Pouchitis

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Disclosures

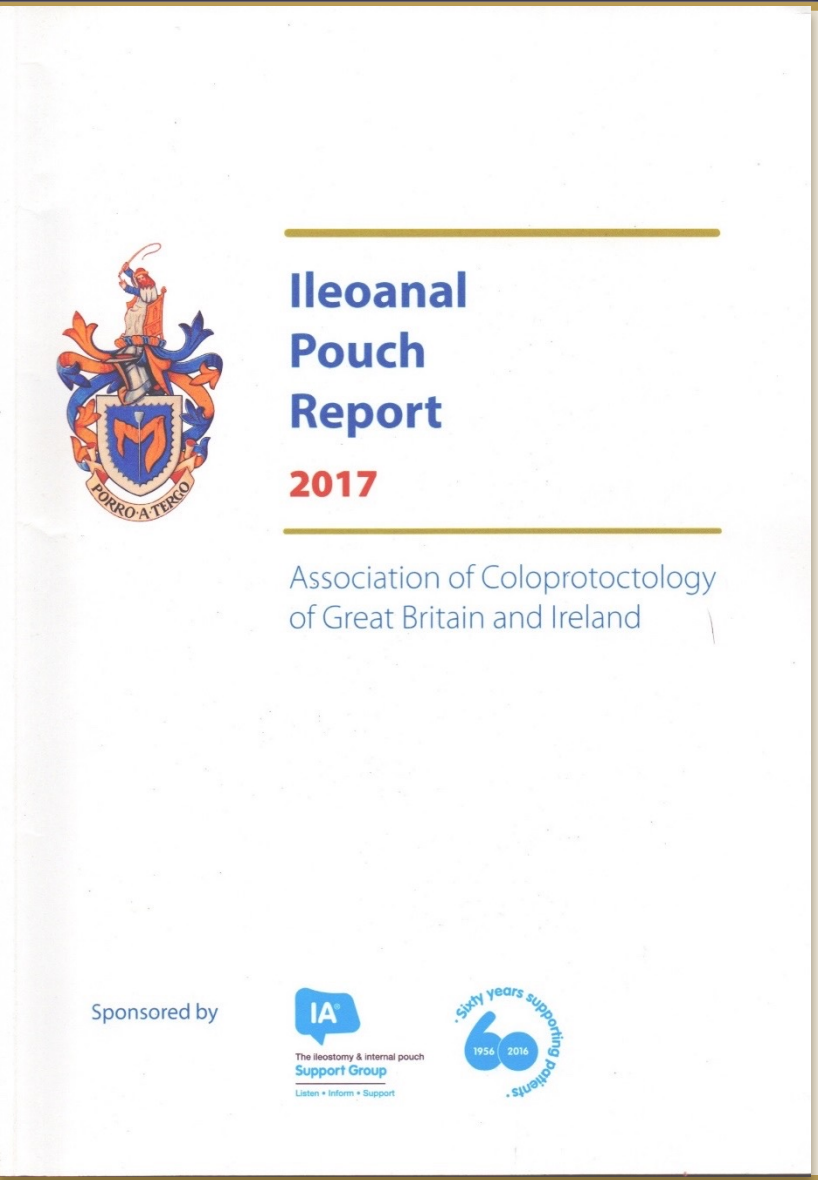
- Professor Travis was the lead author of the UCEIS and has been adviser to, in receipt of educational or research grants from, or invited lecturer for Abacus, AbbVie, Actial, ai4gi, Alcimed, Allergan, Amgen, Apexian, Aptel, Arcturis, Arena, Asahi, Aspen, Astellas, AstraZeneca, Atlantic, Barco, BioCare , Biogen, BL Pharma, Boehringer Ingelheim, Bristol Myers Squibb, Buhlmann, Calcico, Celgene, Cellerix, Celsius, Cerimon, ChemoCentryx, Chiesi, Cisbio, ComCast, Coronado, Cosmo, Dr Falk, Ducentis, Dynavax, Elan, Endpoint Health, Enterome, EQRx, Equillium, Ferring, FPRT Bio, Galapagos, Genentech/Roche, Genzyme, Gilead, GlaxoSmithKline, Glenmark, Grunenthal, GW Pharmaceuticals, Immunocore, Immunometabolism, Indigo, Janssen, Lexicon, Lilly, Medarex, MedTrix, Merck, Merrimack, Mestag, Microbiotica, Millennium, Neovacs, Novartis, Novo Nordisk, NPS-Nycomed, Ocera, Optima, Origin, Otsuka, Palau, Pentax, Pfizer, PharmaVentures, Phesi, Phillips, Procter & Gamble, Pronota, Proximagen, Resolute, Robarts, Sandoz, Sanofi, Santarus, Satisfai, Sensyne Health, Shire, Sigmoid Pharma, Sorriso, Souffinez, Syndermix, Synthon, Takeda, Theravance, TiGenix, Tillotts, Topivert, Trino Therapeutics with Wellcome Trust, TxCell, UCB Pharma, Vertex, VHsquared, Vifor, Warner Chilcott, Zeria

- All advisory boards were suspended while President of ECCO

Synopsis

- Physicians: get it right from the start
- Not all pouch dysfunction = pouchitis
- Types of pouchitis
- First and second line therapies
- Beyond vedo
- Calling for help
- Take home messages

UK Ileoanal Pouch Registry



Salient points

5352 patients

126 units in England in last 5 y (2012-17)

