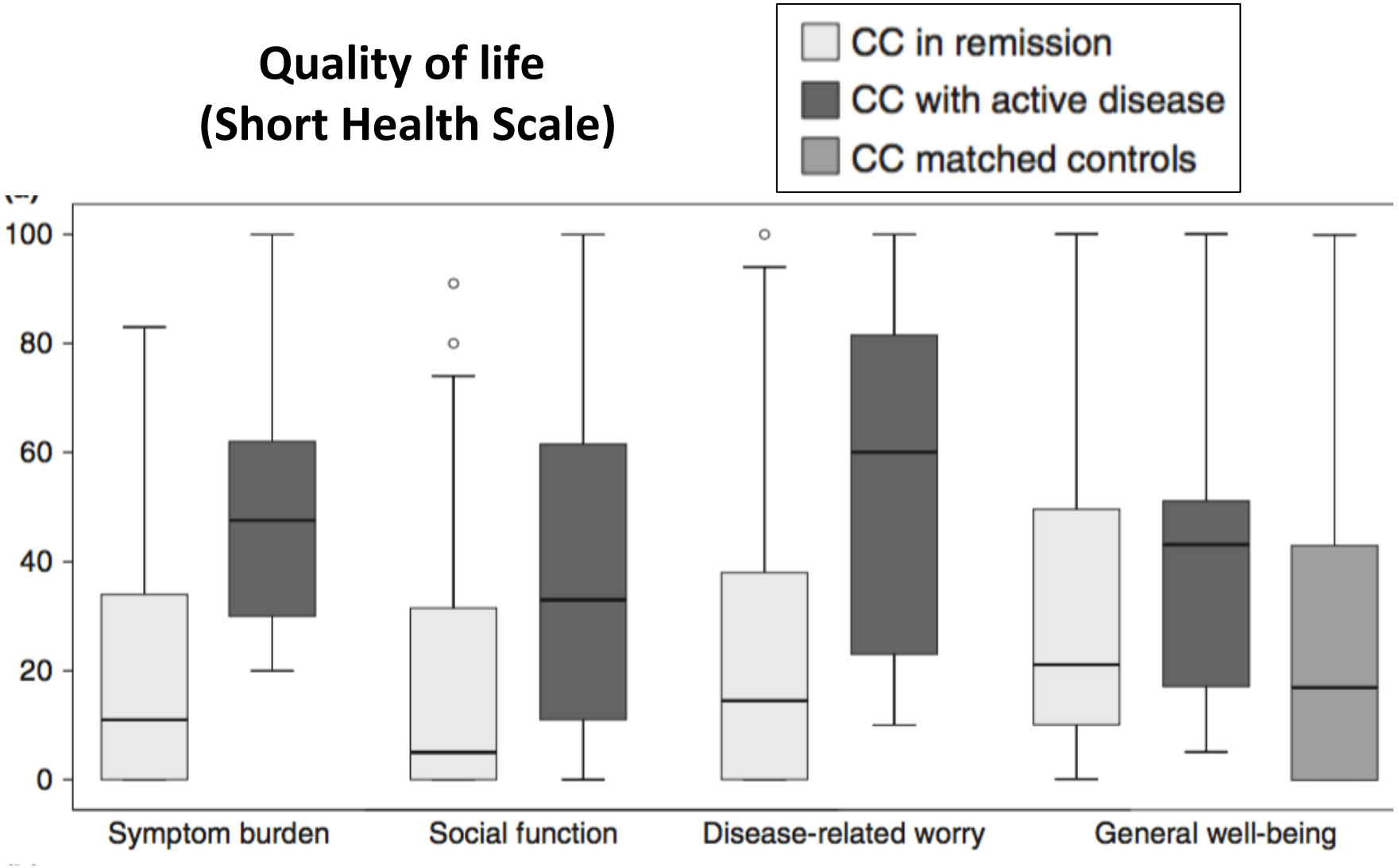
Lymphocytic colitis (n=97)

	LC, *n* = 97 (%)	Matched controls, *n* = 224 (%)	OR	95% CI
Diarrhoea last week	47 (50%)	25 (11%)	7.9	4.4–14.1***
Obstipation	10 (10%)	35 (16%)	0.6	0.3–1.3
Abdominal pain	50 (52%)	57 (26%)	3.1	1.8–5.0***
Fatigue	63 (67%)	84 (39%)	3.2	1.9–5.4***
Arthralgia	48 (50%)	96 (44%)	1.2	0.8–2.0
Myalgia	44 (46%)	95 (44%)	1.1	0.7–1.8
Faecal incontinence	34 (36%)	15 (7%)	7.4	3.8–14.5***
Nocturnal defecation	14 (16%)	4 (2%)	9.7	3.1–30.3***

Nyhlin N et al, Aliment Pharmacol Ther 2014

Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case–control study

Quality of life (Short Health Scale)



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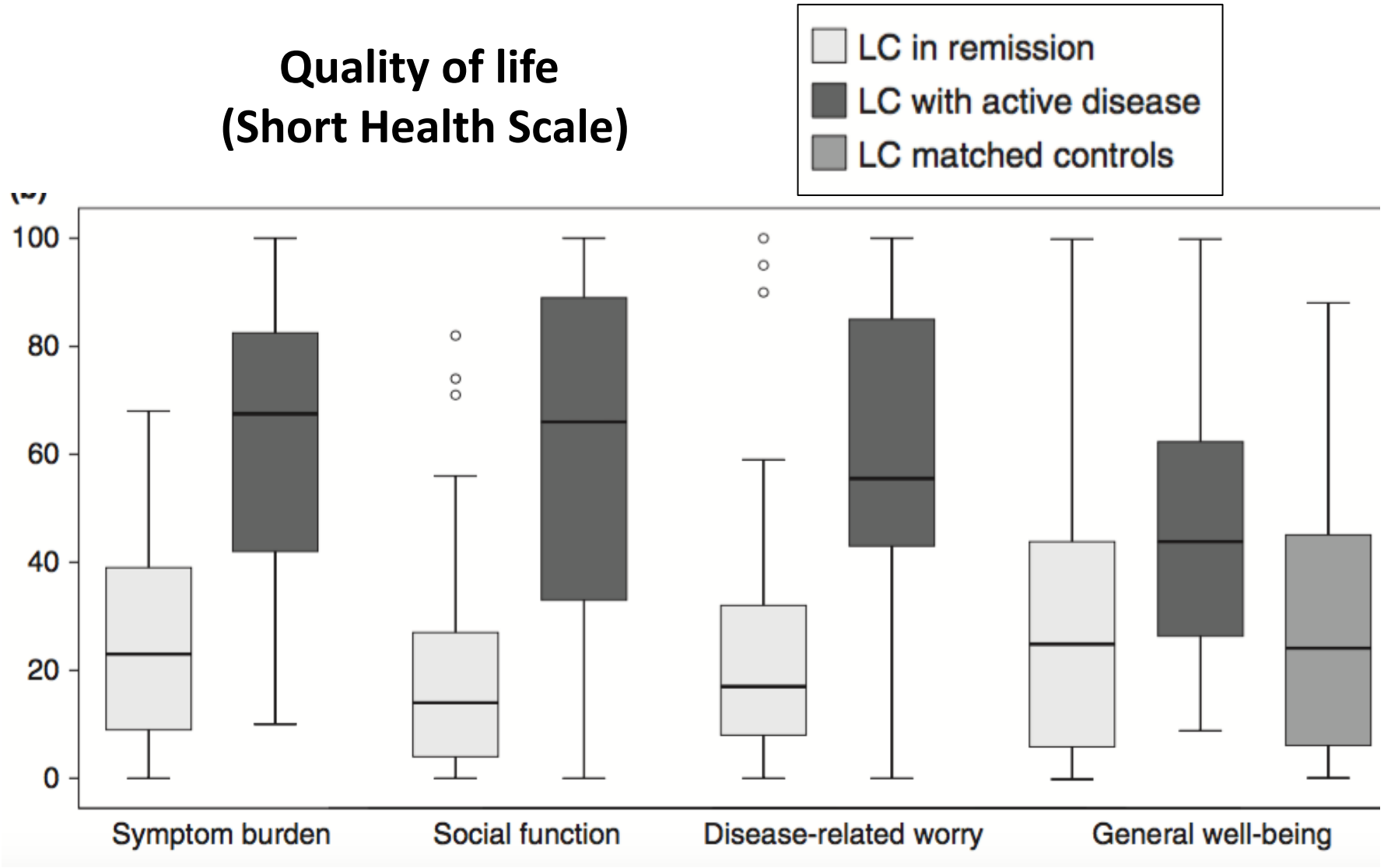
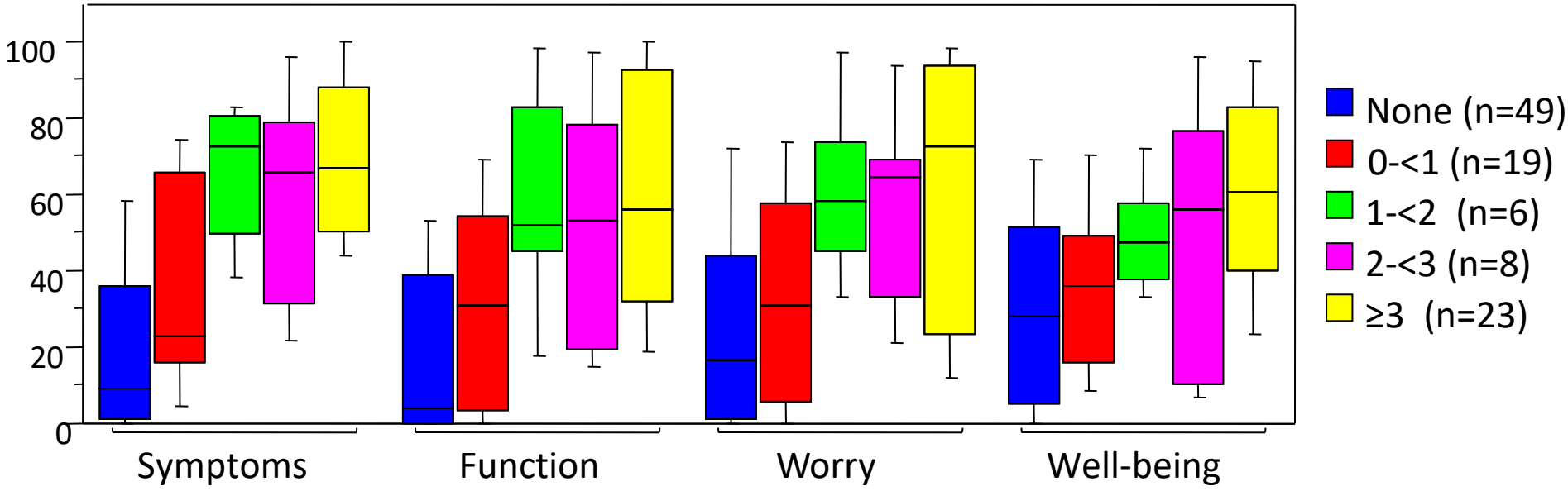


Nyhlin N et al, Aliment Pharmacol Ther 2014

Disease Activity in Microscopic Colitis

Impact of watery stools on QoL (SHS), n=116 CC



Hjortswang criteria	Stools/day		Watery Stools/day
Active disease	≥3	or	≥1
Remission	<3	and	<1

1-week symptom registration

Hjortswang H et al, Dig Liver Dis 2009

Work in progress: Development of the European Microscopic Colitis Disease Activity Index (E-MCDAI)

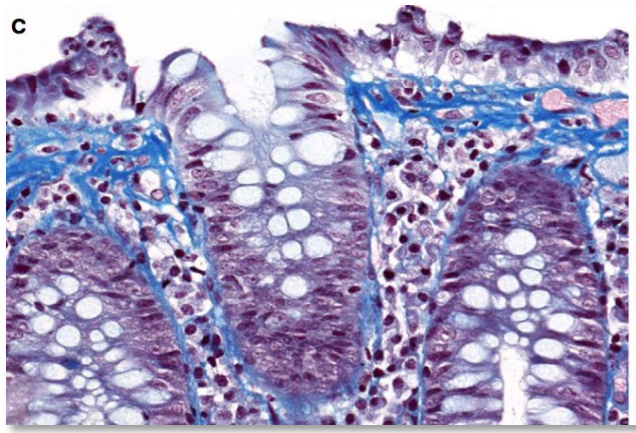
EMCG
EUROPEAN MICROSCOPIC COLITIS GROUP

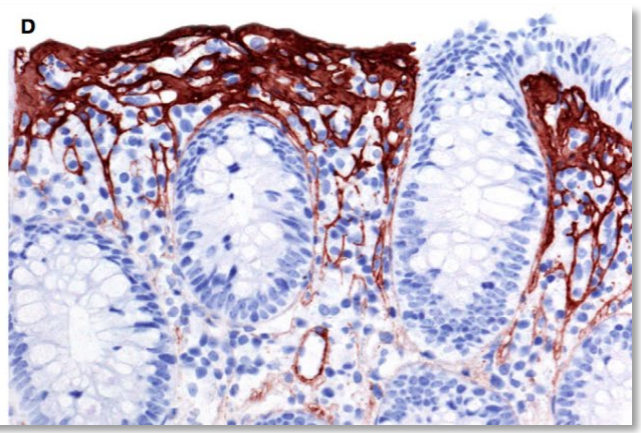
Henrik Hjortswang, Katarina Lesnovska Linköping, Sweden

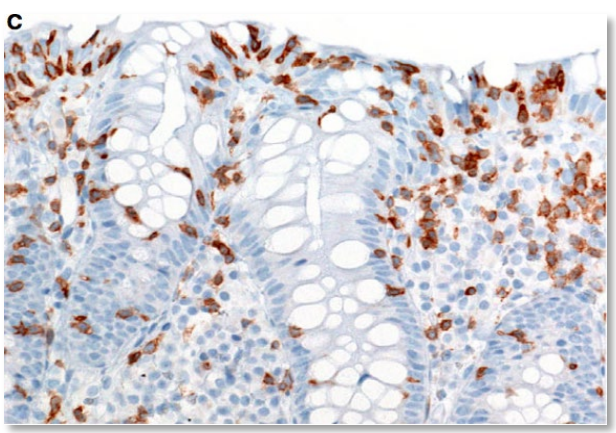
Step 1	Draft of items	Literature review Qualitative interviews Content validity (experts) Translation/cognitive interv.
Step 2	Cross-sectional evaluation of first version	Content validity (patients) Construct validity Reliability
Step 3	Longitudinal Evaluation of second version	Construct validity Responsiveness

Microscopic Colitis

Diagnosis

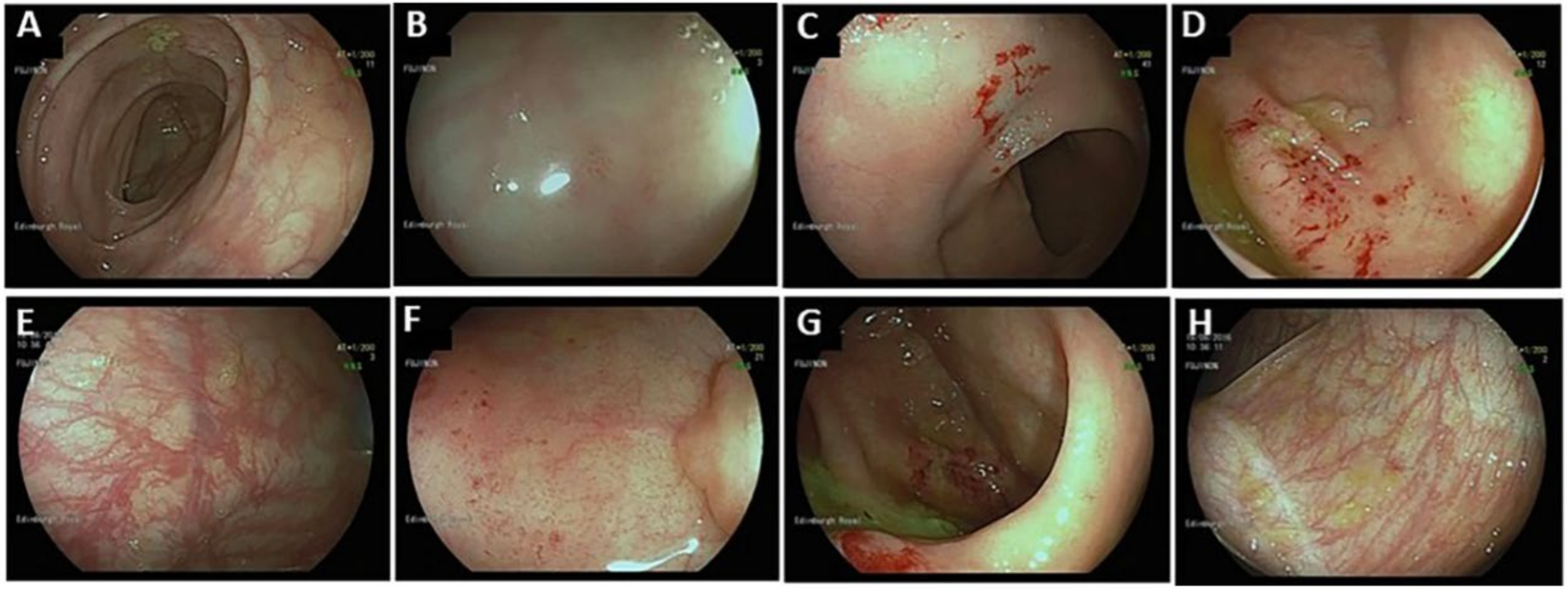






Endoscopic Findings in Microscopic Colitis

Systematic review: 80 articles (49 single case reports), 1582 patients



erythema, edema, friability, contact bleeding, scarring, pseudomembranes,
loss of vascular pattern, distorted hypervascularity, erosions, ulcerations, lacerations ....

... in up to 38 % of cases

Marlicz W et al, Dig Liver Dis 2017

Diagnosis of MC:
multiple colonic biopsies are recommended

EMCG 2012

4.1. Colonoscopy with multiple colonic biopsies is the main diagnostic procedure to establish the diagnosis and to rule out other causes of diarrhoea

SMCG 2016

Recommendation 2:

It is advisable to obtain biopsies from each of the examined colonic segments (ascending, transverse and descending colon, and sigmoid colon) separately, specifying the location corresponding to each biopsy.

Recommendation 3:

At least two biopsies should be obtained from each explored segment.

