

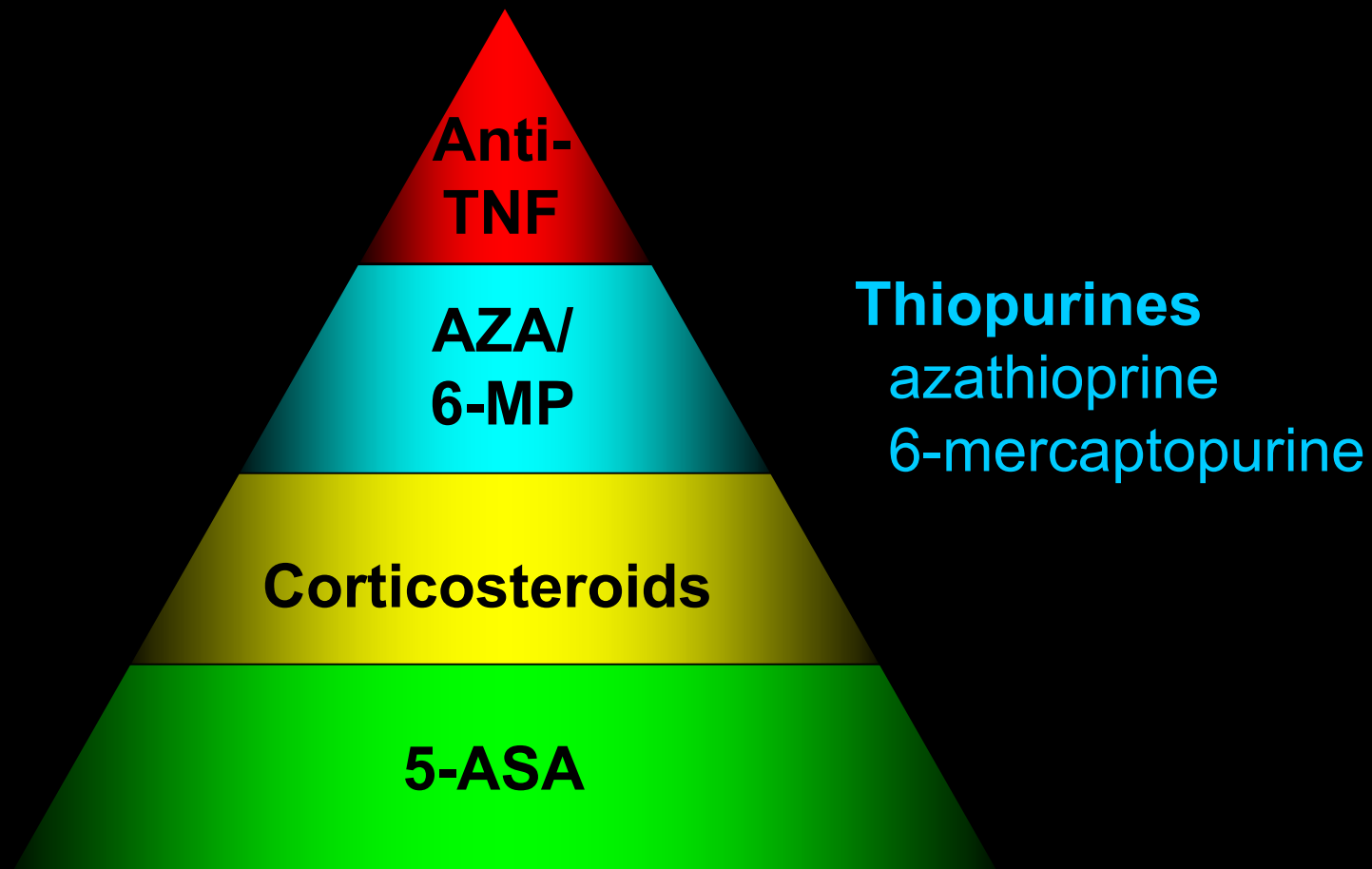


*„No evidence of adrenal tissue was found.“*

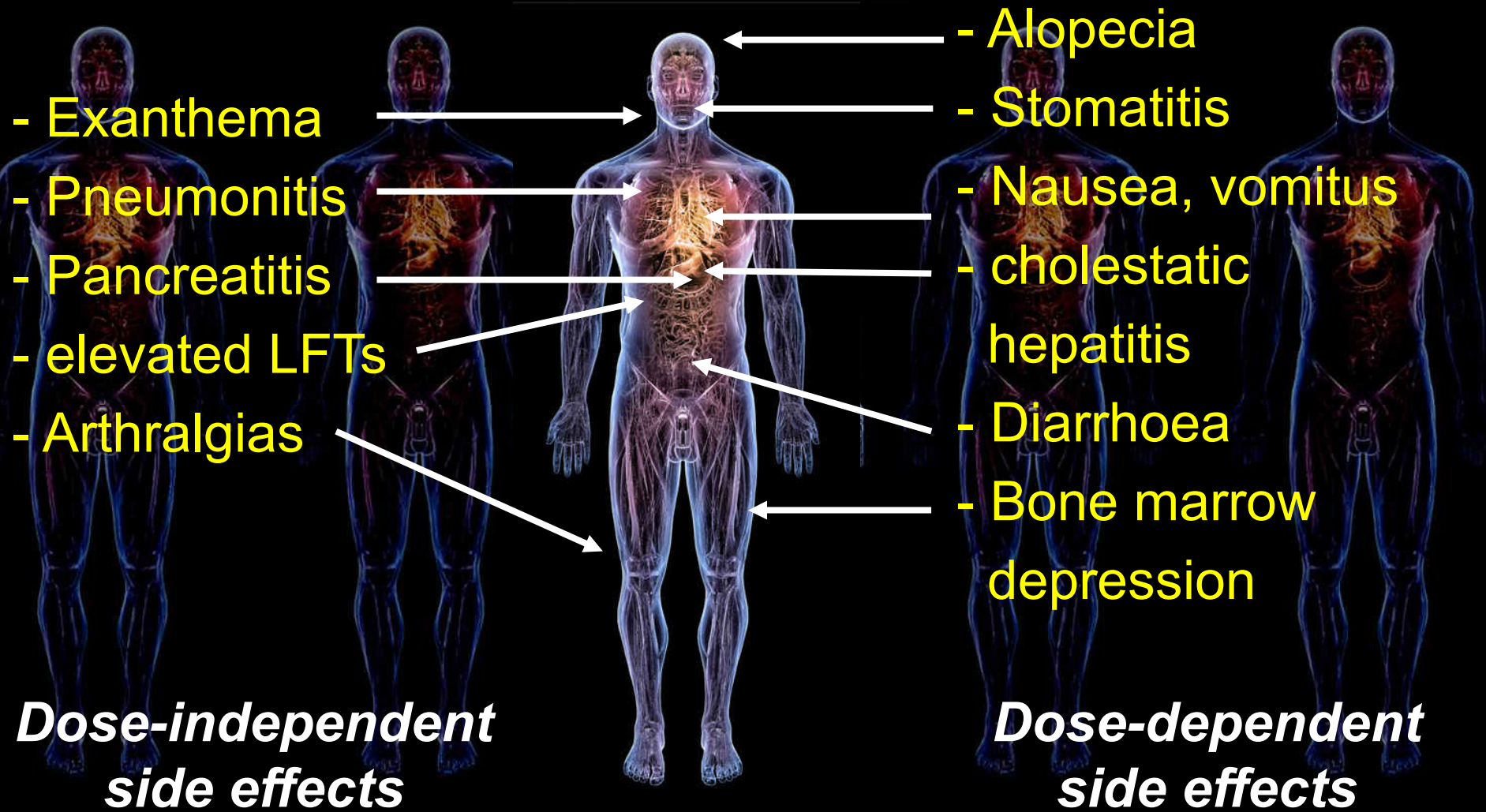
Autopsy report of John F. Kennedy

# Preoperative thiopurines and postoperative complications

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# Side effects in 20% of azathioprine-treated patients