400 operations/y

>50% laparoscopic last 5y

6% performed by trainee under supervision

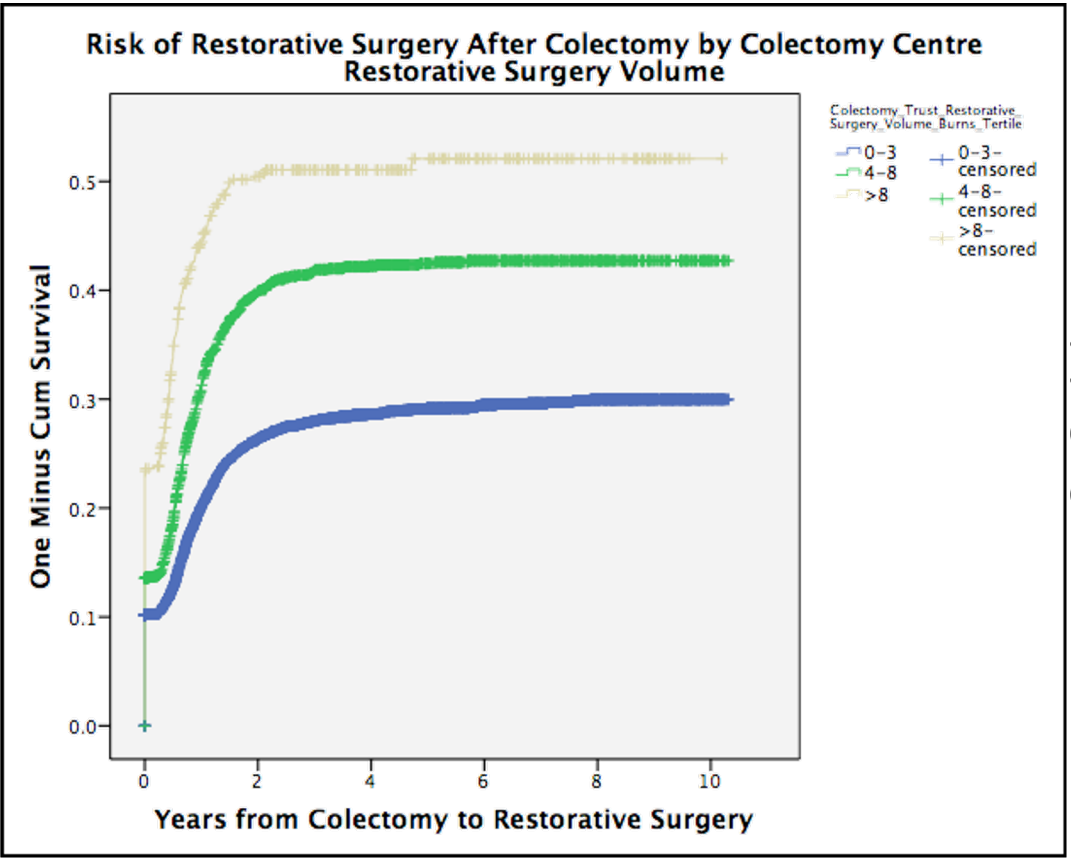
Complications 23%. Failure 5%

- Average IPAA/surgeon = 3/y
- 25% of surgeons performed just 1 in last 5y
- Low volume surgeons more complications and failure

https://www.acpgbi.org.uk/_userfiles/import/2016/07/Ileoanal-Pouch-Report-2017-FINAL.pdf

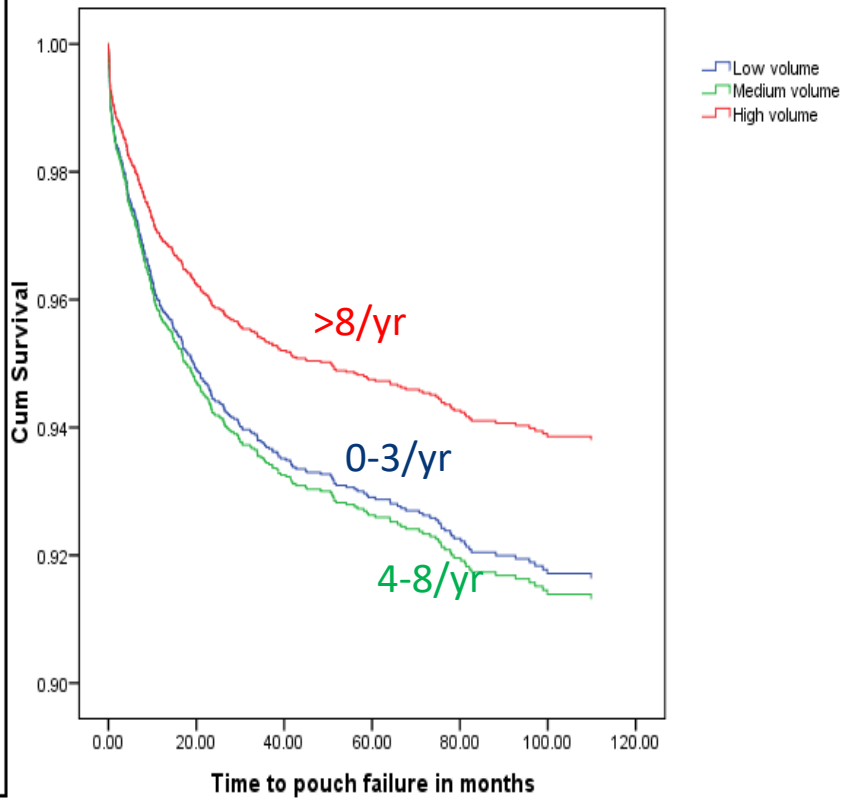
UK high and low volume centres (HES data)

