

# Anti-TNF and Immunomodulators in the Perioperative Setting



Steven Mills, MD

Professor of Clinical Surgery  
Colon and Rectal Surgery  
University of California, Irvine



# Disclosures

**Ethicon Endosurgery – Consultant**  
**Medtronics – Consultant**



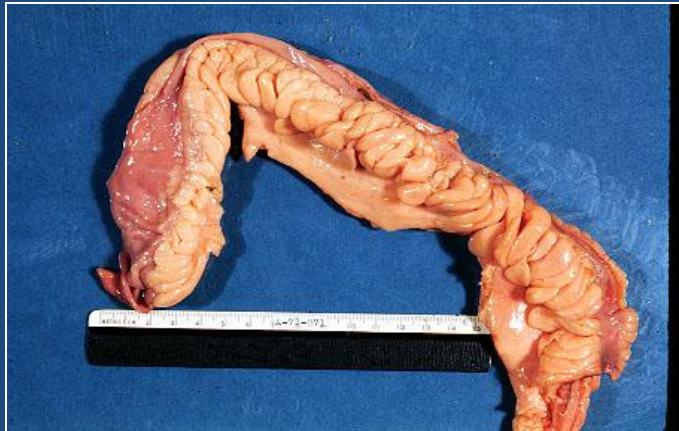
# Surgery for Ulcerative Colitis

- Refractory colitis
- Medication side-effects
- Clinical deterioration during medical therapy
- Dysplasia
- Emergency
  - Toxic Megacolon
  - Perforation
  - Severe hemorrhage



# Crohn's Disease

- **Most commonly for complications**
  - Obstruction (stricture)
  - Fistula
  - Perforation/Abscess



# Inflammatory Bowel Disease

- Patients with IBD generally treated with medications
- Generally speaking, sicker patients are treated more aggressively
  - High dose steroids
  - Immunomodulators
  - Anti-TNF