# Meta-analysis of postoperative complications with preoperative thiopurines: No increased risk

**TABLE 4.** Postoperative outcome in patients with and without preoperative thiopurines

Reference	Drug window	Risk of confounding bias in MA <sup>a</sup>	Cases vs controls, n	Total complications, %	Total infectious complications, %	Anastomotic leak, %	Intra-abdominal abscess, %	Wound infection, %	Septic shock, %	Reoperation, %	Mortality, %
El-Hussuna 2012 <sup>23</sup>	<1 mo	Medium	166 vs 251	–	10 vs 14	–	–	–	–	–	–
Rizzo 2011 <sup>32</sup>	NR	Medium	34 vs 80	15 vs 24	9 vs 18	–	–	–	–	–	–
Aberra 2003 <sup>21</sup>	<2 wk	High (BNE)	18 vs 51	–	72 vs 6	6 vs 0	0 vs 0	17 vs 0	6 vs 4	–	–
Bafford 2012 <sup>12</sup>	<3 mo	High (BNE)	69 vs 127	–	13 vs 28	–	–	–	–	–	–
Canedo 2010 <sup>14</sup>	<1 mo	High (BNE)	85 vs 75	–	33 vs 17	5 vs 1	7 vs 3	7 vs 11	–	8 vs 3	0 vs 0
Colombel 2004 <sup>22</sup>	<1 mo	High (BNR)	105 vs 165	25 vs 22	19 vs 19	–	–	–	–	–	–
Myrelid 2009 <sup>28</sup>	<6 wk	High (BNR)	51 vs 292	–	10 vs 6	–	–	–	–	–	–
Page 2002 (patients <60 y) <sup>16</sup>	NR	High (BNR)	20 vs 55	15 vs 22	–	–	–	–	–	–	–
Page 2002 (patients ≥60 y) <sup>16</sup>	NR	High (BNR)	13 vs 17	54 vs 41	–	–	–	–	–	–	–

Outcome data presented as percentages of cases (%) vs percentages of controls (%).

NR = not reported; MA = meta-analysis.

<sup>a</sup>Medium = not matched, but baseline equivalent between groups. High (BNE) = high risk, baseline not equal between groups. High (BNR) = high risk, baseline not reported.

**Total complications:**

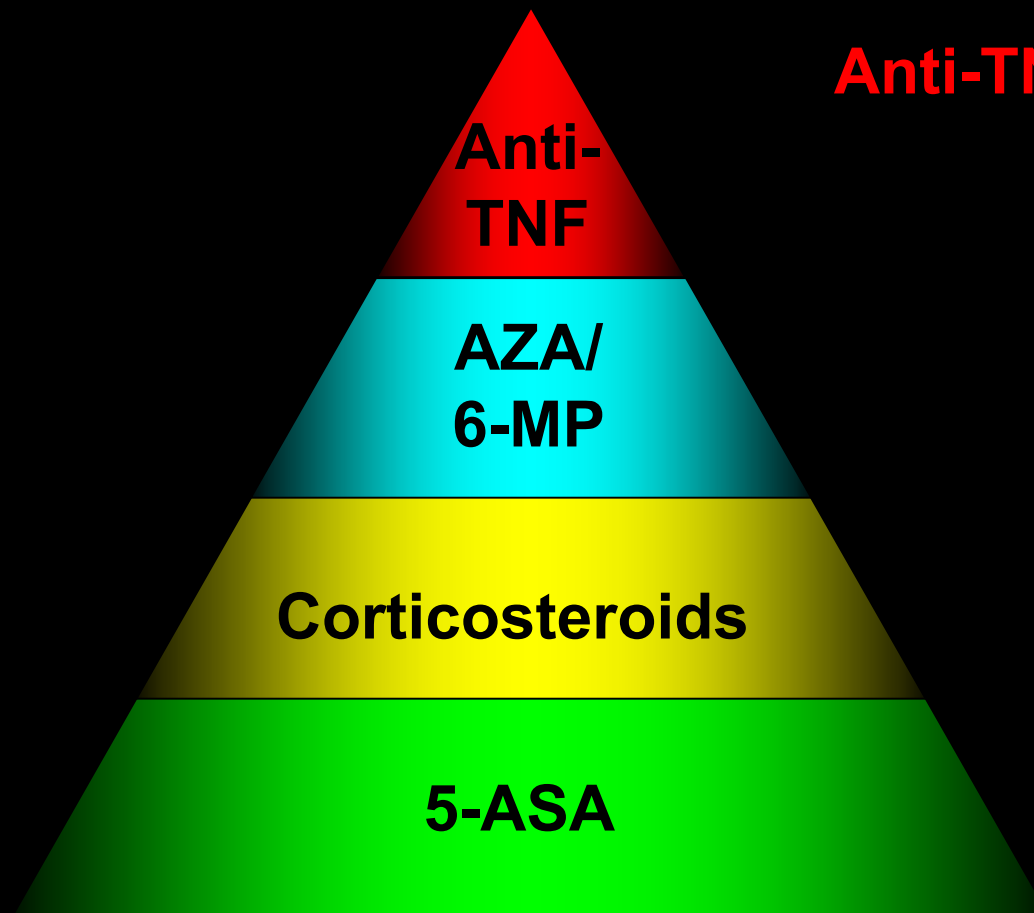
**RR 0.97 (95% CI, 0.69 – 1.36)**

**Infectious complications:**

**RR 1.23 (95% CI, 0.66 – 2.29)**

# Preoperative anti-TNF antibodies and postoperative complications

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## Anti-TNF antibodies

infliximab  
adalimumab  
certolizumab  
golimumab



# Infliximab Does Not Affect Postoperative Complication Rates in Crohn's Patients Undergoing Abdominal Surgery

*Michael S. Kasperek, MD,\* Andreas Bruckmeier, MD,\* Florian Beigel, MD,† Mario H. Müller, MD,\*  
Stephan Brand, MD,† Ulrich Mansmann, PhD,‡ Karl-Walter Jauch, MD,\*  
Thomas Ochsenkühn, MD,† and Martin E. Kreis, MD\**



**Kasperek MS ... Brand S et al. *Inflamm Bowel Dis* 2012;18:1207-13.**

# Complications rates are similar in infliximab-treated and control group

TABLE 3. Number of Minor and Major Complications in Both Groups and Postoperative Outcome

	Infliximab Patients (n=48)	Control Patients (n=48)	P-value
Minor complications	17 in 14 patients	9 in 8 patients	0.23
Wound infection	9 (19%)	7 (15%)	0.78
Urinary tract infection	1 (2%)	0 (0%)	1.0
Paralytic ileus	7 (15%)	2 (4%)	0.16
Major complications	16 in 13 patients	15 in 12 patients	1.0
Anastomotic leak	2 (4%)	6 (13%)	0.27
Intraabdominal abscess	3 (6%)	5 (10%)	0.71
Small bowel leakage following takedown of adhesions	1 (2%)	2 (4%)	1.0
Stoma complication	3 (6%)	1 (2%)	0.62
Postoperative hemorrhage	4 (8%)	1 (2%)	0.36
Enterocutaneous fistula	2 (4%)	0 (0%)	0.50
Death	1 (2%)	0 (0%)	1.0
Patients requiring reoperation	11 (23%)	10 (21%)	1.0
Number of complication-related reoperations / per reoperated patient	2 [1 – 5]	2 [1 – 6]	0.54
Fecal diversion during reoperation	1 (2%)	4 (8%)	0.36
CT-guided drainage	0 (0%)	1 (2%)	1.0
Postoperative hospital stay (d)	13 [5–41]	12 [5–54]	0.64

Data of complications is number (%) of patients developing this complications. Other data are median [range].

# Own data: Infliximab does not affect postoperative complication rates

ORIGINAL ARTICLE

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## Infliximab Does Not Affect Postoperative Complication Rates in Crohn's Patients Undergoing Abdominal Surgery

Michael S. Kasperek, MD,\* Andreas Bruckmeier, MD,\* Florian Beigel, MD,<sup>†</sup> Mario H. Müller, MD,\*  
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Thomas Ochsenkühn, MD,<sup>†</sup> and Martin E. Kreis, MD\*

**Week 0:  
Infliximab**



**Week 4:  
Surgery**



**Week 8:  
Infliximab**



**Kasperek MS ... Brand S et al. *Inflamm Bowel Dis* 2012;18:1207-13.**



# Meta-Analyses: Preoperative Anti-TNF and postoperative complications/infections

## Study Reference

## Risk increase (Odds ratio)



Narula N et al. *Aliment Pharmacol Ther* 2013;  
37:1057-64.