RESTORATIVE SURGERY AFTER INITIAL COLECTOMY



FAILURE

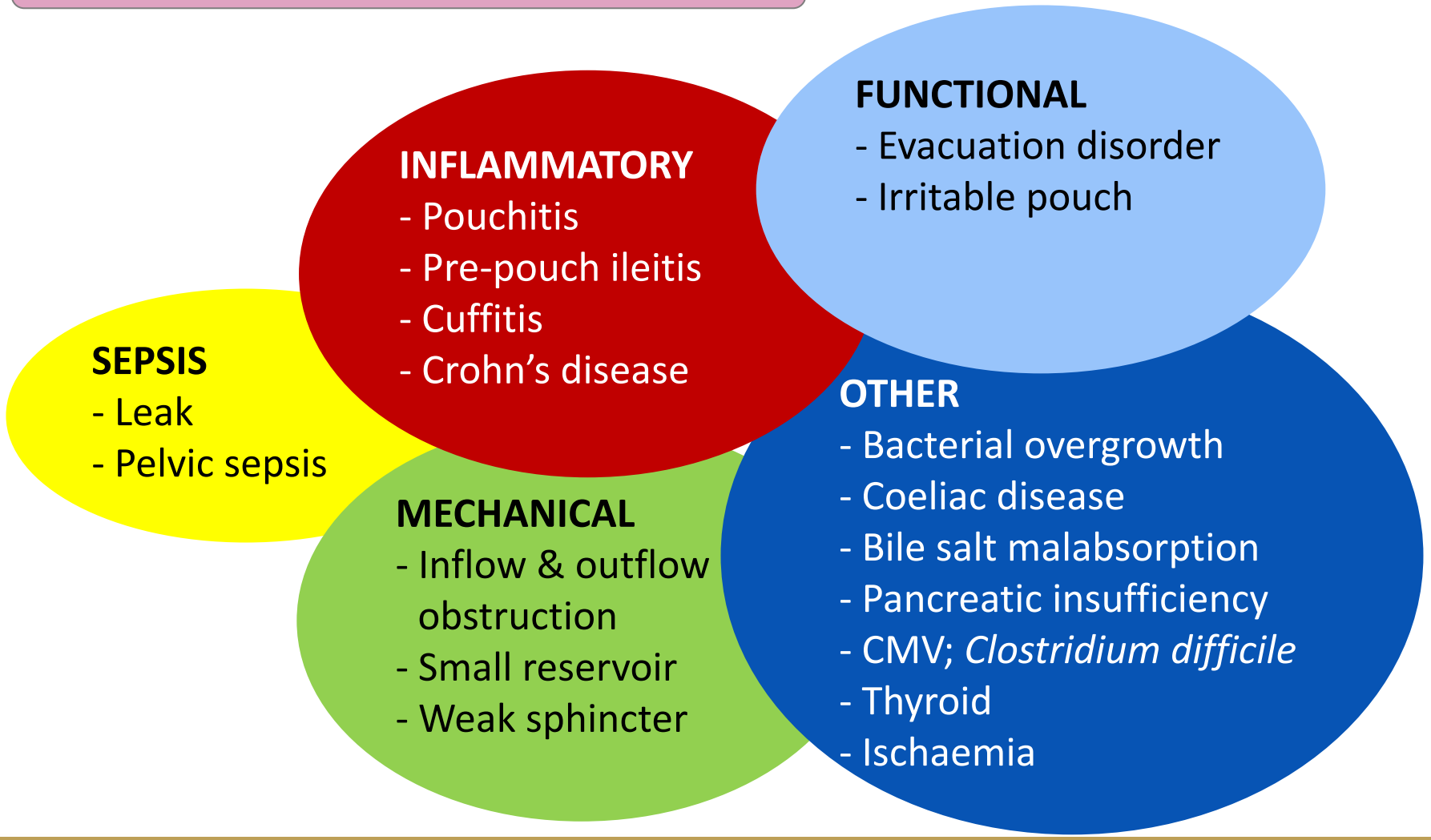
Pouch failure rate and volume for individual institution



https://www.acpgbi.org.uk/_userfiles/import/2016/07/Ileoanal-Pouch-Report-2017-FINAL.pdf

Pouch dysfunction ≠ pouchitis

10% of pouches **fail** over a **10-year** period



Deputy M et al. *Colorectal Dis* 2021;**23:**1193–204

Carefully assess the cause of pouch dysfunction

- Reason for surgery i.e. medically-failed therapy or dysplasia/cancer
- Type of pouch and type of anastomosis
- Review the histopathology of colectomy specimen
- Any EIMs, perianal symptoms, mouth ulcers?
- Is there a long history of bowel symptoms (eg pre-existing IBS)?
- Has the pouch ever worked well from the start?
- Previous episodes of pouch symptoms and response to antibiotics
- Possible gastrointestinal infection (travel history, sexual proclivity etc)
- Current medications, including NSAIDs, PPI
- Ask carefully about bowel symptoms (DF/NF/urgency/DC/NC)…

Deputy M et al. *Colorectal Dis* 2021;**23:**1193–204

Assessment of the causes of pouch dysfunction

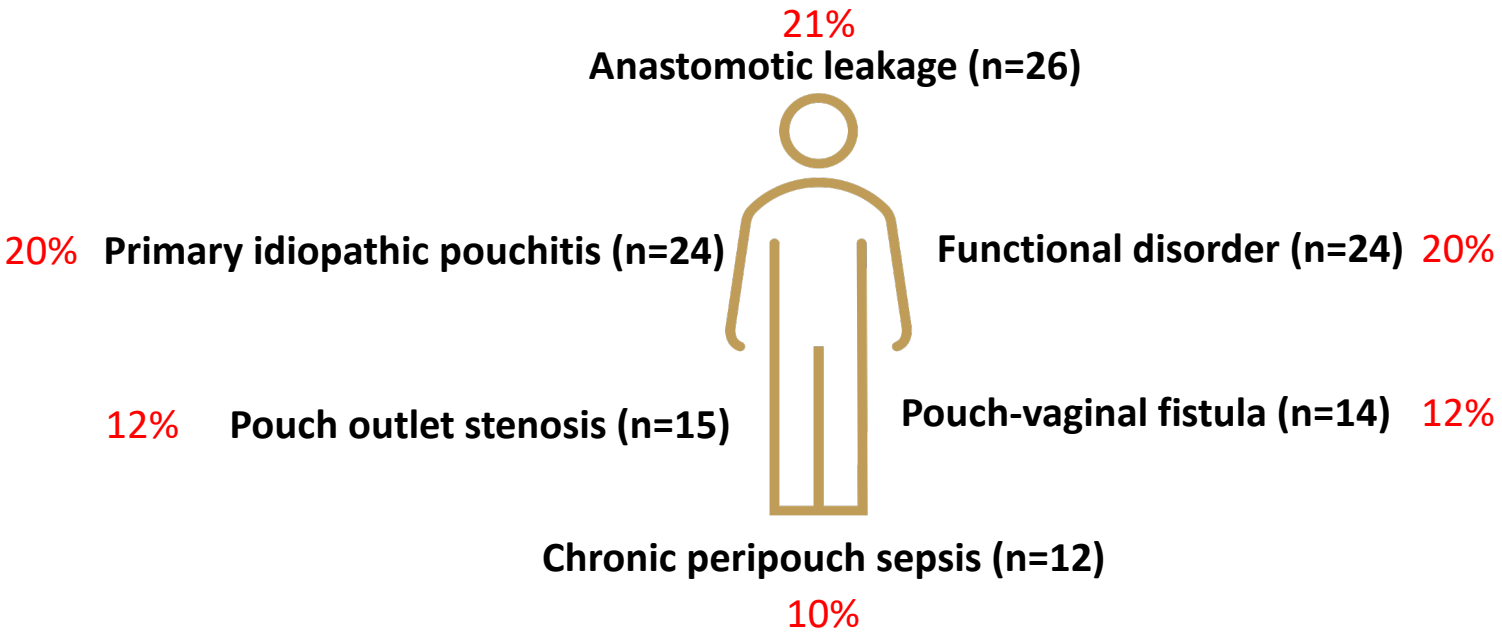
Examination (perianal + digital)	Perianal fissures/ fistula Ileo-anal anastomosis (stricture; high) Sphincter tone
Bloods	FBC, biochemistry, inflammatory markers, haematinics, coeliac serology, thyroid function
Stool cultures Faecal calprotectin	Exclude infections and *Clostridium difficile*
Pouchoscopy + biopsies	Pouchitis, cuffitis, pre-pouch ileitis, strictures, fistula, exclude CMV
MRI pelvis	Peri-pouch sepsis
Defaecating pouchogram	Pouch anatomy; small volume pouch functional outflow obstruction
Examination under anaesthesia +/- pouchoscopy	Assess perianal tissue + pouch
MRI small bowel	Small bowel Crohn's disease