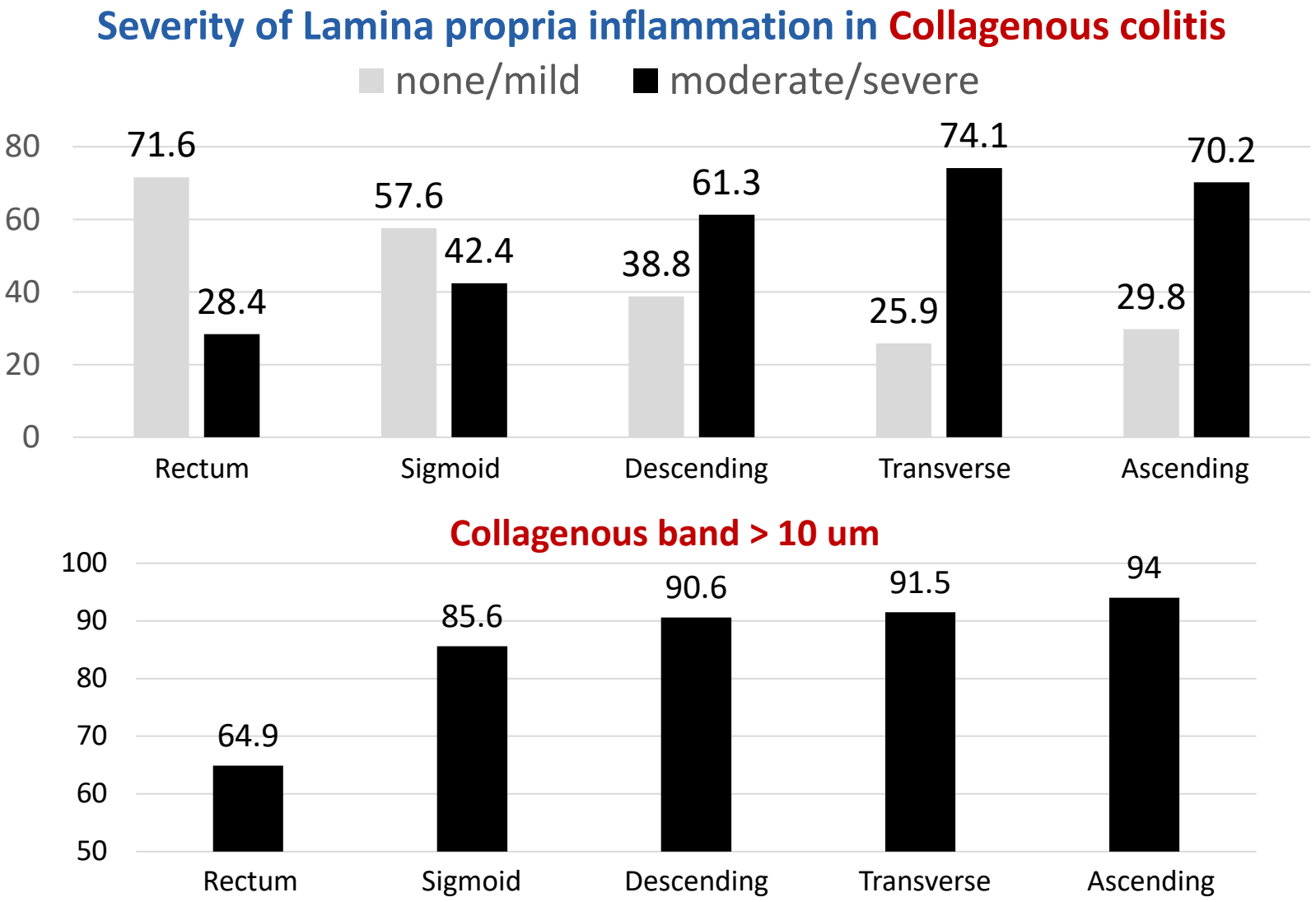
***LE**: Low; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Münch A et al, J Crohn's Colitis 2012

Fernández-Bañares F et al, Aliment Pharmacol Ther 2016

Distribution of Histopathological Features in MC

255 MC (199 CC, 56 LC), baseline biopsies from 3 European RCTs, central reading

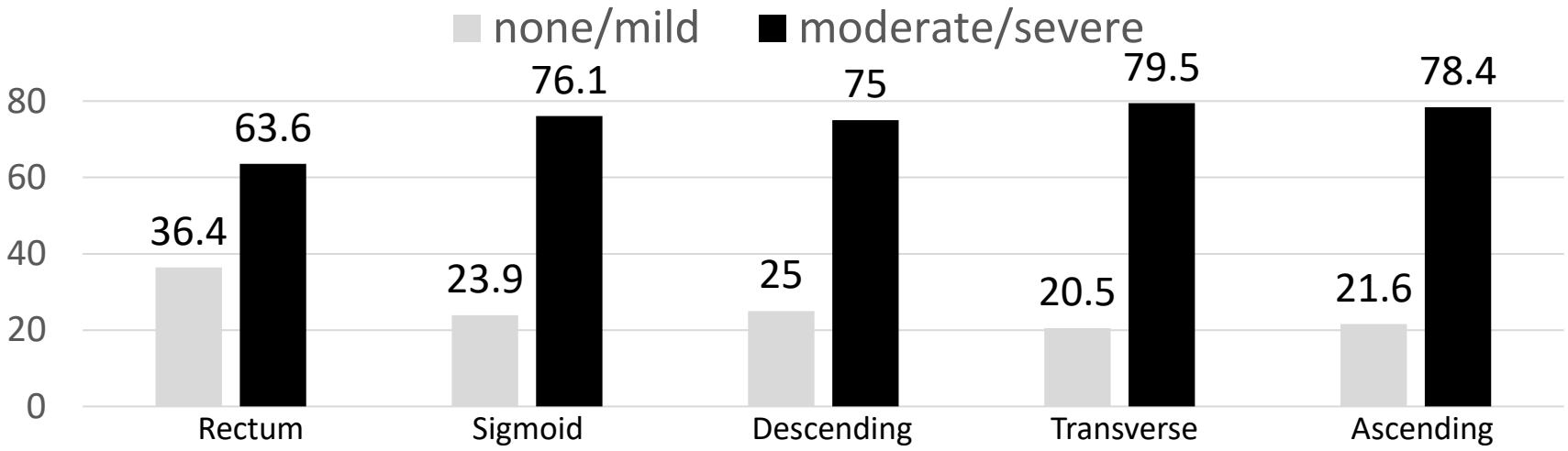


Kanstrup-Fiehn A, Miehlke S et al, manuscript in prep

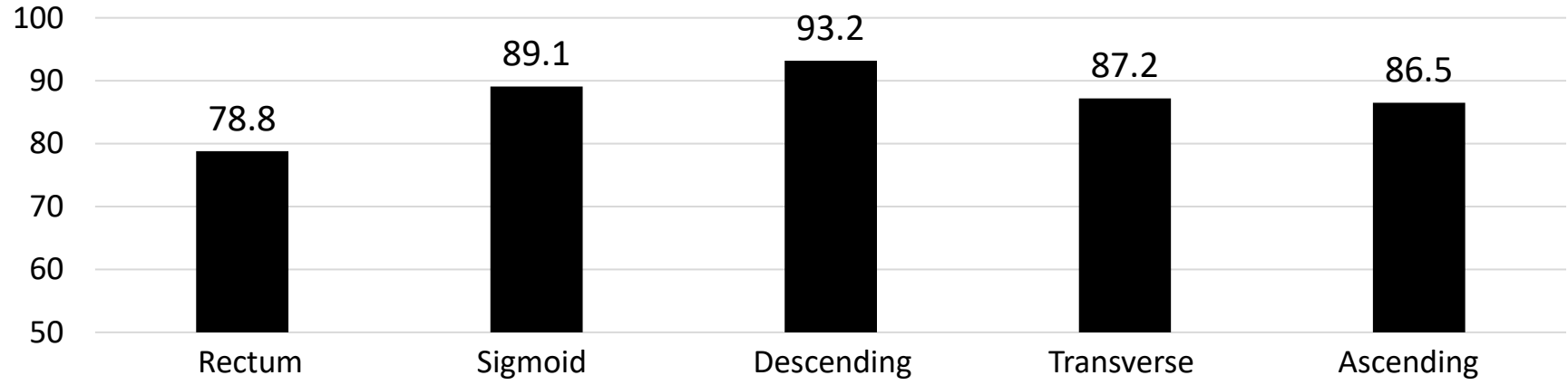
Distribution of Histopathological Features in MC

255 MC (199 CC, 56 LC), baseline biopsies from 3 European RCTs, central reading

Severity of Lamina propria inflammation in Lymphocytic colitis



>20 IEL/100 epithelial cells



Kanstrup-Fiehn A, Miehlke S et al, 2020 manuscript in prep

Biopsies From Ascending and Descending Colon are Sufficient for Diagnosis of Microscopic Colitis

- Retrospective study, **101 MC pts** (52 CC, 42 LC, 7 comb)
- Diagnosis of MC at each biopsy site ?
- **Positive for MC:** Cecum 90.0%; ascending colon 96.9%; transverse colon 95.7%; descending colon 85.0%; sigmoid colon 90.9%; and rectum 82.2%.
- For biopsies labeled random: 95.7% positive for MC
- **Ascending and descending combined -> 100% MC detected**

European guideline on the management of microscopic colitis

EMCG European Microscopic Colitis Group

in association with United European Gastroenterology ueg

„Ileocolonoscopy with biopsies from at least the right and left side sent in separately labeled containers.

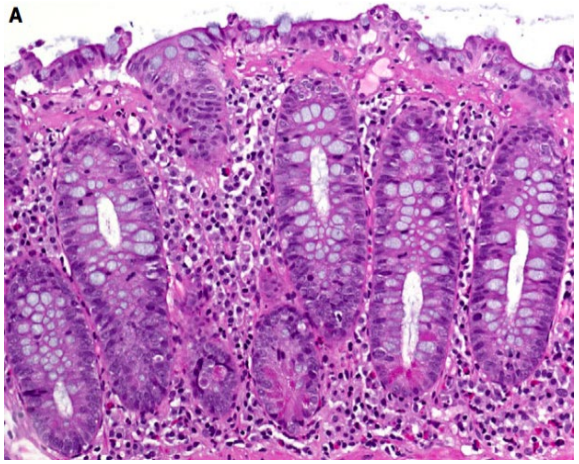
LE: High; GR: Strong in favor; Agreement: 100 %, Strong consensus

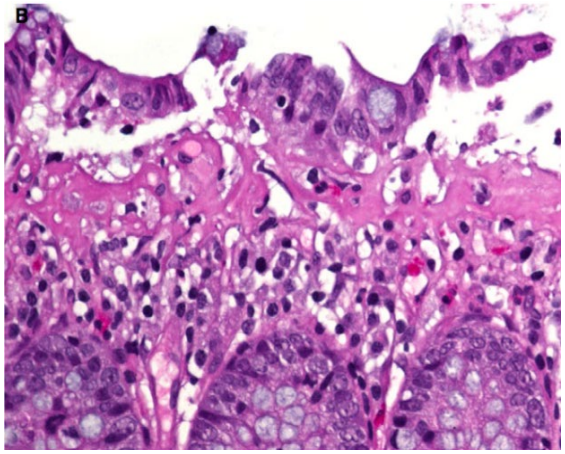
Miehlke S et al. UEG Journal 2020, in preparation

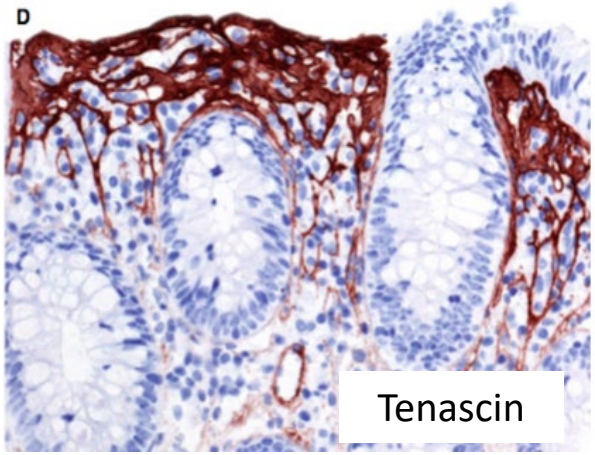
Virine B et al, Clin Gastroenterol Hepatol 2020

Histology of microscopic colitis—review with a practical approach for pathologists (EMCG & ESP)

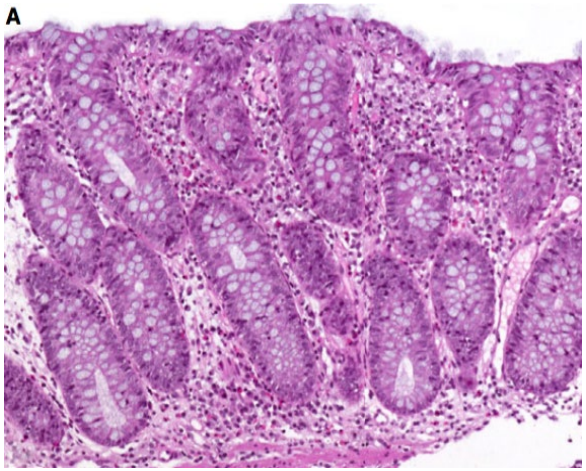
Collagenous colitis

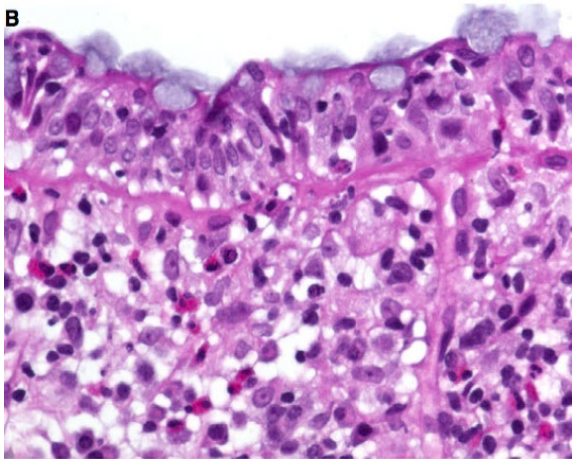


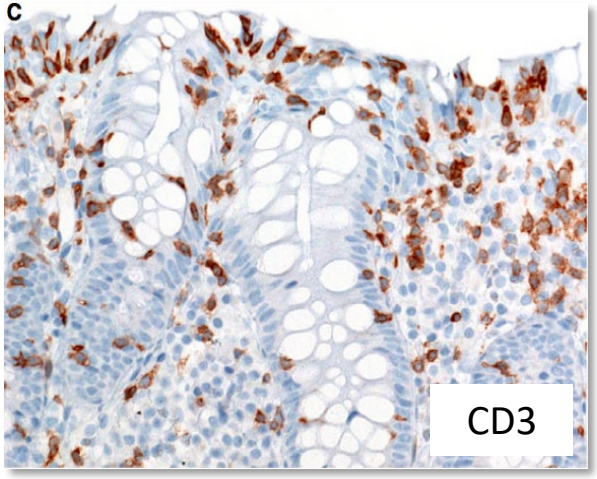




Lymphocytic colitis

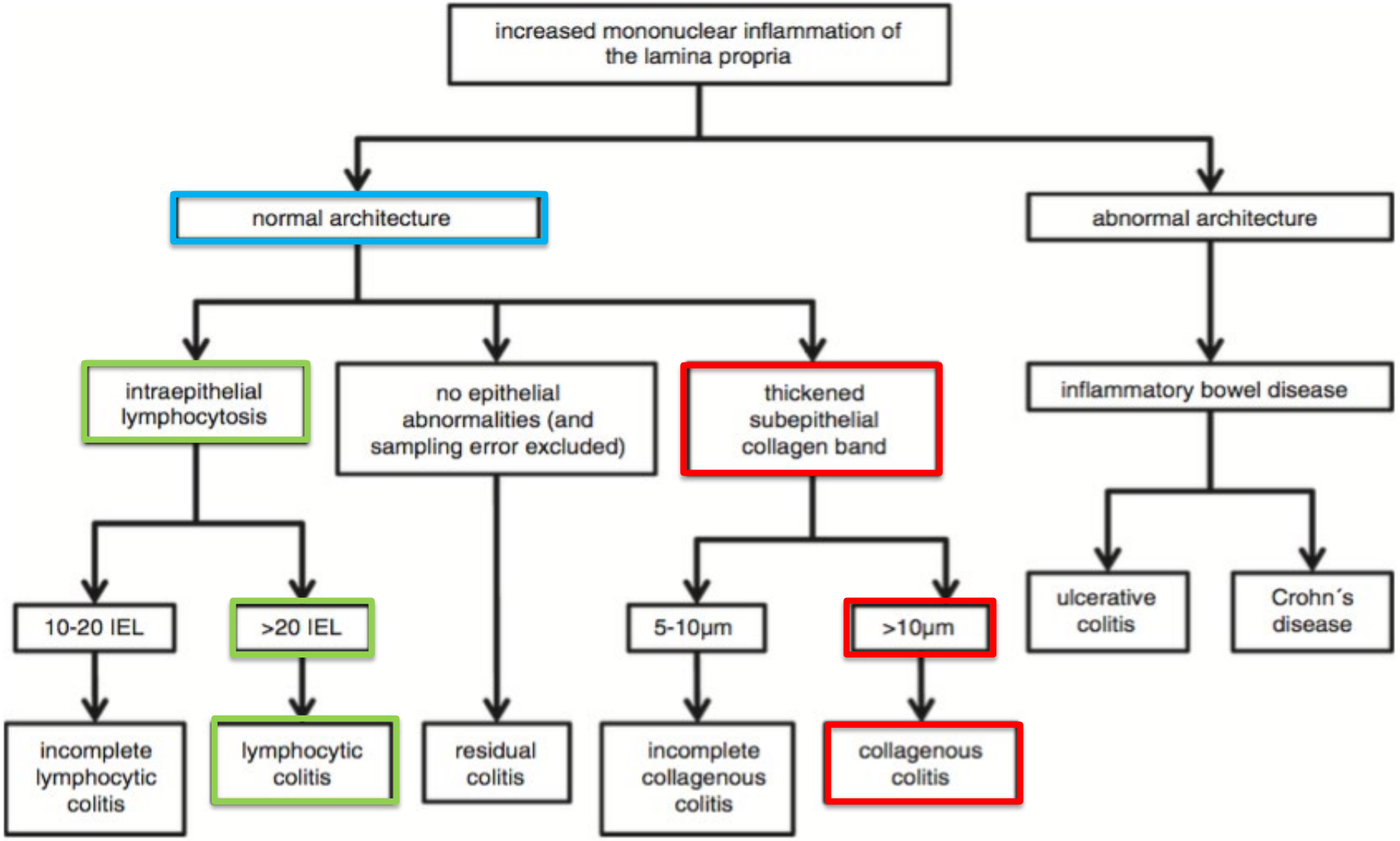






Langner C et al, Histopathology 2015

Histology of microscopic colitis—review with a practical approach for pathologists (EMCG & ESP)



Langner C et al, Histopathology 2015

Foecal Biomarkers in MC

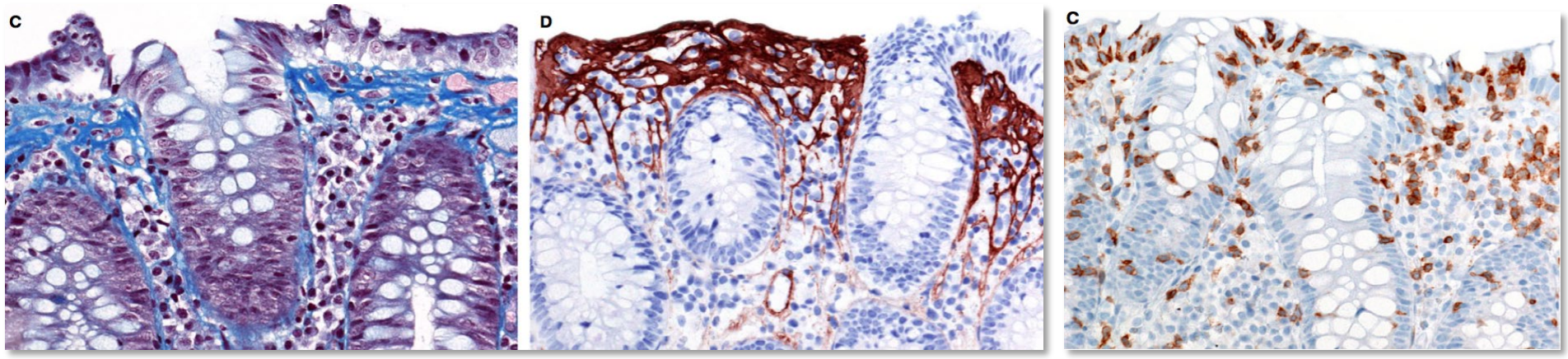
Cell type	Fecal marker	Setting	Findings and statistics	Sample size (*N*)	Reference
Neutrophils	Myeloperoxidase	CC vs. HC	Median 11.7 vs. 2.5 µg/g $p < 0.05$	18 vs. 20	Lettesjö et al. (36)
		CC vs. IBS	Median 11.7 vs. 1.7 µg/g $p < 0.01$	18 vs. 46	Lettesjö et al. (36)
		CC vs. HC	10.4 vs. 4.9 µg/g	9 vs. 45	Wagner et al. (37)
		LC vs. HC	9.6 vs. 4.9 µg/g	4 vs. 45	Wagner et al. (37)
	Calprotectin	Active CC vs. Quiescent CC	Median 80 vs. 26 µg/g $p = 0.025$	21 vs. 12	Wildt et al. (16)
		CC vs.			
		IBD vs.			
		CC vs.			
	Lactoferrin	LC vs.			
		Active			
Eosinophils	Eosinophil protein X	CC vs.			
		CC vs.			
		CC vs.			
		LC vs.			
	Eosinophil cationic protein	CC vs.			
		CC vs.			
		LC vs.			
Mast cells, other leucocytes	Tryptase	CC vs.			
	IL-1ß	CC vs.			
	TNFa	CC vs.			
Endocrine cells	Chromogranin A	CC vs.			
	Chromogranin B	CC vs. IBD	$p < 0.001$	12 vs. 32	Wagner et al. (40)
		CC vs. HC	$p < 0.001$	12 vs. 43	Wagner et al. (40)
		CC vs. IBD	$p < 0.001$	12 vs. 32	Wagner et al. (40)
	Secretoneurin	CC vs. HC	$p < 0.01$	12 vs. 43	Wagner et al. (40)
		CC vs. IBD	$p < 0.001$	12 vs. 32	Wagner et al. (40)

„So far, none of the tested molecules present sufficient accuracy for use in clinical practice....“

