IBD Case Studies

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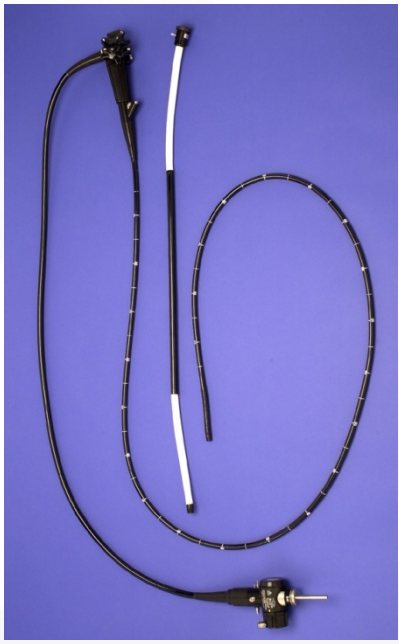

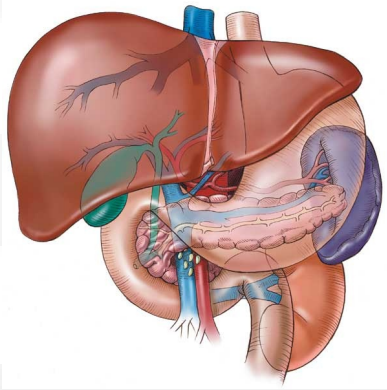

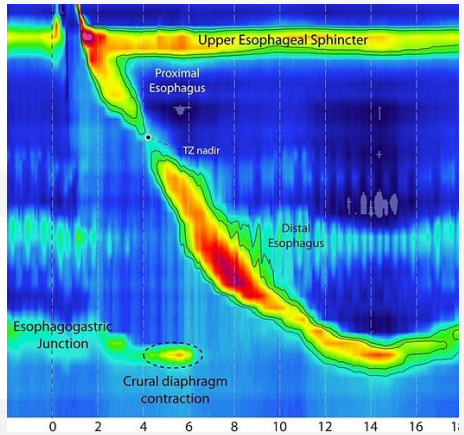

My background ...

- University of Newcastle upon Tyne
- Specialist Gastroenterology Training Leeds/Bradford & London
- Hepatology Training Leeds & London
- Specialist Gastroenterologist & Physician, Auckland Hospital since 1999
- OE (SE London) 2004 – 2007
- Clinical Director & Gastroenterologist 2008

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Case 1

18 year old female presents with rectal bleeding and mucus, with feelings of incomplete evacuation. Rigid sigmoidoscopy reveals active proctitis with normal mucosa above the rectum. The best initial management is ...

A. Oral steroids
B. Azathioprine
C. 5-ASA enema
D. 5-ASA suppository
E. Rectal swab

Case 2

18 year old gay male presents with rectal bleeding and mucus, with feelings of incomplete evacuation. Rigid sigmoidoscopy reveals active proctitis with normal mucosa above the rectum. The best initial management is ...

A. Oral steroids
B. Azathioprine
C. 5-ASA enema
D. 5-ASA suppository
E. Rectal swab

Case 3

30 year old female presents with 3/52 diarrhoea, bleeding and mucus, with weight loss (now 60kg). Stool cultures negative. Rigid sigmoidoscopy shows florid proctitis/colitis. The correct regimen for oral corticosteroids is ...

A. 30mg daily reducing weekly
B. 40mg daily reducing weekly
C. 60mg daily reducing weekly
D. 20mg daily reducing slower
E. 40mg daily reducing slower

When should you introduce corticosteroids and for how long?

The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management

A. Dignass*,1, G. Van Assche*,1, J.O. Lindsay, M. Lémann, J. Söderholm, J.F. Colombel, S. Danese, A. D'Hoore, M. Gassull, F. Gomollón, D.W. Hommes, P. Michetti, C. O'Morain, T. Öresland, A. Windsor, E.F. Stange, S.P.L. Travis for the European Crohn's and Colitis Organisation (ECCO)

ECCO

5.2.1. Mildly active localised Crohn's disease

ECCO Statement 5A

Budesonide 9mg daily is the preferred treatment [EL2a, RG B]. The benefit of mesalazine is limited [EL1a, RG B]. No treatment is an option for some patients with mild symptoms [EL5, RG D].

5.2.3. Severely active localised ileocaecal Crohn's disease

ECCO Statement 5C

Severely active localised ileocaecal Crohn's disease should initially be treated with systemic corticosteroids [EL1a, RG A]. For those who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option for patients with objective evidence of active disease [EL1a, RG B for infliximab]. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. Surgery is a reasonable alternative for some patients and should also be considered and discussed [EL5 RG D].

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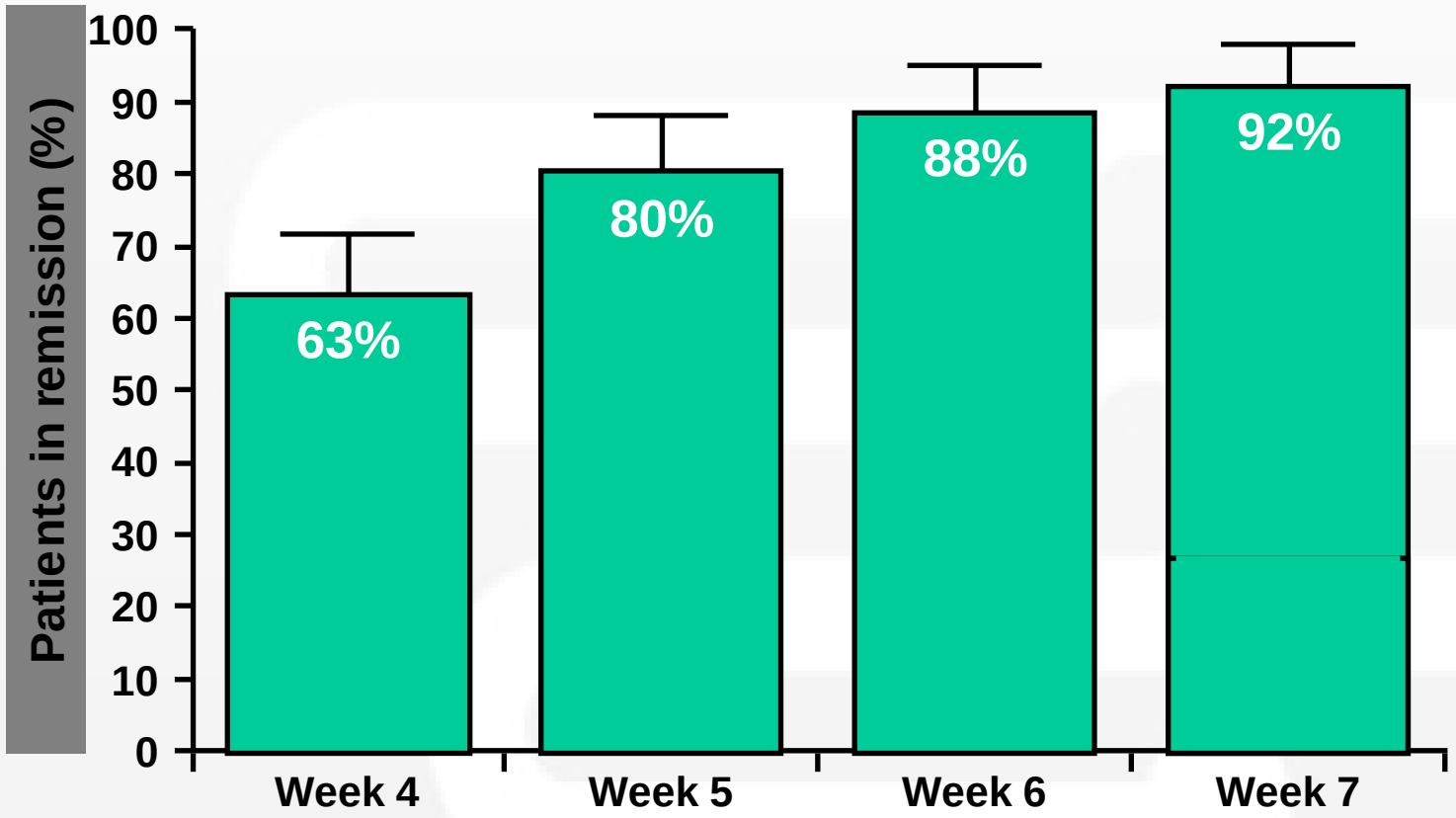
Dignass A *et al. J Crohn's Colitis* 2010; 4:28–62