Occasional
- SIBO breath test
- Faecal elastase
- Anorectal physiology
- Endoanal ultrasound

Deputy M et al. *Colorectal Dis* 2021;**23:**1193–204

Many patients present with ≥ one diagnosis

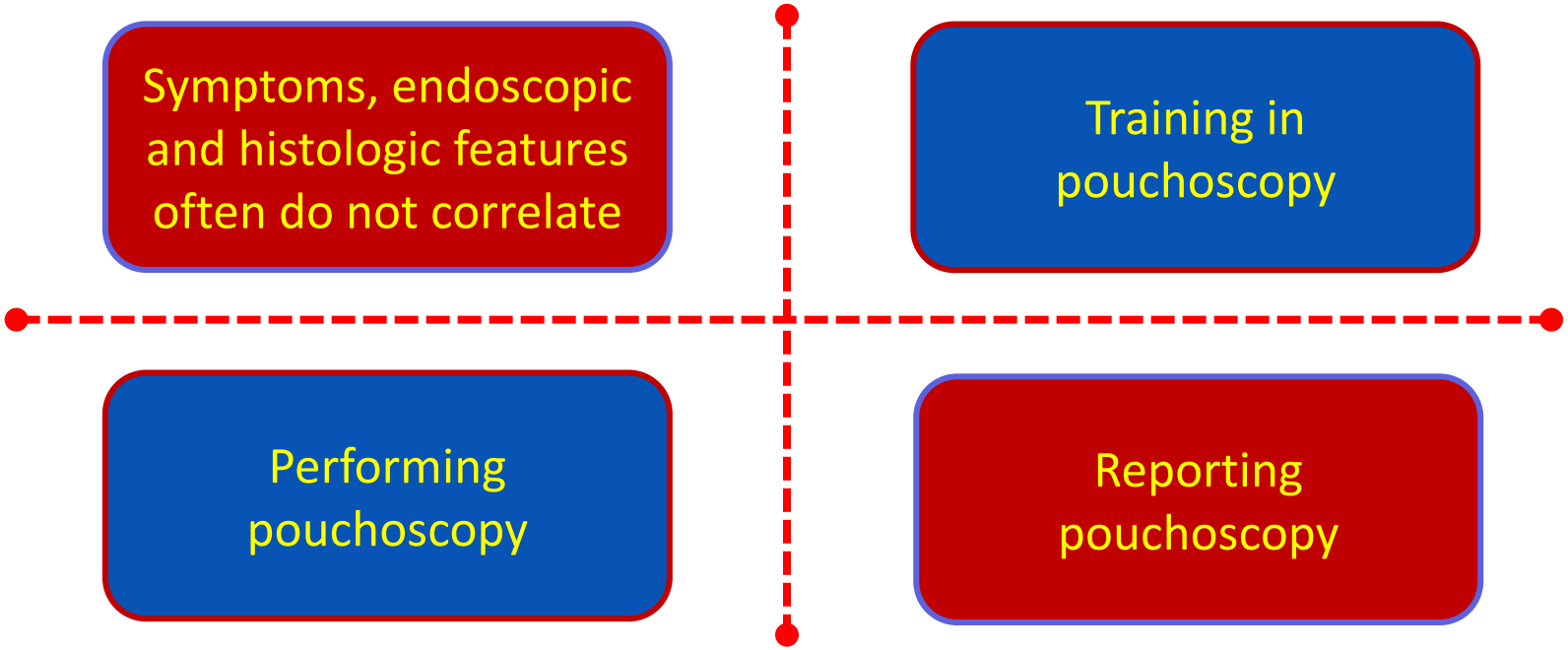
St Mark's study (n=121) on the management of patients with pouch dysfunction, the highest frequency diagnoses observed in the cohort were:



Other diagnoses included bile salt malabsorption, anal fissure and a cohort displaying multiple diagnoses

Speaker's opinion.

Diagnosing pouchitis can be challenging



Pouchitis assessment: PDAI and mPDAI (1)

Criteria	Score
Clinical	
Stool frequency	
Usual postoperative stool frequency	0
1–2 stools/day >postoperative usual	1
3 or more stools/day >postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Faecal urgency or abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature >37.8°C)	
Absent	0
Present	1

Criteria	Score
Endoscopic inflammation	
Oedema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucoid exudate	1
Ulceration	1
Acute histological inflammation	
Polymorphic nuclear leucocyte infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (mean)	
<25%	1
25–50%	2
>50%	3

- PDAI: 18-points, includes histology
- mPDAI: 12 points, excluding histology; no loss of diagnostic sensitivity/specificity

Shen B et al. *Dis Colon Rectum* 2003;**46:**748–53.

