Inflammatory Bowel Disease mimickers

Franck Carbonnel

Service de Gastroentérologie
CHU de Bicêtre
Assistance Publique–Hôpitaux de Paris
Université Paris Sud

Disclosures

Speaker fees
Abbvie, Astra, BMS, Ferring, Janssen, MSD, Pfizer, Pileje, Takeda, Tillots

Advisory Boards
Amgen, BMS, Enterome, Ferring, Janssen, Medtronic, Pfizer, Roche, Takeda,

IBD mimickers

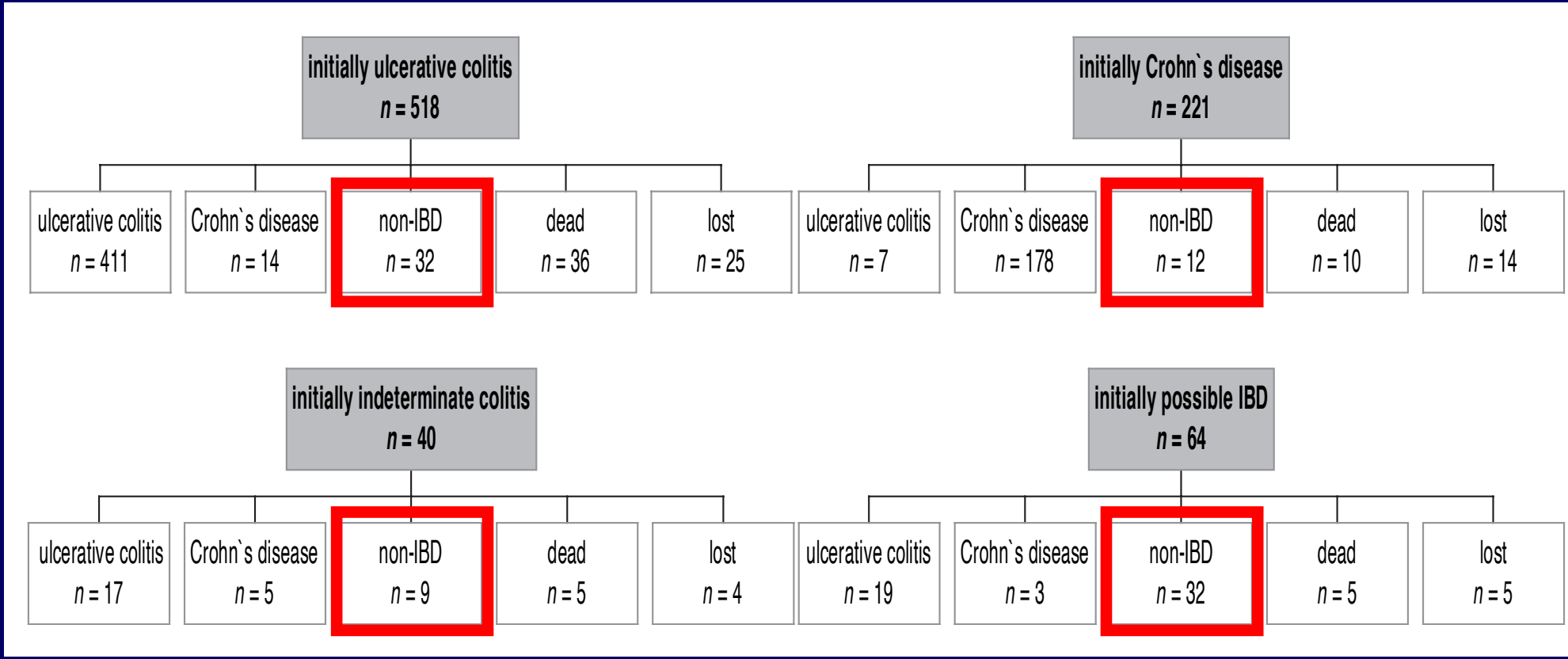
- Differential diagnoses of IBD
- Drug-induced IBD

Differential diagnoses of IBD

Differential diagnosis of a new onset IBD

Differential diagnosis of IBD relapse in a patient with known IBD

Change of diagnosis during the first 5 years after onset of IBD: prospective follow-up study (IBSEN Study)



Henriksen M Scand J Gastroenterol 2006; 41: 1037-1043

Main differential diagnoses of a new-onset IBD *(DiLauro S, Curr Gastroenterol Rep 2010;12:249)*

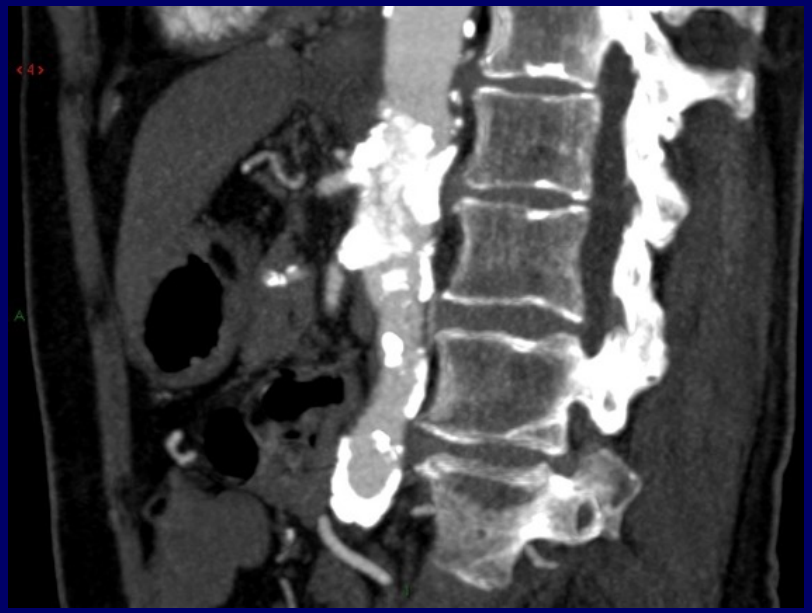
- Infection
- NSAIDs
- Ischemia
- Colitis associated with diverticulosis
- Colitis associated with immune deficiency, typhlitis
- Vasculitis (SLE, microscopic polyangeitis, Henoch-Schonlein, Wegener, Behcet…),
- Sarcoidosis
- Eosinophilic gastroenteritis
- Malignancy
  - Lymphoma:
    - non-IPSID small intestinal B cell lymphomas
    - T cell
    - NK cell
    - mantle cell
    - EBV-positive mucocutaneous ulcer
  - Adenocarcinoma of the small bowel or the appendix
  - NET
- *Proctitis: rectal solitary ulcer syndrome, endometriosis, sexuallly-transmitted disease*

Case history 1 Ms F, 75 year-old, steroid-refractory, Ileocolonic CD

- Past history of breast cancer, smoking, lower extremity peripheral artery disease
- Abdominal pain, weight loss, bloody diarrhea
- Severe, ulcerated Ileocolitis
- Biopsies: non specific inflammation
- IV Corticosteroids : worsening, melena

Case history 1 Ms F, 75 year-old, steroid-refractory, Ileocolonic CD

- Past history of breast cancer, smoking, lower extremity peripheral artery disease
- Abdominal pain, weight loss, bloody diarrhea
- Severe, ulcerated Ileocolitis
- Biopsies: non specific inflammation
- IV Corticosteroids : worsening, melena



Infectious agents that may cause ileitis and/or colitis

Bacteria	Viruses	Parasites	Fungi
Salmonella	CMV	*Entamoeba histolytica histolytica*	Histoplasma
Clostridioides difficile	Herpes (HSV)	*Ballantidium coli*	Candida
Campylobacter jejuni	Adenovirus	*Strongyloïdes stercoralis*	Aspergillus
Shigella		Schistosoma	Basidiobolomycosis
Klebsiella oxytoca		Trichuris trichiura	
E coli (EHEC et EIEC)			
Vibrio parahaemolyticus			
Aeromonas Hydrophila			
Plesiomonas shigelloides			
Yersinia (ileitis)			
BK/atypical mycobacteria			
Actinomycosis			

Most frequent (in Europe)
Immunocompromised
Imported cases
Imported and immunocompromised

IBD or infection ?

Infection

- Positive stool culture
- Favorable evolution with antibiotics (fluoroquinolones ± metronidazole, azithromycin)

IBD

- Negative stool culture
- No improvement with antibiotics
- Colonic biopsies : crypt distorsion, basal plasmocytosis, cryptitis, crypt abscess

IBD or infection ?