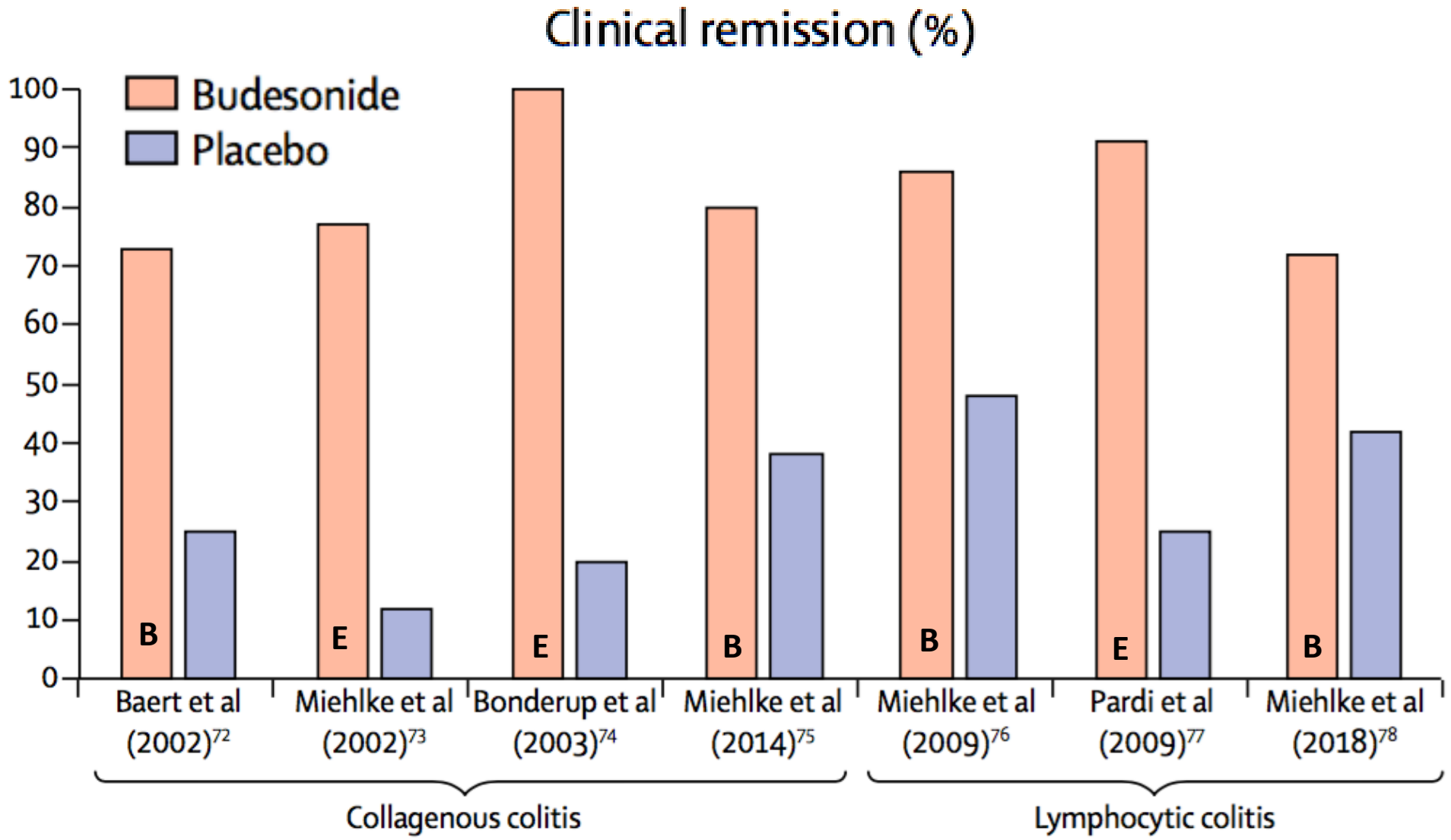
Pisani LF et al, Front Med 2017

Microscopic Colitis

Treatment



Short-term Treatment of MC with oral Budesonide



B = Budenofalk ®

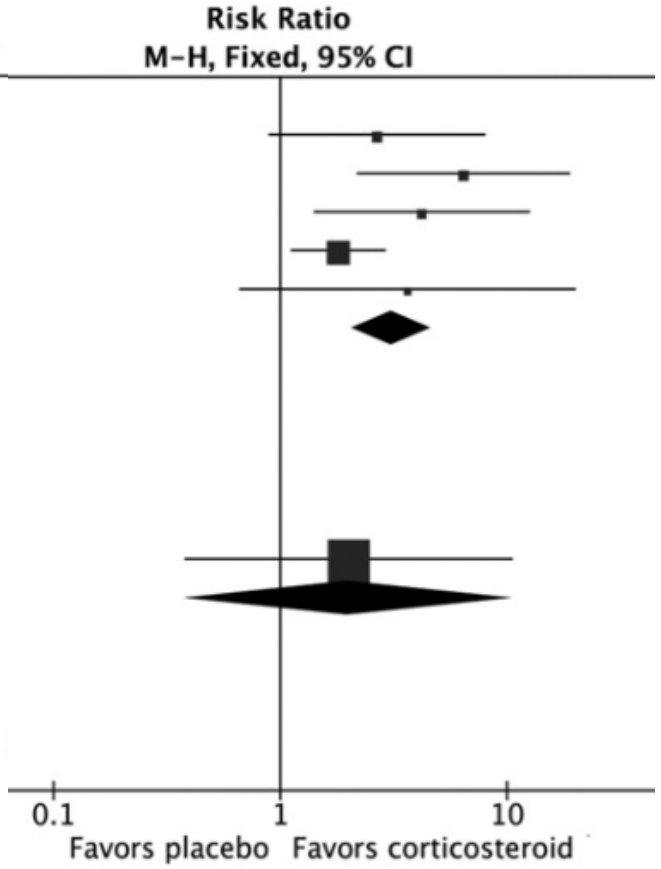
E = Entocort ®

Miehlke S et al. Lancet Gastroenterol Hepatol 2019

Prednisolone and Budesonide for Short- and Long-Term Treatment of Microscopic Colitis: Systematic Review and Meta-analysis

Induction Therapy

Study or Subgroup	Corticosteroid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Budesonide							
BAERT 2002	8	14	3	14	15.0%	2.67 [0.89, 8.02]	2002
MIEHLKE 2002	20	26	3	25	15.3%	6.41 [2.17, 18.92]	2002
BONDERUP 2003	10	10	2	10	12.5%	4.20 [1.40, 12.58]	2003
MIEHLKE 2009	18	21	10	21	49.9%	1.80 [1.11, 2.91]	2009
PARDI 2009	10	11	1	4	7.3%	3.64 [0.66, 20.06]	2009
Subtotal (95% CI)		**82**		**74**	**100.0%**	**3.07 [2.06, 4.57]**	
Total events	66		19				
Heterogeneity: $Chi^2 = 6.91$, df = 4 ($P = .14$); $I^2 = 42\%$							
Test for overall effect: Z = 5.51 ($P < .00001$)							
Prednisolone							
MUNCK 2003	6	9	1	3	100.0%	2.00 [0.38, 10.58]	2003
Subtotal (95% CI)		**9**		**3**	**100.0%**	**2.00 [0.38, 10.58]**	
Total events	6		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.82 ($P = .41$)							



Stewart MJ et al, Clin Gastroenterol Hepatol 2011

Prednisolone and Budesonide for Short- and Long-Term Treatment of Microscopic Colitis: Systematic Review and Meta-analysis

Side Effects

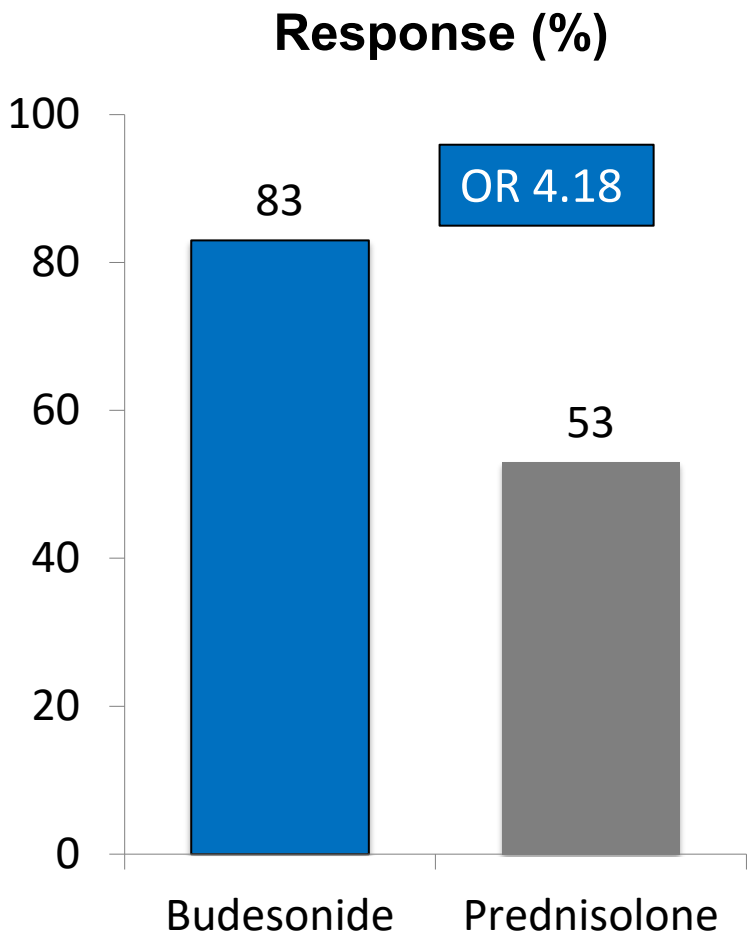
Budesonide side effect[31–33]	Budesonide, n = 66	Control, n = 65
Arthralgia, myalgia, abdominal pain, leg cramps	4	7
Depression/mood changes	1	1
Diaphoresis	1	1
Dizziness	3	0
Fatigue	0	1
Gastrointestinal (nausea, dyspepsia, bloating, flatulence, ulcer)	8	6
Headache	2	1
Hypertension	1	0
Infection (urinary, respiratory, dental)	2	2
Motor vehicle accident	0	1
Obstipation	1	0
Skin erythema or rash	1	2
Sleep disturbance	1	0
Subarachnoid hemorrhage	1	0
Venous thrombosis	0	1
Bruising	1	1
Weight gain	4	0
Worsening of diabetes	2	0
Total	**33**	**24**

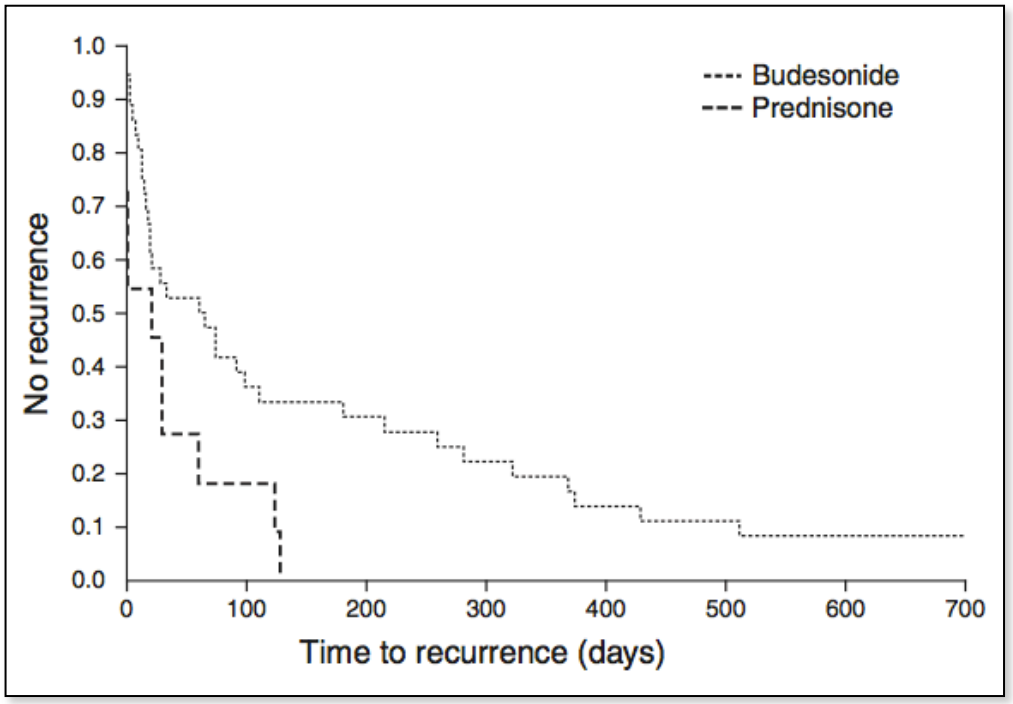
Prednisolone side effect[28]	Prednisolone, n = 9	Control, n = 3
Arthralgia, myalgia, abdominal pain, leg cramps	3	1
Depression/mood changes	4	1
Headache	5	1
Sleep disturbance	8	0
Weight gain	5	1
Total	**25**	**4**

Stewart MJ et al, Clin Gastroenterol Hepatol 2011

Prednisolone vs. Budesonide in MC

retrospective, n=315 MC, 25% with steroids, Mayo Clinic Rochester



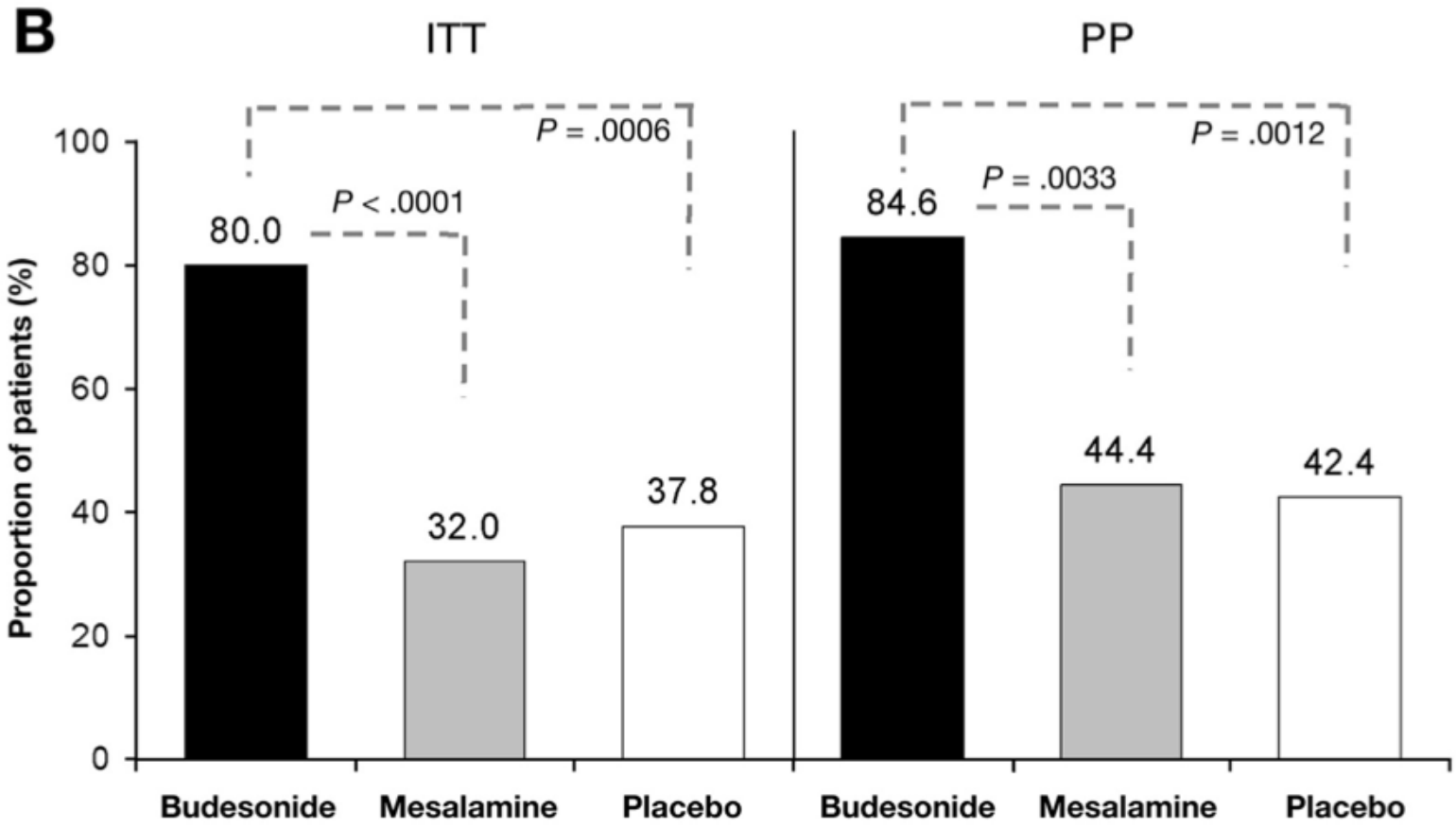


Gentile NM et al, Am J Gastroenterol 2013

Budesonide Is More Effective Than Mesalamine or Placebo in Short-term Treatment of Collagenous Colitis

rx, db, double-dummy multicenter, n=92
Budesonide 9 mg/d vs. Mesalazin 3g/d vs. Placebo, 8 weeks

Clinical Remission (Hjortswang-Criteria)



Miehlke S et al, Gastroenterology 2014

Budesonide Is More Effective Than Mesalamine or Placebo in Short-term Treatment of Collagenous Colitis

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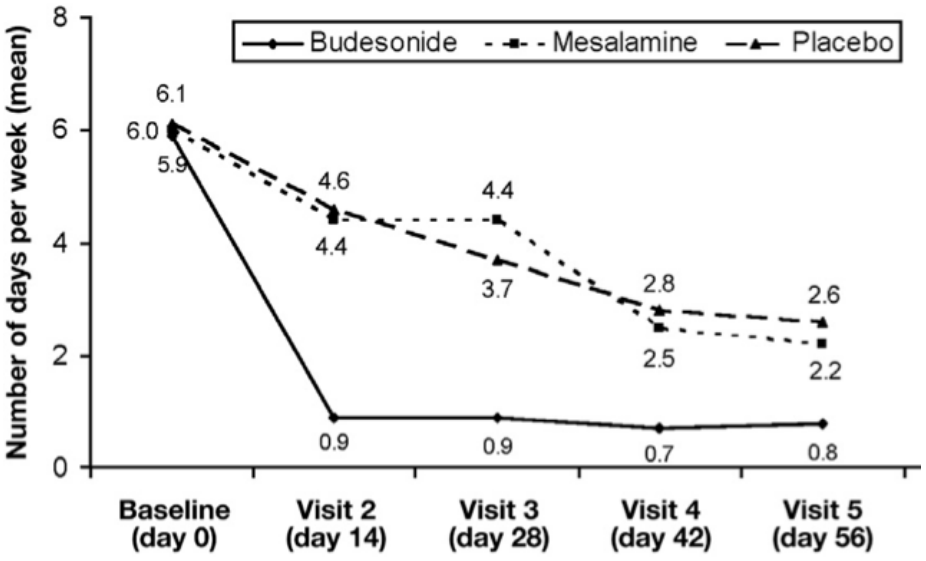
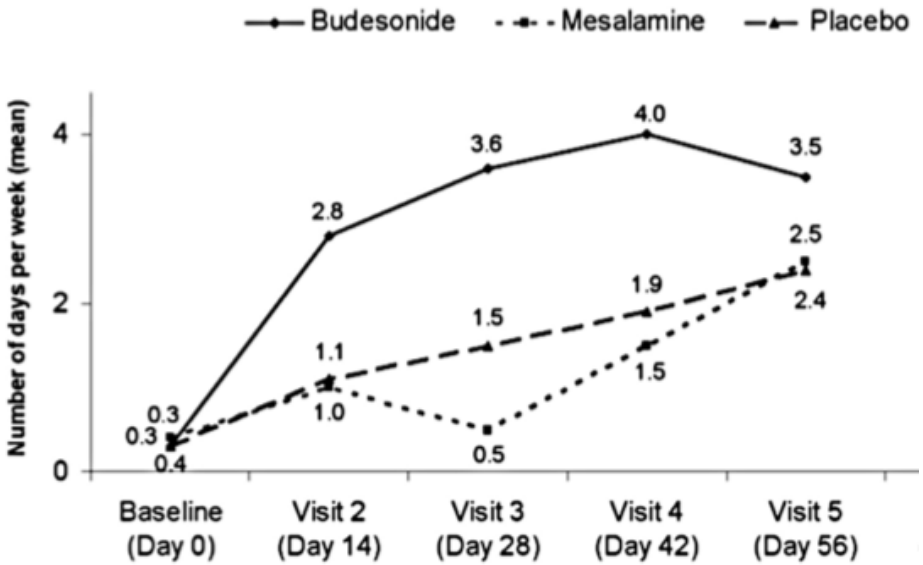
Days with watery stools



Days with solid stools



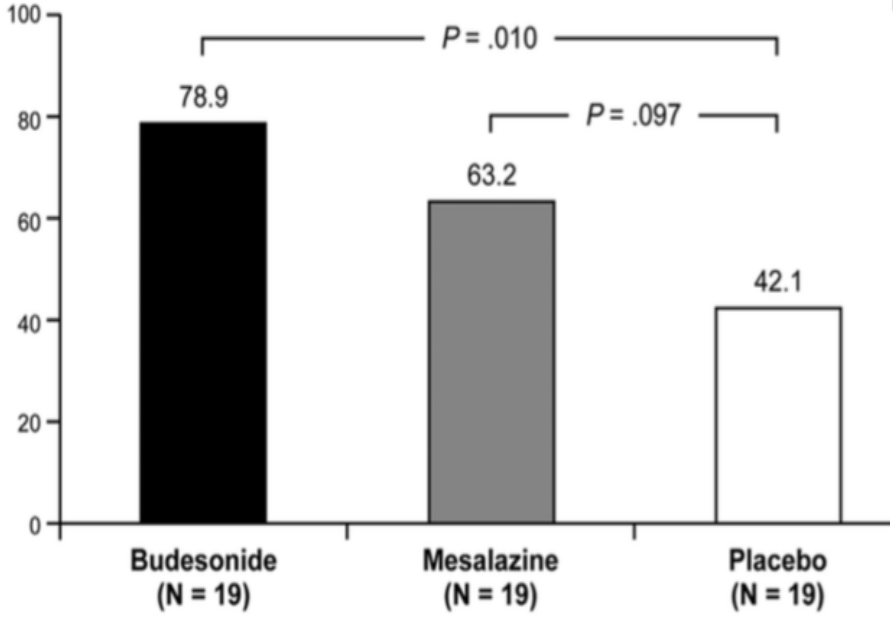
Miehlke S et al, Gastroenterology 2014

Efficacy and Safety of Budesonide, vs Mesalazine or Placebo, as Induction Therapy for Lymphocytic Colitis