Pouchitis assessment: API

- Only ulceration and ulcerated surface have inter-rater reliability
  - Apply SES-CD to pouch endoscopy as a single segment
- Add RHI for histopathology to create novel Atlantic Pouchitis Index
  - Objective, but lacks clinical data

Variable	SES-CD values			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0.1-0.5 cm)	Large ulcers (0.5-2.0 cm)	Very large ulcers (>2.0 cm)
Ulcerated surface (%)	None	<10	10-30	>30
Affected surface (%)	Unaffected segment	<50	50-75	>75
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Index	Item	ICC (95% CI)		AUC (95% CI)	Correlation, r (95% CI), with change in VAS
		Intra-rater	Inter-rater		
Endo PAI	**Total EPAI (0 to 6)**	0.77 (0.68, 0.84)	0.39 (0.24, 0.52)	0.72 (0.6, 0.82)	**0.56** (0.40, 0.68)
SES-CD	**Total SES-CD (0 to 12)**	0.71 (0.57, 0.82)	0.42 (0.26, 0.55)	0.86 (0.76, 0.92)	**0.73** (0.63, 0.81)

Samman MA et al. *Gastrointest Endo* 2018;**88:**360-9; Jairath V, Sedano R et al. *DDW* 2023

Classification of subtypes of pouchitis

Based on symptom duration	
Acute	Less than 4 weeks
Chronic	Greater than 4 weeks
Based on symptom pattern	
Infrequent	<3 episodes per year
Relapsing	≥3 episodes per year or recurrence within 1 month of successful therapy
Based on response to antibiotics	
Antibiotic-responsive	Responds to course of antibiotics
Antibiotic-dependent	Requires antibiotics to maintain response (=CARP)
Antibiotic-refractory	Does not respond to standard course of antibiotics (=CARP)

adapted from Tome J, Raffals L, Pardi DS. *Dis Colon Rectum* 2022;**65:**S69-76

Prevalence of pouchitis

- Cumulative probability of pouchitis after pouch formation:
  - 20% at 1 year
  - 40% at 5 years

Outtier A et al. *Clin Exper Gastroenterol* 2021:14;277–90

- Around 60% get recurrence

Shen B et al. *Gastroenterol Hepatol* 2008;**4:**355–61

- Up to 19% develop chronic pouchitis refractory to antibiotics

Weaver KN et al. Crohns Colitis 360 2019;1:1–7

ECCO and BSG Guidelines: acute pouchitis

ECCO Statement 10B

The majority of **patients respond to metronidazole or ciprofloxacin**, although the optimum modality of treatment is not clearly defined [EL2]. **Side effects are less frequent using ciprofloxacin** [EL2]. Antidiarrhoeal drugs may reduce the number of daily liquid stools, independently of pouchitis [EL5]

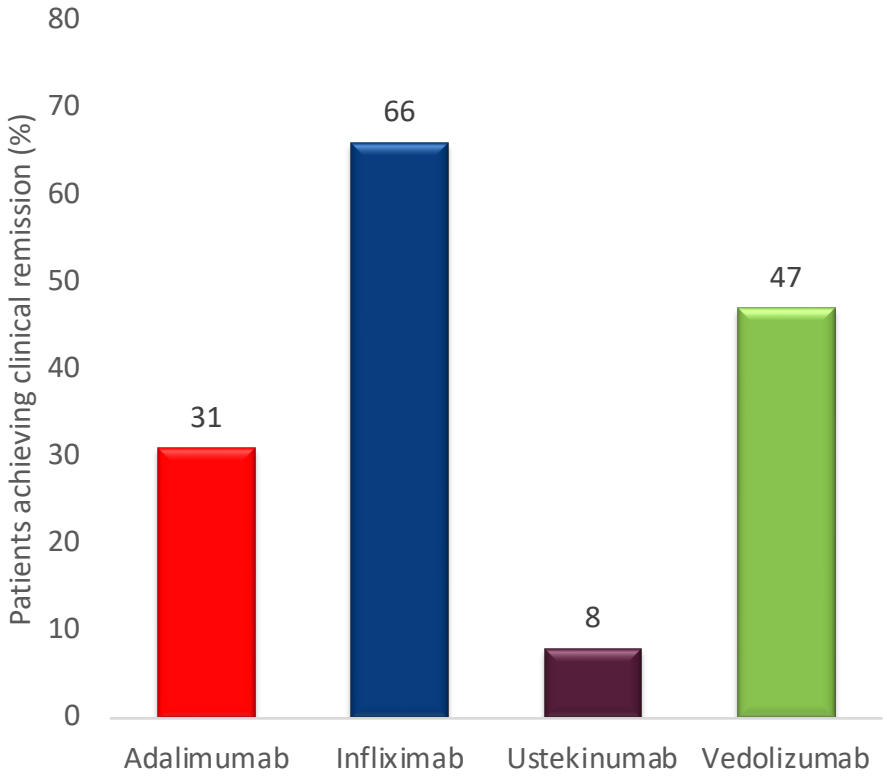
BSG Statement 23

We recommend that a 2-week course of **ciprofloxacin or metronidazole is the first-line treatment of acute pouchitis** (GRADE: strong recommendation, low-quality evidence). We suggest that **ciprofloxacin is better tolerated and may be more effective that metronidazole** (GRADE: weak recommendation, low-quality evidence. Agreement: 97.2%)

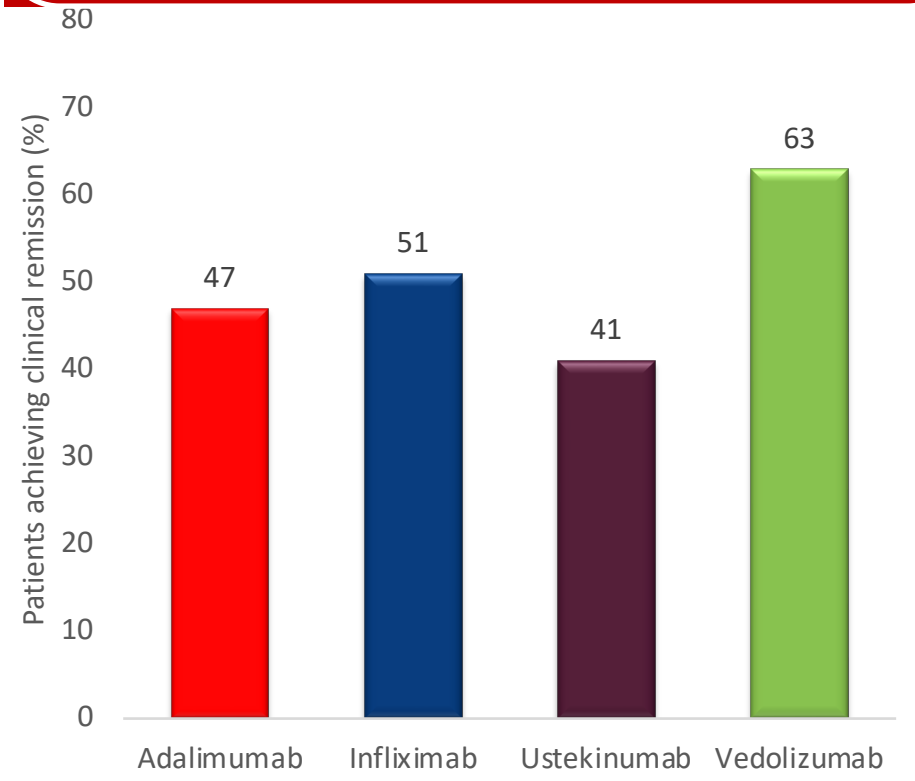
Magro F et al. *J Crohns Colitis* 2017;**11:**649–70; Lamb CA et al. *Gut* 2019;68:s1–s106.