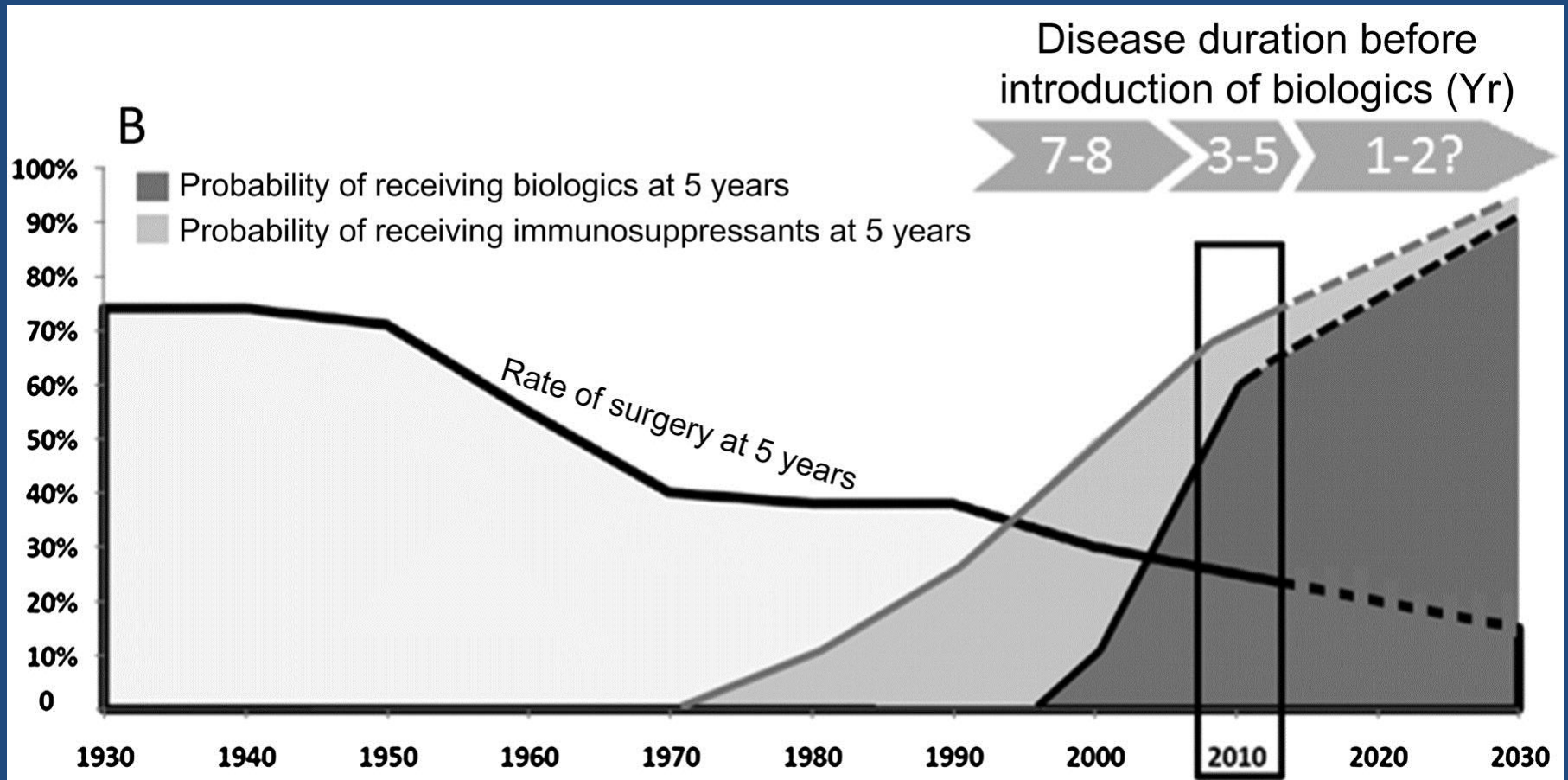
# Surgery and IBD

- There is often a “ramp up” of therapy just before surgery
- These medications are immune suppressants
- Immune system necessary to heal after surgery
  
- What are the risks of surgery in the setting of