GETAID: 92% in remission at 7 weeks with prednisolone

Prednisolone 1mg/kg until in clinical remission



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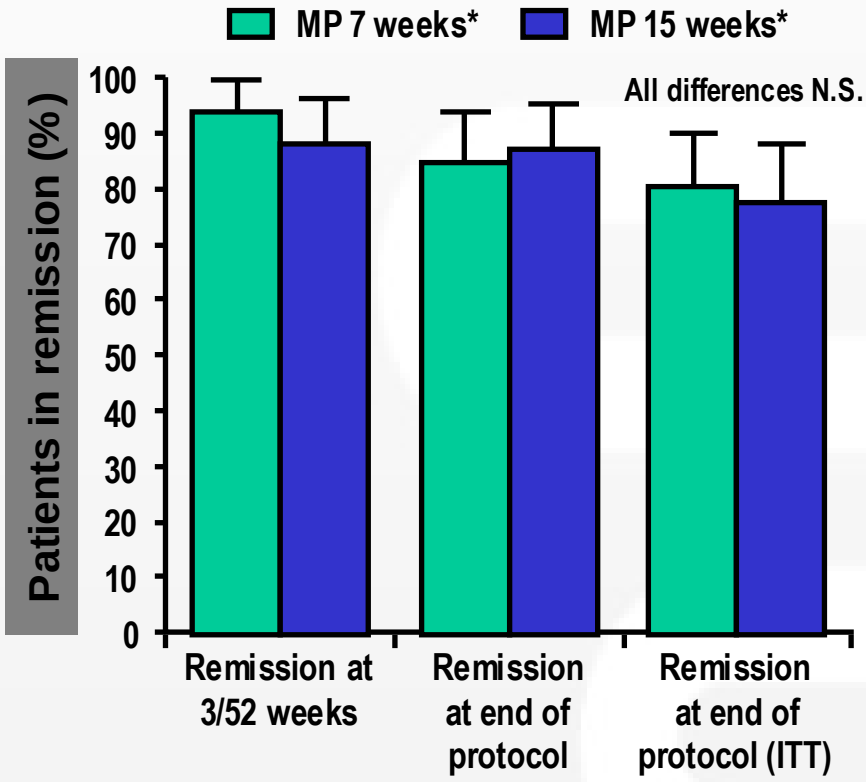
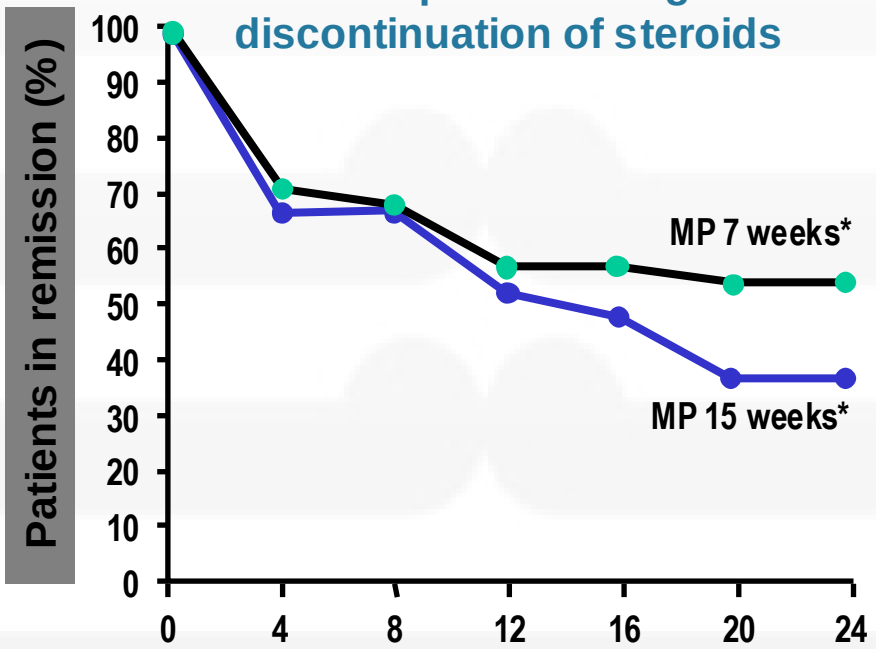
Modigliani R *et al. Gastroenterology* 1990:98;811–18

Does steroid duration affect remission rate?

No significant difference in remission rates between patients treated with methylprednisolone (MP) for 7 weeks *vs.* 15 weeks*





*70 pts with active Crohn's treated with MP 40 mg/day IM for 3/52 and then with two different tapering regimens: one for 4/52 (7/52 total) and another for 12/52 (15/52 total)

Brignola C *et al*. *Aliment Pharmacol Ther* 1994:8;465–8

What is the best dosing strategy; maximum dose duration, tapering, formulation?

ECCO recommendations for use of steroids in CD

ECCO Statement 5H
Patients with objective evidence of active disease refractory to corticosteroids should be treated with anti-TNF therapy, with or without thiopurines or methotrexate [EL1a, RG B for infliximab], although surgical options should also be considered and discussed at an early stage.

ECCO Statement 6B
If a patient has a relapse, escalation of the maintenance treatment can be considered [EL5, RG D]. Steroids should not be used to maintain remission [EL1a, RG A]. Surgery should always be considered as an option in localised disease [EL4, RG D].

ECCO Statement 6A
After the first presentation if remission has been achieved with systemic steroids, a thiopurine [EL1a, RG A] or methotrexate [EL1b, RG A] should be considered. There is no consistent evidence for efficacy of oral 5-aminosalicylic acid [EL1b, RG B]. No maintenance treatment is an option for some patients [EL5 RG D].

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Dignass A *et al. J Crohn's Colitis* 2010; 4:28–62

What about steroid side effects?

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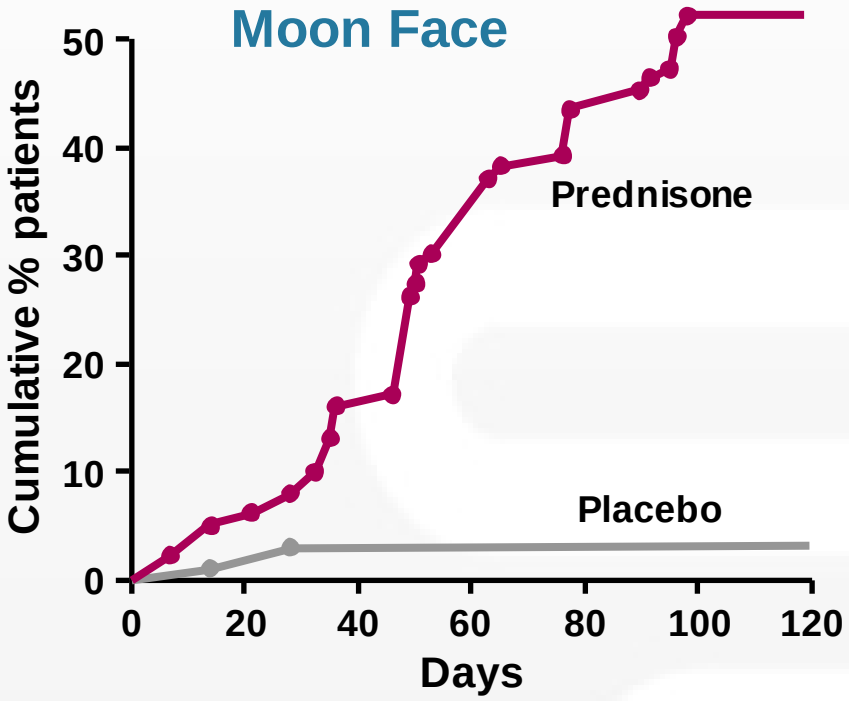
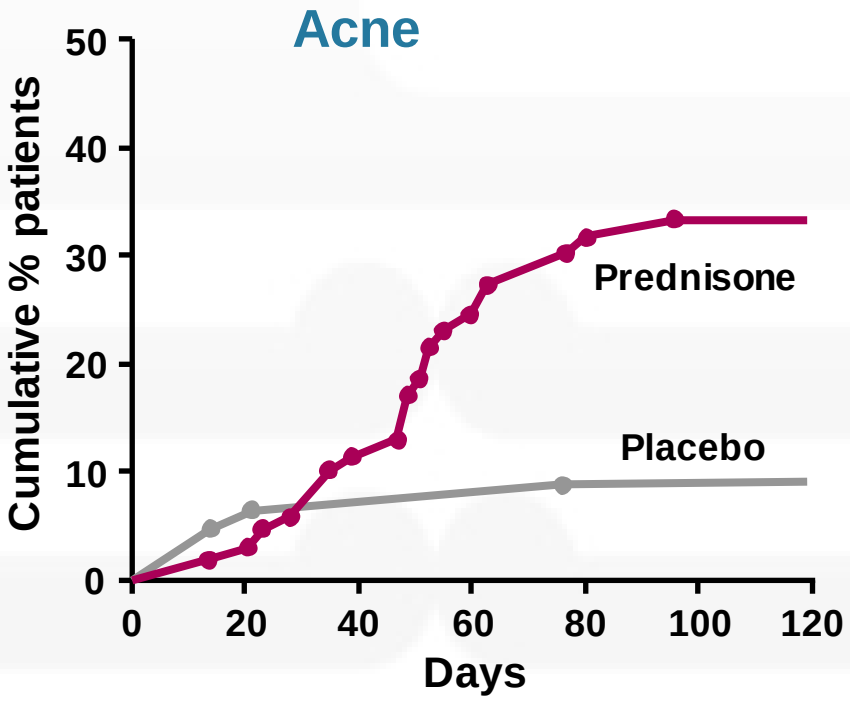
National Cooperative Crohn's Disease Study
Steroid side effects