Meta-analysis of biologics to treat inflammatory IPAA dysfunction: complete clinical response/remission

2021: 15 studies, 311 patients all CARP, only one RCT with ADA (n=13). mPDAI and PDAI definitions differed between studies. Total numbers: ADA=42; IFX=92; UST=33; VDZ=144



2022: 26 studies, 741 patients, with CARP/Crohn's/cuffitis. Complete clinical response definitions varied. Total numbers: ADA=223; IFX=245; UST=126; VDZ=147



Chandan S et al. *J Clin Gastroenterol* 2021;**55:**481–91 Shehab M et al. *J Can Assoc Gastro* 2022;**55:**287-96

EARNEST: RCT in chronic pouchitis

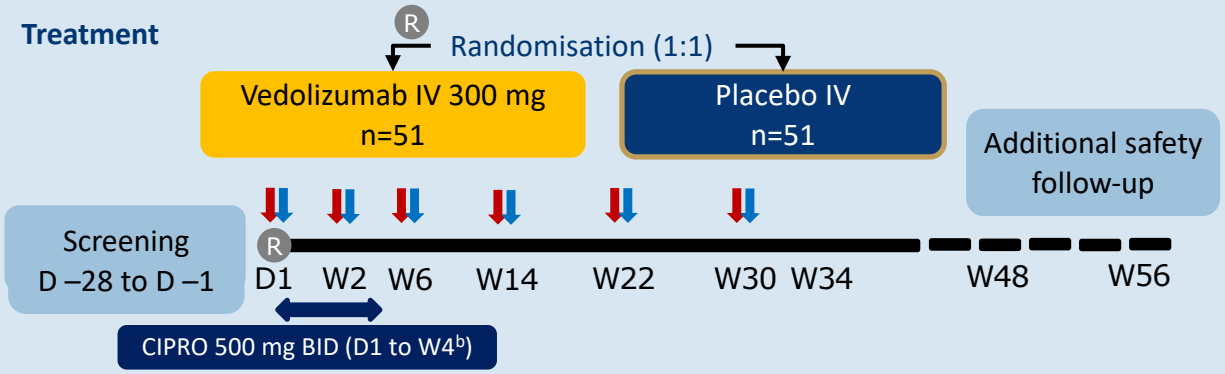
Key Eligibility Criteria

Inclusion

- Aged 18-80 years
- IPAA for UC completed ≥1 year prior to study start
- Active chronic pouchitis[a]

Exclusion

- CD or CD of the pouch (known or suspected), irritable pouch syndrome, mechanical complications of the pouch, active infection or isolated/predominant cuffitis
- Prior treatment with vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab or anti–MAdCAM-1 therapy



Key Endpoints

Primary
- mPDAI remission[c] at W14

Secondary
- mPDAI remission[c] at W34
- PDAI remission[d] at W14 and W34
- mPDAI response[e] at W14 and W34
- Quality of life (IBDQ and CGQL)

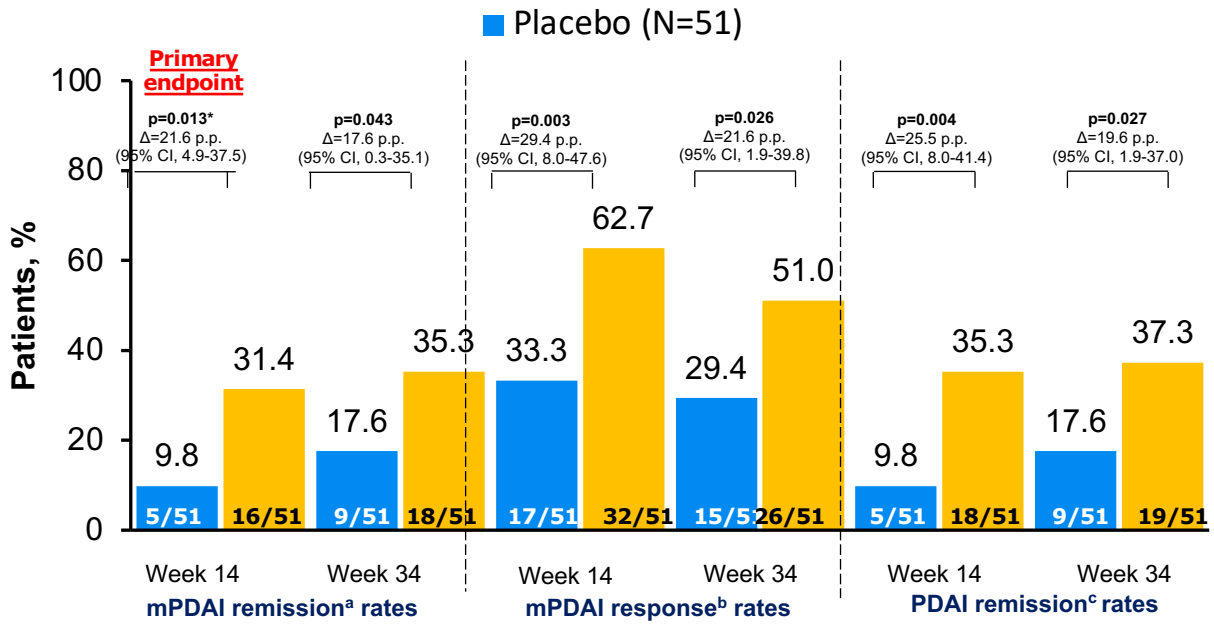
Exploratory
- Endoscopic (change in number of ulcers and SES-CD)

- mPDAI remission comprises clinical symptoms and endoscopic domains
- PDAI remission comprises clinical symptoms, endoscopic and histology domains

[a]mPDAI score ≥5 and endoscopic subscore of ≥2 with either: a) ≥3 recurrent episodes within 1 year before screening visit, each treated with ≥2 weeks of antibiotic or other prescription therapy, or b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to baseline endoscopy. [c]mPDAI score of <5 and a ≥2-point reduction from baseline.