Infection

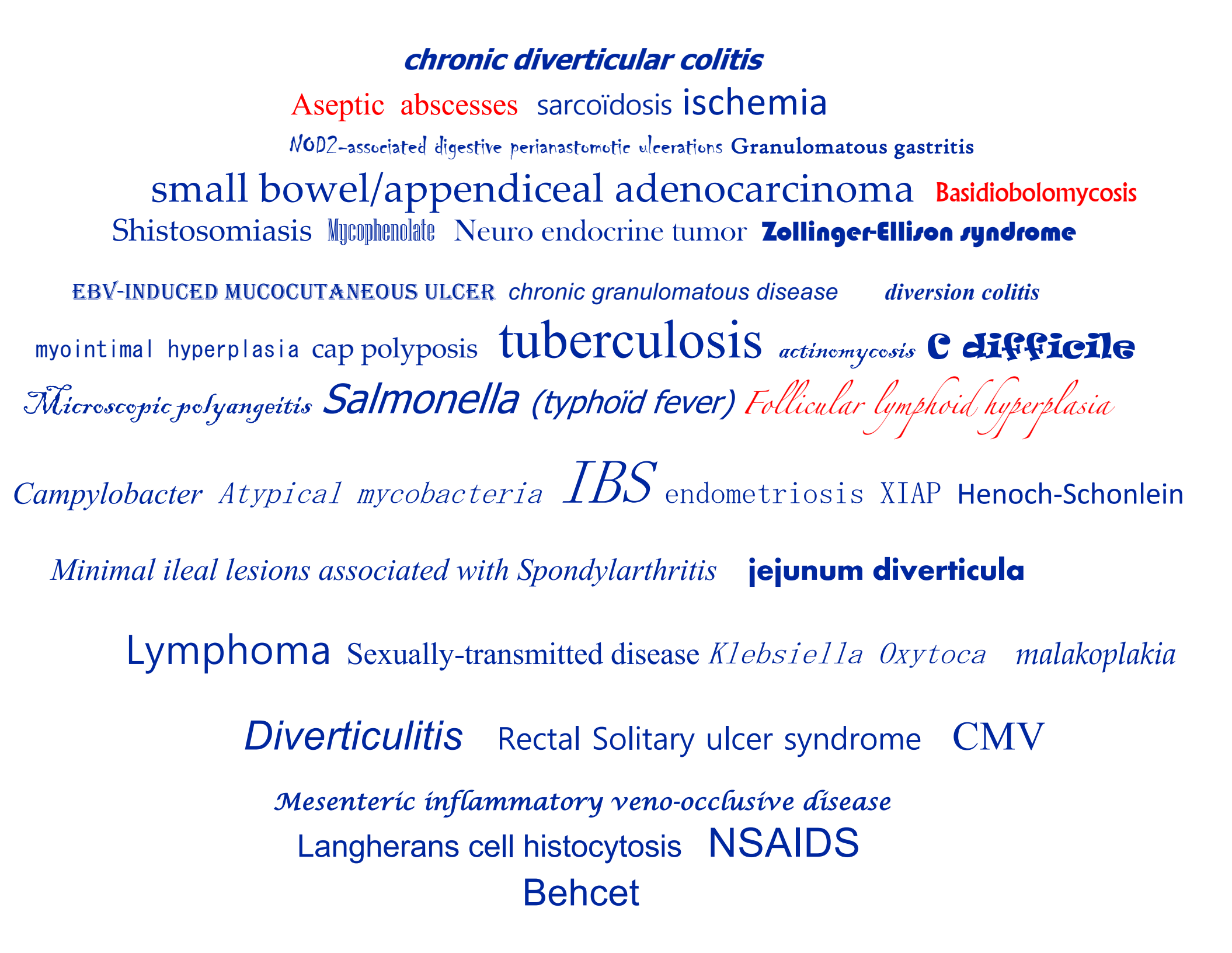
- *Positive stool culture*
- Favorable evolution with antibiotics (fluoroquinolones ± métronidazole, azithromycin)

IBD

- Negative stool culture
- No improvement with antibiotics
- *Colonic biopsies : crypt distorsion, basal plasmocytosis, cryptitis, crypt abscess*

Meta-Analytic Bayesian Model For Differentiating Intestinal Tuberculosis from Crohn's Disease *(Am J Gastroenterol. 2017; 112: 415)*

	Tuberculosis	**Crohn**
Clinical manifestations	Fever, night sweats	Diarrhea, hematochezia, perianal disease, extraintestinal manifestations
Imaging	Short segmental involvement,	Wall stratification, coomb sign, fibrofatty infiltration
Endoscopic findings	Transverse ulcers, patulous IC valve, caecal involvement, IC valve involvement	Aphtous ulcers, longitudinal ulcers, cobblestone, stricture, rectal/sigmoid involvement, skip lesions, mucosal bridge
Histology	Large, confluent granulomas, multiple granulomas/section, submucosal granulomas, lymphocyte cuffing, ulcer lined by histiocytes,	Focally enhanced colitis
Bacteriology	Positive IGRA	


chronic diverticular colitis
Aseptic abscesses sarcoïdosis ischemia
NOD2-associated digestive perianastomotic ulcerations Granulomatous gastritis
small bowel/appendiceal adenocarcinoma Basidiobolomycosis
Shistosomiasis Mycophenolate Neuro endocrine tumor Zollinger-Ellison syndrome
EBV-INDUCED MUCOCUTANEOUS ULCER chronic granulomatous disease diversion colitis
myointimal hyperplasia cap polyposis tuberculosis actinomycosis C difficile
Microscopic polyangeitis Salmonella (typhoïd fever) Follicular lymphoid hyperplasia
Campylobacter Atypical mycobacteria IBS endometriosis XIAP Henoch-Schonlein
Minimal ileal lesions associated with Spondylarthritis jejunum diverticula
Lymphoma Sexually-transmitted disease Klebsiella Oxytoca malakoplakia
Diverticulitis Rectal Solitary ulcer syndrome CMV
Mesenteric inflammatory veno-occlusive disease
Langherans cell histocytosis NSAIDS
Behcet

Differential diagnoses of IBD

Differential diagnosis of a new onset IBD

Differential diagnosis of IBD relapse in a patient with known IBD

Main differential diagnoses of IBD relapse in patients with known IBD

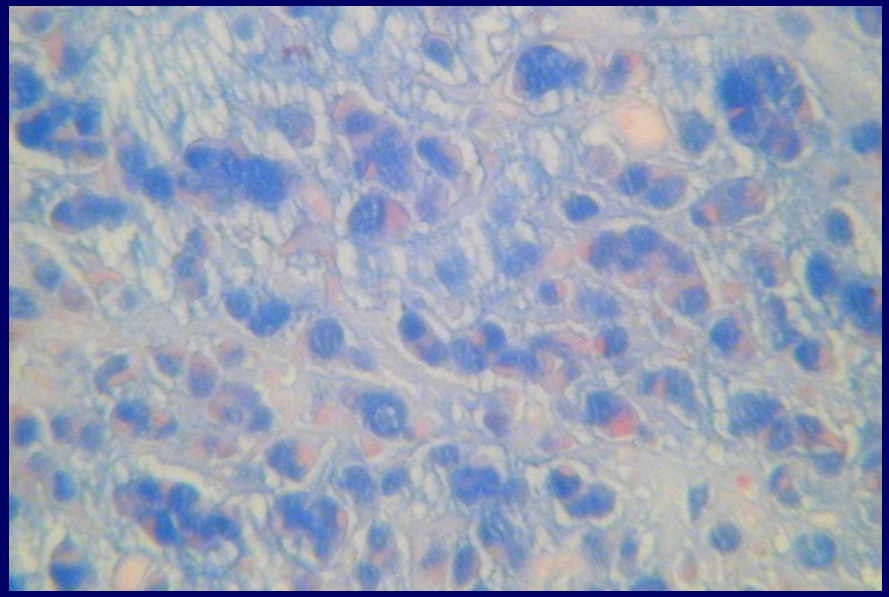
- Infection
- Malignancy (lymphoma, adenocarcinoma, NETs)
- Ischemia
- IBS

Ms F, 53 year-old, refractory, stricturing, longstanding ileal CD

- Right lower quadrant pain
- 15 cm regular, stricture of the terminal ileum
- Elective ileocecal resection.
- Macroscopic examination of the resected specimen : CD.

Ms F, 53 year-old, refractory, stricturing, longstanding ileal CD

- Right lower quadrant pain
- 15 cm regular, stricture of the terminal ileum
- Elective ileocecal resection.
- Macroscopic examination of the resected specimen : CD.



Signet-ring cell adenocarcinoma complicating ileal CD

Main infectious agents that may mimic IBD activity in patients with known IBD

Bacteria	Viruses	Parasites
Salmonella	**CMV**	*Entamoeba histolytica histolytica*
Clostridium difficile	Rotavirus	
Campylobacter jejuni	Adenovirus	
Shigella	Norovirus	Schistosoma
E coli (EHEC et EIEC)		*Cryptosporidium parvum*
Aeromonas Hydrophila		
Plesiomonas shigelloides		
BK		

Am J Gastroenterol 2018;113:1530
Inflamm Bowel Dis. 2015;21:71
PLoS One. 2017 Dec 6;12(12):e0189377.
Inflamm Bowel Dis. 2016;22:1755

Differential diagnosis of IBD

- Of paramount importance, avoids disasters
- Diverse and sometimes, difficult
- Main differential diagnoses of either new onset or established IBD are infection, ischemia and neoplasia
- Differential diagnosis should be suspected in migrants, vascular patients, refractory patients, and in those with atypical manifestations

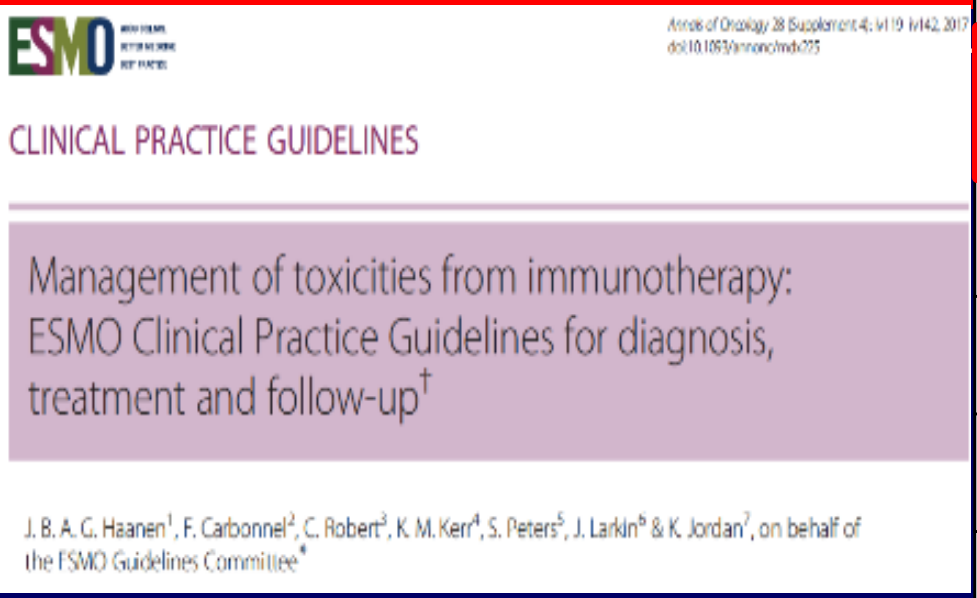
Drug-induced IBD-mimickers

Drug-induced IBD mimickers

- NSAIDs
- Mycophenolate[1]
- Gold compounds
- **Anti CTLA-4 (Ipilimumab, tremelimumab)**
- **Anti PD-1 (nivolumab, pembrolizumab)**
- Idelalisib[2], duvelisib[3]

[1]Liu TC Gastrointest Endosc. 2006;63:707
[2]Weidner A Am J Surg Pathol. 2015;39:1661
[3]Flinn IW Blood. 2018;131:877

Immune-related adverse events (IrAE) of immune checkpoint inhibitors



	Anti CTLA-4	Anti PD-1	Combo
Cutaneous	++	++	+++
GI	+++	+	**++++**
Hypophyse	++	0/+	+++
Thyroid	+	+	++
Diabetes	0/+	++	++
Renal	+	+	++
Hepatic	+	+	++
Pulmonary	+	++	+++
Neurological	+	+	++
Arthritis	0/+	+	
Cardiac	+	+	++

Frequency of Gastrointestinal (GI)-IrAE due to anti CTLA-4 and/or anti PD-1

	Diarrhea	Colitis
Anti CTLA-4	35-40%	8-11%
Anti PD-1	11-17%	0.3-3%
Combotherapy	32%	13.6%

✓Colonic perforation in 1% (melanoma) to 6% (renal cancer)

✓0.6 to 0.8% of patients die of GI IrAE due to anti CTLA-4

Baxi S, BMJ 2018; 360:k793. De Velasco G, Cancer Immunol Res 2017; 5:312. Khoja L, Ann. Oncol. 2017; 28:2377. Komaki Y, Clin. Pharmacol. Ther. 2018; 103:318; Tandon P, J Immunother 2018, 41:8. Wang, D. Y., OncoImmunology 2017, 6:e1344805. Wang PF, Front. Pharmacol 2017; 8:730. Zhang B, International Immunopharmacology 2018; 63:292.