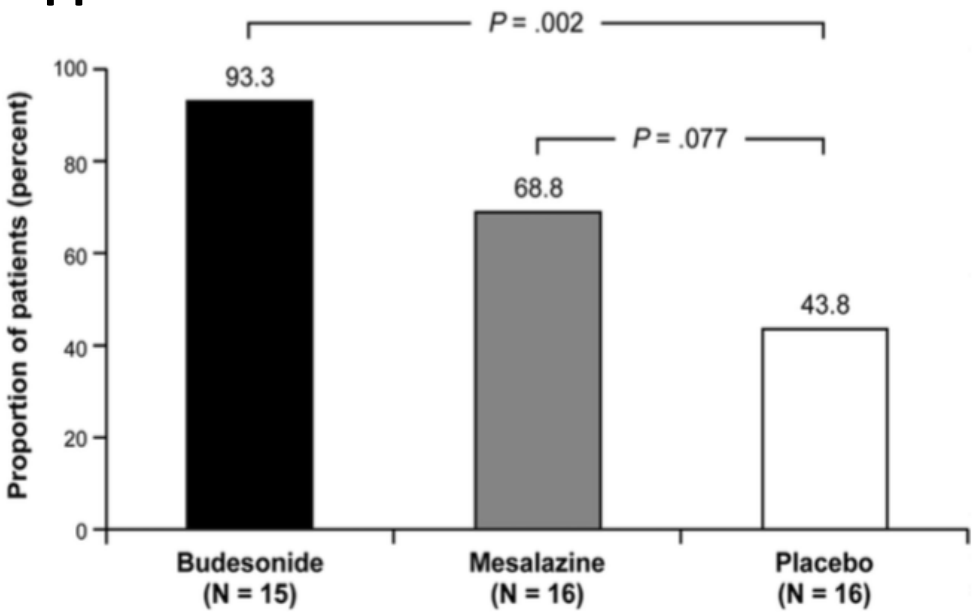
rx, db, double-dummy multicenter, n=57
Budesonide 9 mg/d vs. Mesalazin 3g/d vs. Placebo, 8 weeks

Clinical Remission (Hjortswang-Criteria)

ITT



PP



Miehlke S et al, Gastroenterology 2018

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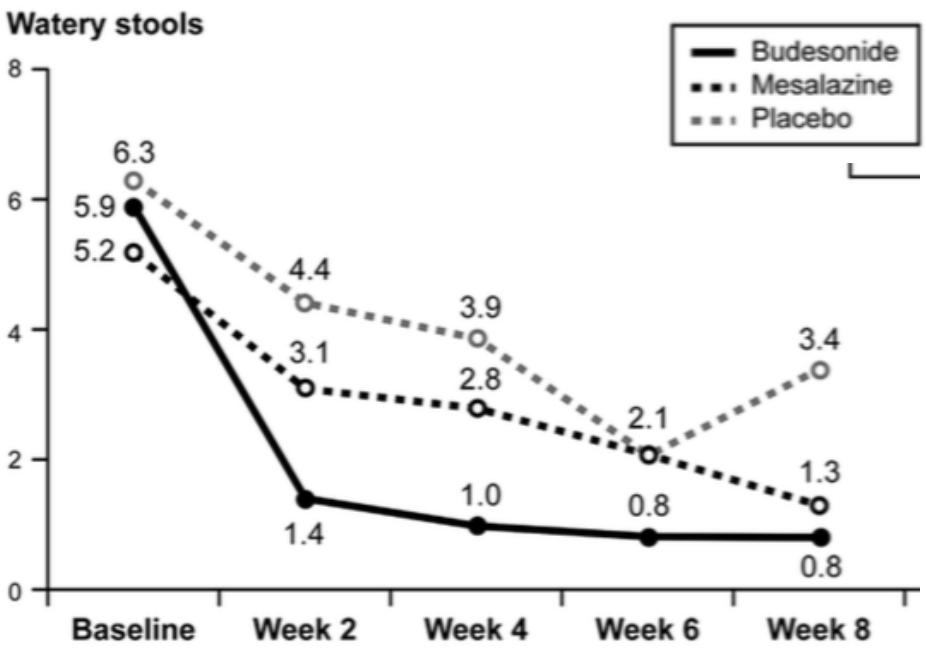
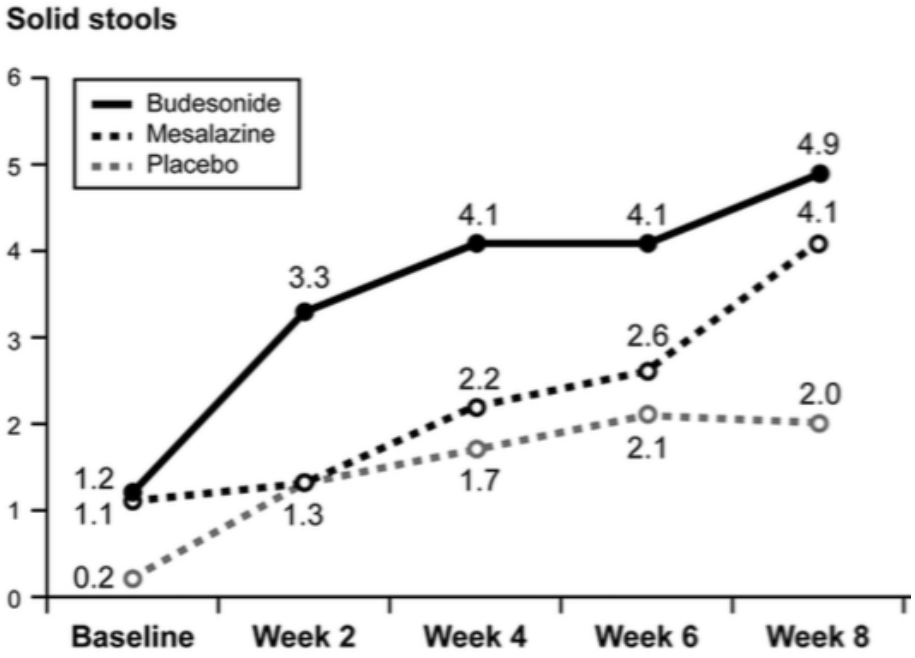
Days with watery stools



Days with solid stools

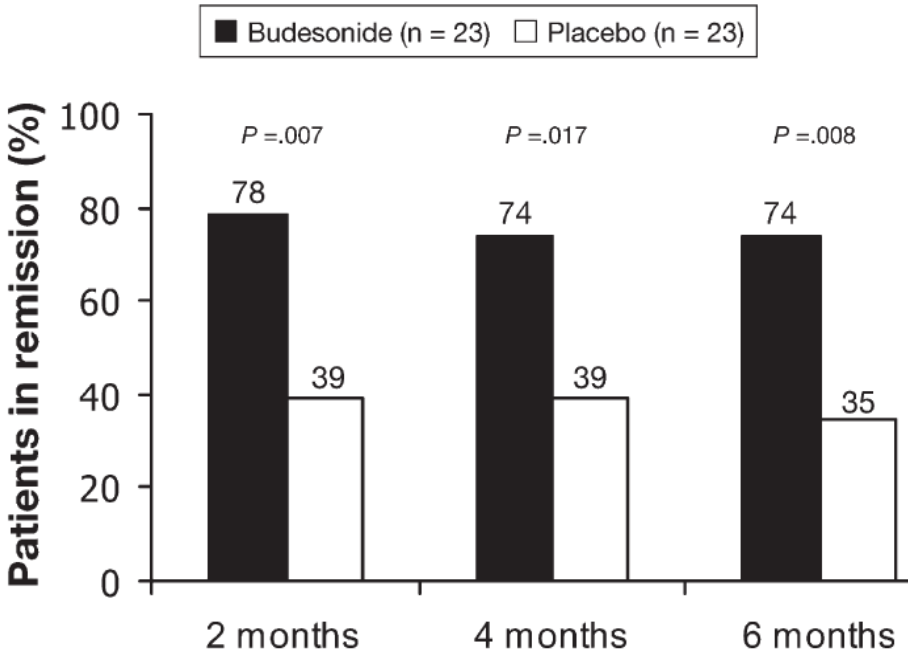


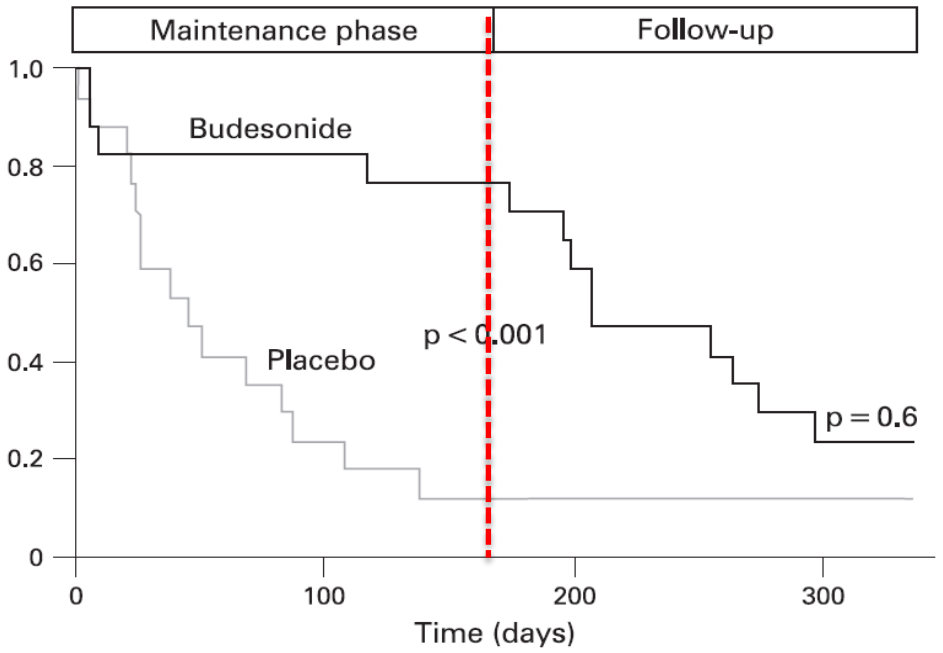
Miehlke et al, Gastroenterology 2018

Maintenance Therapy of Collagenous Colitis with low-dose Budesonide

Budesonide 6 mg/d vs. Placebo, 6 months

Clinical Remission

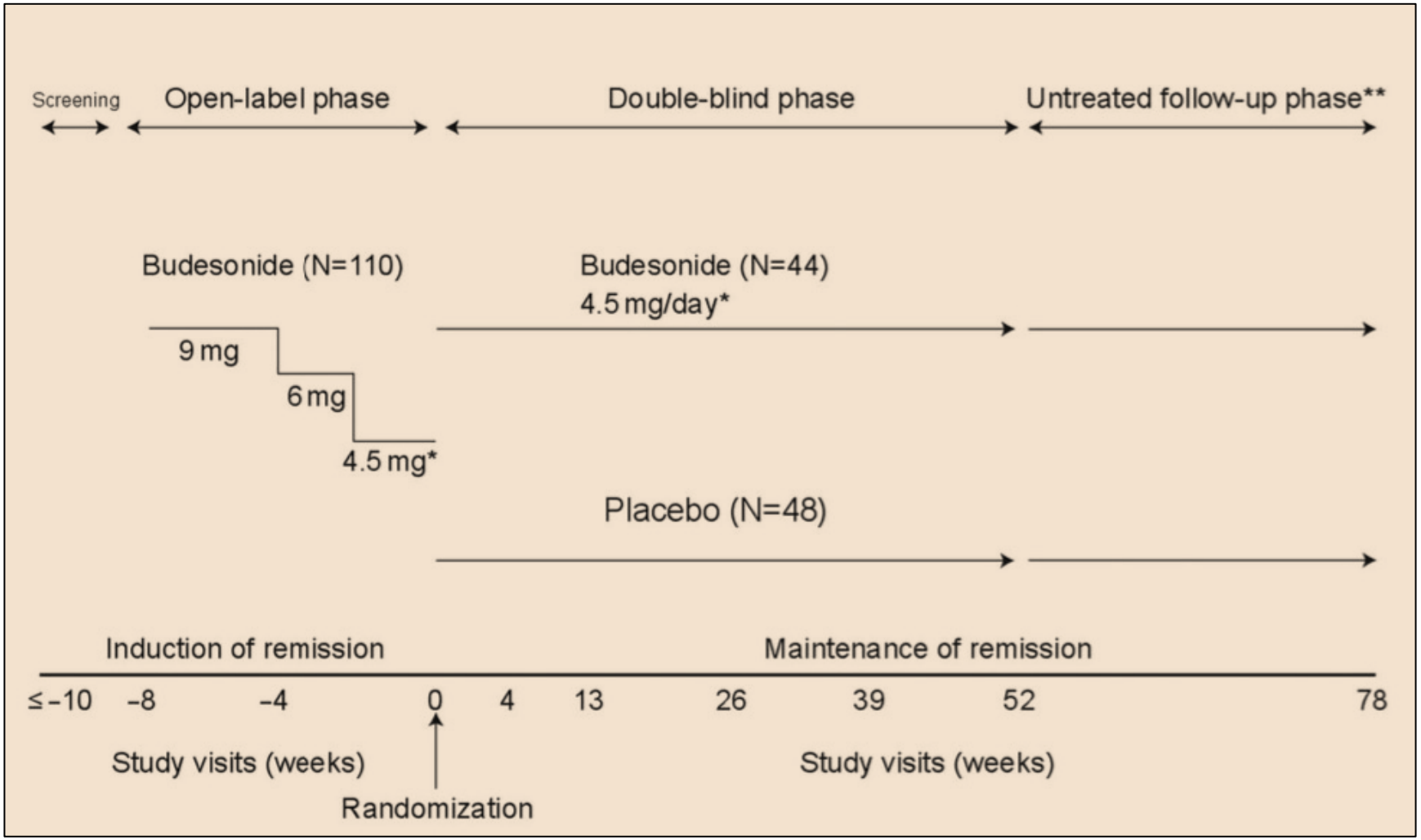




Miehlke et al, Gastroenterology 2008

Bonderup et al, Gut 2009

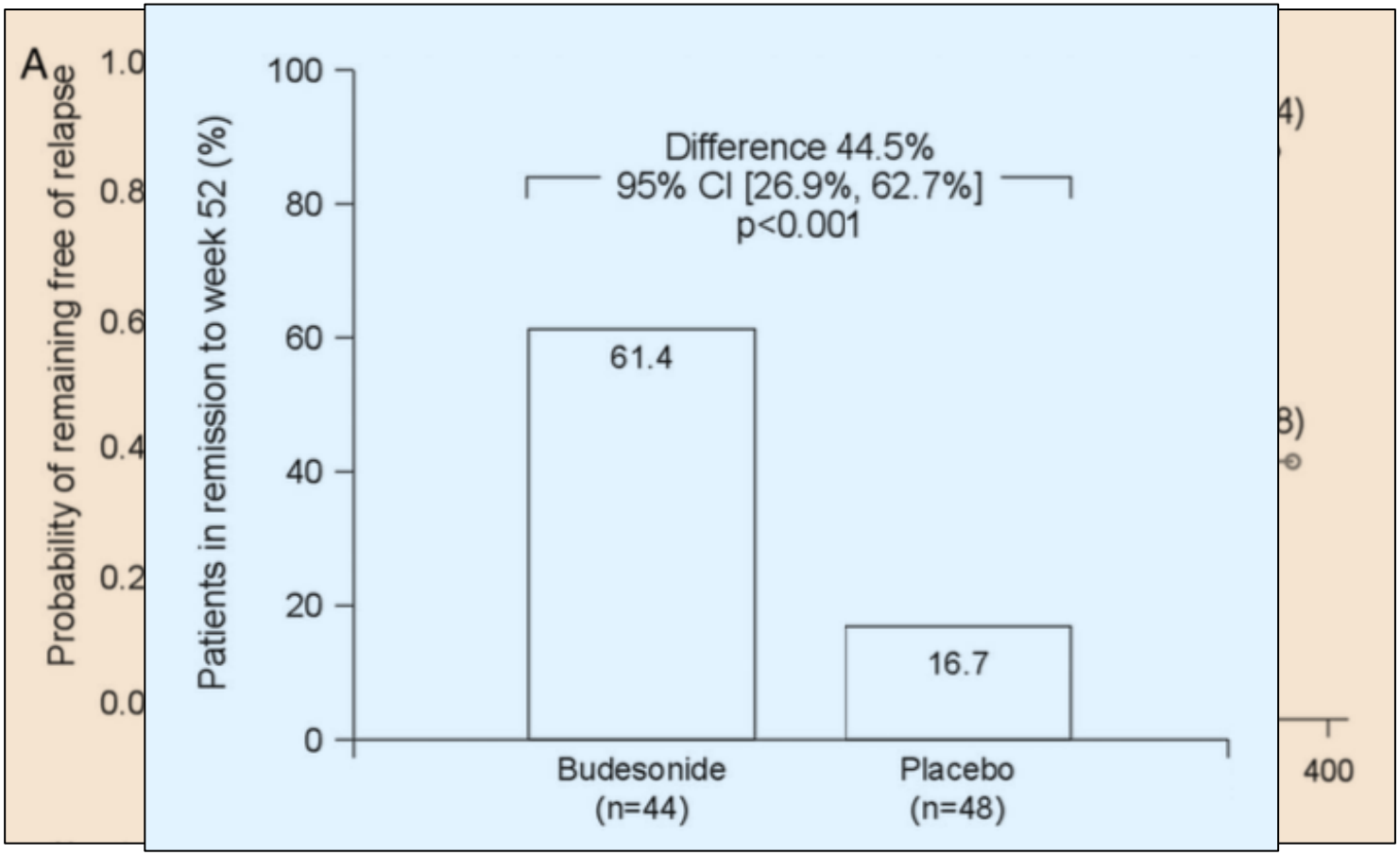
Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial



Münch et al, Gut 2016

Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial

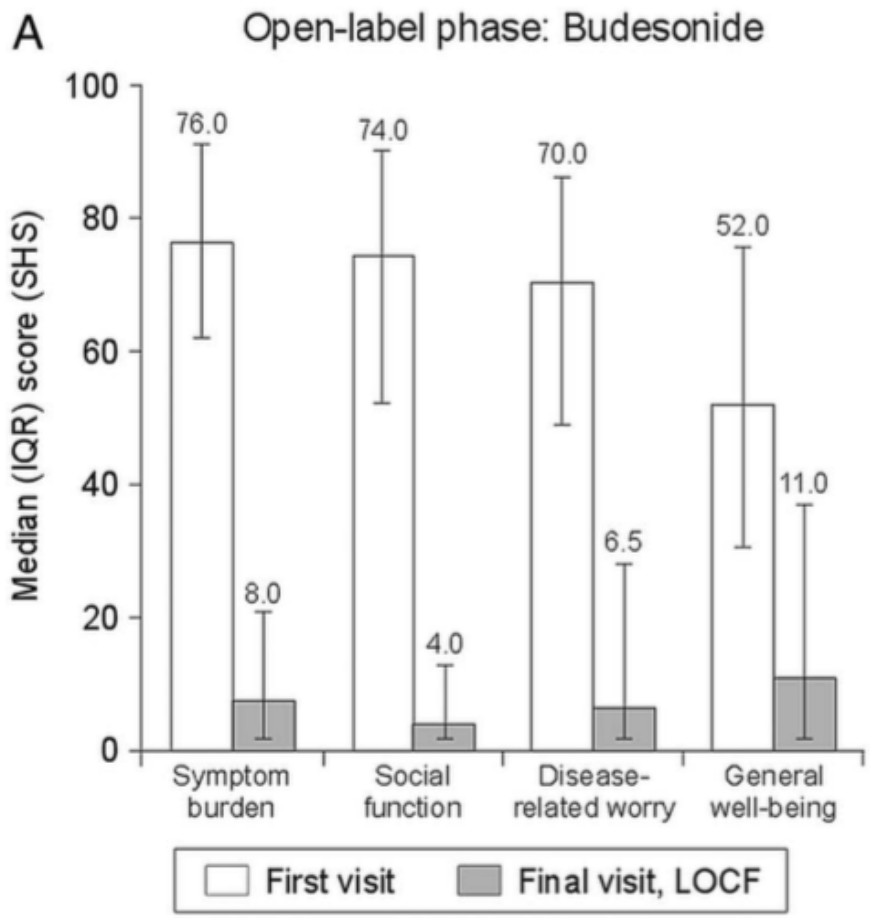
Budesonide 4,5 mg/d vs. Placebo, 12 months