Prednisone*	85	80	78	77	74	65	54	48	45	41	36
Placebo		69		54							

* Number at risk



Prednisone*	73	71	69	62	54	52	47	45
Placebo	69	57				42		

* Number at risk

Cumulative incidence of steroid side-effects during NCCDS Phase 1, Part 1 (induction of remission sub-study)

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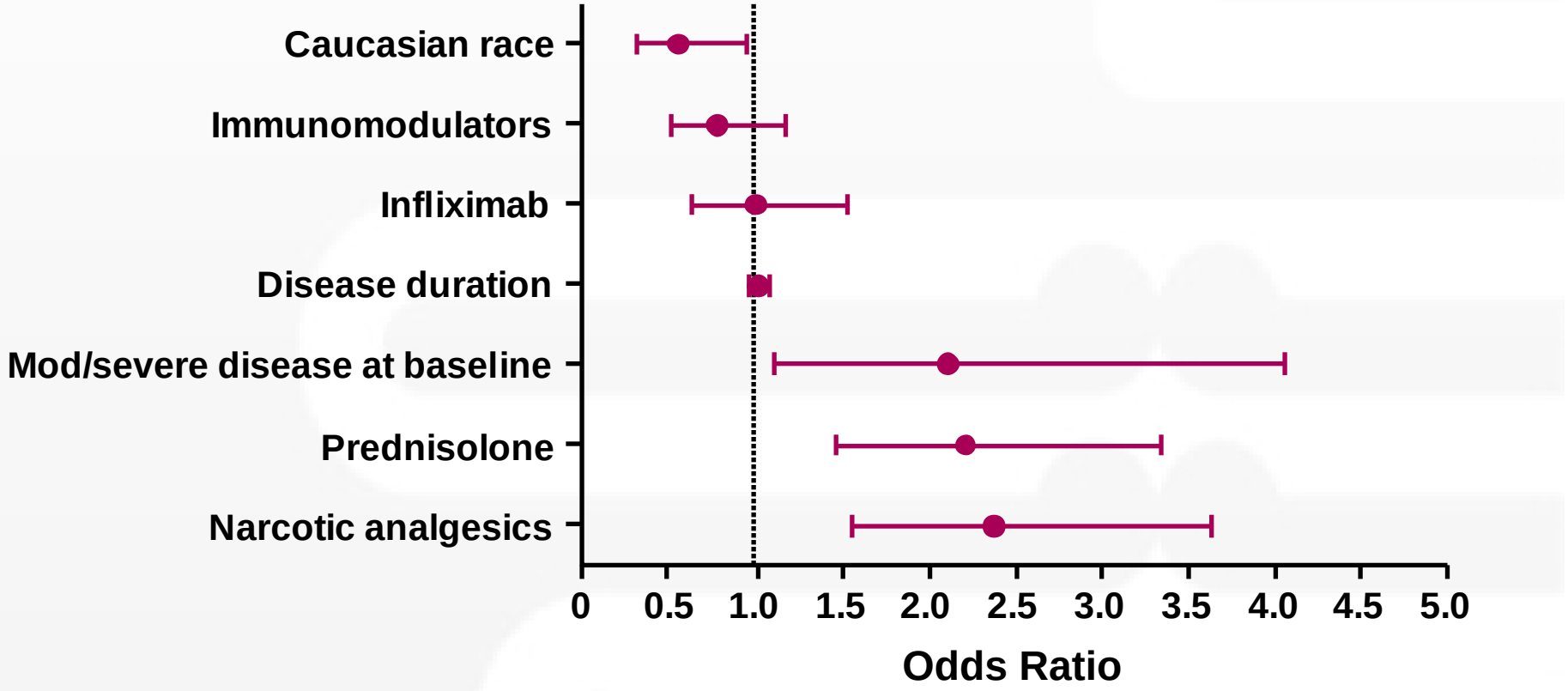
Digestive Diseases & Endoscopy

Singleton JW *et al. Gastroenterol* 1979:77;870–82

Steroids and Infection
TREAT Registry



Multivariate analysis of "serious infections" for patients in the TREAT registry. Sex, age at enrolment and disease distribution are not significant

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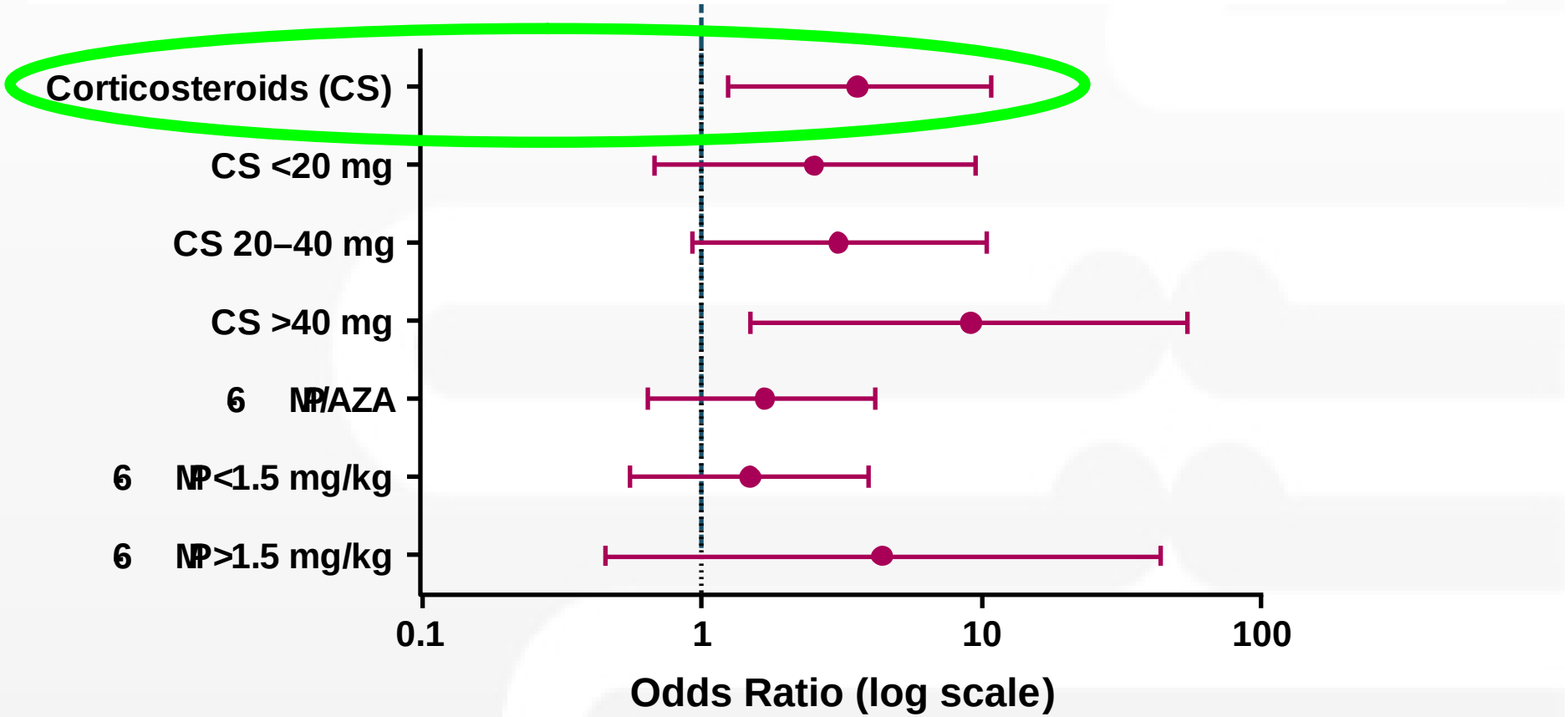
Lichtenstein GR, *et al. Clin Gastroenterol Hepatol* 2006:4;621–30