Risk factors of GI IrAE

Table 1 Risk factors of enterocolitis due to immune checkpoint inhibitors

Risk factors		References
Type of ICI	**Combotherapy>anti-CTLA-4>anti-PD-1**	**Tandon *et al*[9]**
Dose of ICI	Dose-dependant toxicity with anti-CTLA-4	Ascierto *et al*[11]
NSAIDs use	Suggested with anti-CTLA-4	Marthey *et al*[25]
Pre-existing IBD	About 30% risk of relapse with anti-CTLA-4; not reported with anti-PD-1	Johnson *et al*[12] Kähler *et al*[13] Menzies *et al*[15]
Microbiota	Baseline microbiota enriched in Firmicutes and poor in Bacteroidetes with anti-CTLA-4	Chaput *et al*[84]
Tumour histology	Increased risk in melanoma as compared with NSCLC and RCC with anti-PD-1	Khoja *et al*[7] Wang *et al*[8]

Soularue et al. Gut 2018

Cancer Immunotherapy with Anti-CTLA-4 Monoclonal Antibodies Induces an Inflammatory Bowel Disease

L. Marthey[a,b], C. Mateus[c], C. Mussini[d], M. Nachury[e], S. Nancey[f], F. Grange[g], C. Zallot[h], L. Peyrin-Biroulet[h], J. F. Rahier[i], M. Bourdier de Beauregard[j], L. Mortier[k], C. Coutzac[l], E. Soularue[a], E. Lanoy[m,n], N. Kapel[o], D. Planchard[p], N. Chaput[l,q,r], C. Robert[c], F. Carbonnel[a]

Journal of Crohn's and Colitis, 2016, 1–7

Clinical characteristics of patients with anti-CTLA-4 colitis

	N = 39	%
Diarrhoea Median Number of stools/ 24h [extremes]	**36** 10	**92** [1-20]
Hematochezia	**25**	**64**
Abdominal pain	**32**	**82**
Weight loss % usual body weight [extremes]	**8**	**[0-27]**
Extra-intestinal manifestations *Pyoderma gangrenosum* Arthralgia **Total**	 1 4 **5**	 3 13 **20**
Mouth ulcers	**1**	**3**
Perianal ulcers or fistulae	**4**	**10**
Intra-abdominal abscess	**4**	**10**
Colonic perforation	**5**	**13**

Journal of Crohn's and Colitis, 2016, 1–7

Endoscopy of anti-CTLA-4 colitis

Site of lesions	N	%
Ileum	5/25	20
Right Colon	27/33	82
Transverse colon	28/35	80
Left Colon	35/38	92
Sigmoid Colon	36/38	95
Rectum	32/39	82
Extensive Colitis	23/35	66
Skip lesions	18/33	55