1.56 (p<0.05)



Rosenfeld G et al. *J Crohns Colitis* 2013;  
7:868-77.

1.59 n.s.



Yang ZP et al. *Int J Surg* 2014;  
12:224-230.

1.45 (p<0.05)



Ahmed Ali U et al. *Dis Colon Rectum* 2014;  
57:663-74.

1.29 (p<0.05)

# Anti-TNF therapy and postoperative complications

AP&T Alimentary Pharmacology and Therapeutics

## Meta-analysis: peri-operative anti-TNF $\alpha$ treatment and post-operative complications in patients with inflammatory bowel disease

N. Narula, D. Charleton & J. K. Marshall



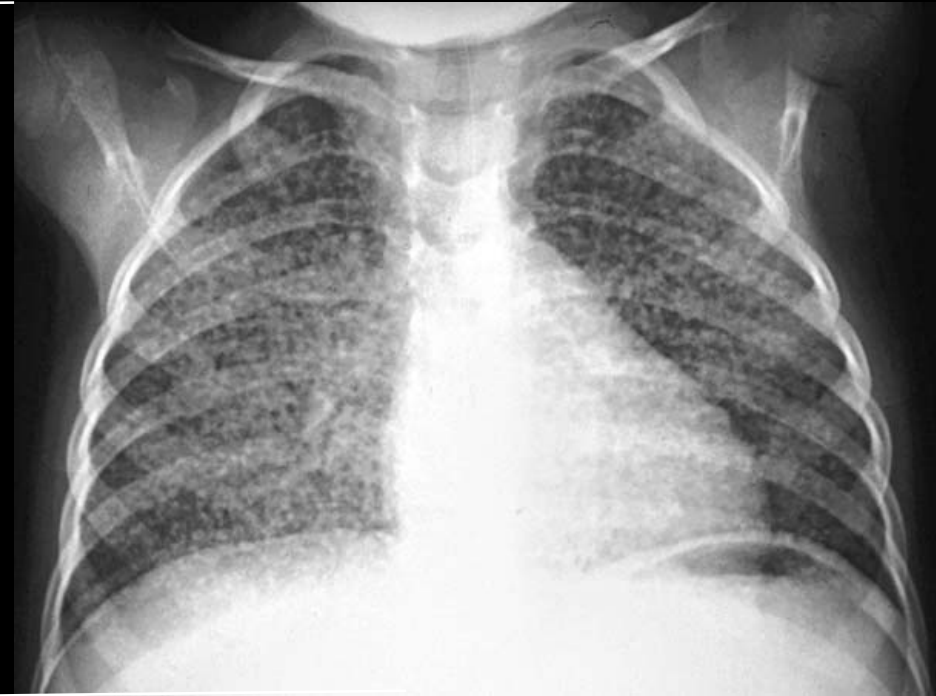
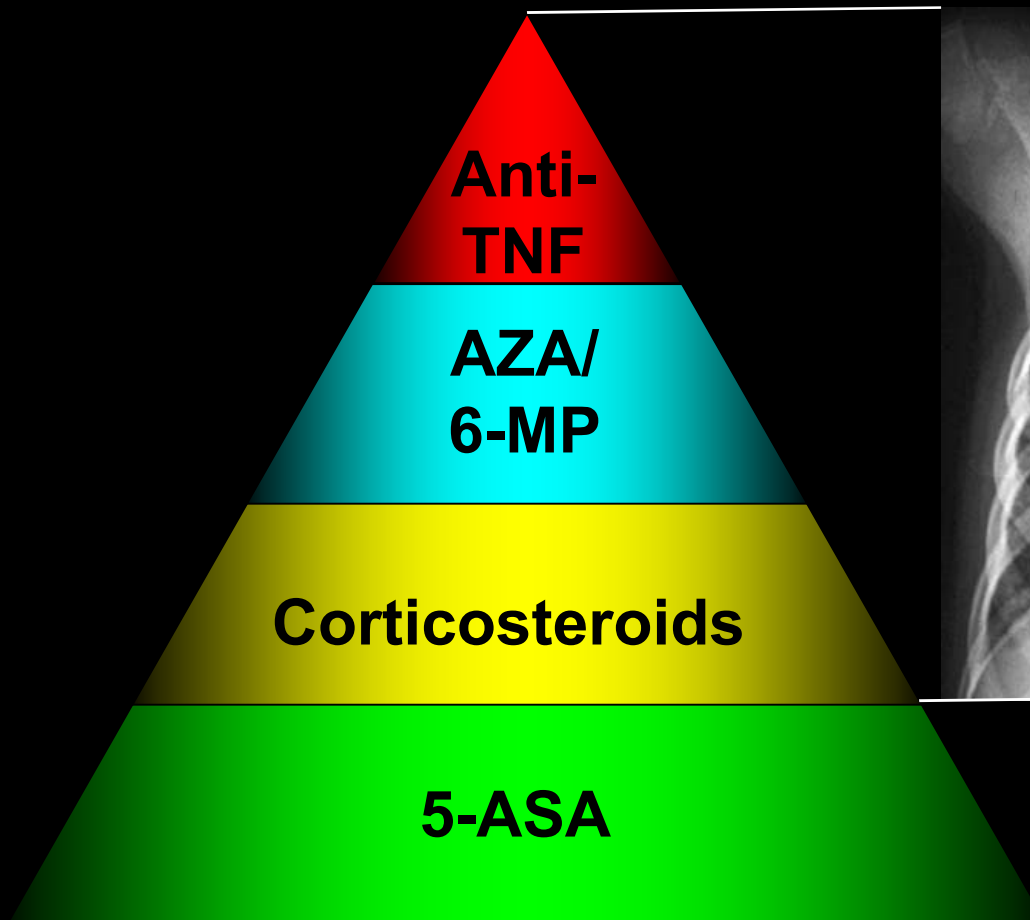
### Conclusion

Anti-TNF $\alpha$  therapies appear to increase the risk of post-operative complications. The increase in risk is small, and may well reflect residual confounding rather than a true biological effect. Nevertheless, physicians should exercise caution when continuing biological therapies during the peri-operative period.

Narula N et al. *Aliment Pharmacol Ther* 2013;37:1057-64.

**Problem of current immunosuppressive therapy: unspecific, resulting in increased rate of opportunistic infections**

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# Novel therapies for Crohn's disease

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2014: Vedolizumab (Anti-Integrin)  
2017: Ustekinumab (Anti-IL-12/IL-23)