Steroids and Post-operative infection



Multivariate analysis of any postoperative infection with pre-operative medicine use from a retrospective case-control study

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Aberra FN, *et al*. *Gastroenterology* 2003:125;320-7

Corticosteroids: Conclusions

1) Optimal initial dose of oral steroids in Crohn's disease ranges from 40–60 mg/day to 1 mg/kg/day.
2) Tapering of steroids generally initiated within a week of starting therapy, and after no more than 3–4 weeks. (But …) No trials assessing different tapering regimens, 'standard' regimens differ amongst centres. Treatment should not exceed 12 weeks except in exceptional circumstances. Early introduction of immunomodulator or anti-TNF appropriate.
3) Oral corticosteroids not effective as maintenance therapy.
4) Steroids increase risk of serious, opportunistic infection, & mortality both independently, or in combination with IM and anti-TNF agents.
5) Prevent corticosteroid-induced loss of bone mineral density, calcium and vitamin D supplements should be provided.

Case 4

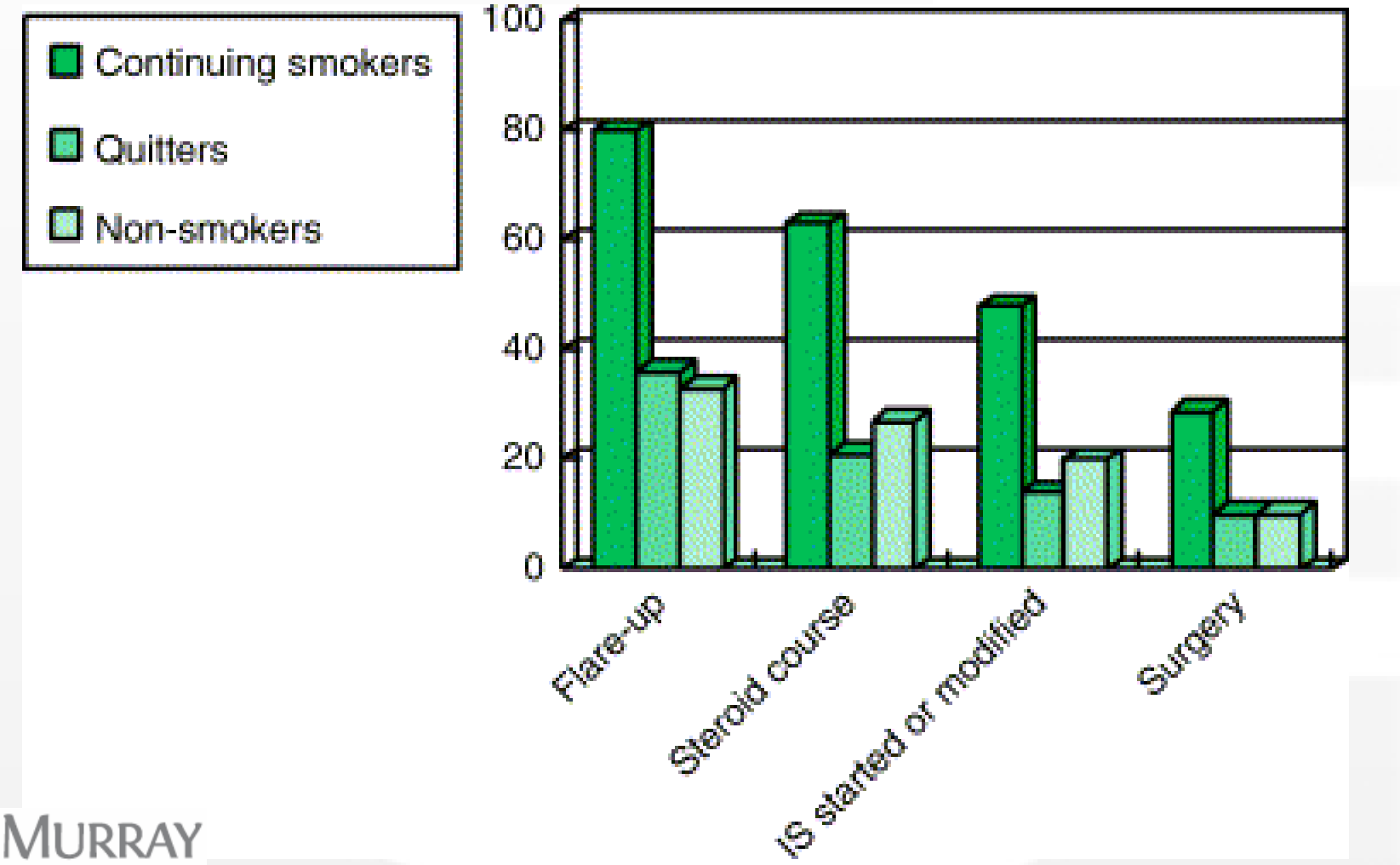
15 year old boy diagnosed with Crohn's: weight loss (55kg), deep colonic ulcers, small bowel disease. Cigarette smoker 20/day. What is the best thing you can prescribe for him …?

Case 4

15 year old boy diagnosed with Crohn's: weight loss (55kg), deep colonic ulcers, small bowel disease. Cigarette smoker 20/day. What is the best thing you can prescribe for him …?

A. Colifoam
B. 5-ASA
C. Prednisone
D. Azathioprine
E. Bupropion (*Zyban*)

Effect of smoking on Crohn's disease course



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Smoking and recurrent Crohn's disease

	5 year recurrence	10 year recurrence
Non-smoker	20%	41%
Smoker	36%	70%

Worse in those with small bowel disease and in women

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Sutherland, *Gastroenterology* 1990

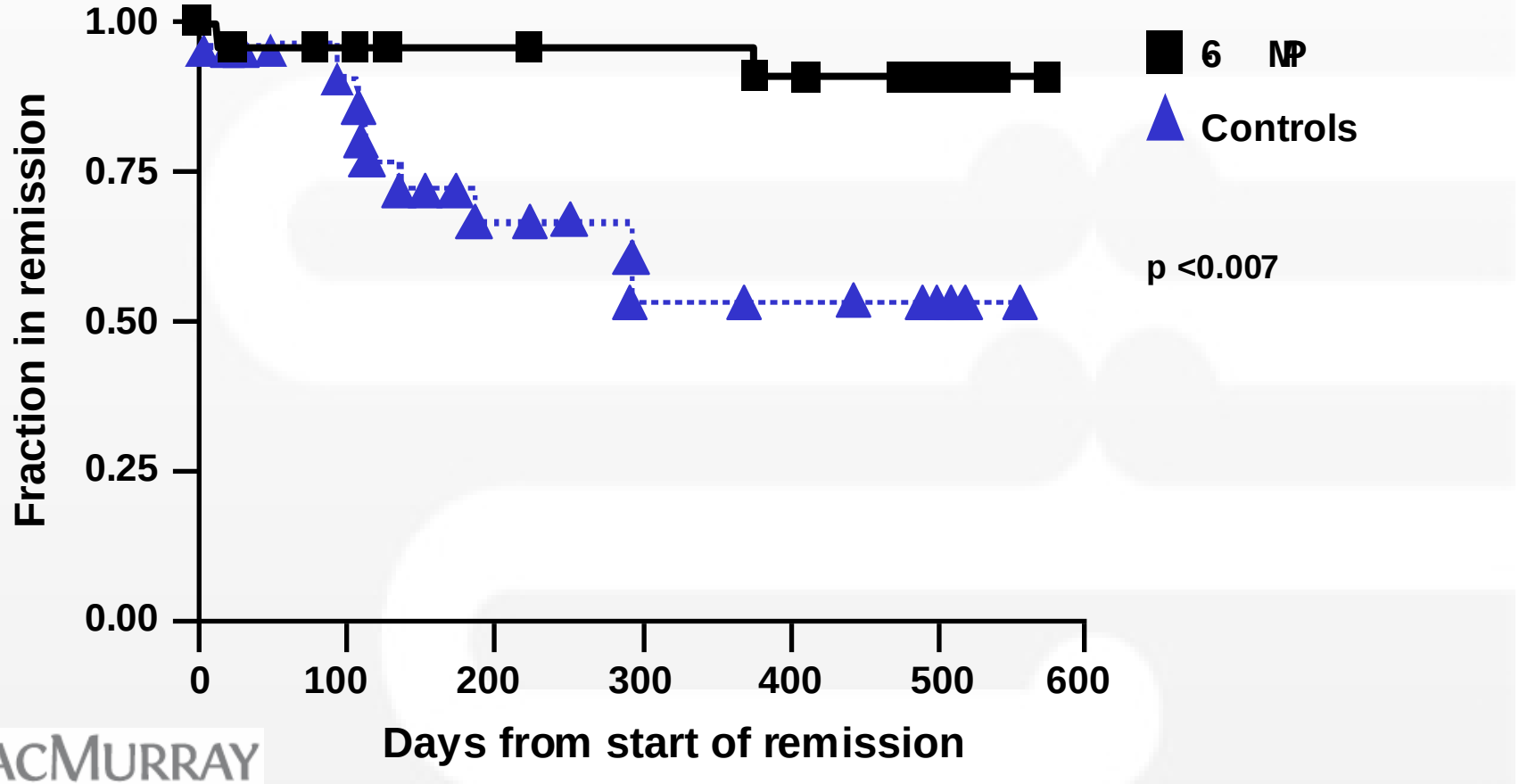
Case 4 (again)