Journal of Crohn's and Colitis, 2016, 1–7

Endoscopy of anti-CTLA-4 colitis

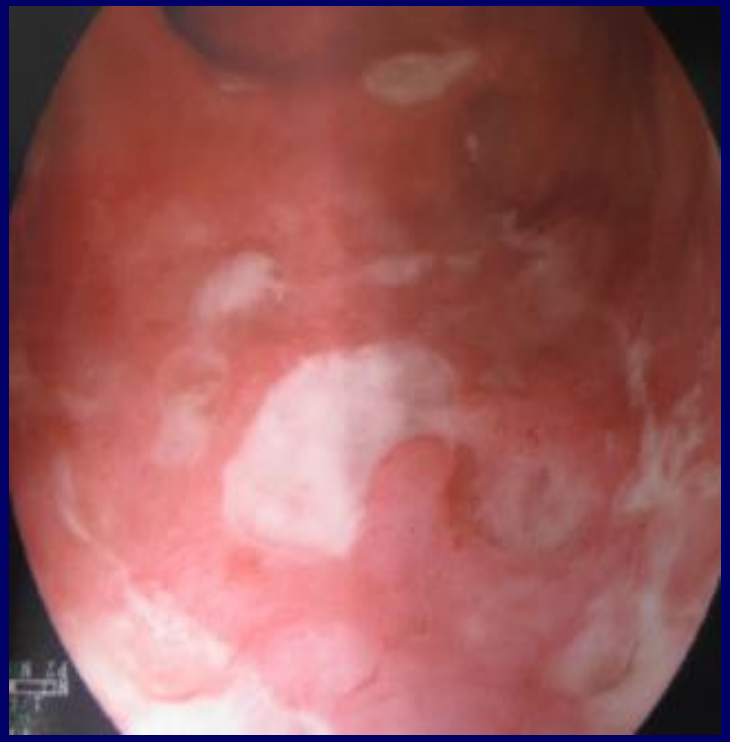
- 8% with erythema

- 13% with erosions

Journal of Crohn's and Colitis, 2016, 1–7

Endoscopy of anti-CTLA-4 colitis

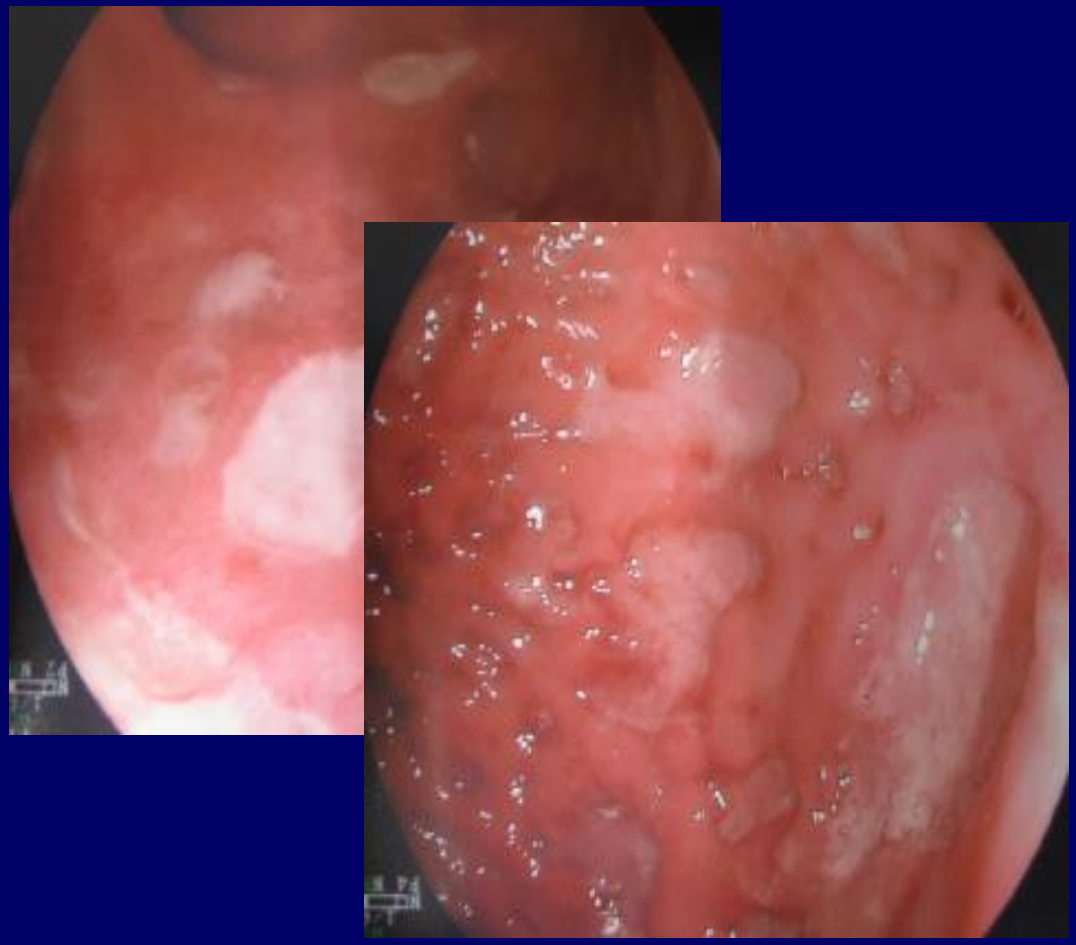
- 79% with ulcerations



Journal of Crohn's and Colitis, 2016, 1–7

Endoscopy of anti-CTLA-4 colitis

- 79% with ulcerations

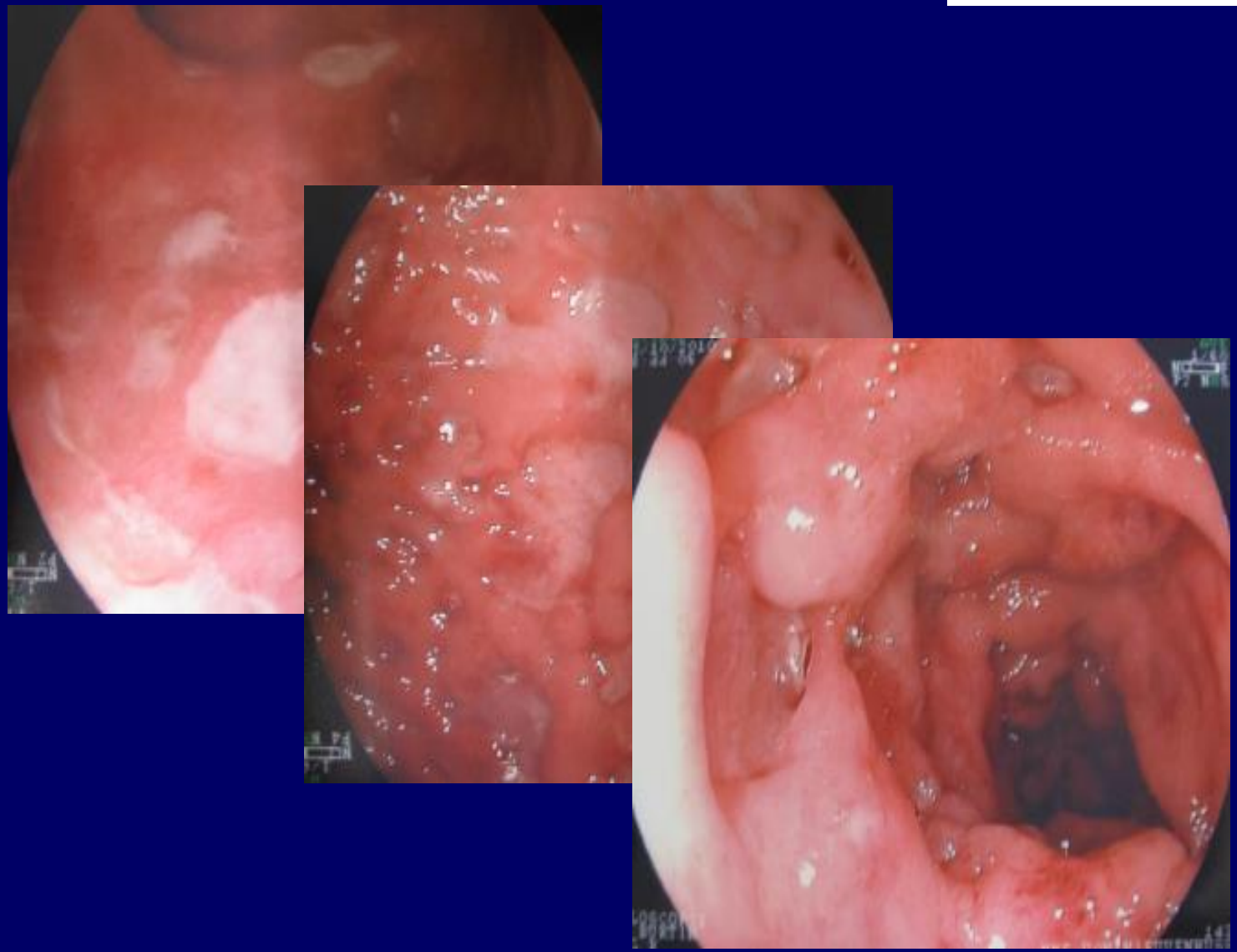


Journal of Crohn's and Colitis, 2016, 1–7

Endoscopy of anti-CTLA-4 colitis

- 79% with ulcerations

Journal of Crohn's and Colitis, 2016, 1–7

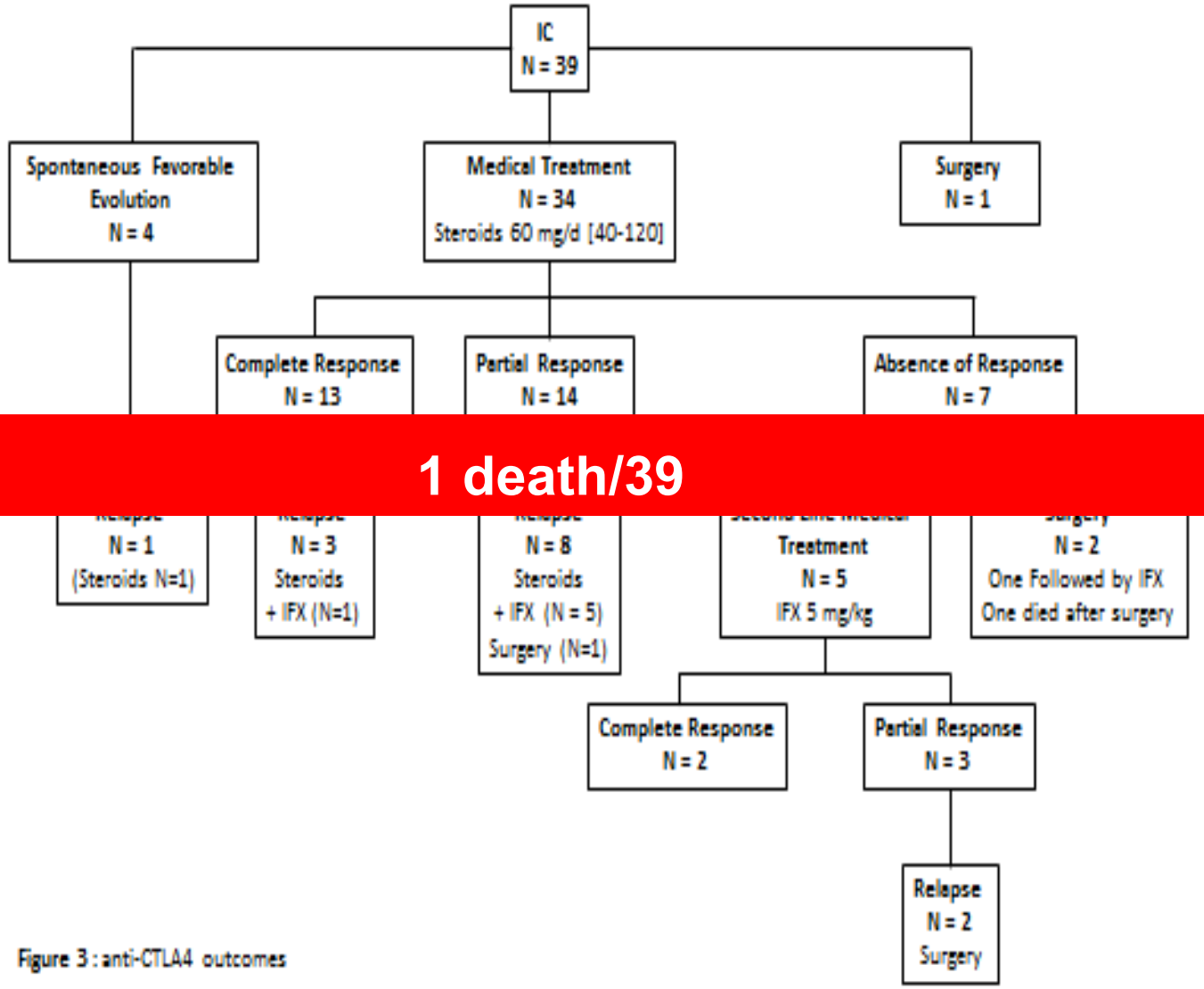


Blood and stool tests in patients with diarrhoea treated with immune checkpoint inhibitors

- Serum electrolyte and creatinine levels
- Search for stool enteropathogens
- *Clostridioides difficile* toxin
- CBC
- CRP
- Albumin serum level
- Fecal calprotectin
- Interferon-g-release assay screening for tuberculosis, HBV and HIV serology (in patients with a severe form, who may need infliximab).