Immunomodulators and Anti-TNF therapy?





# Rates of Surgery with Crohn's



Bouguen G , and Peyrin-Biroulet L Gut 2011;60:1178-1181

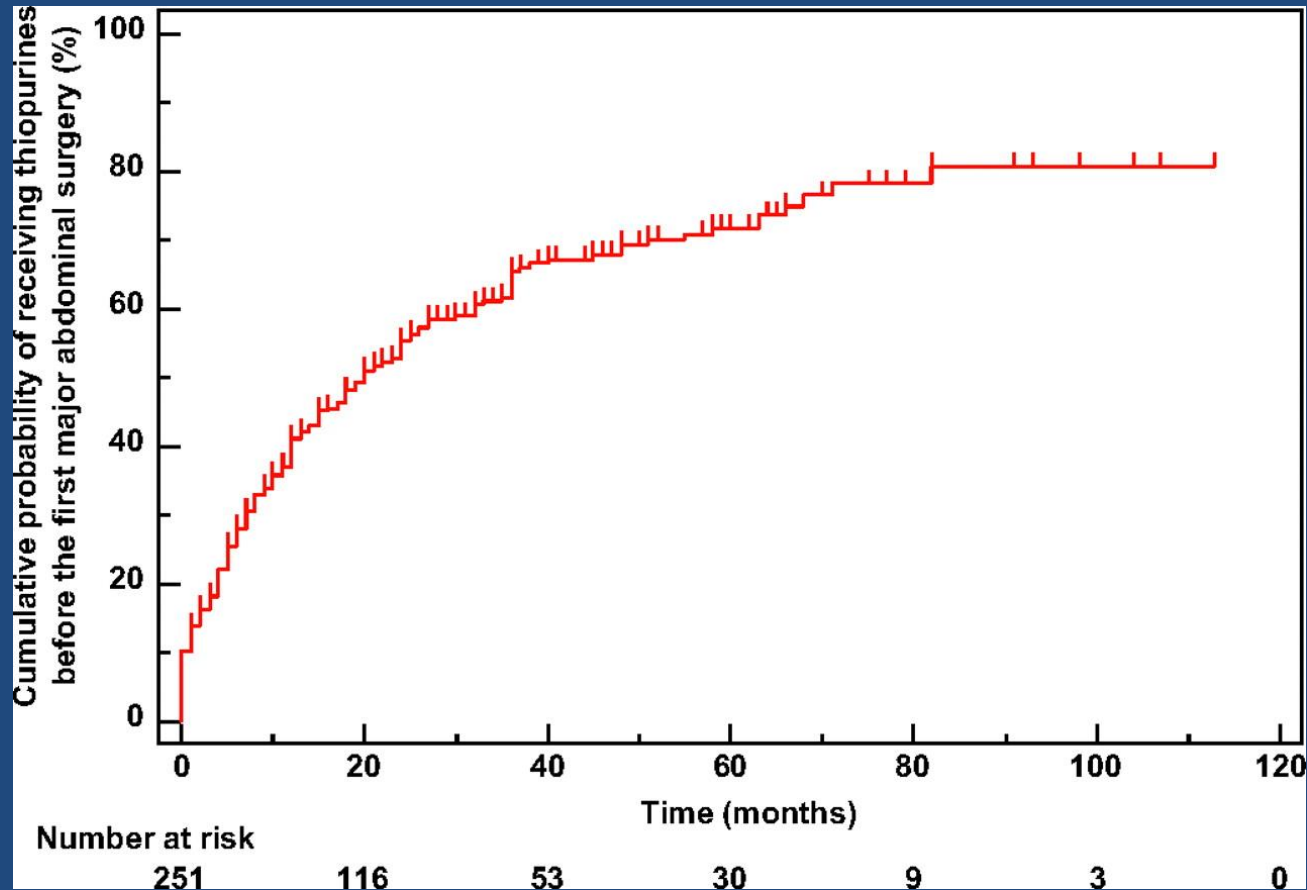
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# Immunomodulators prior to Surgery