15 year old boy diagnosed with Crohn's: weight loss (55kg), deep colonic ulcers, small bowel disease, smoker. You commence him on oral 5-ASA and Azathioprine. What are the appropriate doses …?

A. 5-ASA 1g bd; Azathioprine 100mg daily
B. 5-ASA 1.5g bd; Azathioprine 100mg daily
C. 5-ASA 2g bd; Azathioprine 75mg daily
D. 5-ASA 500mg bd; Azathioprine 125mg daily
E. 5-ASA 2g bd; Azathioprine 150mg daily

Immunomodulators: How early and which regimen?

Start immunomodulator early: effect of MP on remission in children with newly diagnosed CD



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Markowitz J *et al. Gastroenterology* 2000;119:895

Early biological treatment (<3 yrs) associated with lower risk of Crohn's-related hospitalisation

	Sample size, n		6 Month Hospitalization Rate		12 Month Hospitalization Rate	
	Treatment		Treatment		Treatment	
Disease duration	ADA	Placebo	ADA	Placebo	ADA	Placebo
<3 years	64	31	0.0%	11.8%	3.2%	11.8%
≥3 years	193	100	6.9%	11.4%	7.9%	14.8%

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CHARM study
Loftus E , *et al. Am J Gastroenterol* 2008; 103(Suppl 1):S383

Which Immunomodulator: Azathioprine/6-MP *vs.* Methotrexate?

Only one randomised comparison

- Oral MTX 15 mg/week *vs.* 6-MP 1.5 mg/kg/day *vs.* 3 g/day 5-ASA
- 72 steroid-dependent patients (34 UC, 39 Crohn's)

Remission rate at 30 weeks

- 79% for 6-MP
- 58% for MTX
- 25% for 5-ASA

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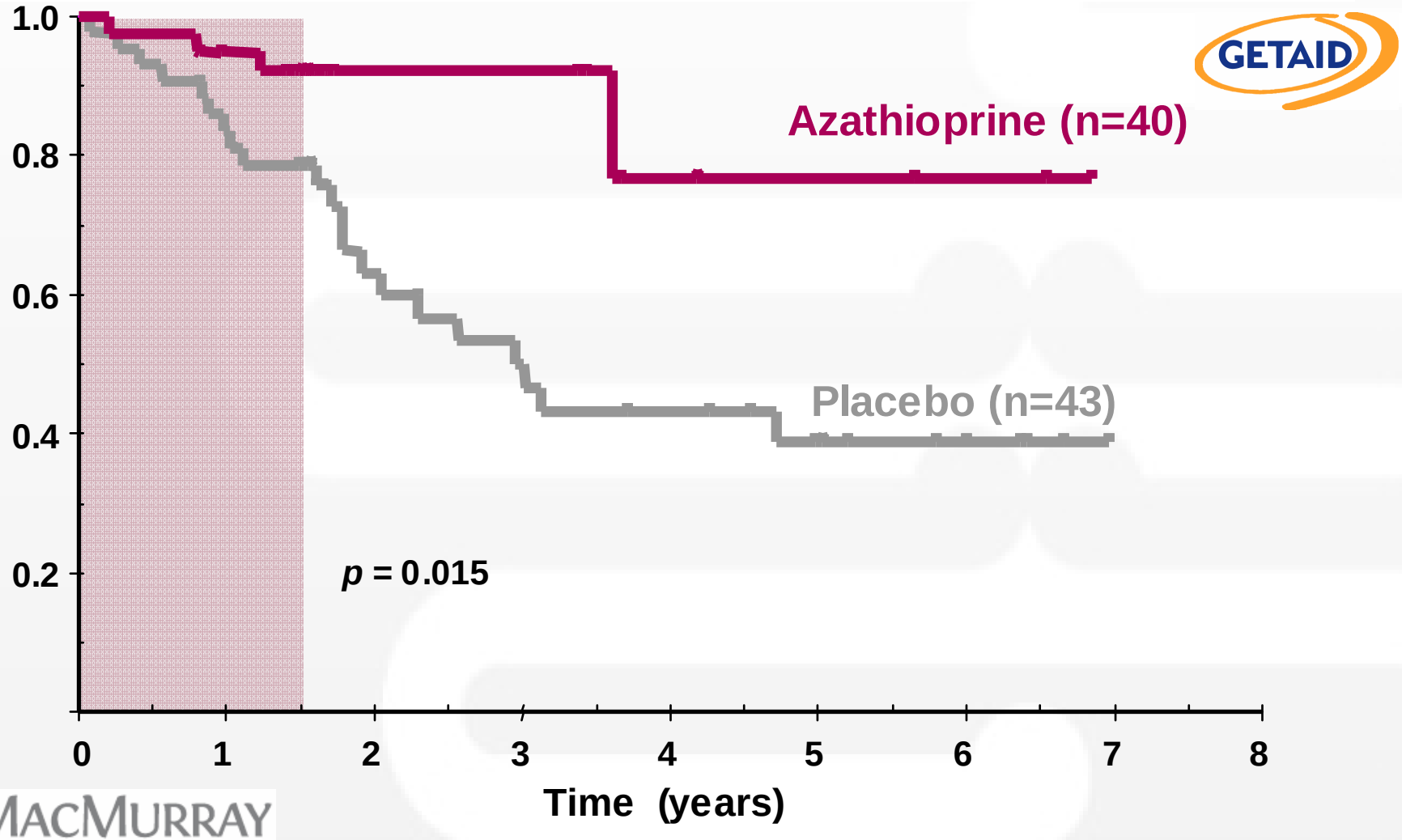
Mate-Jimenez J *et al. Eur J Gastroenterol Hepatol* 2000;12:1227–33

What about Azathioprine withdrawal?