Soularue et al. Gut 2018

Evolution

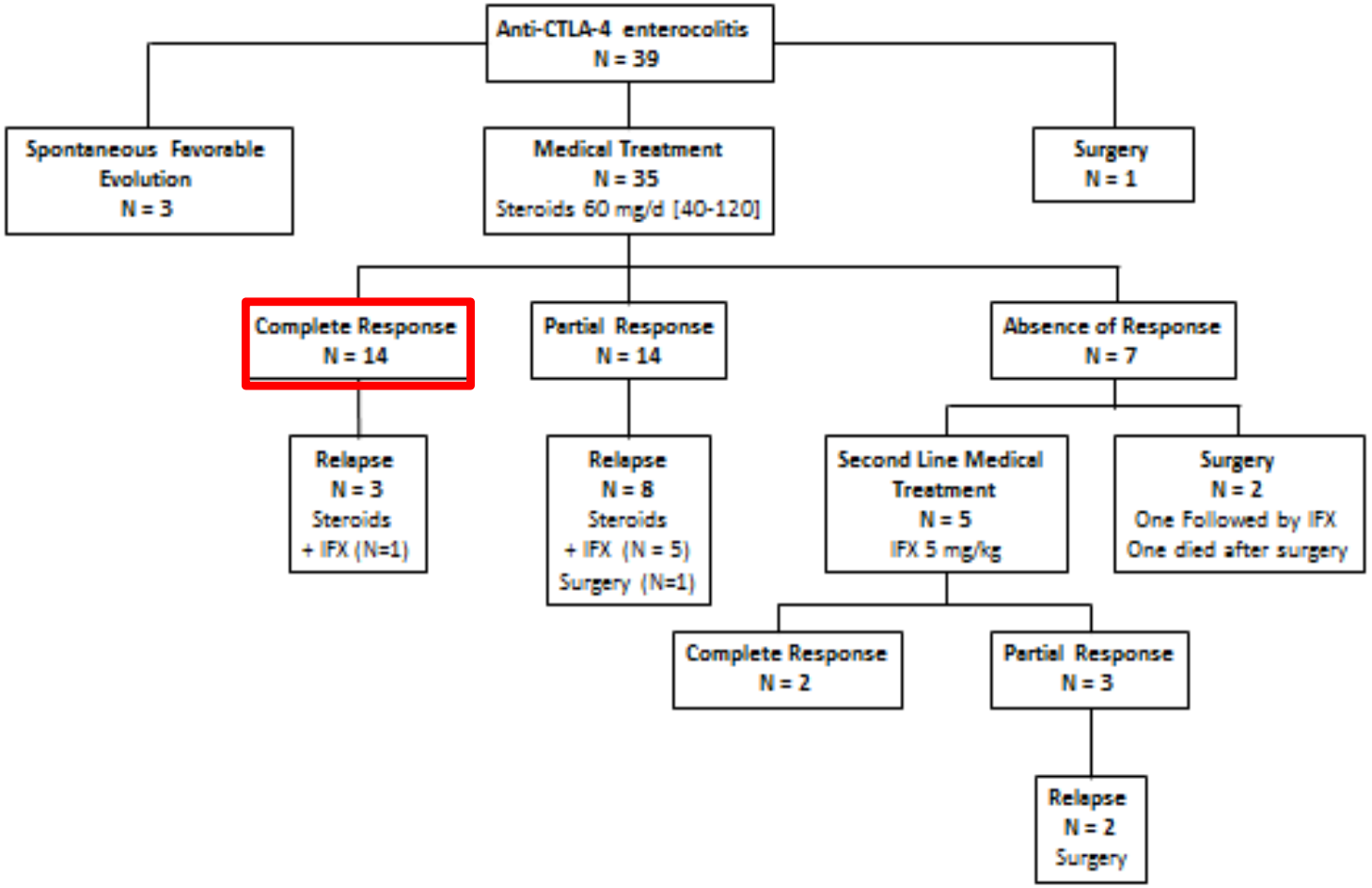


1 death/39

Figure 3 : anti-CTLA4 outcomes

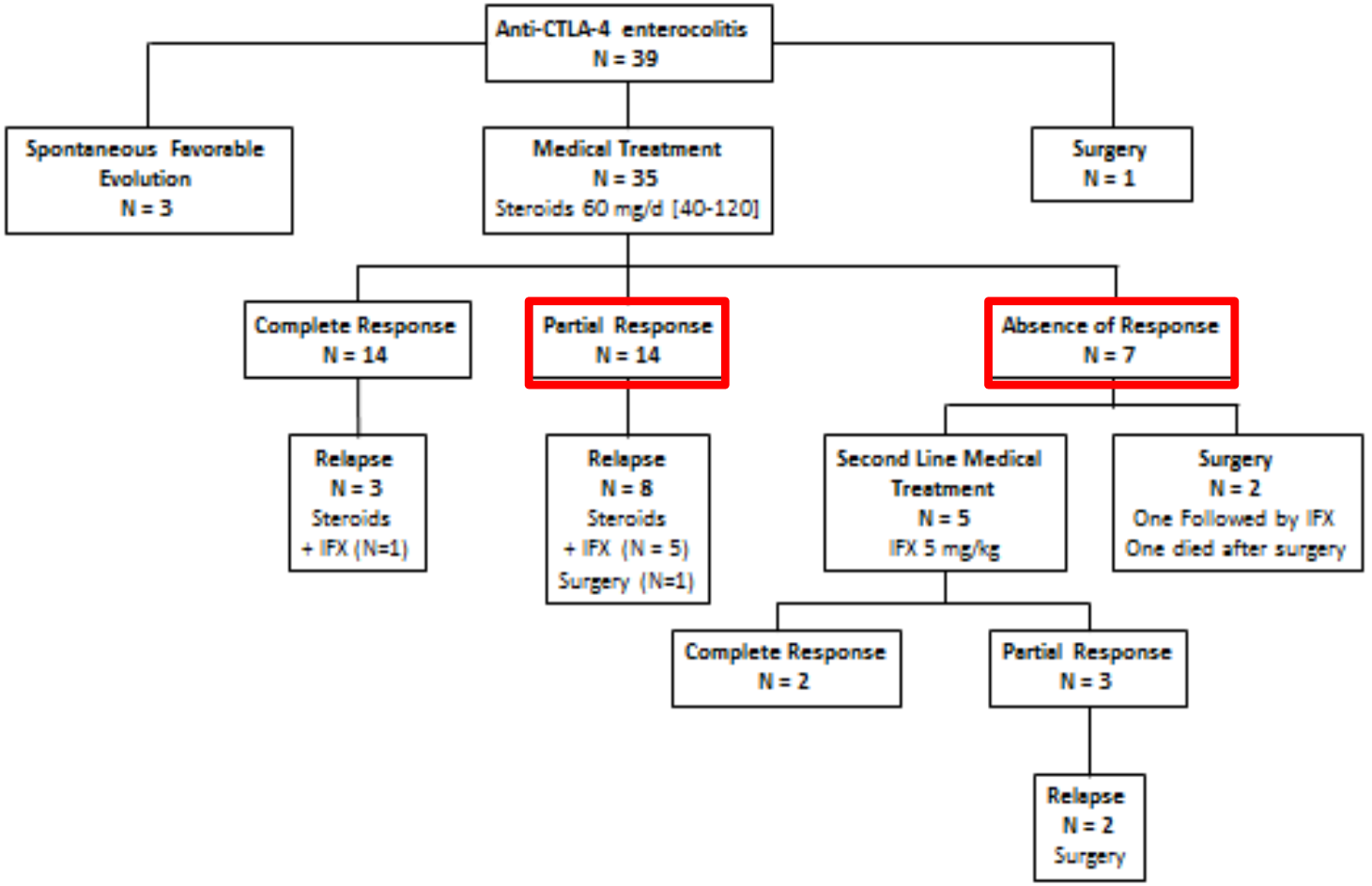
Journal of Crohn's and Colitis, 2016, 1–7

Evolution



Journal of Crohn's and Colitis, 2016, 1–7

Evolution



Journal of Crohn's and Colitis, 2016, 1–7

Management of severe colitis due to anti CTLA-4

- Stop anti CTLA-4
- IV Corticosteroids (1 to 2 mg/kg)
- Close medical and surgical supervision
- Decision making at Day 3 to 7
  - Responders: oral corticosteroids with tapering in 8 to 12 weeks
    1/3 to 2/3 of patients do not respond to IV steroids or relapse during tapering
    They should be treated with infliximab
  - Non responders: Infliximab
    1 to 3 infusions are enough in most cases. Some patients may require additional infusions

Haanen JBAG, et al. Management of toxicities from immunotherapy: ESMO Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl4):iv119-iv14

Management of severe colitis due to anti CTLA-4

If relapse or corticosteroid resistance :
ALWAYS look AGAIN
for differential diagnosis

- Responders: oral corticosteroids with tapering in 6 to 12 weeks
  1/3 to 2/3 of patients do not respond to IV steroids or relapse during tapering
  They should be treated with infliximab
- Non responders: Infliximab
  1 to 3 infusions are enough in most cases. Some patients may require additional infusions

Haanen JBAG, et al. Management of toxicities from immunotherapy: ESMO Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl4):iv119-iv14

When is diarrhoea severe ?

National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase in stool number **<4/d** or mild increase in stomal output as compared to normal	Increase in stool number **4 -6/j** or moderate increase in stomal output as compared to normal	Increase in stool number **≥ 7/d incontinence, hospitalisation** or severe increase in stomal output as compared to normal	Life-threatening complication Need for emergency intervention	Death

Severe Diarrhoea = grade 3 or 4
Grade 1 or 2 with dehydration, fever, tachycardia or hematochezia

Adapted from CTCAE v5.0, NIH
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Management of a patient with grade 1 diarrhea due to anti CTLA-4

- Loperamide
- Rehydration
- Continue anti CTLA-4
- Budesonide or prednisone 40 mg in some selected cases
- Supervision

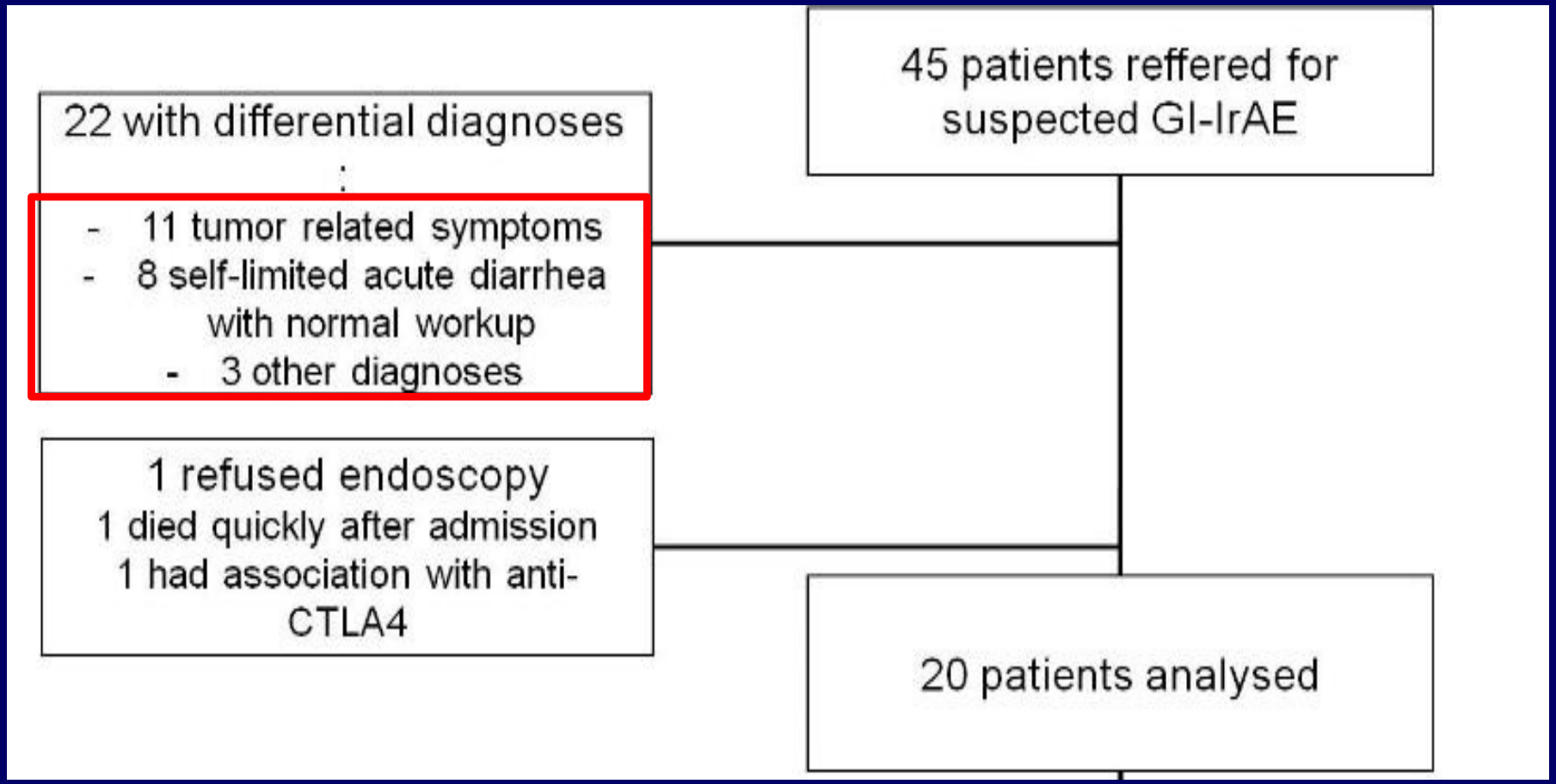
Haanen JBAG, et al. Management of toxicities from immunotherapy: ESMO Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl4):iv119-iv14

Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies

M. Collins[1,2†], J. M. Michot[3†], F. X. Danlos[3], C. Mussini[2,4], E. Soularue[1,2], C. Mateus[5], D. Loirat[6], A. Buisson[7], I. Rosa[8], O. Lambotte[2,9,10,11], S. Laghouati[12], N. Chaput[2,13], C. Coutzac[2,13], A. L. Voisin[12], J. C. Soria[3], A. Marabelle[3], S. Champiat[3], C. Robert[5] & F. Carbonnel[1,2*]

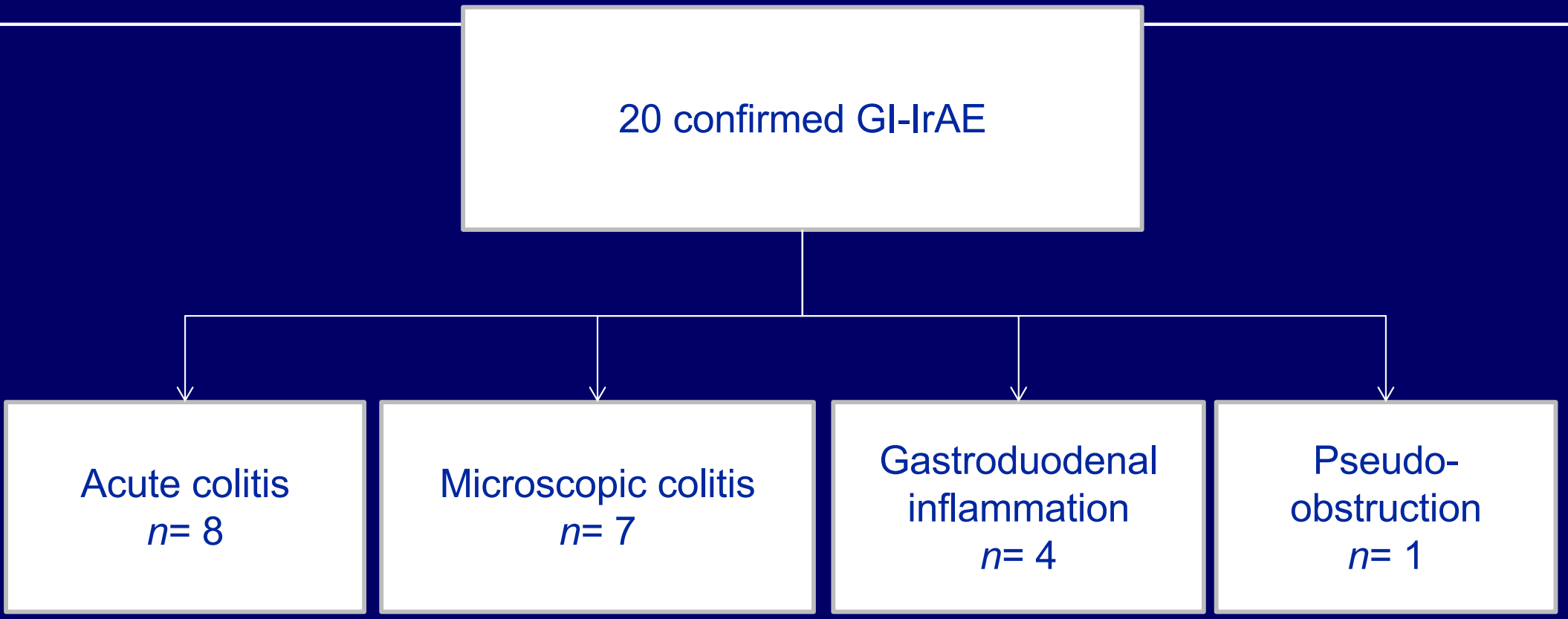
Annals of Oncology 0: 1–6, 2017
doi:10.1093/annonc/mdx403
Published online 3 October 2017

Half of patients referred for GI symptoms associated with anti PD-1 have a differential diagnosis

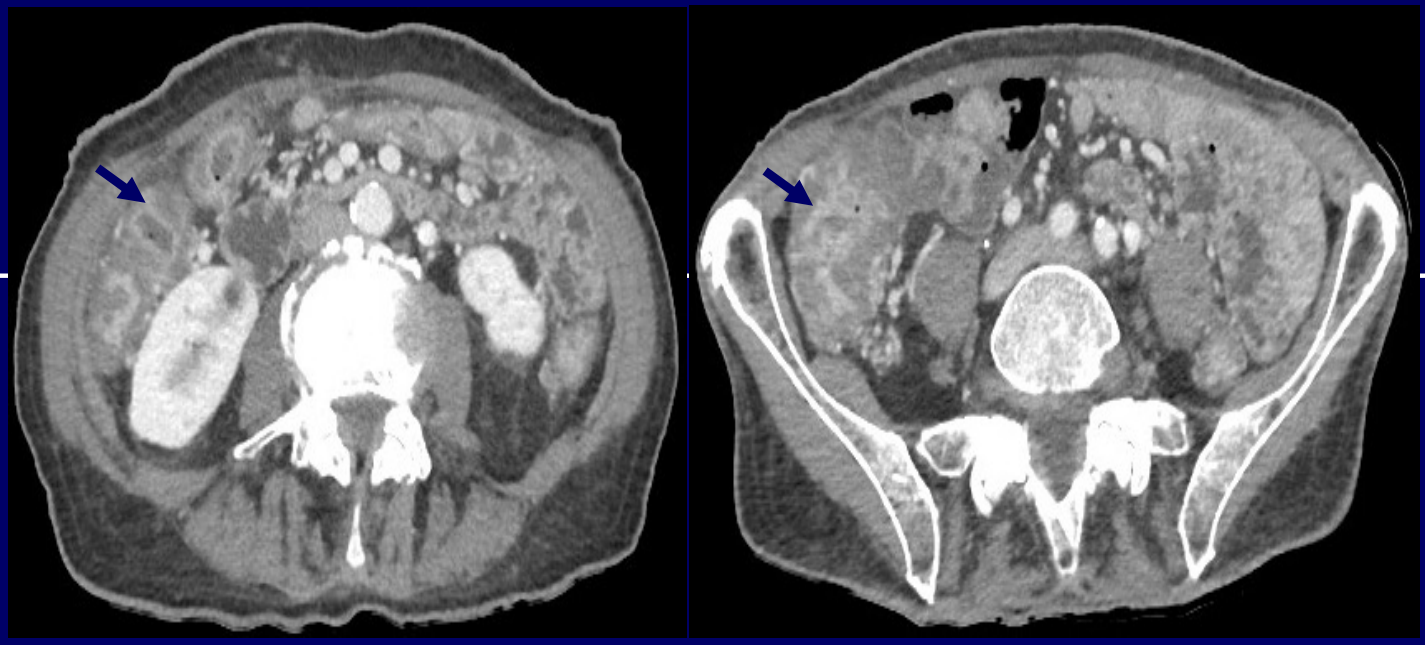


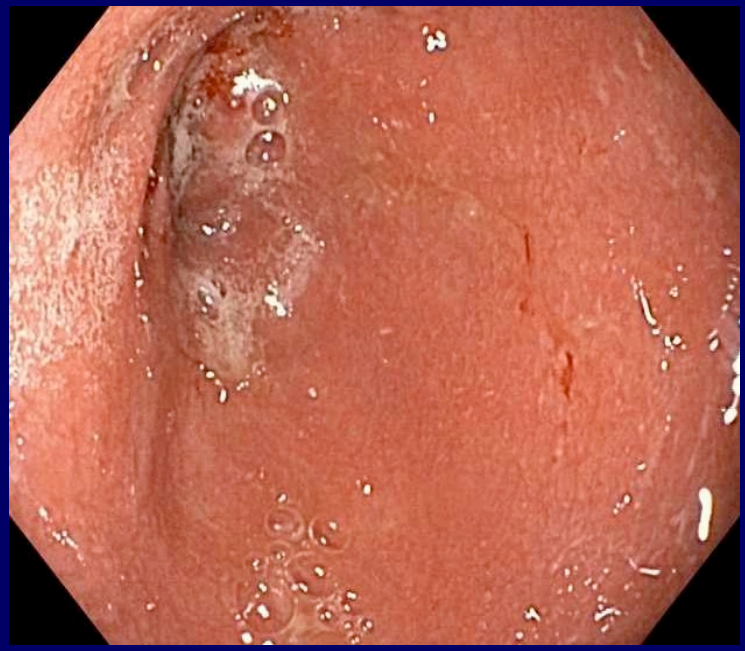
Collins M, et al. Ann Oncol. 2017 1;28:2860-2865
Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies.