Anti-TNF

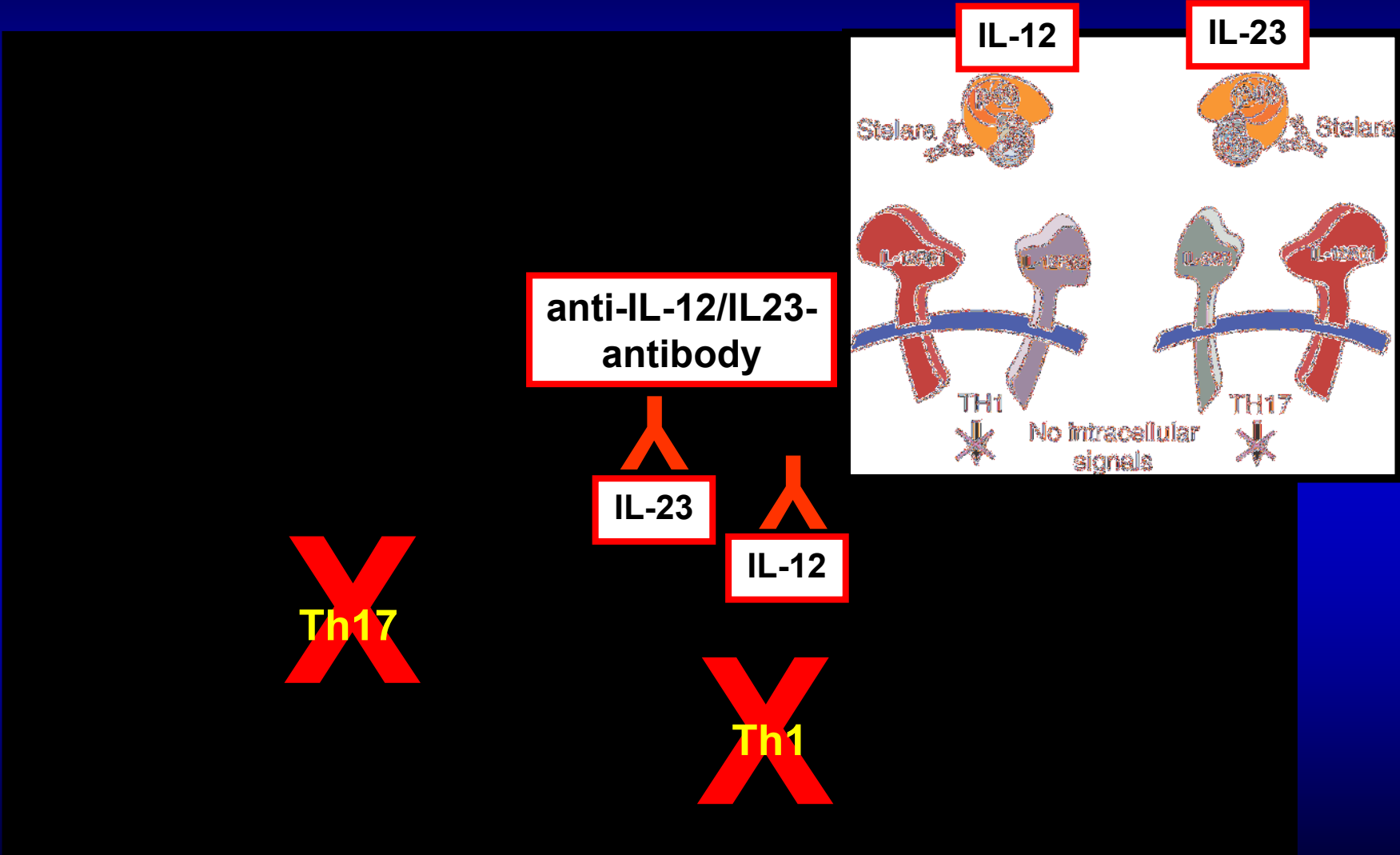
Immun-suppressiva

Kortikosteroide

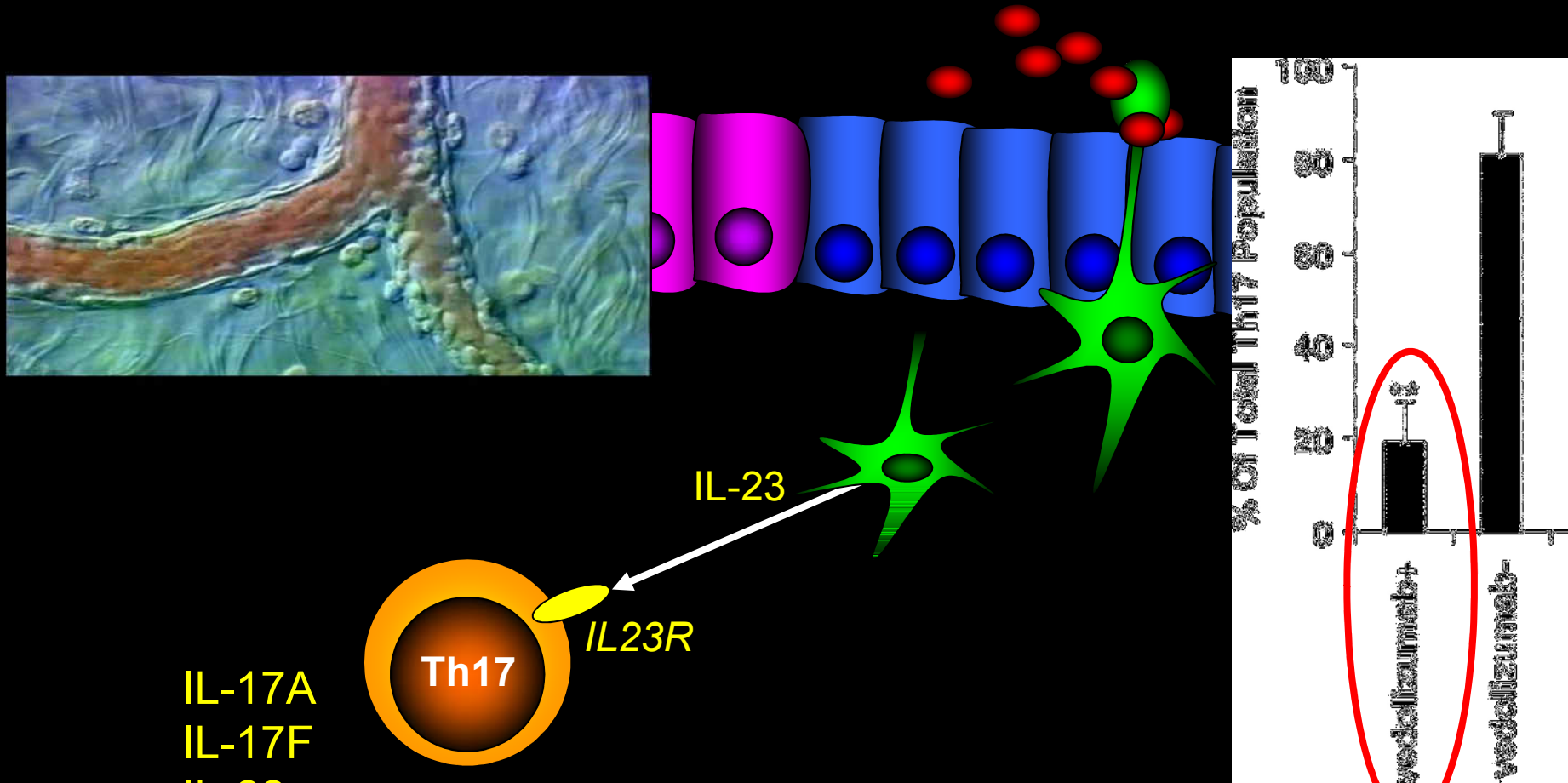
5-ASA



# Ustekinumab inhibits via IL-12 Th1 cells and via IL-23 Th17 cells



# Vedolizumab inhibits Th17 cells

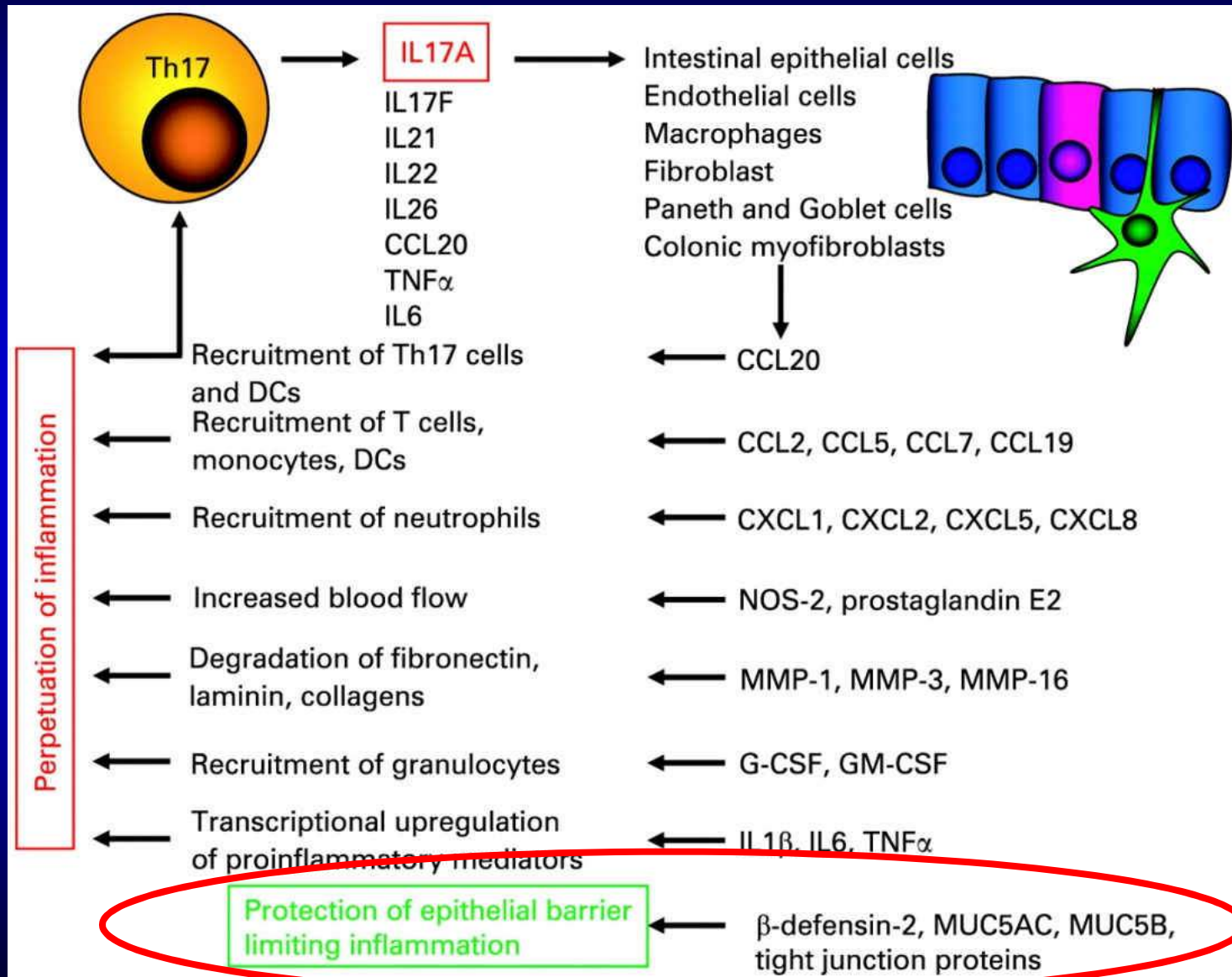


IL-17A  
 IL-17F  
 IL-22  
 IL-26  
 CCL20



Soler D et al. *J Pharmacol Exp Ther* 2009;330(3):864–875.  
 Brand S et al. *J Cell Biochem* 2006;97:709-23.  
 Brand S et al. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G827-38.  
 Dambacher J ... Brand S. *Gut* 2009;58:1207-17.

# But: Th17 cells have also protective effects!



Brand S. *Gut* 2009;58:1152-67.

## **Summary (2): Safety of peri-operative immunosuppression**

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- **Avoid high-dose steroids!**
- **There might be a slight increase of postoperative complications with anti-TNF agents; however, the effect is likely biased due to disease severity and co-medication**



# Immunosuppression and Surgery in Crohn's Disease

- Surgery in Crohn's disease
- Safety of peri-operative immunosuppression
- **Efficacy of immunosuppression preventing postsurgical recurrence of Crohn's disease**
- Role of biomarkers predicting the postsurgical recurrence of Crohn's disease

# Summary of postoperative randomized controlled trials in Crohn's disease

Postop Prevention RCTs	Clinical Recurrence	Endoscopic recurrence