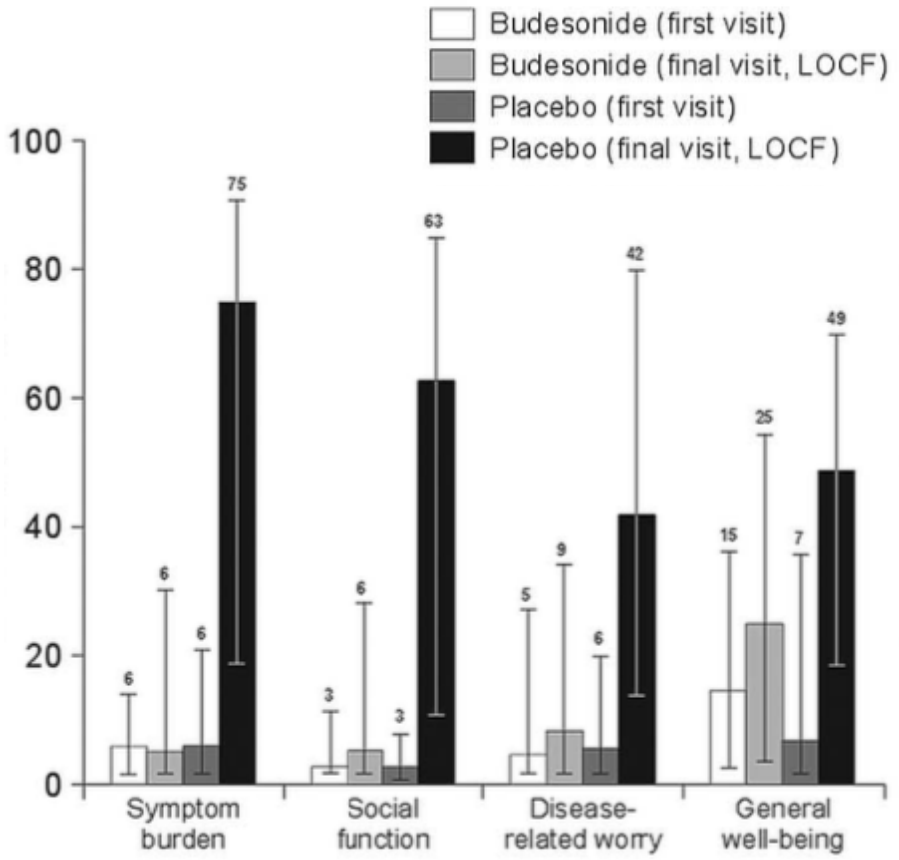
Münch et al, Gut 2016

Budesonide improves Quality of Life in Collagenous Colitis

Budesonide induction 8 weeks (open-label)



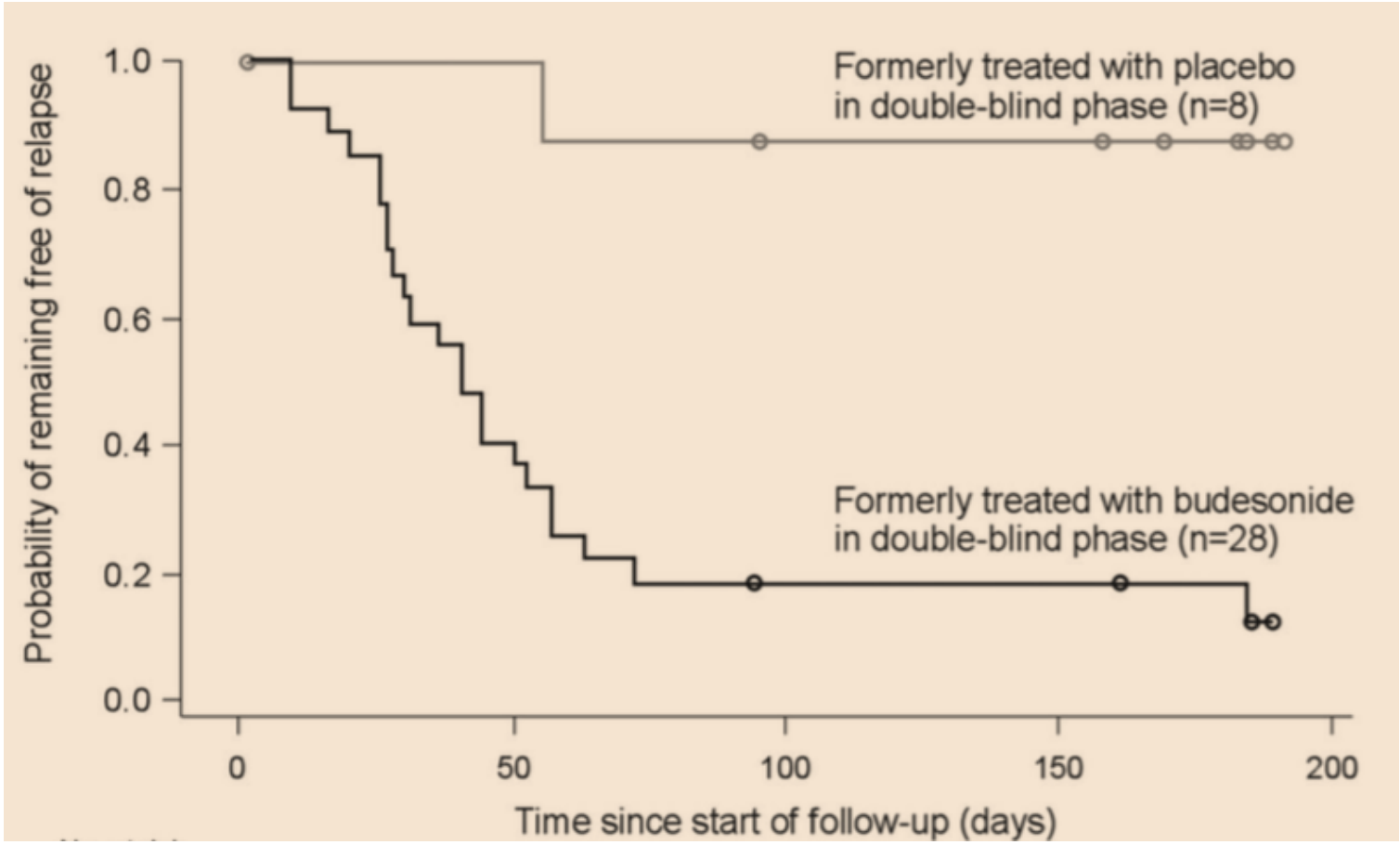
Budesonide maintenance 12 months (double-blind)



Münch et al, Gut 2016

Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial

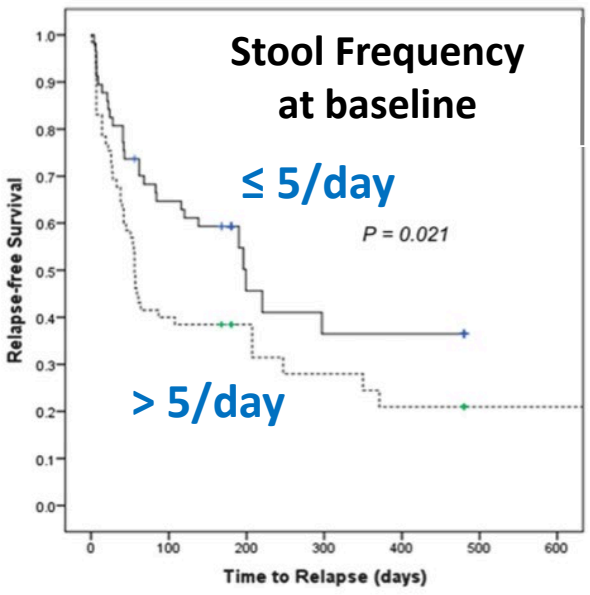
Clinical Relapse after cessation of 12-month maintenance therapy

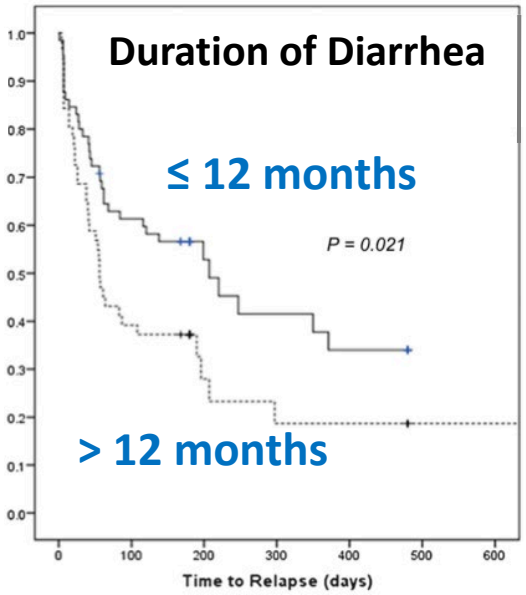


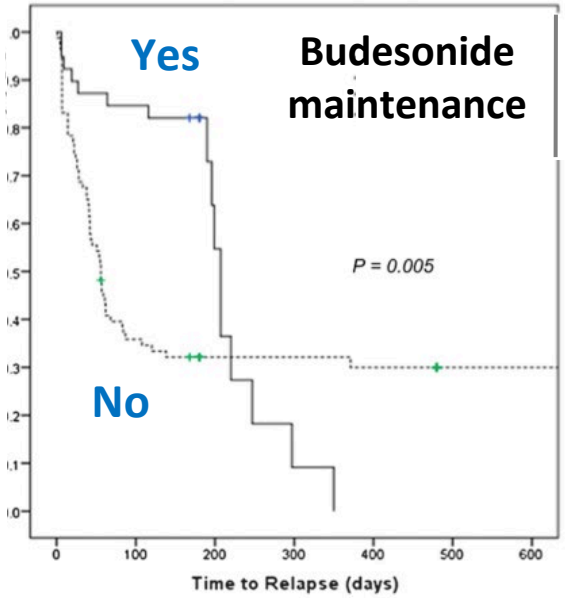
Münch A et al, Gut 2016

Risk Faktors for Clinical Relapse in Collagenous Colitis

post-hoc analysis, 4 RCTs, 123 CC patients in CR after budesonide







Factor (multivariat)	HR (95% CI)	*P*
>5 stools per day	3.95 (1.08–14.39)	0.037
Duration of diarrhea >12 mo	1.77 (1.04–3.03)	0.036
No maintenance therapy	2.71 (1.37–5.36)	0.004

Miehlke et al, Inflamm Bowel Dis 2013

Oral budesonide in gastrointestinal and liver disease: A practical guide for the clinician

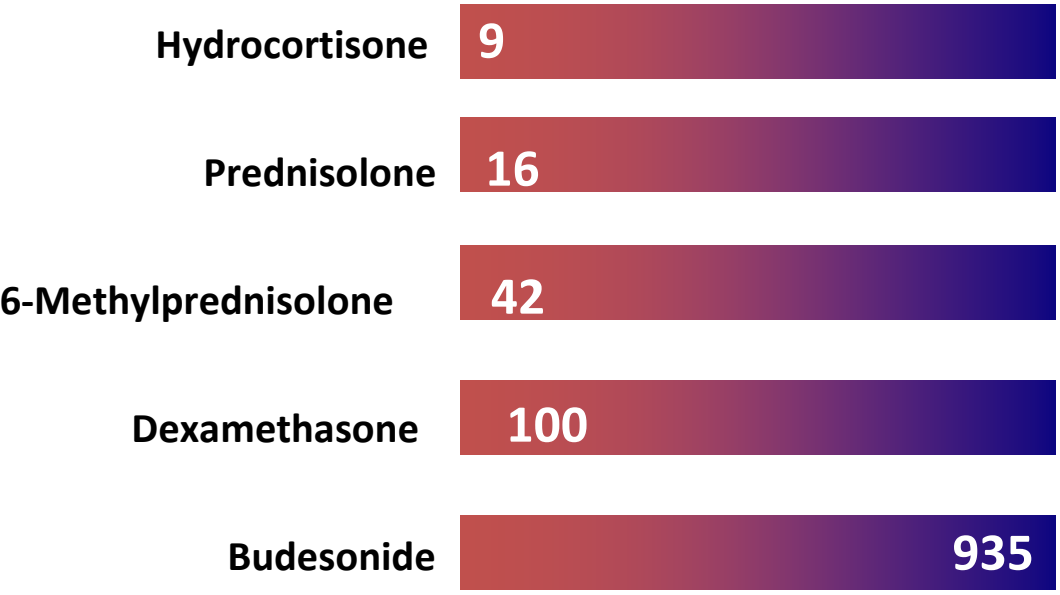
Stephan Miehlke,* Manuel Barreiro-de Acosta,† Gerd Bouma,‡ Daniel Carpio,§ Fernando Magro,¶,** Tom Moreels†† and Chris Probert‡‡

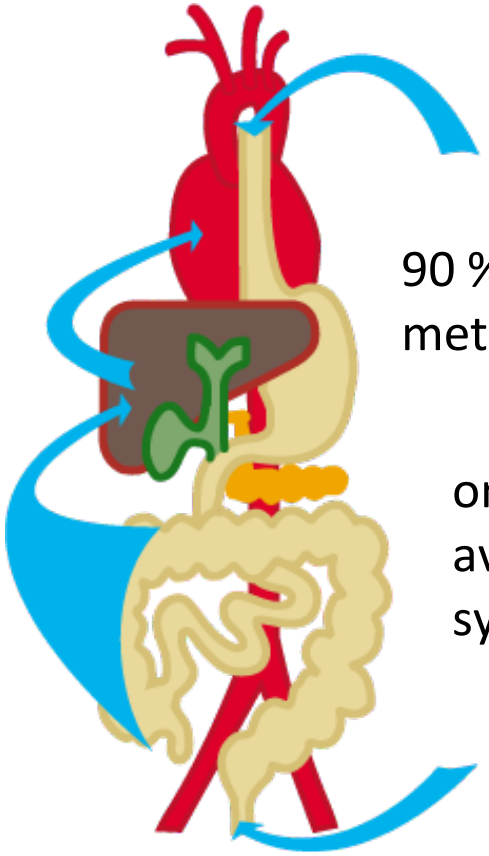
Is there a need for tapering of oral budesonide for safety reasons ?

J Gastroenterol Hepatol 2018

Pharmacological Properties of Budesonide

Relative receptor binding affinity





90 % first pass metabolism

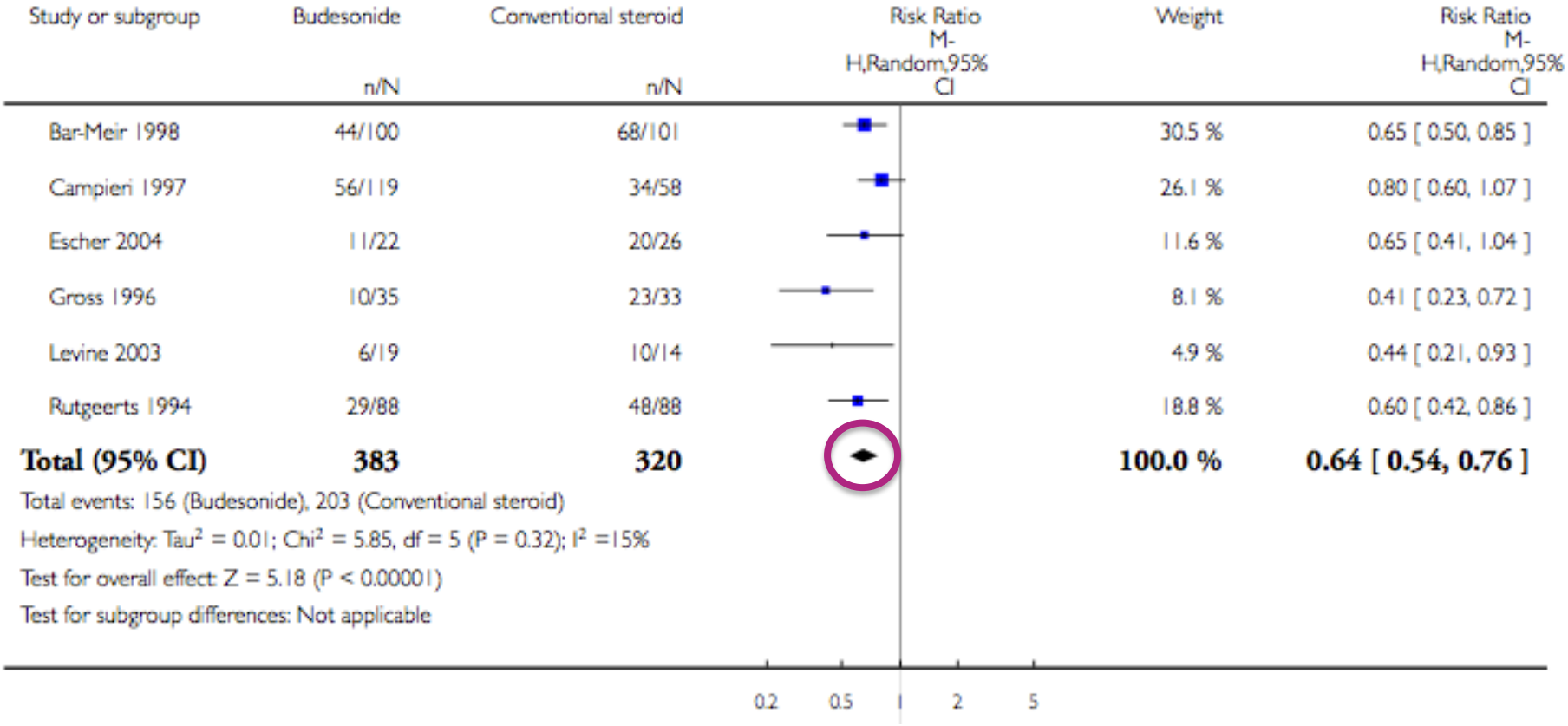
only 10 % available systemically

Budesonide for induction of remission in Crohn's disease (Review)

Budesonide 9 mg/d vs. Conventional steroids

Cochrane Library

Corticosteroid-related adverse events

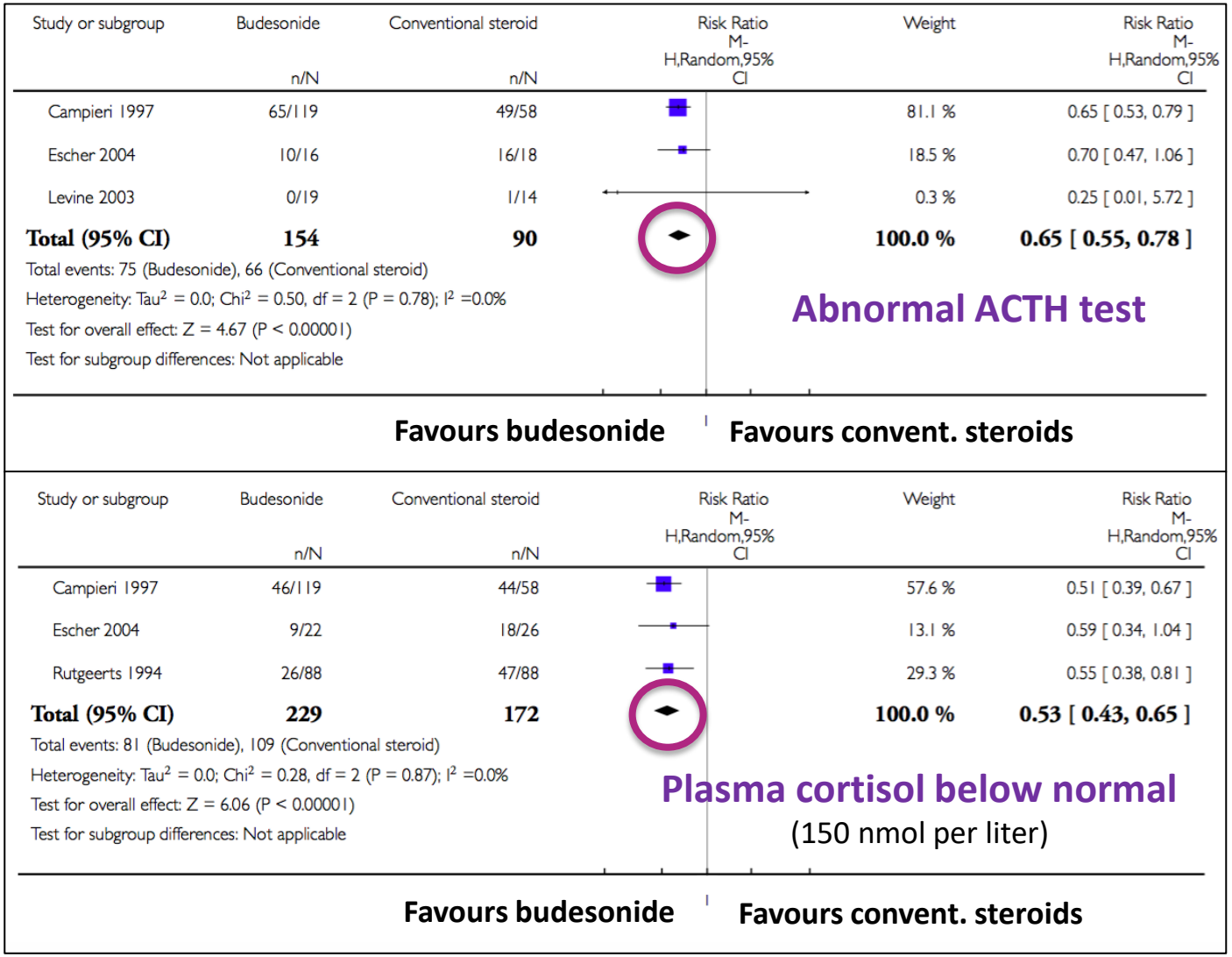


Rezaie A et al. Cochrane Database of Systematic Reviews 2015

Budesonide for induction of remission in Crohn's disease (Review)