GETAID

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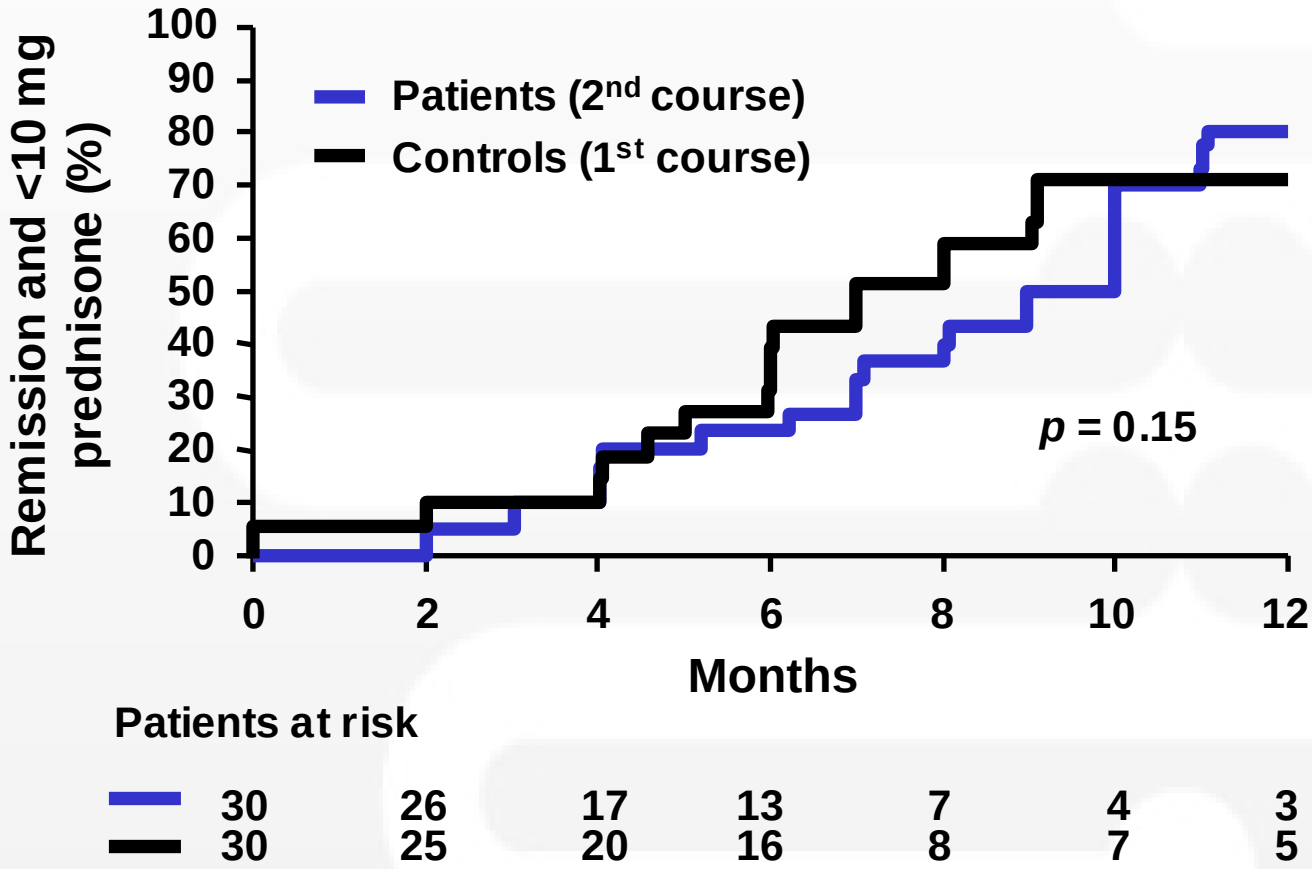
Treton X *et al. Clin Gastroenterol Hepatol* 2009;7 :80–85

What about retreatment with Azathioprine?

Re-treatment with Azathioprine associated with good response



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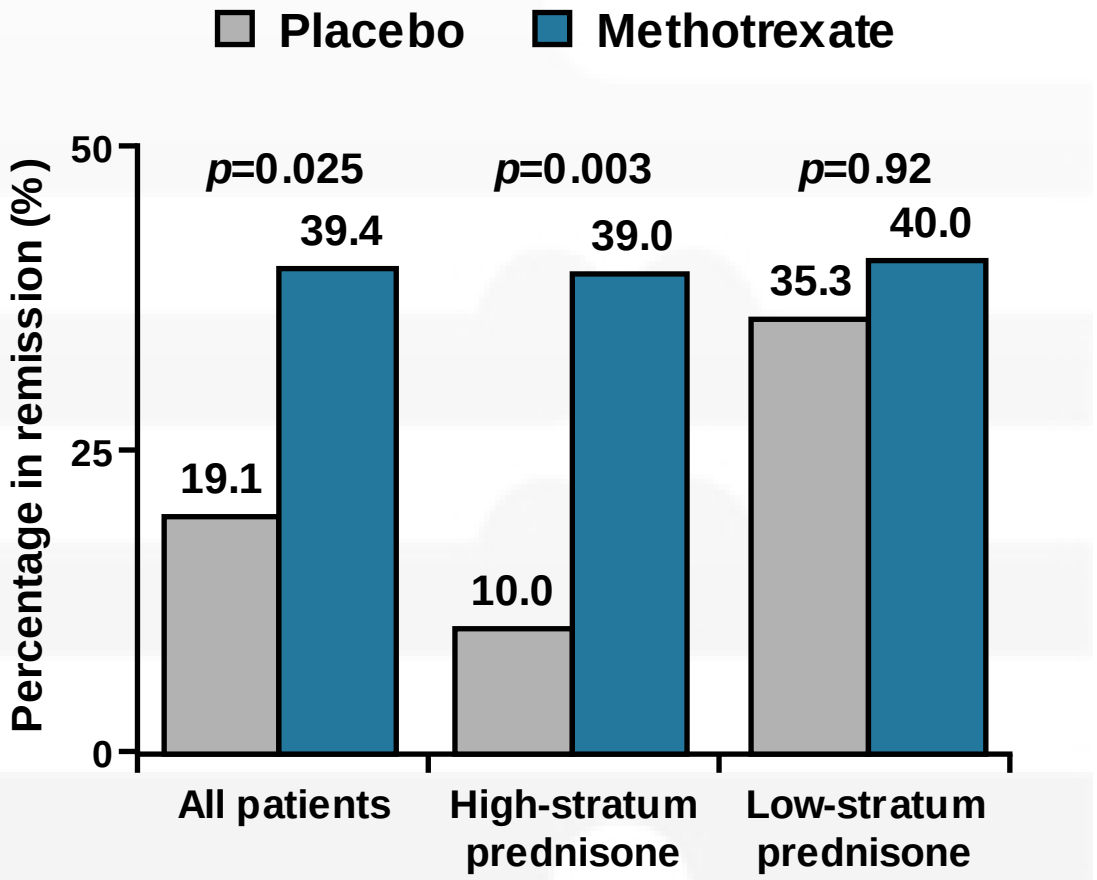
Nachury M, *et al. Gastroenterol* 2003;124(Suppl 1): A-522 (abstr T1381)

Methotrexate for steroid-dependant active Crohn's disease

Randomised double-blind placebo controlled trial
141 patients
Chronically active CD
Steroids for >3 months

Methotrexate IM 25 mg/week *vs.* placebo
16 weeks

Primary end point
CDAI<150 without steroids



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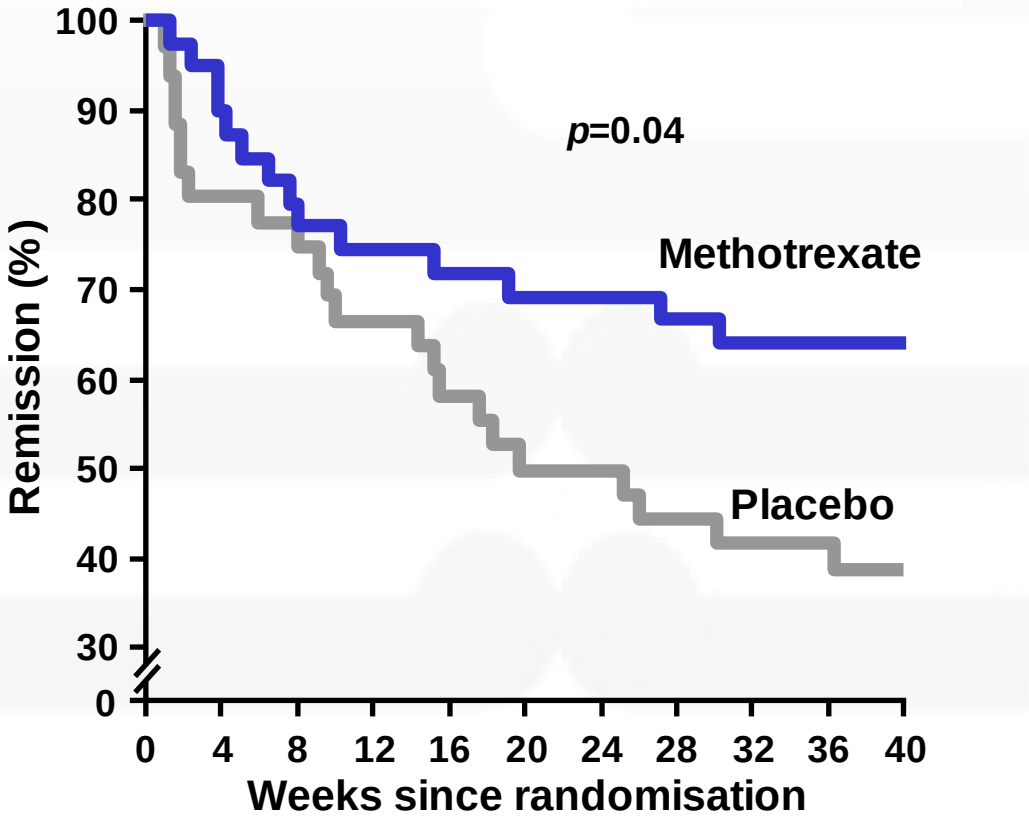
Feagan B, *et al. NEJM* 1995 ;332:292–7