Placebo	25% – 77%	53% - 79%
5 ASA	24% - 58%	63% - 66%
Budesonide	19% - 32%	52% - 57%
Nitroimidazole	7% - 8%	52% - 54%
AZA/6MP	34% – 50%	42 – 44%



# Endoscopic recurrence rates under Anti-TNF

<b>PO- Endo Recur</b>	<b>antiTNF</b>	<b>Control</b>
Sorrentino <sup>1</sup> (MTX/IFX v 5ASA 2yr)	0%	100% (5ASA)
Regueiro <sup>2</sup> (IFX vs PBO RCT 1 yr)	9%	85% (PBO)
Yoshida <sup>3</sup> (IFX vs PBO Open 1 yr)	21%	81% (5ASA)
Armuzzi <sup>8</sup> (IFX vs AZA Open 1 yr)	9%	40% (AZA)
Fernandez-Blanco <sup>4</sup> (ADA)	10%	N/A
Papamichael <sup>5</sup> (ADA 6m)	0%	N/A
Savarino <sup>6</sup> (ADA 3yr)	0%	N/A
Aguas <sup>7</sup> (ADA 1 yr)	21%	N/A
De Cruz <sup>9</sup> (ADA vs AZA 6mos)	6%	38% (AZA)
Savarino <sup>10</sup> (ADA vs AZA vs 5ASA 2 yrs)	6%	65% (AZA), 83%(5ASA)

# Infliximab in postoperative Crohn's disease (PREVENT study)

## Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection



Miguel Regueiro,<sup>1</sup> Brian G. Feagan,<sup>2</sup> Bin Zou,<sup>3</sup> Jewel Johanns,<sup>3</sup> Marion A. Blank,<sup>4</sup> Marc Chevrier,<sup>3</sup> Scott Plevy,<sup>3</sup> John Popp,<sup>4</sup> Freddy J. Cornillie,<sup>5</sup> Milan Lukas,<sup>6</sup> Silvio Danese,<sup>7</sup> Paolo Gionchetti,<sup>8</sup> Stephen B. Hanauer,<sup>9</sup> Walter Reinisch,<sup>10,11</sup> William J. Sandborn,<sup>12</sup> Dario Sorrentino,<sup>13,14</sup> and Paul Rutgeerts,<sup>15</sup> for the PREVENT Study Group