Travis SPL et al. *N Engl J Med* 2023;**388:**1191-1200

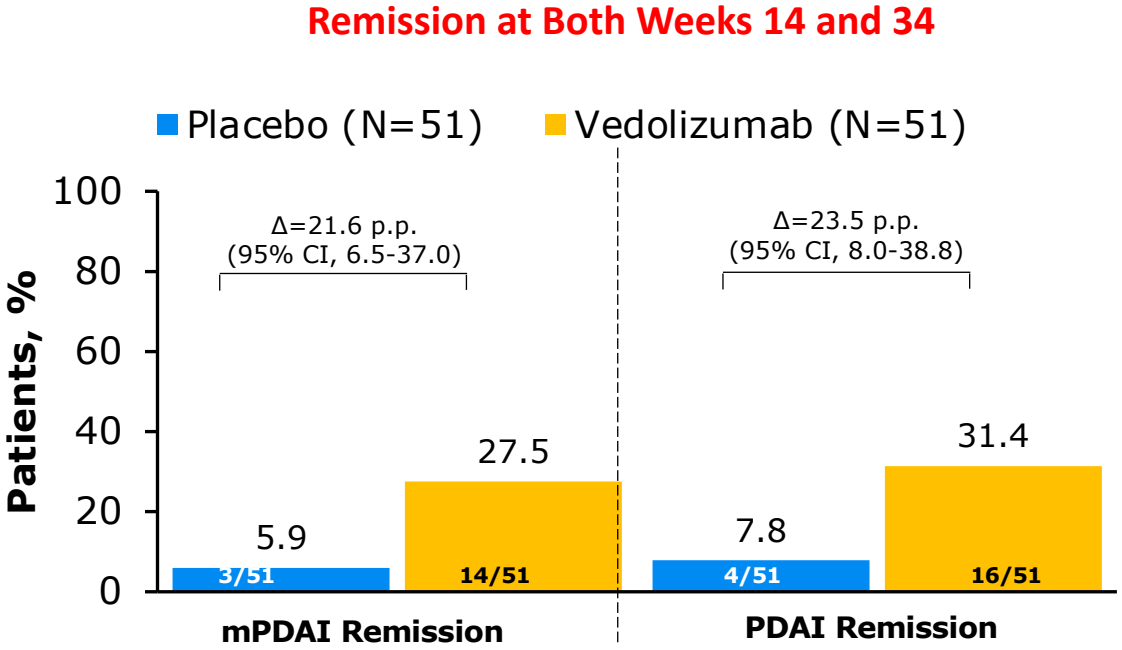
Significant differences in favour of vedolizumab over placebo were observed in the primary and key secondary efficacy endpoints



Δ=vedolizumab–placebo (exact 95% CI). Patients with missing data for determination of response status at a time point were considered to be non-responders (non-response imputation). *Statistically significant at α=0.05 (2-sided). INominal p value shown for secondary endpoints (no multiplicity adjustment performed).

Travis SPL et al. *N Engl J Med* 2023;**388:**1191-1200

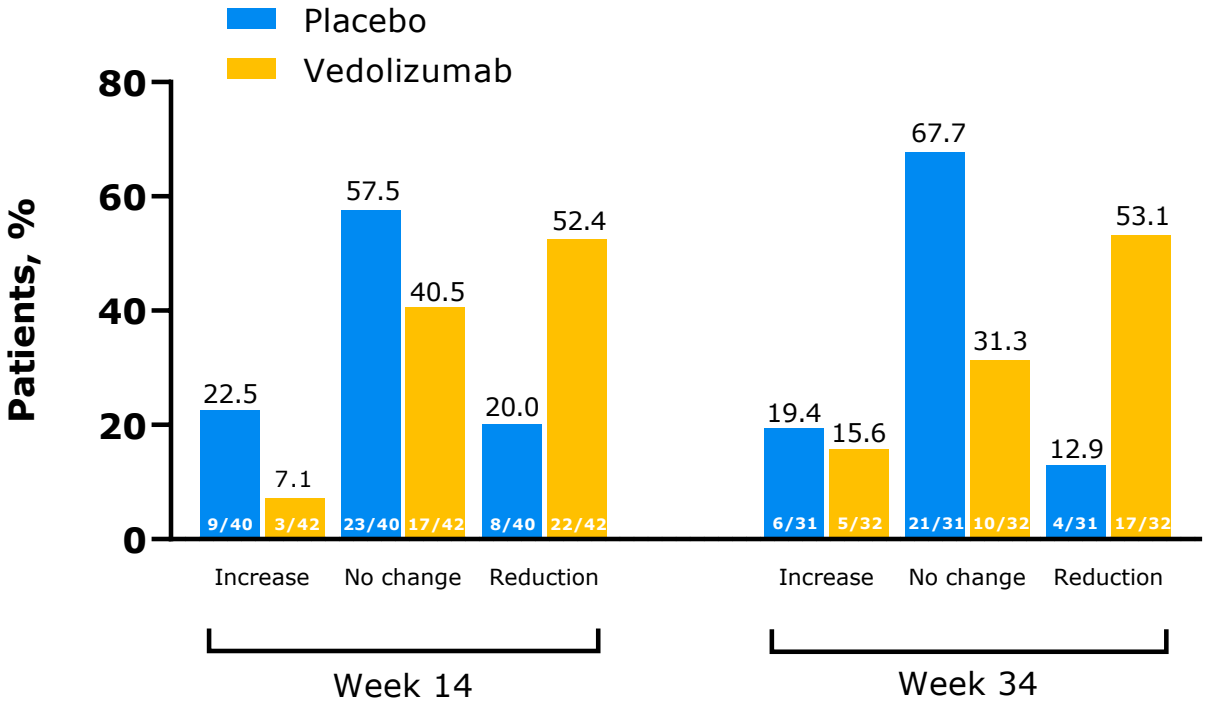
The rate of sustained remission was significantly higher for vedolizumab versus placebo



Δ=vedolizumab–placebo (exact 95% CI). Patients with missing data at a visit were counted as non-remitters. Sustained remission is defined as remission at both W14 and W34.

