

# Microscopic colitis and Proton Pump Inhibitors – use of the Null Hypothesis

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## Background

- Many studies have shown a strong association with proton pump inhibitor (PPI) usage and the development of microscopic colitis (MC).
- Due to the association of PPIs and diarrhoea there is a risk of confounding bias due to increased investigation with colonoscopy and biopsies
- This has resulted in a controversy in case-control studies with regard to using a control group from the background population (BP) or a control group with investigated chronic diarrhoea (ICD)
- This abstract evaluates the use of the null hypothesis for MC and PPIs with relation to published case-control studies of MC and PPIs and with discussion of potential mechanisms

## Methods

- The Null Hypothesis for MC and PPIs can be categorised according to MC being largely clinical and investigated or a largely subclinical uninvestigated disease
- Hypothesis 1: PPIs and MC are unrelated and MC is always overt and investigated by colonic biopsies
- Hypothesis 2: PPIs and MC are unrelated and MC is always subclinical
- For age and sex matched groups – those with clinical MC (hypothesis 1) that are detected will have the same percentage on PPIs as those from the background population (BP), whereas those with subclinical MC (hypothesis 2) that are detected will have the same percentage on PPIs as those with investigated chronic diarrhoea (ICD)

- There are 6 published case-control studies and a recent abstract that provide adjusted odds ratios (AORs)/ odds ratios (ORs) for PPIs and MC.
- Some of the larger studies have divided MC patients into the 2 subgroups; collagenous colitis (CC) & lymphocytic colitis (LC)

## Results

	MC/subtype	n	%PPIs	BP %PPIs	AOR/OR	ICD %PPIs	AOR/OR
<b>Bonderup 2014</b>	CC	3474	55.7	14.2	7.04		3.47
	LC	2277	36.7	12.9	3.37		3.57
<b>Bonderup 2017 (abstract)</b>	CC	6254			8.75		
	LC	4398			5.03		
<b>Banares 2013</b>	CC	120	33.3	14.8			
	LC	70	31.4	14.8			
<b>Kesthelyi 2010</b>	MC	95	37.9	12.6	4.5		
<b>Pascua 2010</b>	MC	26	12	45	0.21	34	0.29
<b>Verhaugh 2016</b>	MC	1211	41.8	17.5	3.79		
<b>Masclée 2015</b>	MC	218	30	2.4	7.3	6.3	10.6

## Discussion and conclusion

- MC is unlikely to be always investigated and there is some evidence that MC can be detected in asymptomatic individuals. However, it is also unlikely that MC is largely subclinical and not investigated
- All but one case-control studies have shown increased AORs for MC and PPIs for BP controls and similarly in 2 of 3 studies for ICD controls. The only study not showing an association included only 26 cases with MC and a very high usage of PPIs in the control BP of 45%.
- The mechanisms of how PPIs can cause MC are unclear but theories include increased epithelial permeability, alteration of colonic bacterial flora and increased production of collagen by colonocytes
- The association of MC with medications including PPIs should not be ignored and cessation of potentially causative medications requires consideration.