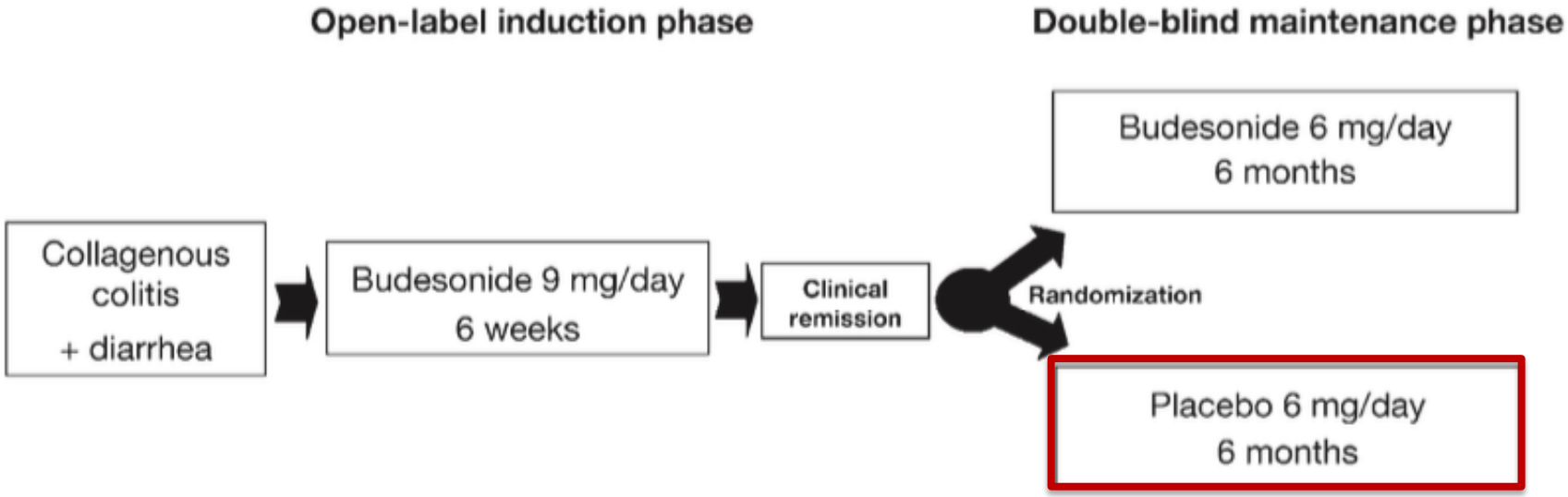
Budesonide 9 mg/d vs. Conventional steroids

Cochrane Library



Rezaie A et al, Cochrane Database of Systematic Reviews 2015

Budesonide withdrawal in MC



Maintenance phase	Budesonide 6 mg/d (n = 23)	Placebo (n = 23)
Patients with AEs, n (%)	8 (35)	8 (35)
AE-related withdrawals, n (%)	3 (13)	1 (4)
AEs among patients discontinuing treatment, n	Dizziness (1); sleep disturbance (1); muscle pain (1); gastric ulcer (1); skin erythema (1)	Thrombosis (1); respiratory infection (1)
AEs among patients continuing treatment, n	Headache (2); urinary infection (1); respiratory infection (1); back pain (1); abdominal pain (1); increased body weight (1); hypertension (1)	Abdominal pain (3); bloating (2); respiratory infection (1); nausea (1); back pain (1); dental pain (1); skin erythema (1); car accident (1)

No cases of adrenal insufficiency

Miehlke S et al. Gastroenterology 2008

Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial

Safety data	Budesonide	Placebo
Drug exposure time, Days (mean)	291	138
AE, total	70,5% (31/44)	50% (24/48
Suspected ADR	15.9% (7/44) all non-serious	
Drug withdrawel due to AE	n = 4	n= 7
Morning cortisol level below normal at 12 months	**3.7% (1/27)**	**5.6% (1/18)**
HbA1c increase in pts with known diabetes	n = 2	n = 2
Body weight increase (kg, mean)	0,4	0,1
No clinically significant changes in blood pressure, fasting glucose, sodium, potassium		

Münch et al, Gut 2016

No Need for Budesonide Tapering !

- Tapering of conventional systemic steroids after induction of remission is required to avoid adrenal insufficiency
- **Oral budesonide has markedly reduced effect on endogenous cortisol production -> tapering before discontinuation not necessary**

Gomollón F, et al. ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management.
J Crohns Colitis 2017; 11: 3–25.

Nguyen GC et al. Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on the Medical Management of Microscopic Colitis. Gastroenterology 2016; 150: 242–6.

Risk for Osteoporosis in Microscopic Colitis ?

Prospective cohort study	MC (n = 50)	Controls (n = 49)
Sex, n (female, male)	44/6	42/7
Age	67 (45–93)	67 (49–85)
CC/LC (n)	35/15	
Disease duration (months)	28 (2–163)	
Cumulative budesonide dose (mg)	702 (0–5400)	
Remission; Hjortswang scale, n (%)	36 (72%)	
SHS value	10 (0–38)	
Substituted with calcium and D3, n (%)	26 (52%)	3 (6%)*
Treatment with alendronate or denosumab (n)	3	
Treatment with inhalative steroids (n)	7 (14%)	1 (2%)
Smokers, n (%)	17 (34%)	5 (10%)#
Menopause at age <45 years, n (%)	12 (24%)	3 (6%)#
BMI <19 kg/m^2 (n)	3	1
BMI (kg/m^2)	24 (16 – 34)	25 (17–34)
Family history of osteoporosis, n (%)	9 (18%)	7 (14%)
ACTH (pmol/L)	3 (0.5–11)	3 (0.5–9)
Serum D2 + D3 (nmol/L)	71 (11–170)	67 (11–127)

Maintenance	15
Episodic	29
No treatment	6

Wildt S et al, Postgrad Med 2018

Risk for Osteoporosis in Microscopic Colitis ?

Bone mineral measurements and markers

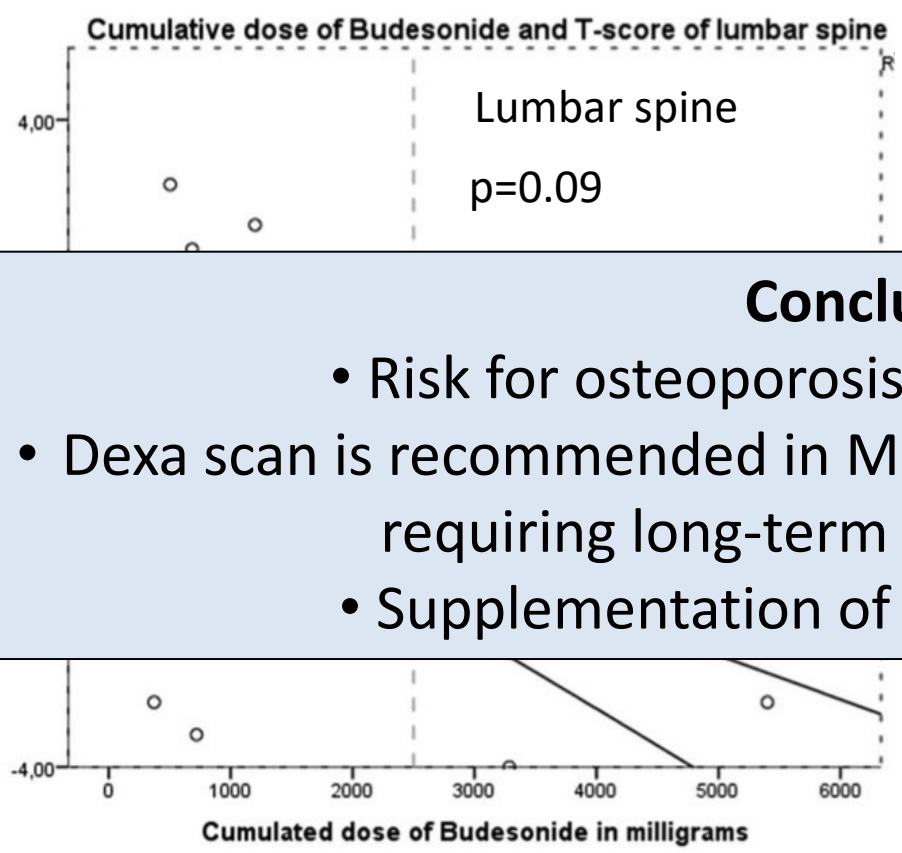
	MC (n = 50)	Controls (n = 49)
Osteopenia[†], n (%)	22 (44%)	15 (31%)
Osteoporosis[§], n (%)	7 (14%)	4 (8%)
BMD hip (g/cm^2)	0.849 (0.571–1.197)	0.866 (0.091–1.101)
BMD spine (g/cm^2)	0.966 (0.613–1.453)	1.021 (0.718–1.242)
Alkaline phosphatase (µg/L)	12 (5–69)	16 (10–35)*
PINP (µg/L)	36 (10 – 125)	43 (19 – 97)#
CTX (µg/L)	0.31 (0.03 – 1.12)	0.37 (0.10 – 0.84)
Osteocalcin (µg/L)	16 (5 – 69)	20 (8 – 48)

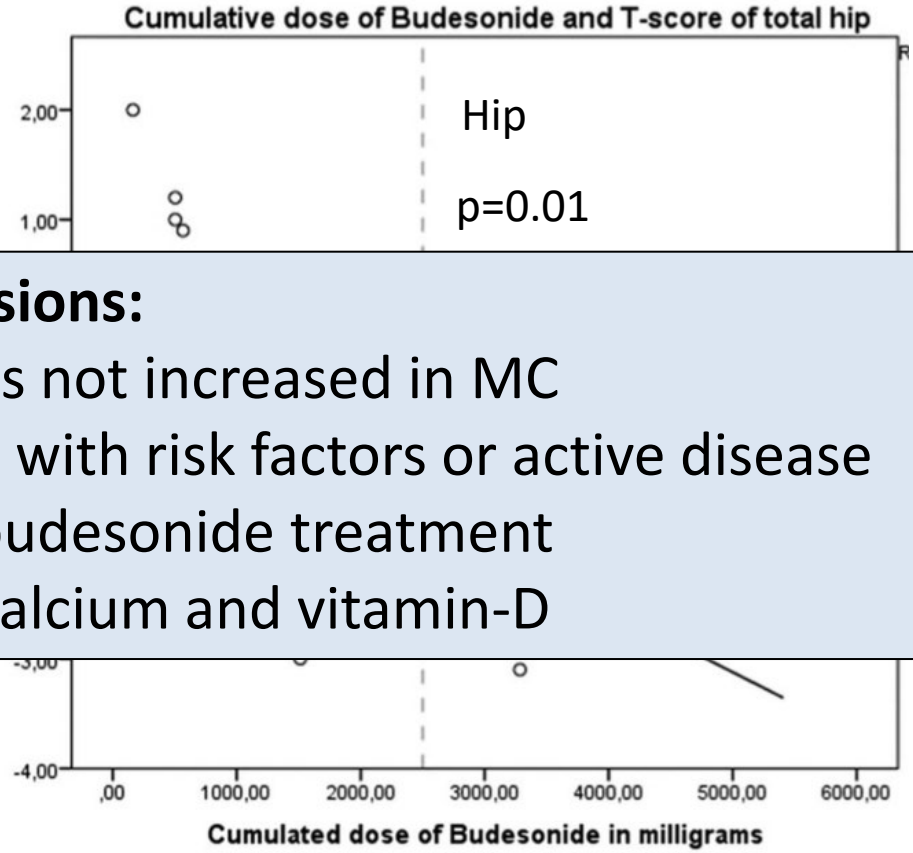
* $p<0.005$ # $p<0.05$

Wildt S et al, Postgrad Med 2018

Risk for Osteoporosis in Microscopic Colitis ?

Cumulative dose of Budesonide and T-scores





Conclusions:

- Risk for osteoporosis is not increased in MC
- Dexa scan is recommended in MC with risk factors or active disease requiring long-term budesonide treatment
- Supplementation of calcium and vitamin-D

Wildt S et al, Postgrad Med 2018

Azathioprine and mercaptopurine in the management of patients with chronic, active microscopic colitis

- Retrospective case series (Sweden, Denmark, Spain)
- 46 MC pts (32 CC and 14 LC), 32 female; median age 59 years, median disease duration of3 yrs

- **Long-term clinical remission on AZA therapy: 28%**
- AZA failure due to intolerance: 67%, due to nonresponse 4 %

- 13 of 31 AZA-intolerant pts switched to MP
  -> 6 pts (46%) clinical remission with MP

- **Overall response to thiopurines 19/46 (41%)**
- main side effects nausea/vomiting, elevated liver enzymes

Münch A et al, Aliment Phramacol Ther 2013

Immune modulator therapy for microscopic colitis in a case series of 73 patients

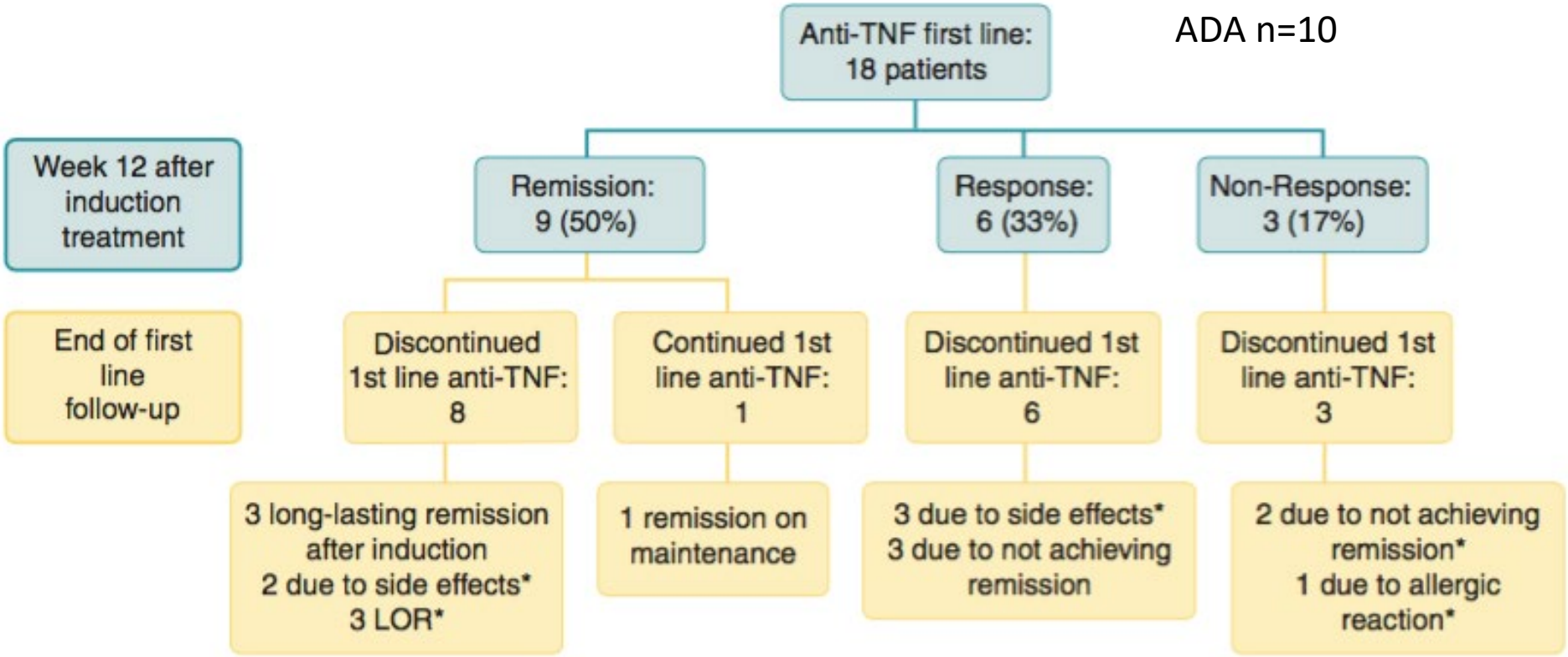
	Thiopurines[a] (N=49)	Methotrexate (N=12)	Calcineurin inhibitors (N=2)	Anti-TNF therapy (N=10)
Median age at diagnosis, years (range)	48.9 (40.5-63.7)	53.5 (49.8-59.5)	40 (32.7-43.2)	39.3 (36.1-45.6)
Median age at treatment start, years (range)	51.8 (43.6-64.6)	55 (52.8-60.9)	41 (36.7-45.2)	45 (42-49)
Female, n (%)	41 (84%)	10 (83%)	2 (100%)	8 (80%)
White race, n (%)	49 (100%)	12 (100%)	2 (100%)	10 (100%)
Collagenous colitis, n (%)	34 (69%)	7 (58%)	2 (100%)	8 (80%)
Treatment indication				
Budesonide dependence, n (%)	18 (37%)	3 (25%)	0 (0%)	0 (0%)
Budesonide intolerance, n (%)	3 (6%)	0 (0%)	0 (0%)	1 (10%)
Budesonide-refractory disease, n (%)	28 (57%)	9 (75%)	2 (100%)	9 (90%)
	4 months (1.5-15) **CR 43 % PR 22 % steroid-free 41 %**	14 months (3-18.8) **CR 58 % PR 17 % Steroid-free 50 %**	4 months (1.5-15) **1x CR with tacrolimus**	4 months (2.3-5.5) **CR 40 % PR 40 %**

Cotter TG et al, Aliment Pharmacol Ther 2017

Single-centre experience with anti-tumour necrosis factor treatment in budesonide-refractory microscopic colitis patients

Niki Daferera[1], Henrik Hjortswang[1], Simone Ignatova[2] and Andreas Münch[1]

IFX n=8
ADA n=10

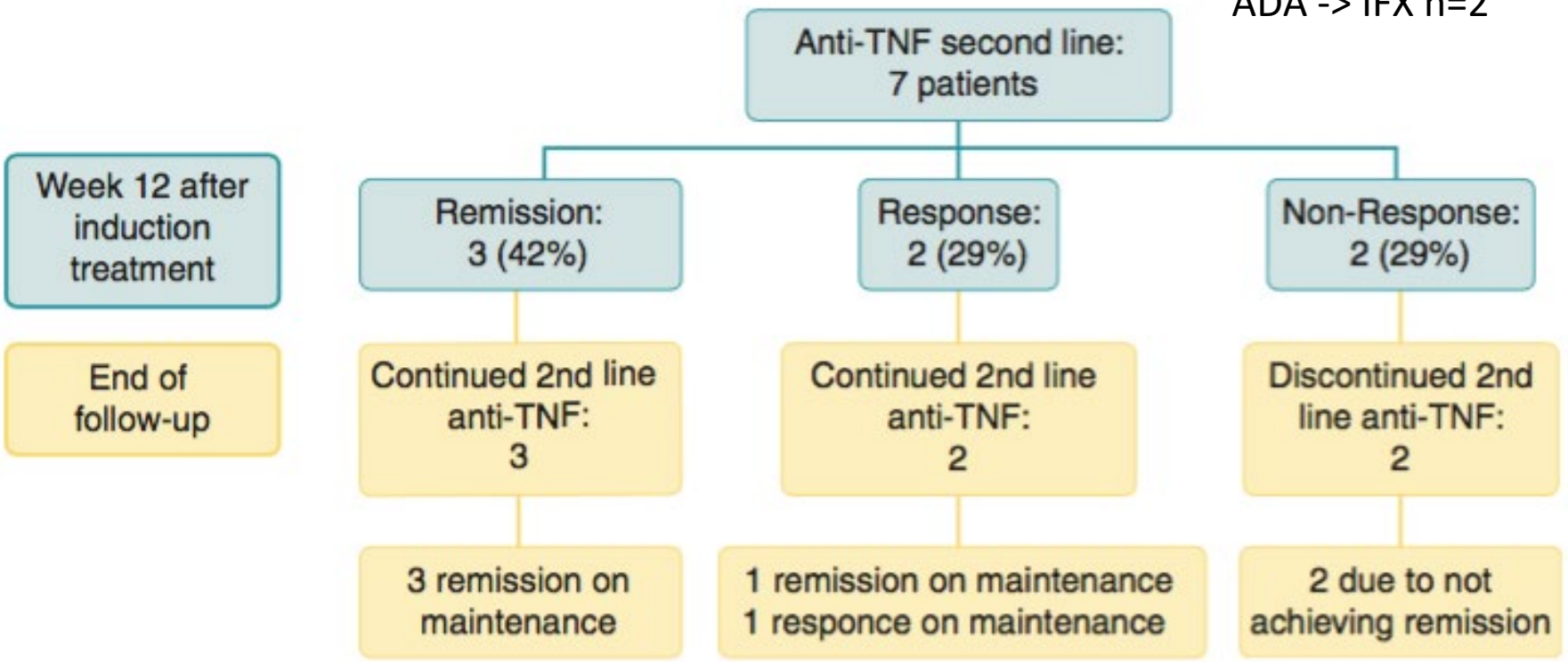


Daferera N et al, UEG Journal 2019

Single-centre experience with anti-tumour necrosis factor treatment in budesonide-refractory microscopic colitis patients

Niki Daferera[1], Henrik Hjortswang[1], Simone Ignatova[2] and Andreas Münch[1]