Travis SPL et al. *N Engl J Med* 2023;**388:**1191-1200

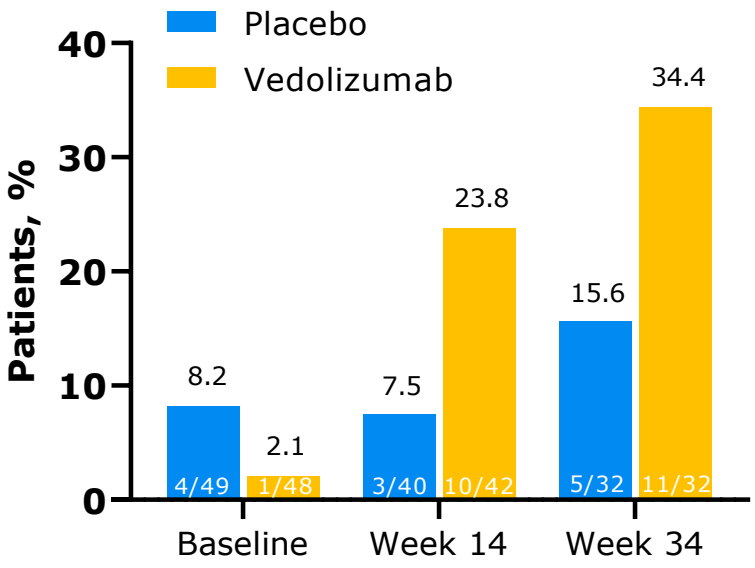
Greater reduction in ulcerated surface area with vedolizumab versus placebo



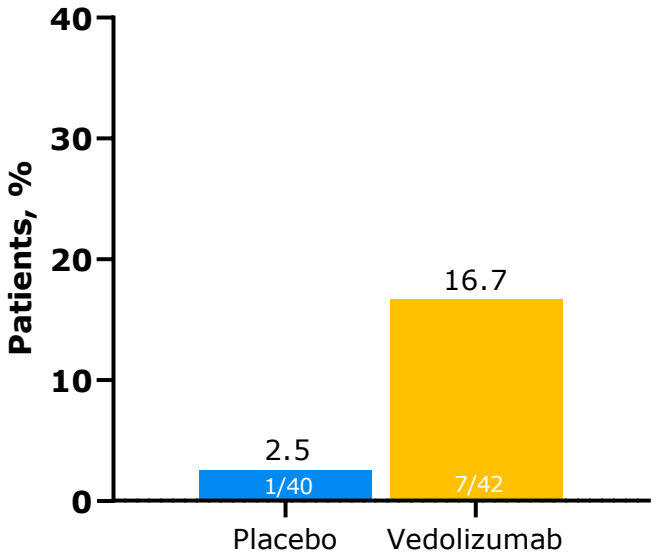
Full analysis set includes all randomised patients who received ≥1 dose of study treatment. No imputation of missing data applied. Four patients without any ulceration assessment done were excluded from the analysis.

Higher rates of SES-CD remission and mucosal healing with vedolizumab versus placebo

SES-CD Remission Rate (SES-CD ≤2)



Mucosal Healing at Week 14 (SES-CD=0 & PDAI histology score ≤1)



PDAI, Pouchitis Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Mucosal healing is defined as a SES-CD score of 0 plus PDAI histology score of ≤1 (none/mild polymorphic nuclear leukocyte infiltration and no ulceration).
Full analysis set includes all randomised patients who received ≥1 dose of study treatment. SES-CD remission is defined as a total SES-CD of ≤2. SES-CD was adapted to assess size and surface of ulcer in ulcerative colitis pouchitis. Four patients without any SES-CD assessment done were excluded from the analysis.

Beyond vedolizumab

- JAKi: TOFA (no data for FIL or UPA)
  - GETAID: 12 patients with CARP all bio-exp; steroid-free remission in 4/12 at 8w
    Uzzan M et al *Dig Liver Dis* 2023;**55:**1158-60
  - MSSM-Chicago: 14 patients with CARP (1 bio-naive); response in 3/13 at 12w
    Akiyama S et al *IBD* 2023;ePub Feb 6
- aIL23
  - SOCRATES: Stelara fOr ChRonic AntibioTic rEfractory pouchitiS NCT04089345 KUL
- aS1PR: No data
- Various
  - Probiotics variable response to VSL3 in RCT
  - FMT NCT03378921 Helsinki. Clinical remission in 4/13 FMT vs 5/13 PBO (2021)
  - Alicaforsen enema NCT02525523
    - 3/65 vs 3/61 endo remission
    - 22/65 vs 16/61 reduction in stool frequency

When to call for help

- Share the burden
  - Imagine treatment refractory UC, surgery, then pouch dysfunction
- Multidisciplinary team approach of specialist centres helps QoL patients (pouch specialist nurses, psychology etc)improve
- Antibiotic-dependence
  - Has a peripouch sepsis been excluded?
- Pouch dysfunction refractory to antibiotics and/or advanced-therapies
  - Have all potential causes of pouch dysfunction been considered?
  - Is QoL so poor that diversion will improve QoL?
  - Are there anatomical causes that might respond to redo (eg long rectal remnant) of K-pouch?

Take Home Messages

- Ultimately pouches are meant to offer ‘quality of life’
- Pouch dysfunction ≠ pouchitis
  - Stool culture
  - MRI pelvis to exclude 2^{o} sepsis
  - Pouchoscopy
  - There may be more than one cause of pouch dysfunction
- Ciprofloxacin +/- metronidazole for acute pouchitis
- Vedolizumab now licensed in Europe for chronic pouchitis
  - Unclear if it works in patients who had VDZ before colectomy
  - Only biologic (bar alicaforsen) yet subject to a powered RCT
- Call for help if dysfunction persists

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