Clinical picture is diverse



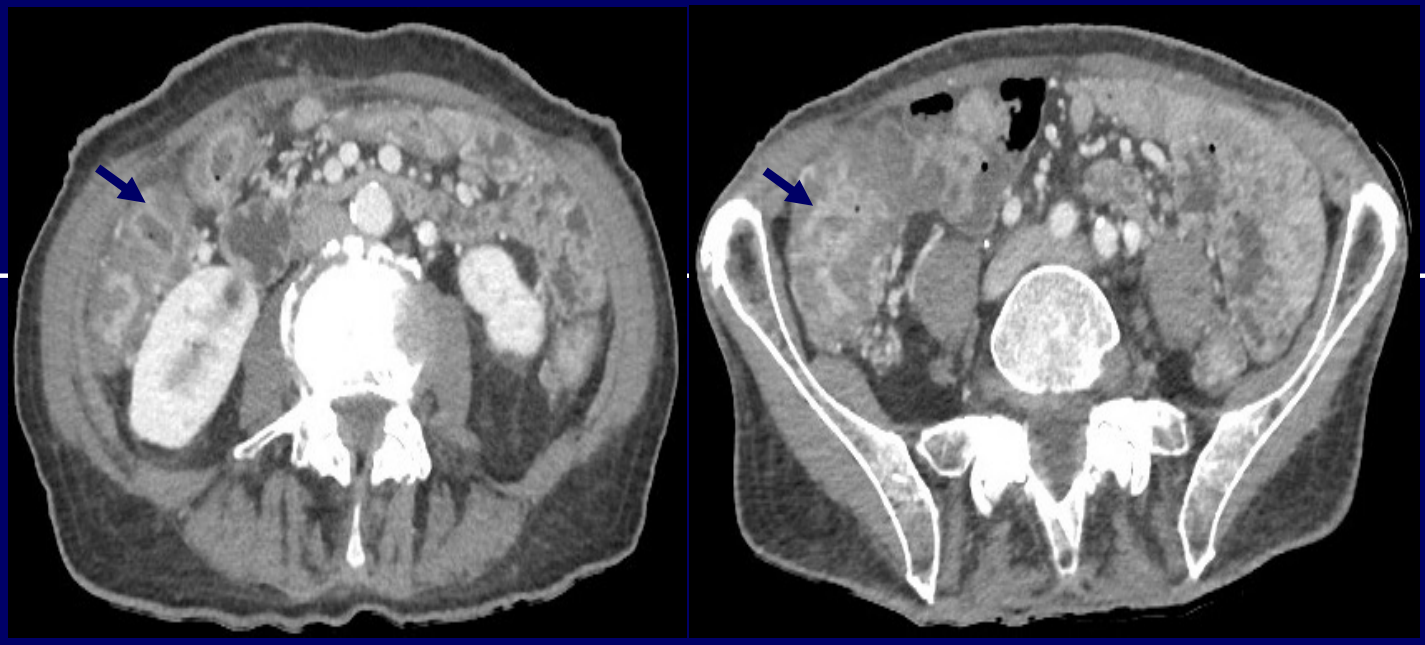
Collins M, et al. Ann Oncol. 2017 1;28:2860-2865
Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies.





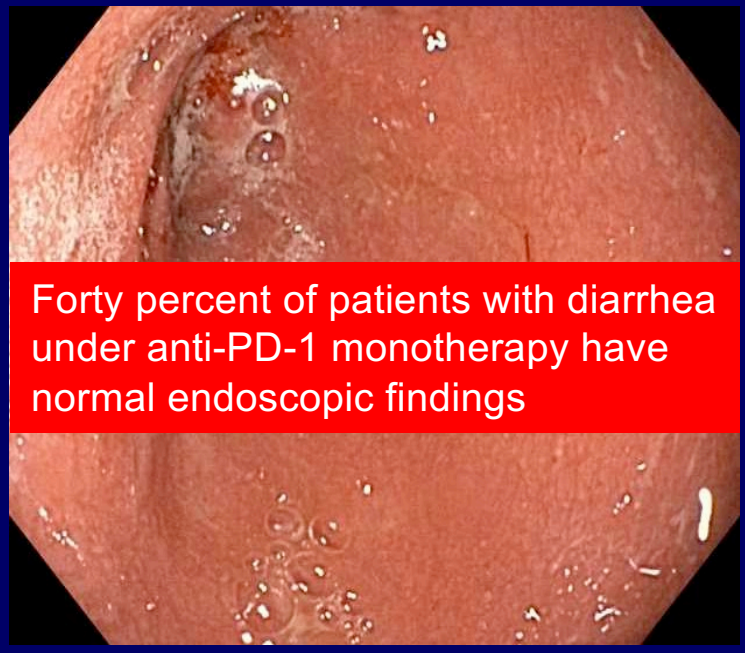
CT scan of a patient with anti-PD-1 induced colitis: thickening of the right colon wall (arrow), mucosal enhancement, and vessel engorgement

Sigmoidoscopy in the same patient: mild bleeding, loss of vascular pattern



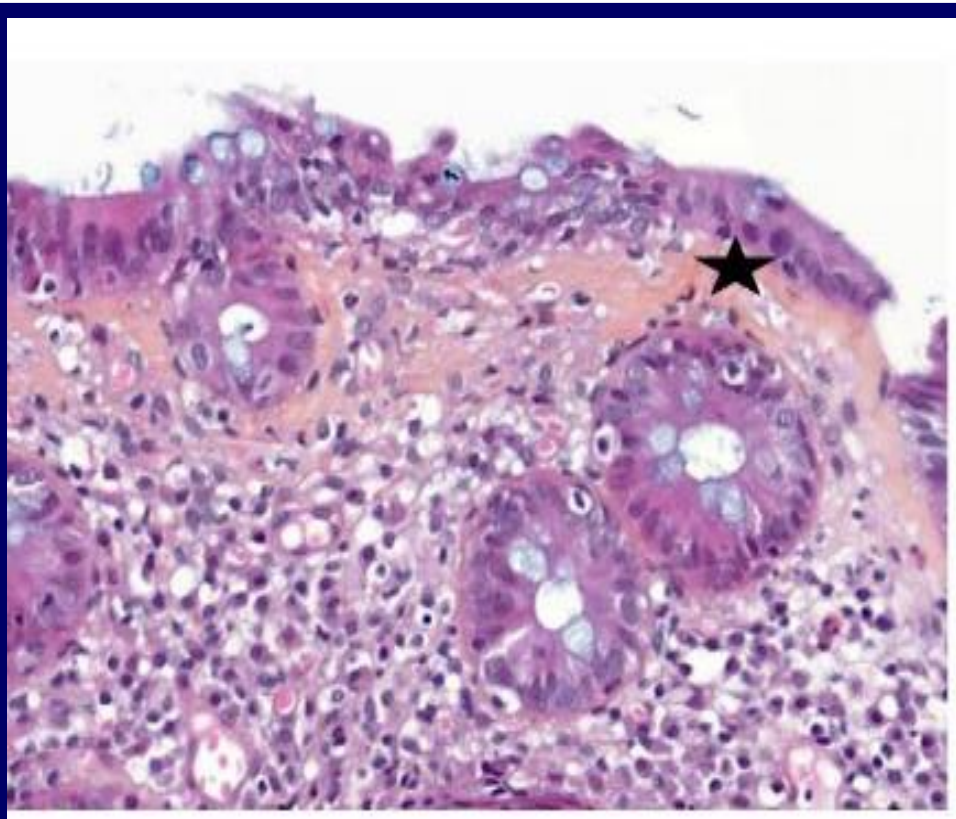
CT scan of a patient with anti-PD-1 induced colitis: thickening of the right colon wall (arrow), mucosal enhancement, and vessel engorgement

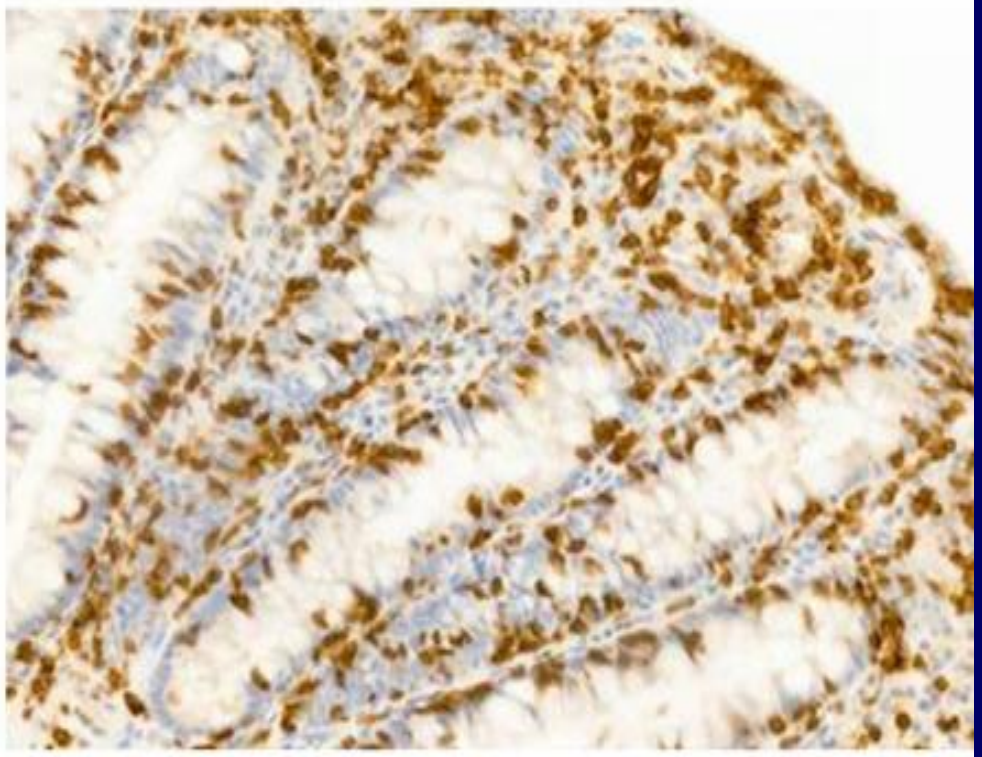
Sigmoidoscopy in the same patient: mild bleeding, loss of vascular pattern



Forty percent of patients with diarrhea under anti-PD-1 monotherapy have normal endoscopic findings