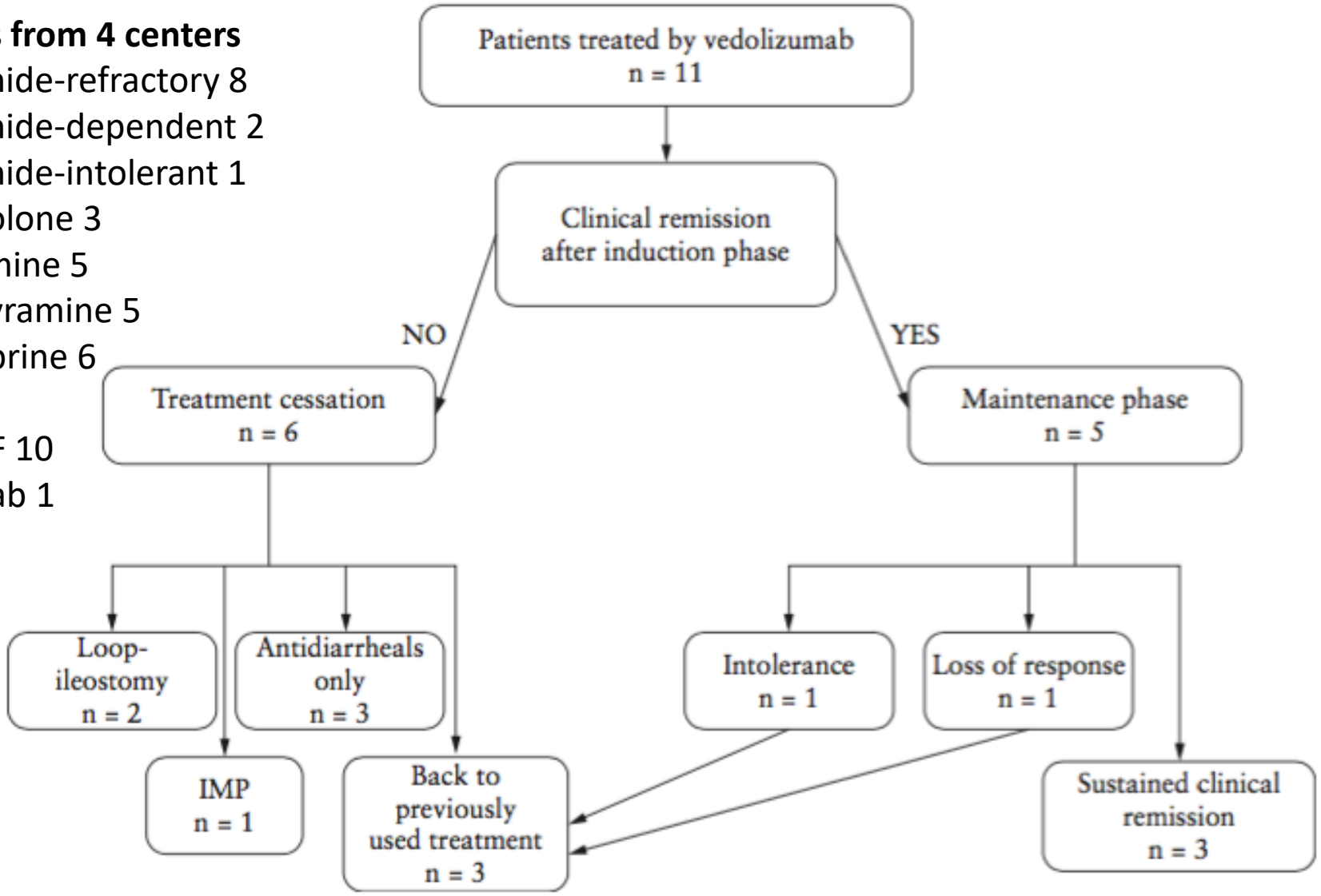
IFX -> ADA n=5
ADA -> IFX n=2



Daferera N et al, UEG Journal 2019

Vedolizumab in Refractory Microscopic Colitis: An International Case Series

- **11 cases from 4 centers**
- Budesonide-refractory 8
- Budesonide-dependent 2
- Budesonide-intolerant 1
- Prednisolone 3
- Mesalamine 5
- Cholestyramine 5
- Azathioprine 6
- MTX 3
- Anti-TNF 10
- Rituximab 1
- FMT 1



Rivière P et al, J Crohn' Colits 2018

European guideline on the management of microscopic colitis

Brief description of the initiative: In order to harmonize and standardize the clinical management of MC across Europe, a pan-European Clinical Practice Guideline on MC is essential. Topics: MC concept and epidemiology, aetiology and pathogenesis, clinical manifestation, diagnosis, histopathology, treatment.

Project type: Guideline development

Participating UEG Member Societies: German Society of Gastroenterology (DGVS), Swedish Society of Gastroenterology, Lithuanian Society of Gastroenterology, Hungarian Society of Gastroenterology, Danish Society of Gastroenterology and Hepatology, Netherlands Association of Hepatogastroenterologists (NVMDL), Spanish Society of Gastroenterology (AEG), ESP

Lead Coordinator: Stephan Miehlke

UNITED EUROPEAN GASTROENTEROLOGY ueg quality of care

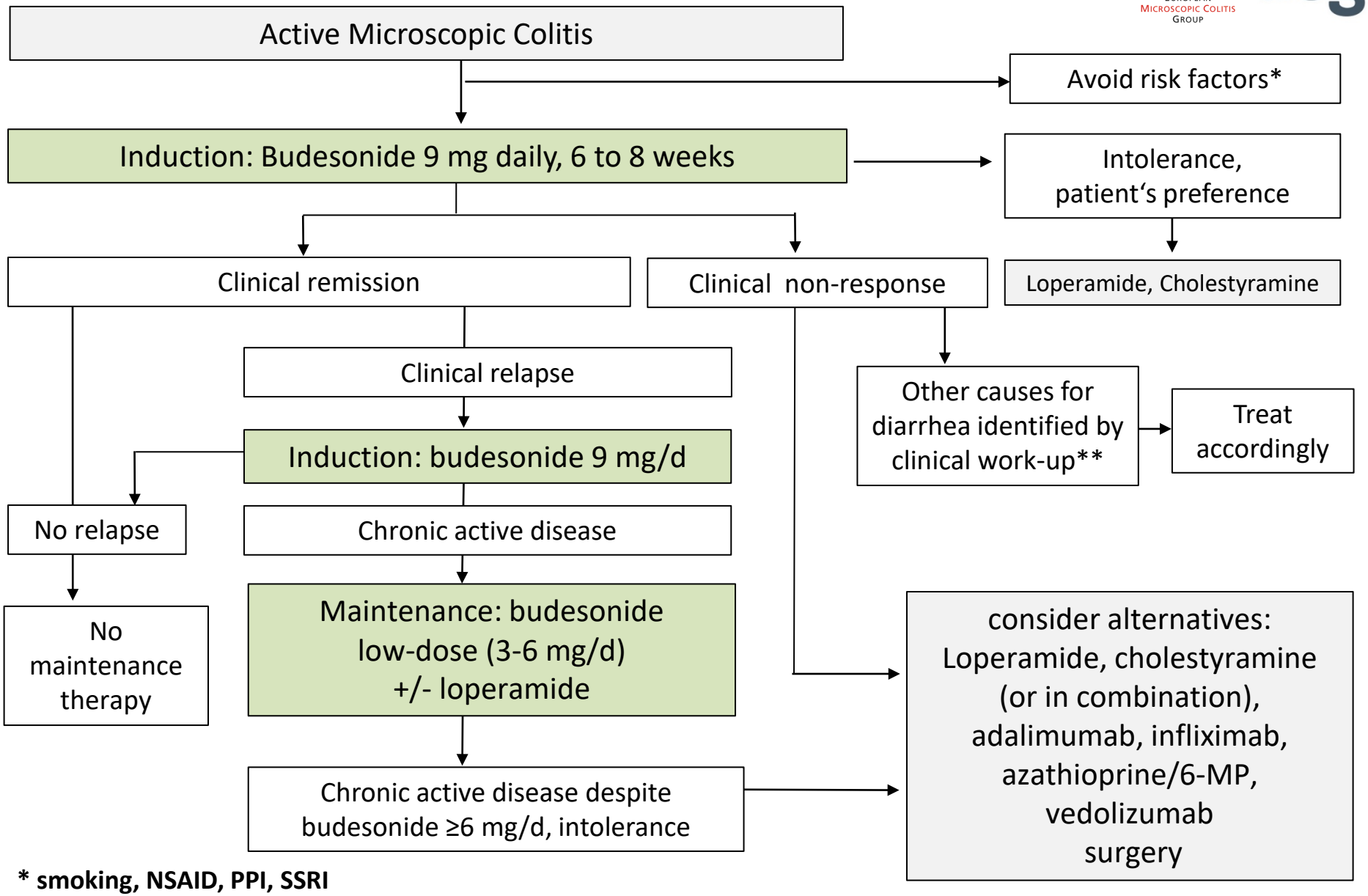
Authors: Stephan Miehlke, Danila Guagnozzi, Yamile Zabano Abdo, Gian E Tontini, Anne-Marie Kanstrup-Fiehn, Signe Wildt, Johan Bohr, Ole Bonderup, Gerd Bouma, Mauro D'Amato, Peter Engel, Fernando Fernandez-Banares, Gilles Macaigne, Henrik Hjortswang, Elisabeth Hultgren-Hörnquist, Anastasios Koulaouzidis, Jouzas Kupcinskas, Stefania Landolfi, Giovanni Latella, Alfredo Lucendo, Ivan Lyutakov, Ahmed Madisch, Fernando Magro, Wojciech Marlicz, Emese Mihaly, Lars Kristian Munck, Ann-Elisabeth Ostvik, Arpad Patai, Plamen Penchev, Karolina Skonieczna-Żydecka, Bas Verhaegh, Andreas Münch

EMCG
EUROPEAN MICROSCOPIC COLITIS GROUP

14 countries (alphabetical): Bulgaria, Denmark, France, Germany, Hungary, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Scotland, Spain, Sweden

Miehlke S et al. manuscript in in preparation (UEG Journal 2020)

European guideline on the management of microscopic colitis



*** smoking, NSAID, PPI, SSRI**

**** i.e. bile acid diarrhea, coeliac disease**

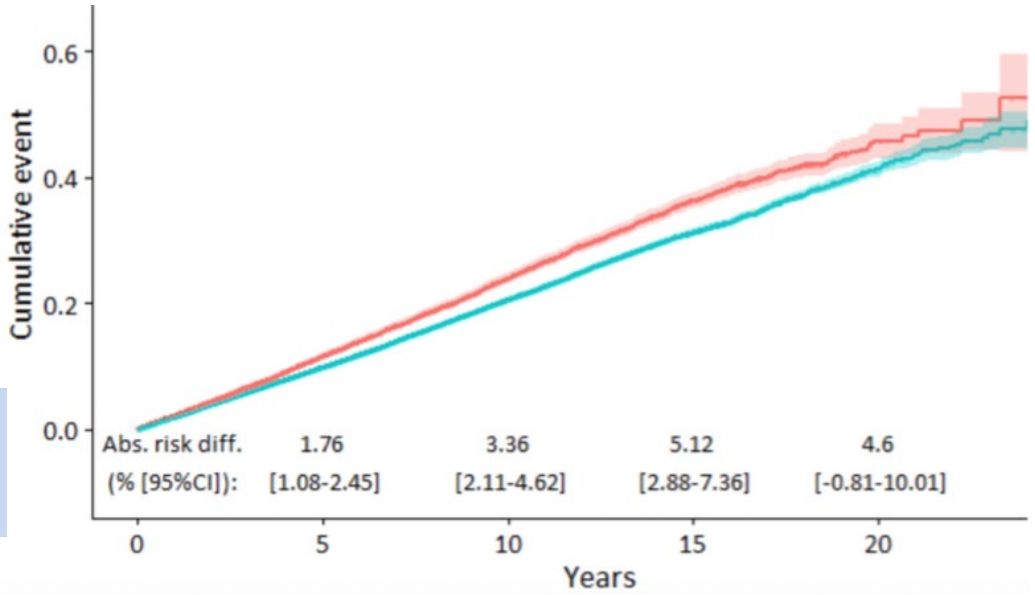
Miehlke S et al. manuscript in in preparation (UEG Journal 2020)

Back up slides

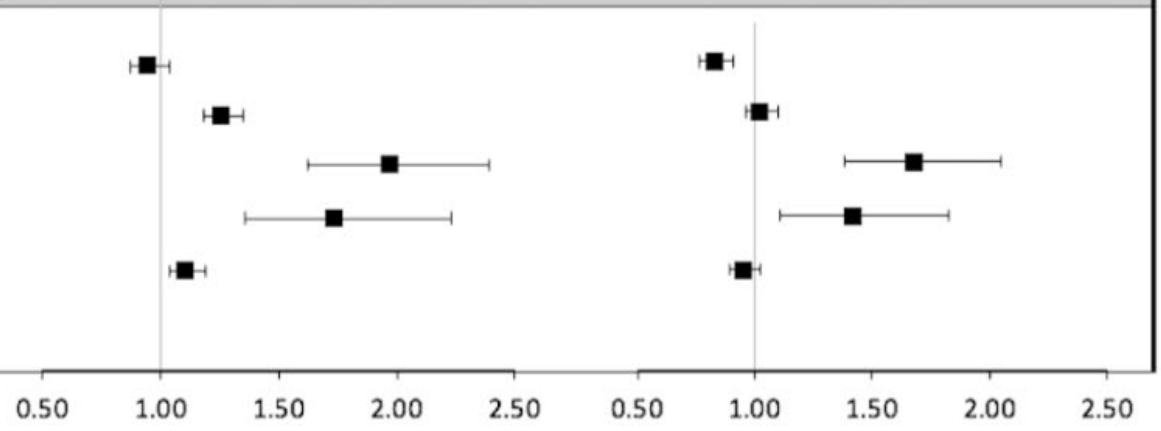
Mortality of Patients with Microscopic Colitis in Sweden

- Nationwide cohort study
- **14.333 MC cases** from 1990-2017
  -> 3014 deaths
- 68.700 matched comparators
  ->12.534 deaths

10-year risk difference 3.4% (2.14.6)
aHR 1.17 (1.12–1.22).



Cause of Death	Deaths¶	Incidence/100K Person-Years
Cancer	578	5.2
Cardiovascular	1114	10.0
Gastrointestinal	143	1.3
Infection	86	0.8
Others	1093	7.6

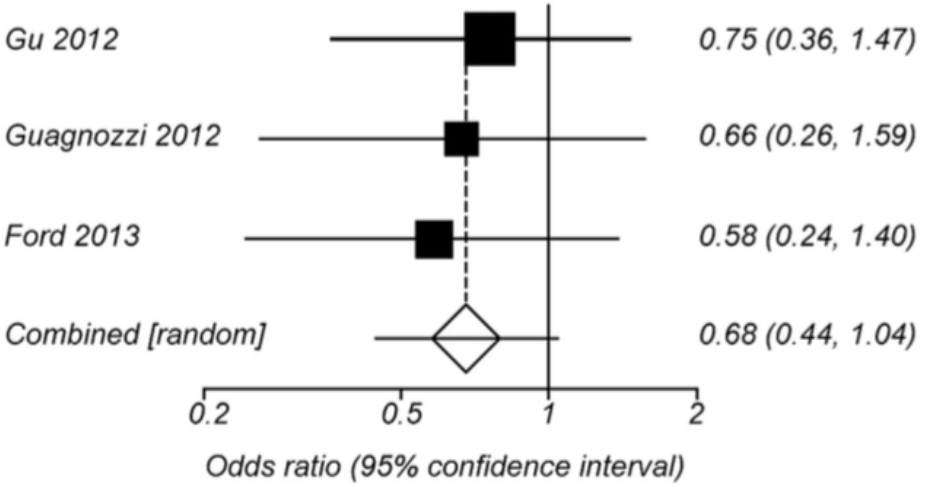


Kjalili H et al, Clin Gastroenterol Hepatol 2020

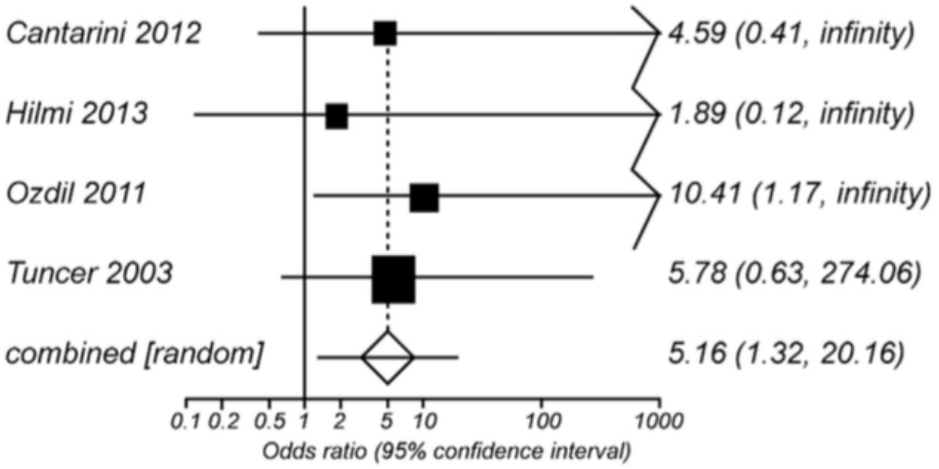
Irritable Bowel Syndrome and Microscopic Colitis: A Systematic Review and Meta-analysis

Odds ratios for MC among patients with IBS vs patients without IBS

Cross-sectional surveys



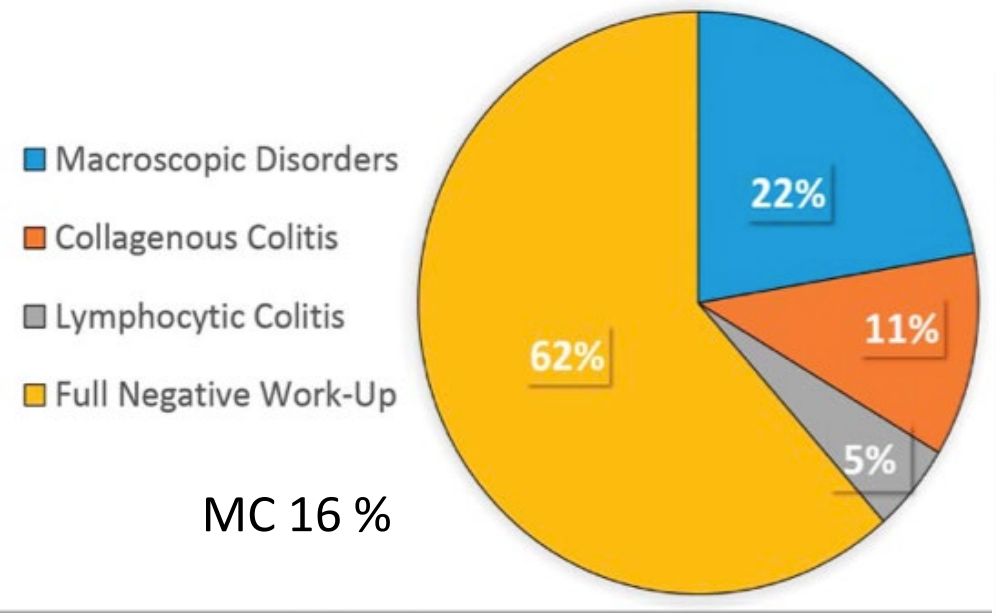
Case-control studies



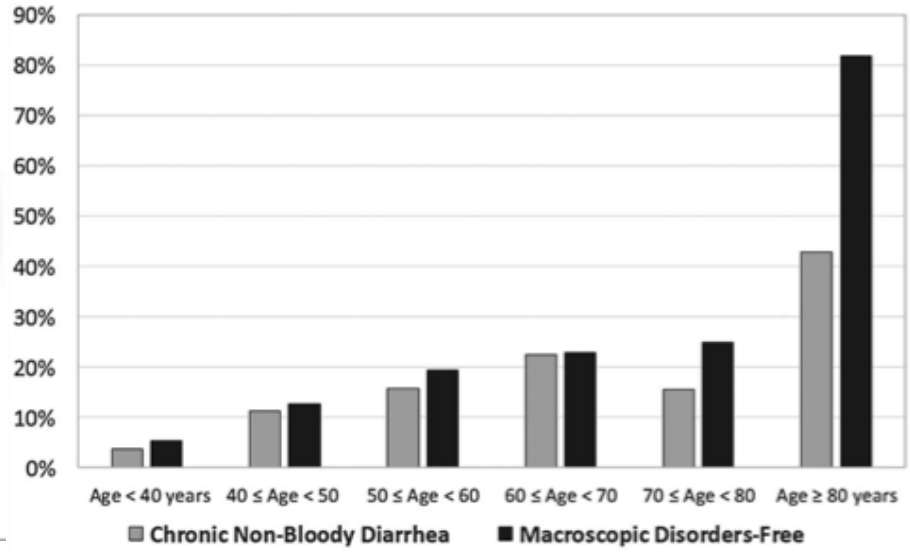
Kamp E et al, Clin Gastroenterol Hepatol 2016