Methotrexate as maintenance therapy in Crohn's disease

Randomised double-blind placebo controlled trial
76 patients
Chronically active CD
Remission after MTX 25 mg/wk

Methotrexate IM 15 mg/week
***vs.* placebo**
40 weeks

Primary end point
CDAI<150 without steroids



No. at risk:											
Methotrexate	40	36	30	29	28	27	27	26	25	24	19
Placebo	36	29	28	24	21	18	18	16	15	15	12

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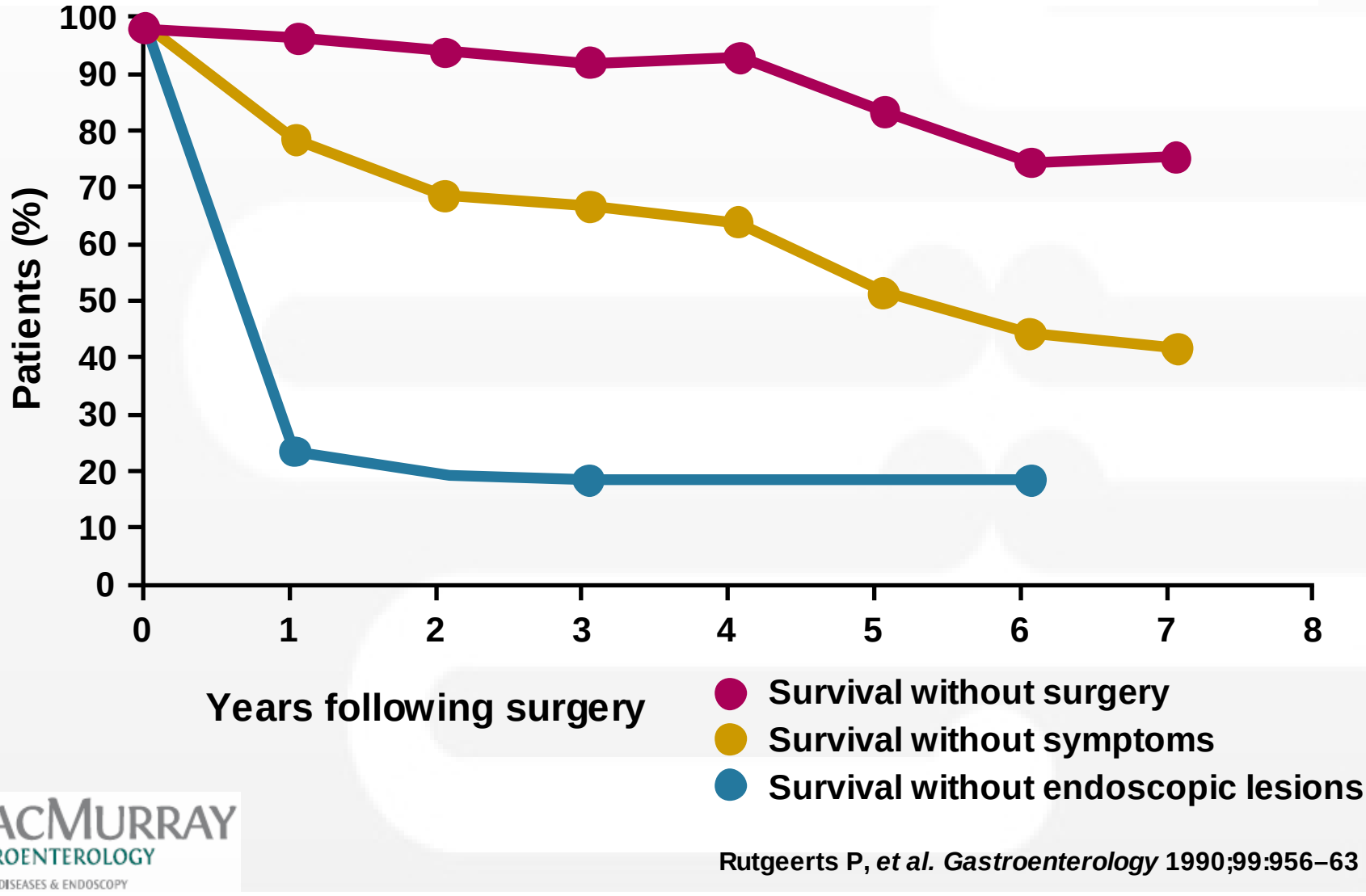
Feagan B. *et al. NEJM* 2000;342:1627–32

Surgery is not a cure:
CD recurrence following resection



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Rutgeerts P, *et al. Gastroenterology* 1990;99:956–63

Immunomodulators: Conclusions

1. Initiation of IM (+/- anti-TNF) early in disease course for pts with severe disease, paeds, and pts at high risk of progression to disabling disease.
2. Start thiopurines or MTX in IM-naïve patients who have a relapse, are steroid-dependent, or who need repeated (2) courses of steroids.
3. Thiopurines are currently indicated for post-operative prophylaxis immediately after surgical resection of ileocolonic disease if there is high risk of recurrence; in other pts thiopurines should be introduced if there is evidence of recurrence at 6–12 months.
4. Most effective dose: Aza 2.5–3.0 mg/kg/day, 6-MP 1.0–1.5 mg/kg/day.

   MTX 25 mg/week for 8–12 weeks and 15 mg/week for maintenance.
5. Azathioprine generally used as first-line IM.
6. Aza/6-MP treatment best maintained for several years. High relapse rates in patients with Crohn's disease if these drugs are discontinued.

Case 5

30 year old woman with UC (left sided). Diagnosed 2 years ago. Difficult to settle colitis initially, but now stable on 5-ASA and Azathioprine. She arrives at your surgery and reveals she is 7 weeks pregnant. Do you ...

A. Stop the 5-ASA
B. Stop the Azathioprine
C. Stop both
D. Recommend termination
E. Commence folic acid

What about the risks of lymphoma?

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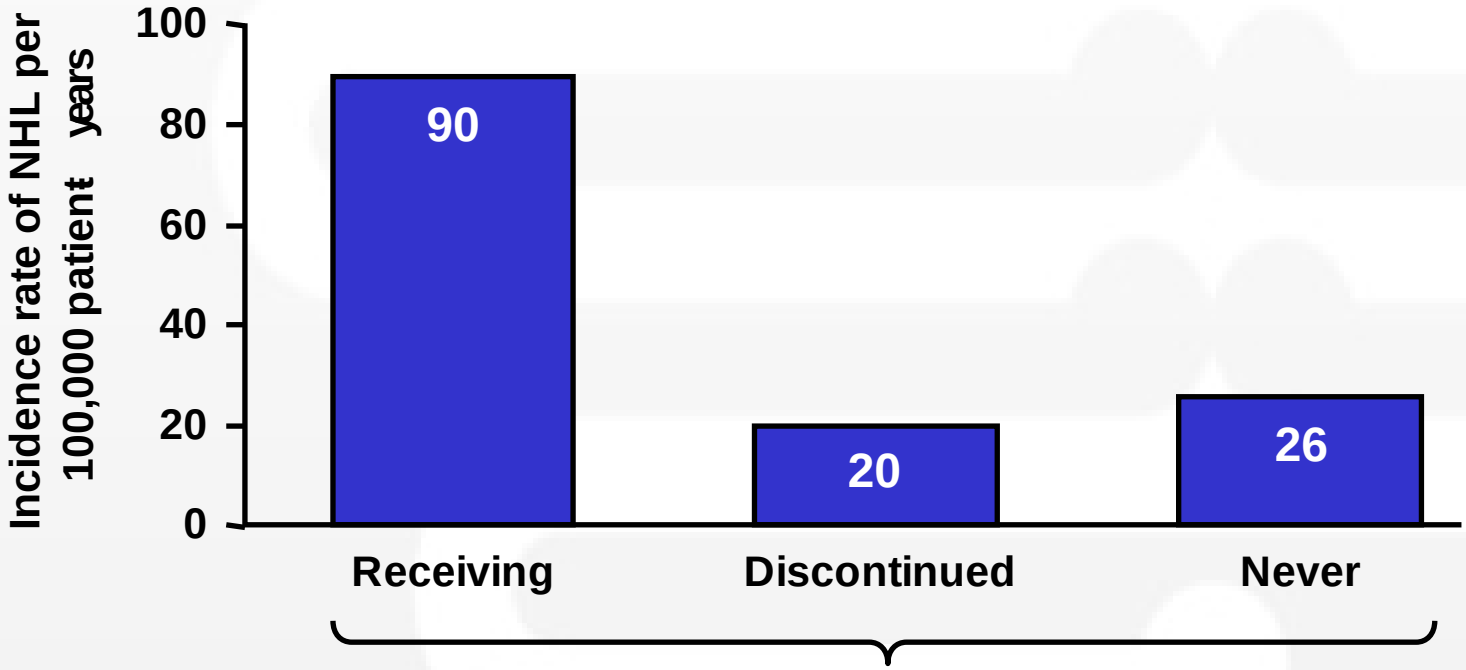
Lymphoproliferative disorders in patients receiving thiopurines for IBD