Microscopic colitis under anti PD-1



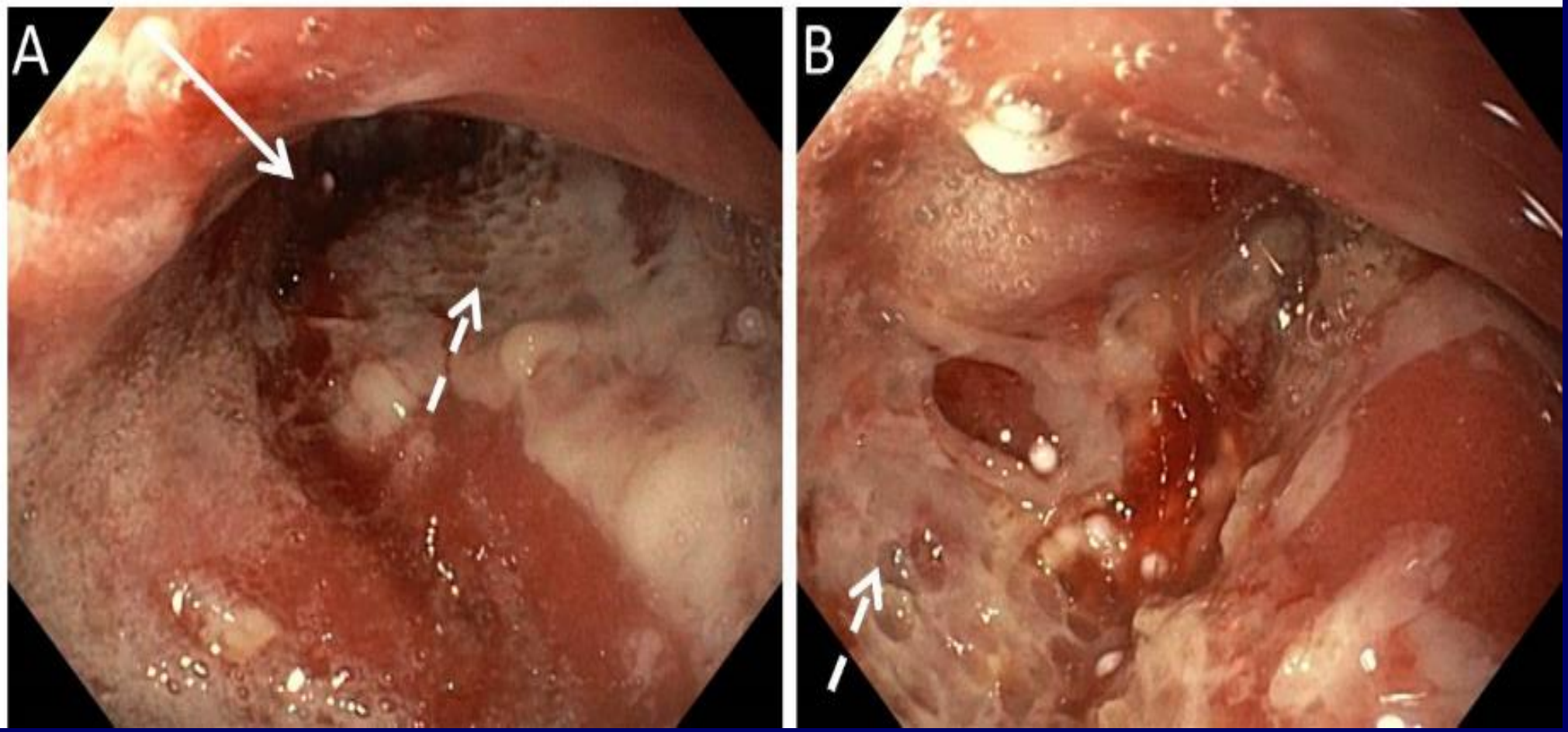


Collagenous colitis

Lymphocytic colitis

Collins M, et al. Ann Oncol. 2017 1;28:2860-2865
Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies.

Gastroduodenal inflammation in a patient treated with anti PD-1



Collins M, et al. Ann Oncol. 2017 1;28:2860-2865
Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies.

Risk of recurrent GI irAE after rechallenge with immune checkpoint inhibitors

- The risk of recurrence of GI IrAE during a second line of ICI, is 23-32%, including 33% patients with grade 3-4 GI irAE.
- Risk factors for GI-irAE are the use of anti-CTLA-4 second line, the requirement for immunosuppressive therapy for the first episode and first line use of anti-PD-1.
- The decision to reintroduce ICI should be made on a case-by-case basis, and discussed within a multidisciplinary team.

de Malet A, European Journal of Cancer 2019, 106:106

Abu-Sbeih H, J Clin Oncol. 2019 Jun 4:JCO1900320

Thank you for your attention

Case history 2 Ms B, 38 year-old, stricturing ileal CD

- Ankylosing spondylarthritis for 5 years, treated with NSAIDs and salazosulfapyridine
- Right lower quadrant pain for 1 month
- Referred for intestinal obstruction

Case history 2 Ms B, 38 year-old, stricturing ileal CD

- Ankylosing spondylarthritis for 5 years, treated with NSAIDs and salazosulfapyridine
- Right lower quadrant pain for 1 month
- Referred for intestinal obstruction

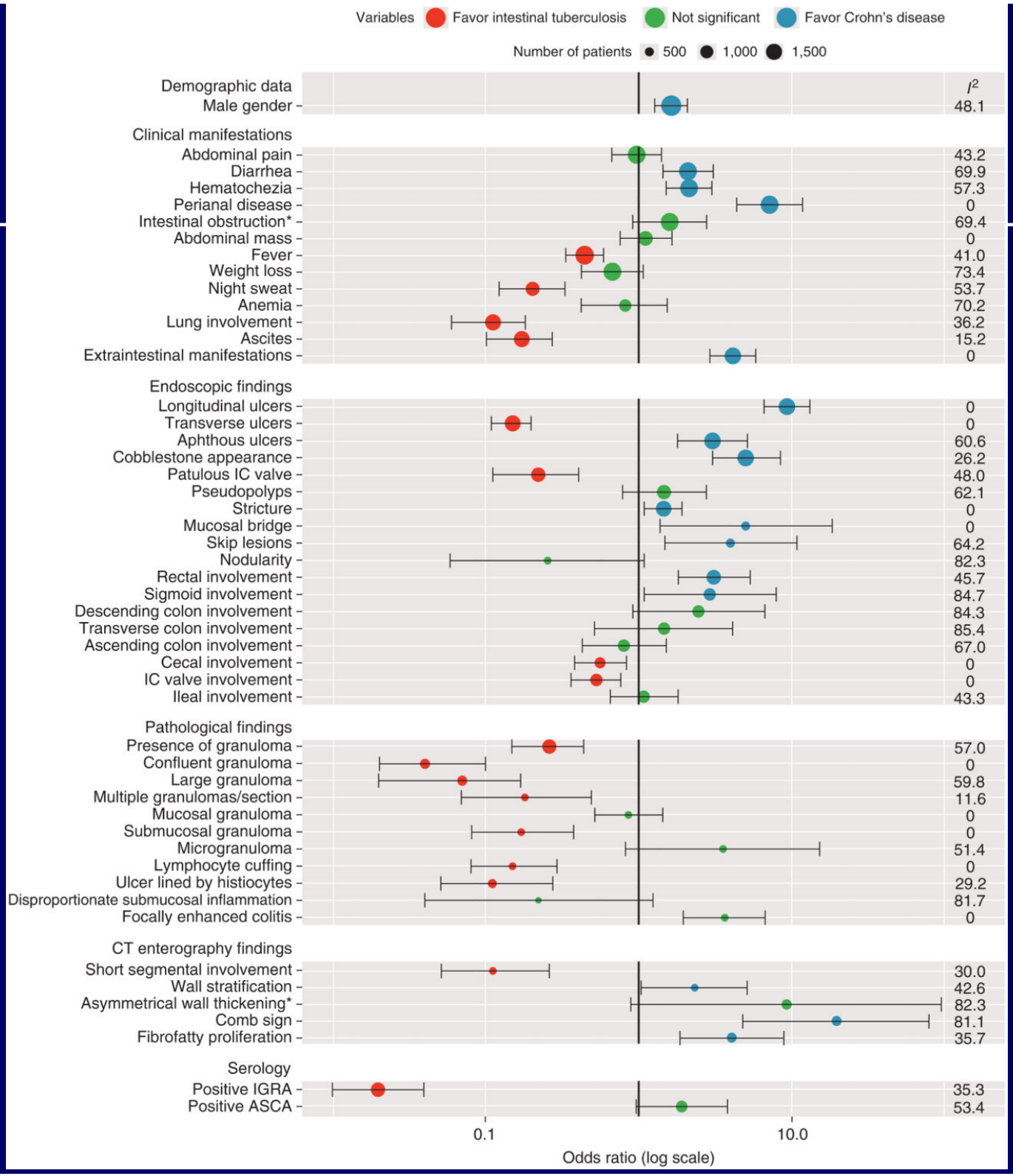
- Carcinoma of the appendix

CD or tuberculosis?

(Pulimood AB Gut 1999 ; Makharia GK Am J Gastro 2010 ; Almadi MA Am J Gastro 2009)

	Tuberculosis	Crohn
Clinical signs	Fever, night sweats, no anoperineal lesion, no hematochezia	QS
Imaging	Necrotic MLN, lung or peritoneal involvement (20-30%)	Coomb sign Fibrofatty infiltration
Endoscopy	Stomach, sigmoid, rectum, anus uninvolved	Aphtoid ulcerations
Histology	Caseous necrosis or acid-fast bacilli (15%) confluent granulomas	
Bacteriology	Positive IGRA PCR (mucosal or in stools) + in 60% of the cases. Culture of biopsies (3 to 8 weeks).	

Meta-Analytic Bayesian Model For Differentiating Intestinal Tuberculosis from Crohn's Disease *(Am J Gastroenterol. 2017; 112: 415)*



Infectious agents that may cause ileitis/ileocolitis *(DiLauro S, Curr Gastroenterol Rep 2010;12:249)*

Bacteria	Virus	Parasites	Fungi
Salmonella	CMV	Anisakiasis	Histoplasma
			Basidiobolomycosis
Campylobacter jejuni			
Yersinia			
BK			
Atypical mycobacteria			
Actinomycosis			
Clostridioides difficile			