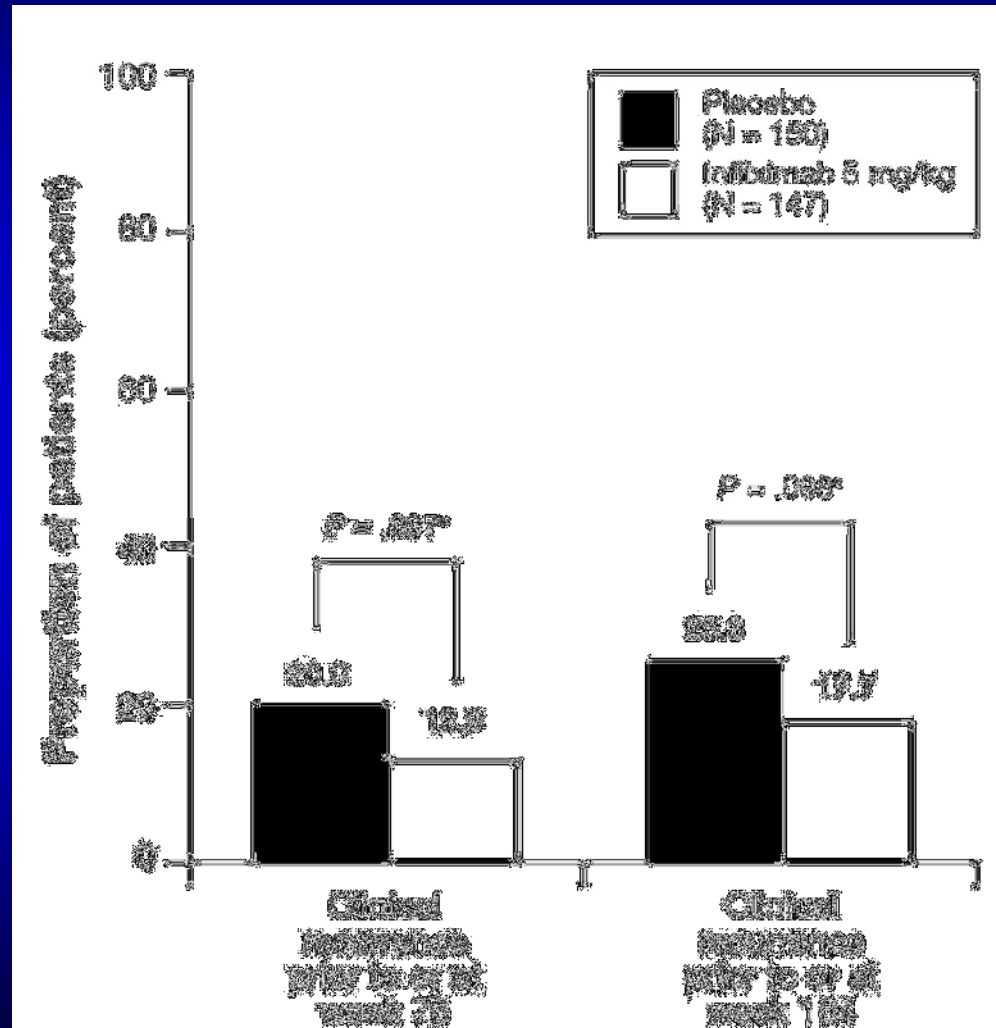
CLINICAL AT

<sup>1</sup>Inflammatory Bowel Disease Center and Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; <sup>2</sup>Robarts Research Institute, University of Western Ontario, London, Ontario, Canada; <sup>3</sup>Janssen Research & Development, LLC, Spring House, Pennsylvania; <sup>4</sup>Janssen Scientific Affairs, LLC, Horsham, Pennsylvania; <sup>5</sup>MSD International, Luzern, Switzerland; <sup>6</sup>Charles University, Prague, Czech Republic; <sup>7</sup>Istituto Clinico Humanitas, Milan, Italy; <sup>8</sup>S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; <sup>9</sup>Feinberg School of Medicine, Northwestern University, Chicago, Illinois; <sup>10</sup>McMaster University, Hamilton, Ontario, Canada; <sup>11</sup>Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; <sup>12</sup>University of California San Diego, La Jolla, California; <sup>13</sup>Virginia Tech, Carilion School of Medicine, Roanoke, Virginia; <sup>14</sup>Department of Clinical and Experimental Pathology, University of Udine School of Medicine, Udine, Italy; and <sup>15</sup>University Hospital Gasthuisberg, Leuven, Belgium

Regueiro M et al. *Gastroenterology* 2016;150:1568-78.



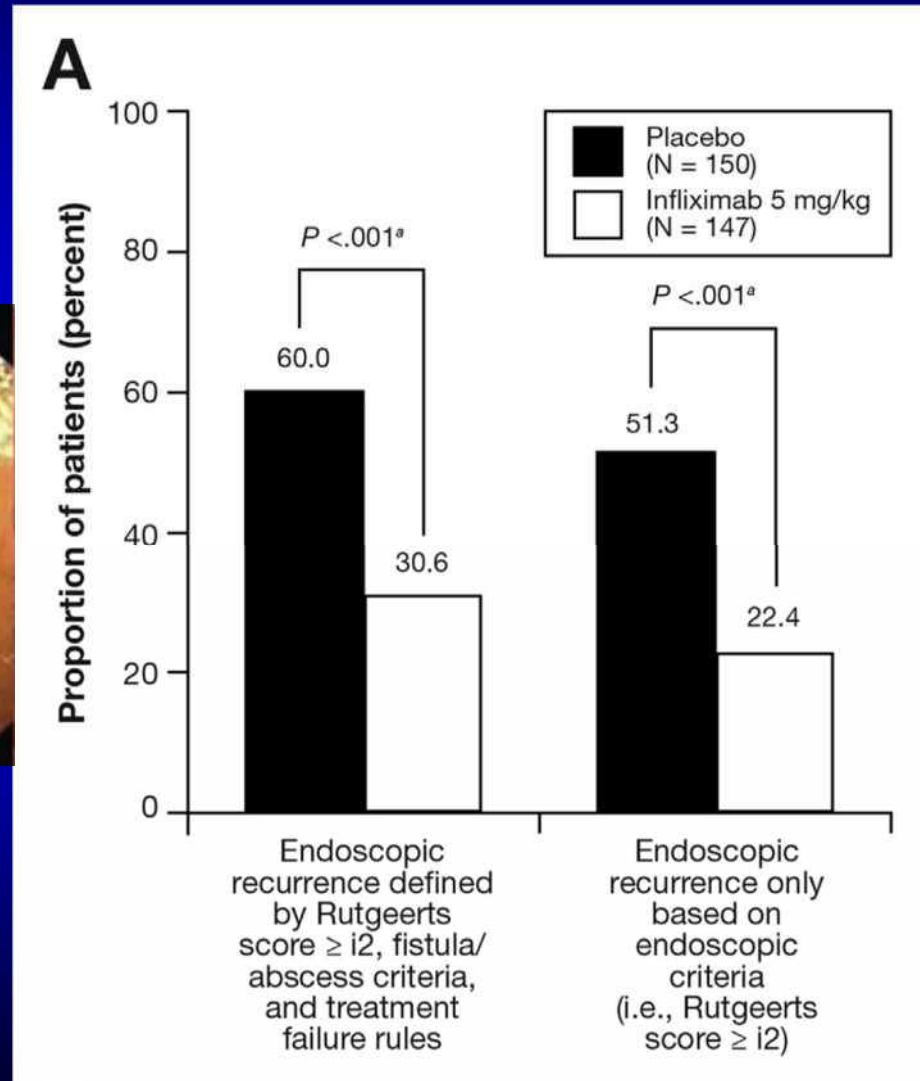
# Infliximab: No difference in clinical postoperative recurrence



Regueiro M et al. *Gastroenterology* 2016;150:1568-78.

# Infliximab significantly reduces endoscopic recurrence of postoperative Crohn's disease

No recurrence



Recurrence



# Safety of postoperative infliximab



Infliximab (dose increase)

Variable	Infliximab, 5 mg/kg <sup>a,b</sup>		Infliximab (dose increase)		All infliximab <sup>d</sup> (N = 170)
	Placebo <sup>a</sup> (N = 146)	Infliximab, 5 mg/kg <sup>a,b</sup> (N = 145)	Placebo/infliximab, 5 mg/kg <sup>c</sup> (n = 25)	Infliximab 5 mg/kg/infliximab, 10 mg/kg <sup>c</sup> (n = 9)	
Mean duration of follow-up, wk	85.4	85.7	50.6	39.4	82.6
Mean duration of treatment, wk	75.9	74.3	32.4	13.9	68.9
Patients with >1 adverse events, n (%)	132 (90.4)	133 (91.7)	19 (76.0)	7 (77.8)	152 (89.4)
Patients with ≥1 serious adverse events, n (%)	32 (21.9)	28 (19.3)	3 (12.0)	2 (22.2)	32 (18.8)
Patients who discontinued study agent because of ≥1 adverse events, n (%)	13 (8.9)	35 (24.1)	10 (40.0)	5 (55.6)	50 (29.4)
Patients who died, n (%)	1 (0.7)	0	0	0	0
Patients with 1 or more malignancies, <sup>e</sup> n (%)	2 (1.4)	0	0	0	0
Patients with ≥1 infections, n (%)	85 (58.2)	84 (57.9)	8 (32.0)	4 (44.4)	93 (54.7)
Patients with >1 serious infections, n (%)	9 (6.2)	7 (4.8)	1 (4.0)	1 (11.1)	9 (5.3)
Patients with ≥1 infusion reaction, <sup>f</sup> n (%)	12 (8.2)	26 (17.9)	7 (28.0)	1 (11.1)	33 (19.4)