- IBD patients 19,486: 11759 (60·3%) CD, 7727 (39·7%) UC or indeterminate IBD
- Thiopurine use: 5867 (30·1%) receiving, 2809 (14·4%) discontinued, 10810 (55·5%) never received
- Lymphoproliferative disorders: 1 Hodgkin's lymphoma and 22 NHL



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Beaugerie L *et al.* *Lancet*. 2009 Nov 7;374:1617–25

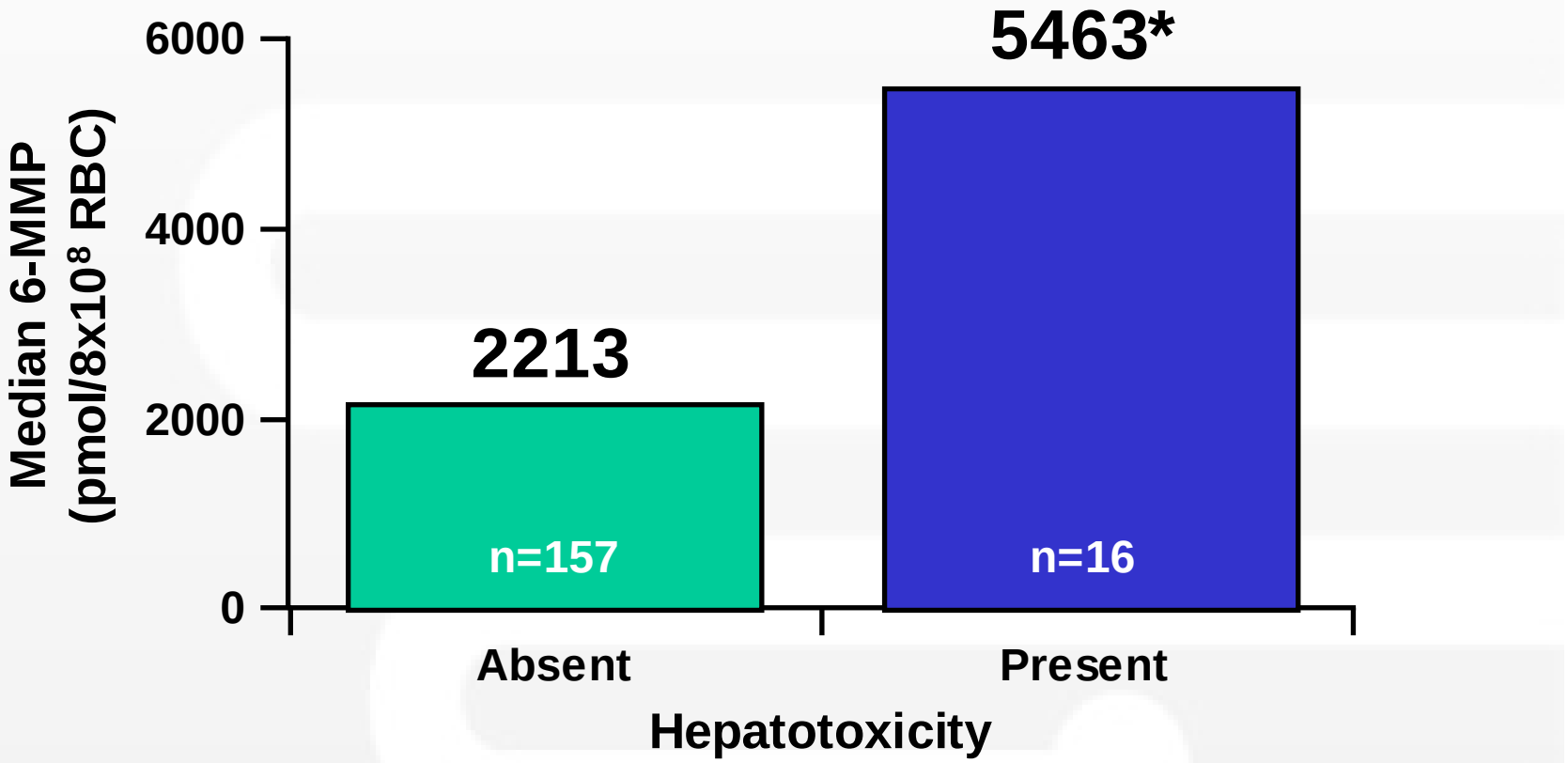
Hepatosplenic T cell lymphoma

Case	Diagnosis	Anti-TNF	Concomitant drugs	Age	Sex	Outcome	HSTCL therapy
1	CD	IFX	6-MP, ST	31	M	Death	CHMT+SCT
2	CD	IFX	AZA, ST	15	M	Death	CHMT
3	CD	IFX	AZA	12	M	Death	CHMT
4	CD	IFX	6-MP, ST	17	F	Death	CHMT
5	CD	IFX	AZA, 6-MP, ST	19	M	Death	CHMT+SCT
6	CD	IFX	AZA, 6-MP, ST	18	M	Death	CHMT
7	CD	IFX	AZA	19	M	Death	CHMT+SCT
8	UC	IFX	AZA, ST	22	M	Death	CHMT+BMT
9	RA	ADA	ST	61	F	Death	–
10	UC	IFX+ADA	6-MP	21	M	Death	–
11	CD	IFX+ADA	AZA	29	M	Unknown	CHMT+BMT
12	CD	IFX	6-MP, ST	22	M	Death	CHMT
13	CD	IFX	6-MP, ST	31	M	Death	CHMT
14	CD	IFX	6-MP, AZA, ST	31	M	Death	CHMT
15	CD	IFX	AZA, ST	40	M	Death	CHMT+BMT
16	CD	IFX	6-MP	19	M	Death	–
17	UC	IFX	AZA	58	M	Unknown	–

Mackey *et al. J Pediatr Gastroenterol Nutr* 2007;44:265-7; Shale *et al. Gut* 2008;57:1639–41

What about shunting?

Higher 6-MMP levels are associated with increased hepatotoxicity



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Dubinsky M, *et al. Gastroenterology* 2000;118:705–13

Case 6

Regular intake of probiotics have been shown to ...

A. Reduce the number of flare-ups of IBD
B. Reduce IBS symptoms (eg: bloating)
C. Reduce risk of *Clostridium difficile* diarrhoea
D. All of the above
E. None of the above

Case 7

Regular intake of probiotics have been shown to ...

A. Reduce the number of flare-ups of IBD
B. Reduce IBS symptoms (eg: bloating)
C. Reduce risk of *Clostridium difficile* diarrhoea
D. All of the above
E. None of the above

Case 8

Azathioprine/6-MP are ...

A. Safe in pregnancy but not breastfeeding
B. Safe in breastfeeding but not pregnancy
C. Safe in both
D. Unsafe in both
E. Known teratogens

Tips for GPs

Management of IBD flares in the community

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Tips

- Exclude infection

Tips

- 5-ASA dose
  - at least 4g daily for flares
  - I regularly use >6g daily
  - can be once daily dosing
- 5-ASA route(s)
  - oral + topical

Tips

- Probiotics
  - acidophilus
  - lactobacillus
  - bifidobacteria
- Diet & Lifestyle
  - triggers?
  - irritants?

Tips

- Supplements (“natural” remedies)
  - Aloe vera juice
  - Spirulina
  - Evening primrose oil
- Beware “Womens Magazines”!

Tips

- Disease modifying drugs - ?dose
  - Azathioprine
  - 6-MP
  - MTX

Tips

- Corticosteroids
  - ?topical
  - in conjunction with 5-ASA
- Oral steroids
  - dose
  - duration

Take home messages

- Exclude infection
- Suppositories Rx the rectum
- Enemas Rx the left hemi-colon
- Topical 5-ASAs *as effective* as topical steroids
- Think 5-ASA first and last
- Steroids (last) resort (dose/duration)
- If worried ..., call/refer

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