Epidemiology of Microscopic Colitis

prospective, multicenter study (Italy), n=305, chronic non-bloody diarrhea



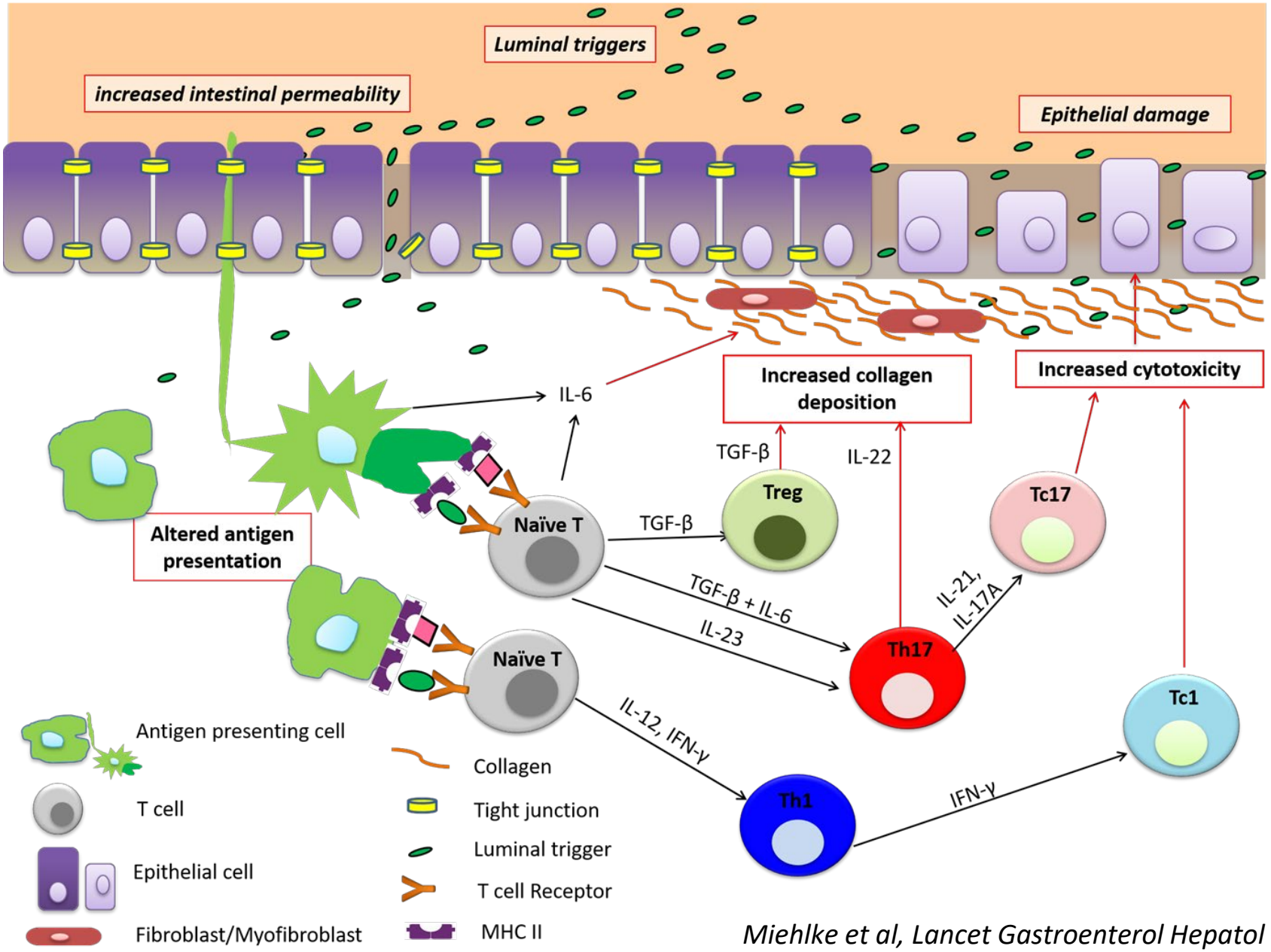
MC 16 %



	MC	Non-MC	OR	95% CI	*P*
Screened patients	43	201	—	—	—
Age, median ± SD	67 ± 15	58 ± 17.3	NA	NA	<0.001
Gender distribution (M/F)	17/26	86/115	1.14	0.58–2.24	0.736
Neoplastic patients	2 (4.6%)	36 (17.9%)	0.22	0.05–0.97	0.035

Tontini et al, Inflamm Bowel Dis 2014

Pathogenesis of Microscopic Colitis



Miehlke et al, Lancet Gastroenterol Hepatol 2019

Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case–control study

CC - active

CC - in Remission

	CC Active disease, *n* = 24 (%)	Matched controls, *n* = 53 (%)	OR	95% CI	CC remission, *n* = 72 (%)	Matched controls, *n* = 160 (%)	OR	95% CI
Diarrhoea last week	22 (92%)	5 (10%)	101.2	18.2–563.3***	10 (15%)	16 (10%)	1.5	0.7–3.6
Constipation	1 (4%)	7 (14%)	0.3	0.0–2.4	11 (15%)	16 (10%)	1.6	0.7–3.7
Abdominal pain	17 (74%)	9 (18%)	13.2	4.1–42.9***	25 (36%)	33 (21%)	2.1	1.1–3.9*
Fatigue	16 (67%)	27 (53%)	1.8	0.6–4.9	39 (54%)	54 (34%)	2.3	1.3–4.0**
Arthralgia	13 (57%)	15 (30%)	3.0	1.1–8.4*	43 (61%)	65 (41%)	2.2	1.3–3.9**
Myalgia	11 (48%)	17 (35%)	1.7	0.6–4.7	38 (53%)	58 (37%)	1.9	1.1–3.3*
Faecal incontinence	14 (58%)	4 (8%)	15.8	4.3–58.1***	18 (27%)	15 (10%)	3.3	1.5–7.0**
Nocturnal defecation	14 (64%)	0 (0%)	–	–	0 (0%)	6 (4%)	–	–

Nyhlin N et al, Aliment Pharmacol Ther 2014

Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case–control study

LC - active

LC - in Remission

	LC Active disease, *n* = 27 (%)	Matched controls, *n* = 71 (%)	OR	95% CI	LC remission, *n* = 60 (%)	Matched controls, *n* = 135 (%)	OR	95% CI
Diarrhoea last week	26 (96%)	7 (10%)	230.3	27.0–1966.6***	18 (31%)	16 (12%)	3.3	1.6–7.2**
Obstipation	0 (0%)	12 (18%)	–	–	8 (13%)	18 (14%)	1.0	0.4–2.4
Abdominal pain	22 (82%)	17 (25%)	13.2	4.3–40.3***	23 (38%)	36 (27%)	1.7	0.9–3.2
Fatigue	23 (89%)	28 (41%)	11.0	3.0–40.0***	32 (54%)	49 (37%)	2.0	1.1–3.7*
Arthralgia	16 (59%)	28 (41%)	2.1	0.9–5.3	26 (43%)	60 (45%)	0.9	0.5–1.7
Myalgia	16 (59%)	27 (39%)	2.3	0.9-5.6	23 (39%)	62 (47%)	0.7	0.4–1.3
Faecal incontinence	16 (59%)	4 (6%)	22.9	6.4–81.5***	12 (20%)	10 (8%)	3.1	1.2–7.6*
Nocturnal defecation	13 (48%)	1 (2%)	62.2	7.5–515.2***	1 (2%)	3 (2%)	0.7	0.1–7.2

Nyhlin N et al, Aliment Pharmacol Ther 2014

Development of a Microscopic Colitis Disease Activity Index: a prospective cohort study

Table 1 Demographic and clinical features of microscopic colitis study cohort (N=162) at baseline

Female, n (%)	120 (74)
Age (years), median (range)	66.4 (56.7–73.1)
Collagenous colitis, n (%)	80 (49.4)
White race, n (%)	161 (99.5)
Out of state of Minnesota, n (%)	79 (49.4)
Average number of unformed stools daily (range)	5.6 (3–8)
Nocturnal bowel movements, n (%)	97 (60)
Presence of abdominal pain, n (%)	105 (64.8)
Presence of weight loss, n (%)	84 (51.9)
Faecal urgency, n (%)	146 (90.1)
Faecal incontinence, n (%)	101 (62.3)
On antidiarrhoeal, n (%)	120 (74)

Cotter TG et al, Gut 2018

Development of a Microscopic Colitis Disease Activity Index: a prospective cohort study

Table 3 Multivariable-adjusted linear regression model (R^2=0.80) in the study cohort at baseline, with PGA score as dependent variable n=162

Variable	β-coefficient	95% CI	p Value
Number of unformed stools/day	0.309	0.26 to 0.36	<0.001
Nocturnal stools present	0.777	0.38 to 1.17	<0.001
Rate of abdominal pain (1–10)	0.216	0.15 to 0.29	<0.001
Weight loss per month (in pounds)	0.109	0.07 to 0.15	<0.001
Urgency prior to BM	0.929	0.31 to 1.55	0.004
Number of episodes of FI/month	0.011	0.01 to 0.02	<0.001

BM, bowel movement; FI, faecal incontinence; PGA, physician global assessment.

Cotter TG et al, Gut 2018

Development of a Microscopic Colitis Disease Activity Index: a prospective cohort study

MICROSCOPIC COLITIS DISEASE ACTIVITY INDEX (MCDAI) SCORECARD

ITEM	SCORE	WEIGHTED COEFFICIENT	TOTAL ITEM SCORE
Average number of unformed stools daily over past week		x 0.31	
Nocturnal stools over past week (0 = absent, 1 = present)		x 0.78	
Maximum abdominal pain over past week (score 1 – 10)		x 0.22	
Average weight loss per month (lbs*)		x 0.11	
Fecal urgency over past week (0 = absent, 1 = present)		x 0.93	
Number of episodes of fecal incontinence over past month		x 0.01	
		6 ITEM SCORE	
			+ 1.1
*Kg x 2.2 = lbs		MCDAI SCORE	

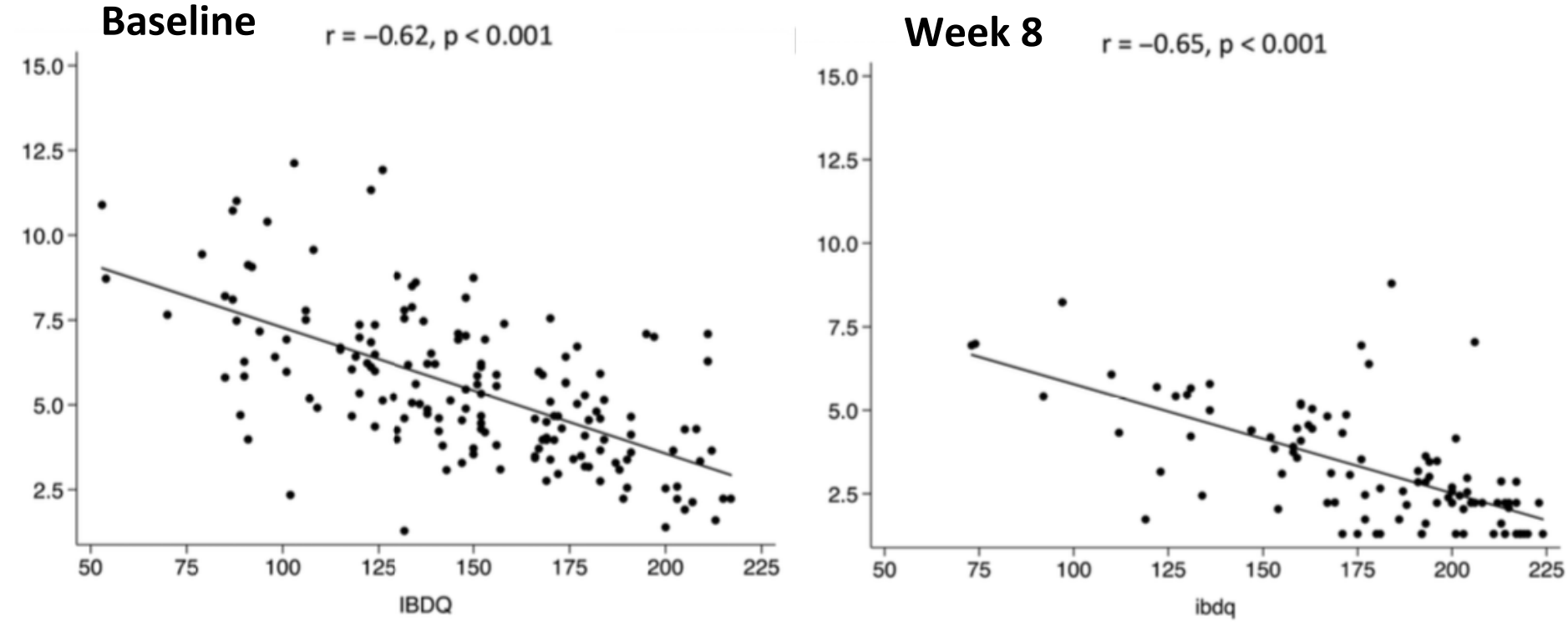
Median Score baseline: 5.14, week 8: 2.85

Patients with no symptoms: 1.32; Meaningful change with 2 points

Cotter TG et al, Gut 2018

Development of a Microscopic Colitis Disease Activity Index: a prospective cohort study

Correlation MCDAI vs IBDQ

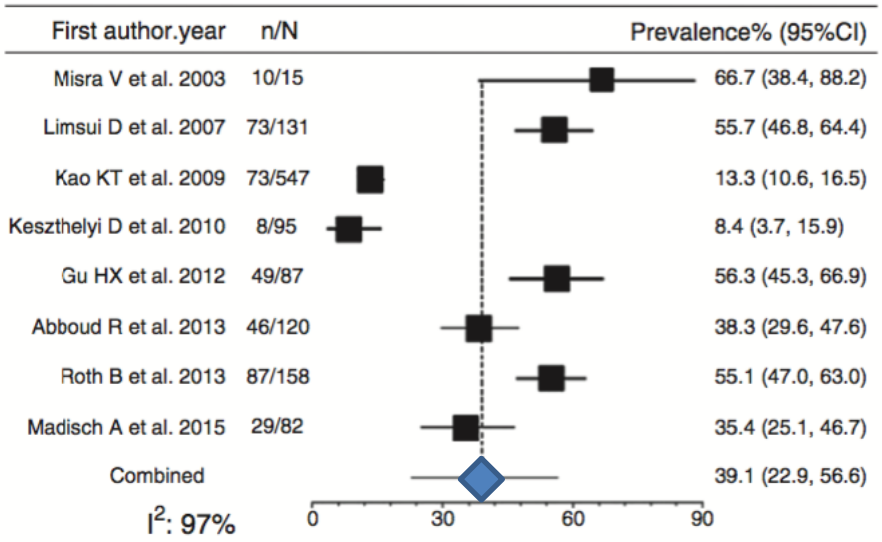


1-unit decrease in MCDAI = 9 point increase in IBDQ

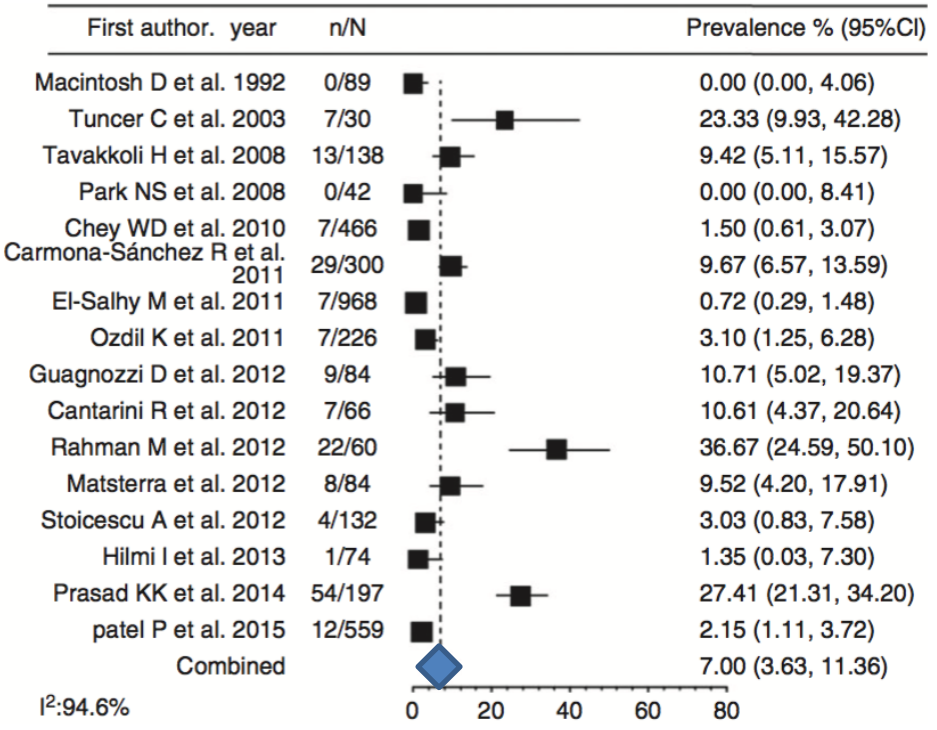
Cotter TG et al, Gut 2018

Systematic review with meta-analysis: diagnostic overlap of microscopic colitis and functional bowel disorders

26 studies, 5099 patients



Criteria of IBS-D in MC
39.1 %



Prevalence of MC in IBS-D
9.8 %

Guagnozzi D et al, Aliment Pharmacol Ther 2016

Development and Validation of a Scoring System to Identify Patients With Microscopic Colitis

	Derivation cohort (n = 476)		Validation cohort (n = 460)	
	Chronic diarrhea patients with MC (n = 85)	Chronic diarrhea patients without MC (n = 391)	Chronic diarrhea patients with MC (n = 74)	Chronic diarrhea patients without MC (n = 386)
Mean age, *y* (standard deviation)	65.8 (14.2)	51.0 (17.2)	65.6 (12.2)	50.4 (16.3)
Age ≥50 y (%)	76 (89.4)	214 (54.7)	65 (87.8)	208 (53.9)
Female gender (%)	64 (75.3)	239 (61.1)	51 (68.9)	224 (58.0)
Current PPI use (%)	34 (40.0)	98 (25.1)	35 (47.3)	101 (26.2)
Current NSAID use (%)	14 (16.5)	16 (4.1)	12 (16.2)	28 (7.3)
Celiac disease (%)	6 (7.1)	12 (3.1)	2 (2.7)	8 (2.1)

Item	OR	95% CI	Regression coefficient	Used within the scoring system	Item score
Female gender	1.94	1.14–3.30	0.662	Yes	+4
Age ≥50 y	6.98	3.40–14.3	1.944	Yes	+13
Current PPI use	2.47	1.46–4.16	0.903	Yes	+6
Current NSAID use	5.28	2.44–11.4	1.664	Yes	+11
Weight loss present	1.89	1.11–3.24	0.639	Yes	+4
Abdominal pain present	0.28	0.16–0.47	−1.283	Yes	−8
Celiac disease present	2.35	0.85–6.51	0.854	No	N/A
Nocturnal diarrhea present	1.17	0.54–2.53	0.155	No	N/A

Score range -8 to +38

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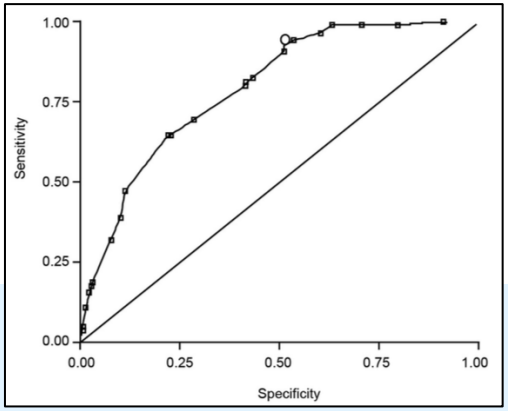
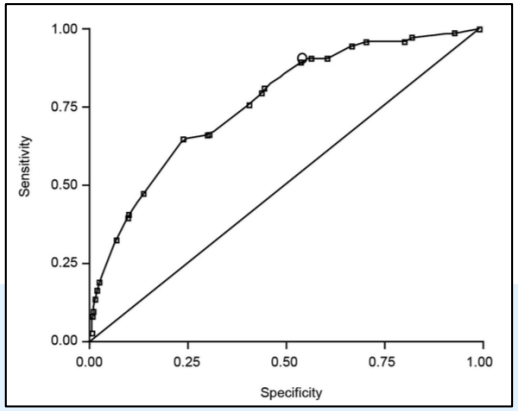
Development and Validation of a Scoring System to Identify Patients With Microscopic Colitis

Derivation cohort



Validation cohort



	No. with MC with a score above the cutoff	No. without MC with a score above the cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Derivation cohort						
Score of ≥+8	80/85	201/391	94.1% (86.8%–98.1%)	48.6% (43.5%–53.7%)	28.5% (23.5%–34.0%)	97.4% (94.1%–98.9%)
Score of ≥+4	84/85	246/391	98.8% (93.6%–99.8%)	37.1% (32.4%–42.0%)	25.5% (21.1%–30.4%)	99.3% (96.2%–99.9%)
Validation cohort						
Score of ≥+8	67/74	211/386	90.5% (81.7%–95.3%)	45.3% (40.3%–50.5%)	24.1% (19.2%–29.6%)	96.2% (92.2%–98.4%)
Score of ≥+4	70/74	260/386	94.6% (86.9%–97.9%)	32.6% (28.0%–37.6%)	21.2% (16.9%–26.0%)	96.9% (92.3%–99.2%)

Detection of pts with MC with >90% sensitivity

Exclusion of MC and potential reduction of colonic biopsies and costs

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