# “Active“ or standard (step-up) therapy?: POCER Study

Articles



## Crohn's disease management after intestinal resection: a randomised trial

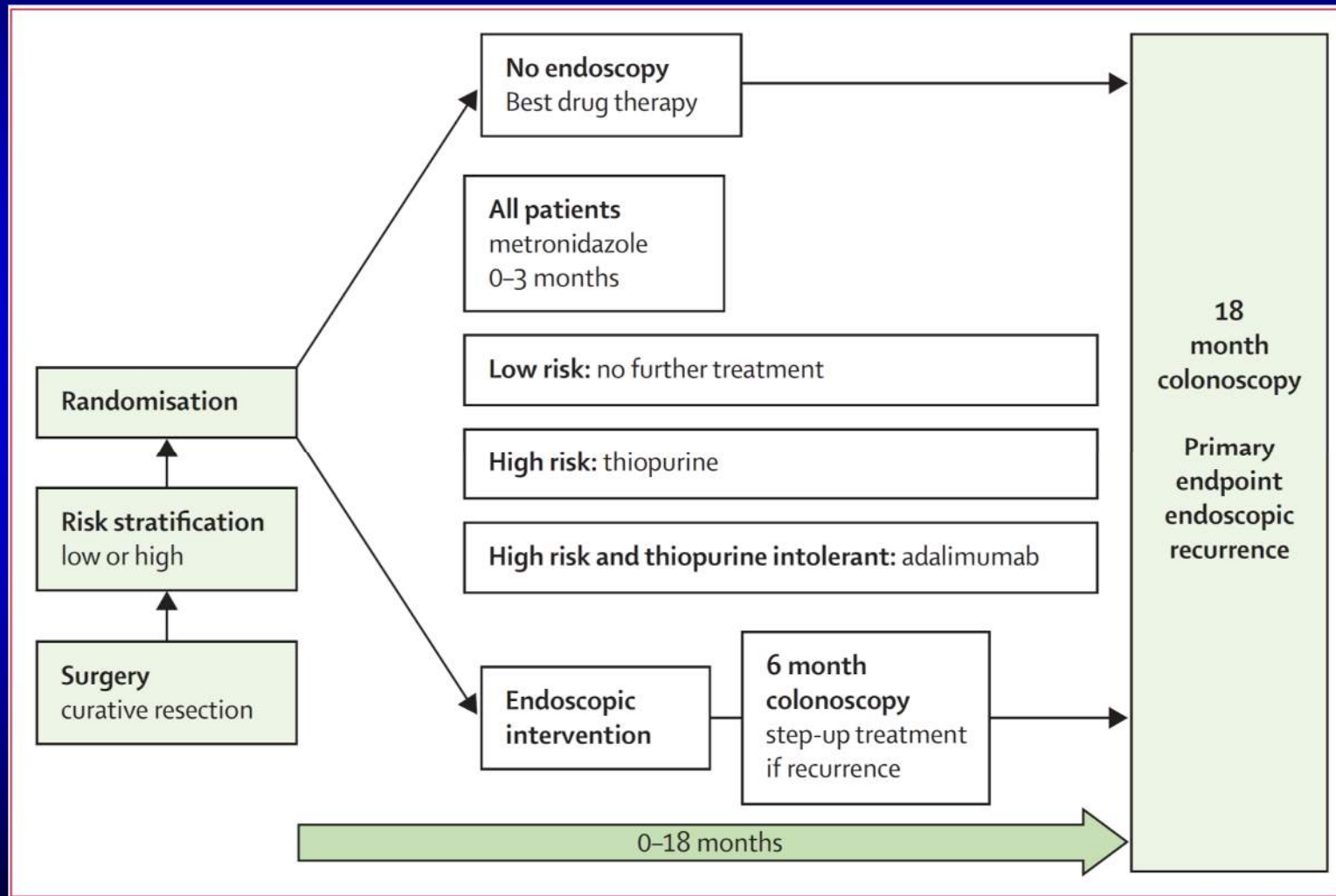


*Peter De Cruz, Michael A Kamm, Amy L Hamilton, Kathryn J Ritchie, Efrosinia O Krejany, Alexandra Gorelik, Danny Liew, Lani Prideaux, Ian C Lawrance, Jane M Andrews, Peter A Bampton, Peter R Gibson, Miles Sparrow, Rupert W Leong, Timothy H Florin, Richard B Geary, Graham Radford-Smith, Finlay A Macrae, Henry Debinski, Warwick Selby, Ian Kronborg, Michael J Johnston, Rodney Woods, P Ross Elliott, Sally J Bell, Steven J Brown, William R Connell, Paul V Desmond*

De Cruz P et al. *Lancet* 2015;385:1406-17.



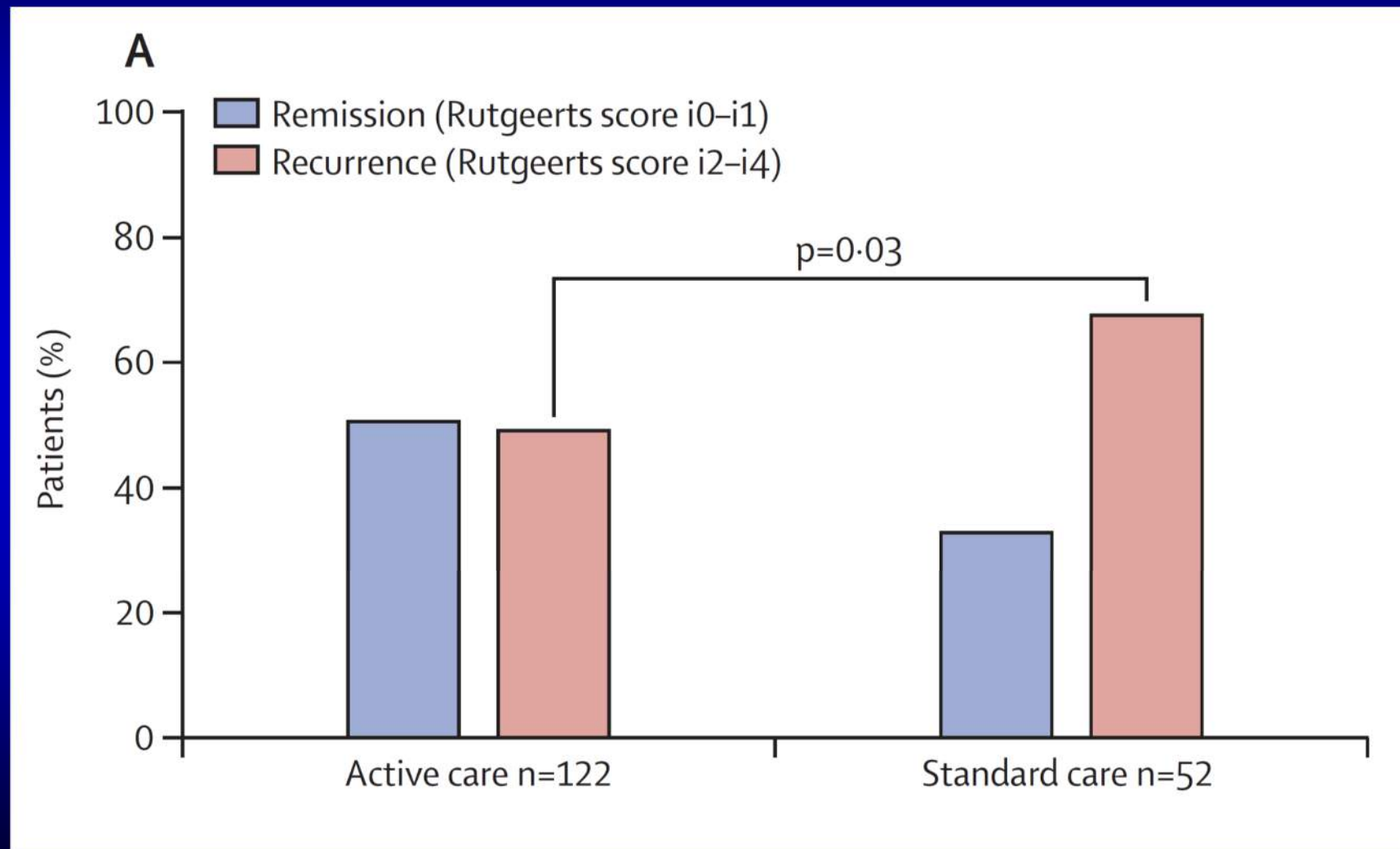
# POCER Study



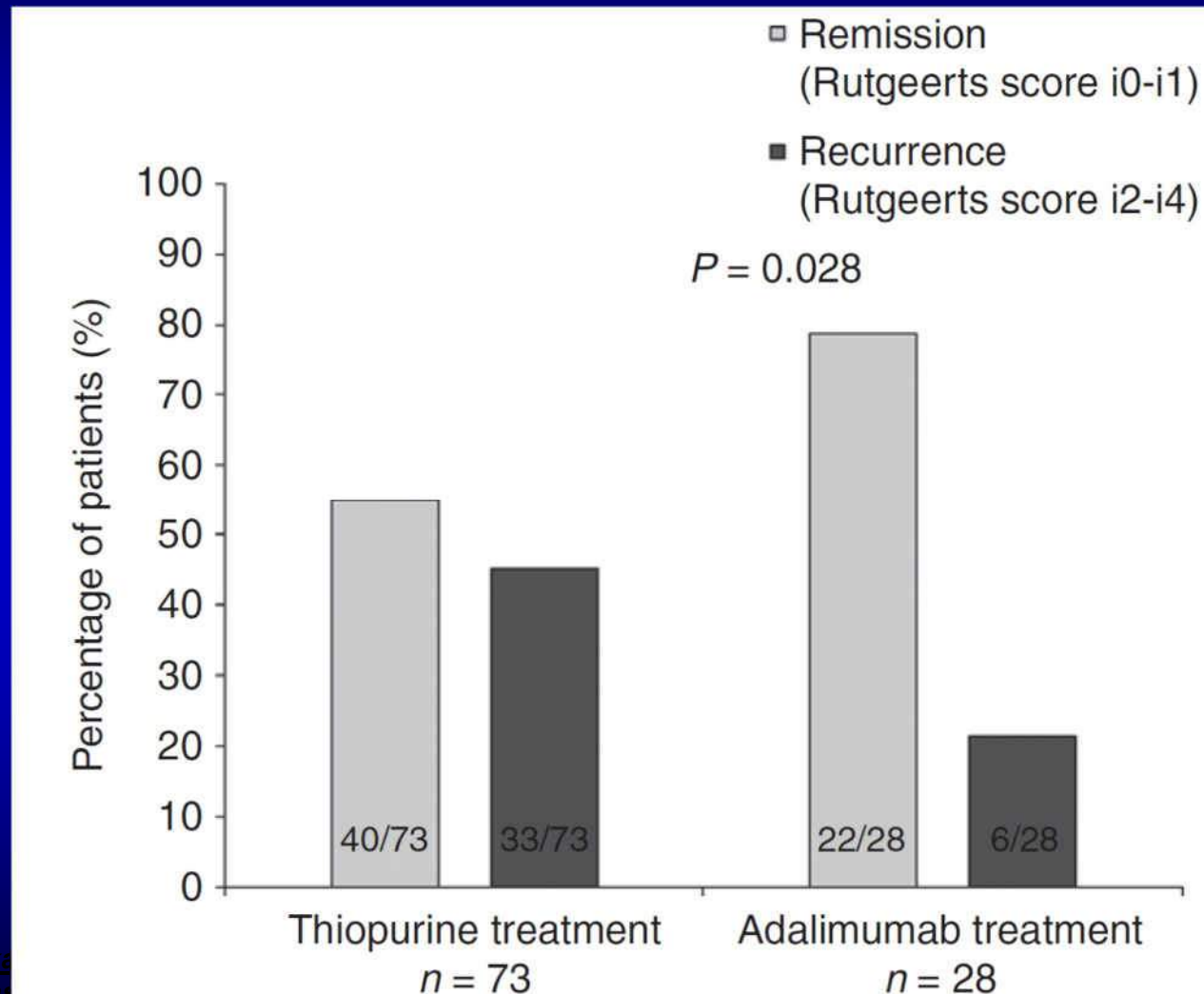
De Cruz P et al. *Lancet* 2015;385:1406-17.



# Lower recurrence rate in endoscopically, “active“ care group compared to standard care



# Adalimumab is more effective than azathioprine for preventing postoperative recurrence of CD



Taka  
Gas

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De Cruz P et al. *Aliment Pharmacol Ther* 2015;42:867-79.

## **Summary (3): Efficacy of immunosuppression**

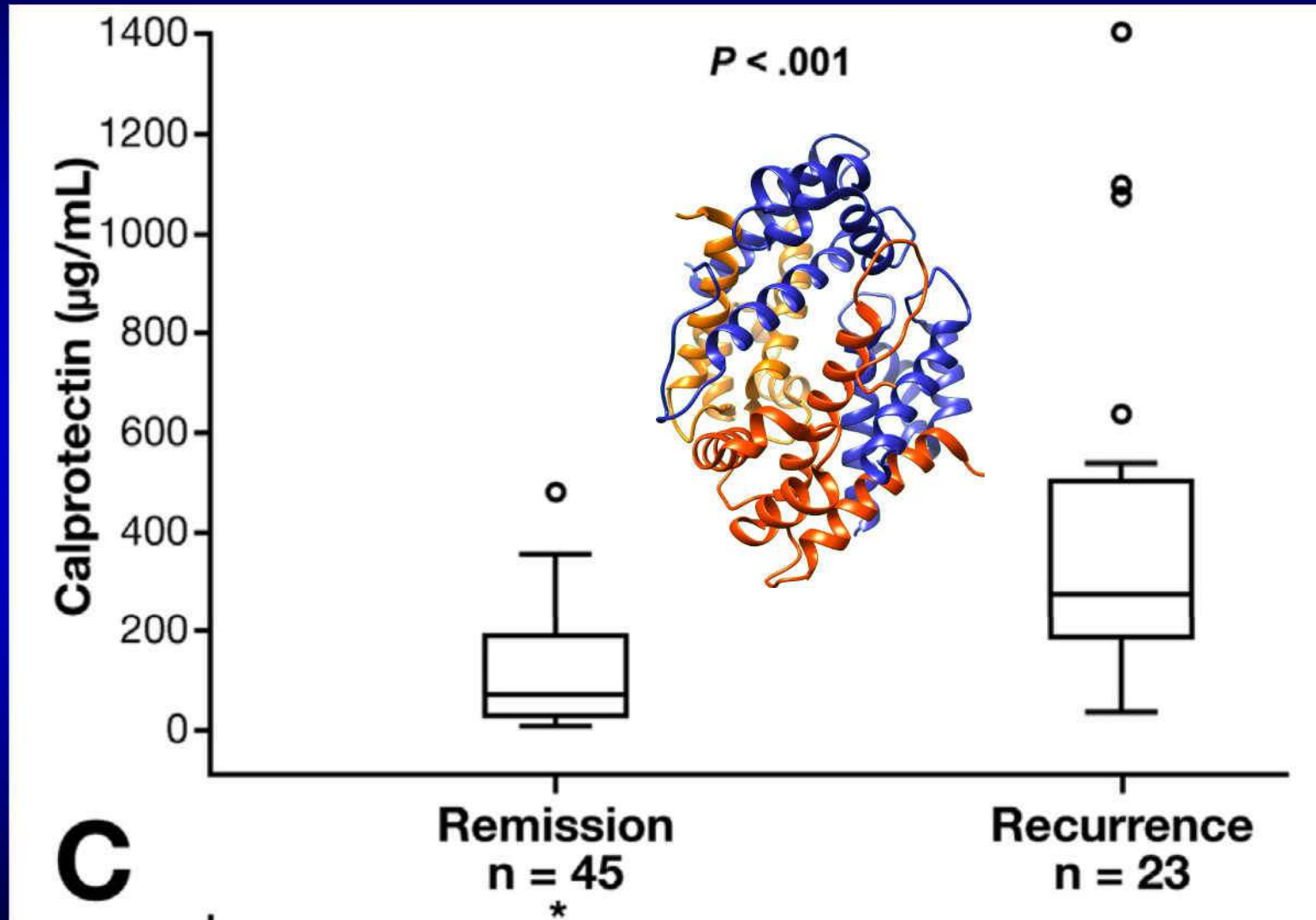
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- **Infliximab and adalimumab prevent endoscopic recurrence in CD**
- **“Active” endoscopic control 6 (- 12) months after surgery and treatment adjustments recommended**

# Immunosuppression and Surgery in Crohn's Disease

- Surgery in Crohn's disease
- Safety of peri-operative immunosuppression
- Efficacy of immunosuppression preventing postsurgical recurrence of Crohn's disease
- **Role of biomarkers predicting the postsurgical recurrence of Crohn's disease**

# Role of calprotectin in postoperative CD



Wright EK et al. *Gastroenterology* 2015;148:938-947.