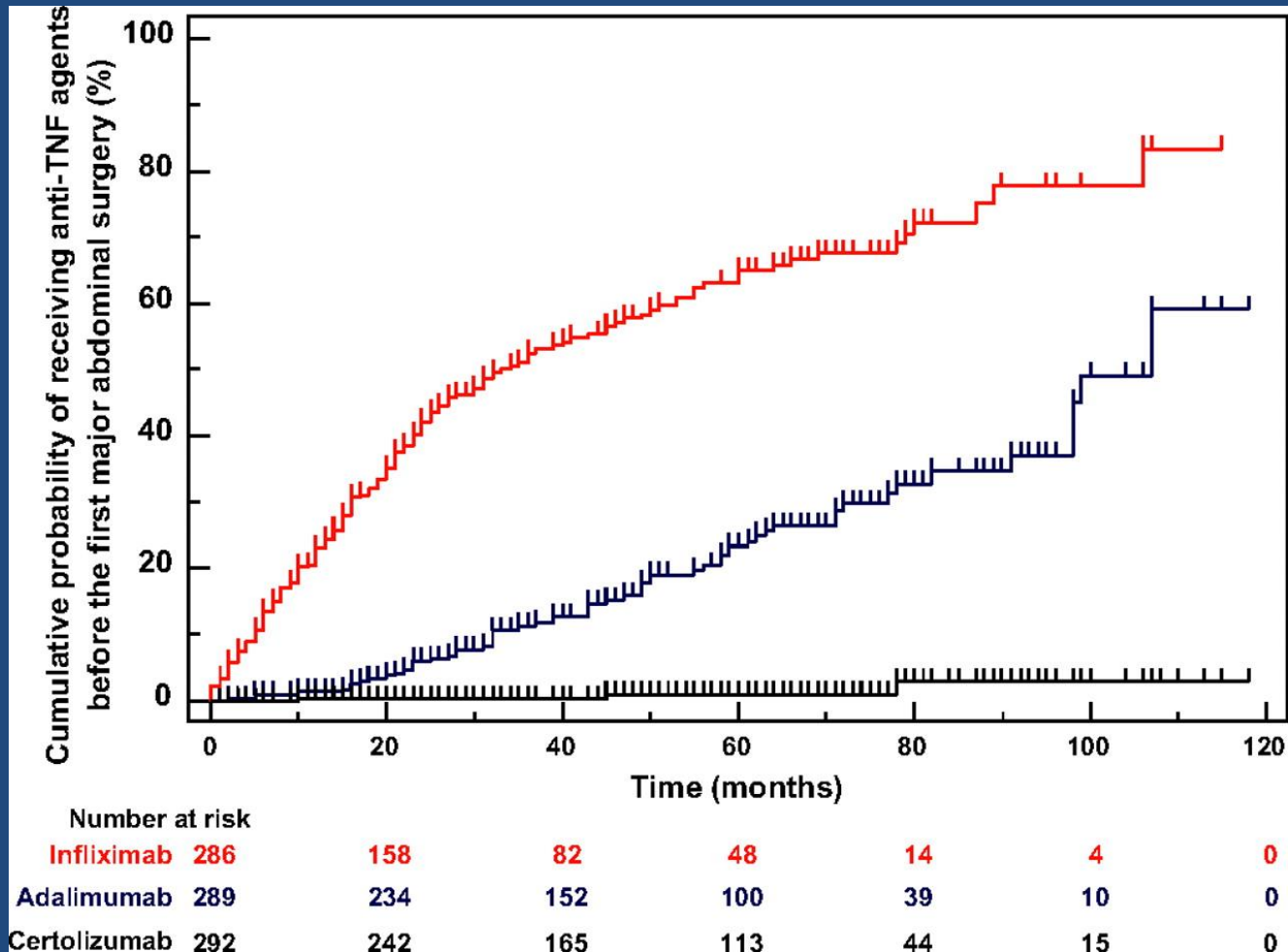


Peyrin-Biroulet L et al. Gut 2011;60:930-936





# Anti-TNF Prior to Surgery



Peyrin-Biroulet L et al. Gut 2011;60:930-936

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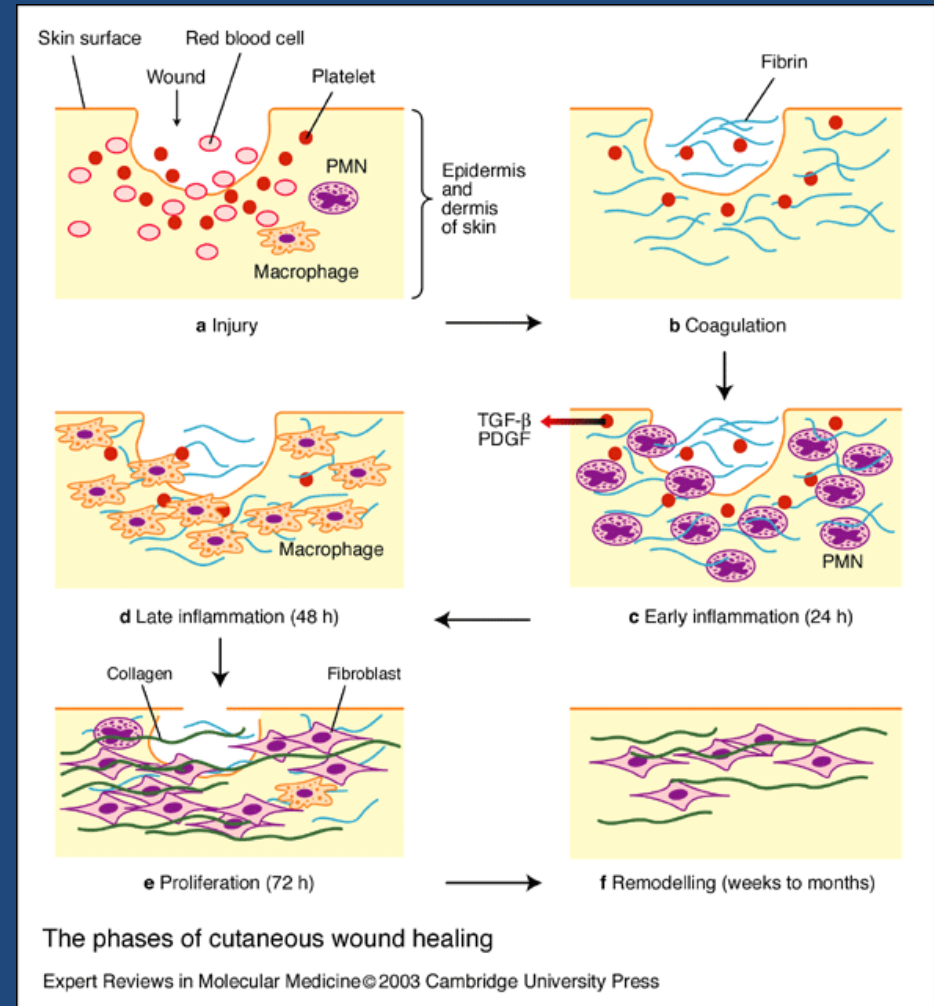
# Anti-TNF Prior to Surgery

- **Most IBD patients undergoing surgery are taking Immunomodulators and/or Anti-TNF**
- **Is it safe to operate?**



# Postoperative Healing

- Immune system is required for wound healing
- Inflammatory response
- Collagen



# Risks of Surgery

- **Wound Infections**
  - Deep or superficial
- **Anastomotic leak**
- **Incisional hernia**
- **Sepsis**
- **VTE**



# Causality?

- **Difficult to assign blame for complications in IBD cases. Too many confounders:**
  - **Severity of IBD**
  - **Malnutrition**
  - **Concomitant therapies**
  - **Time from last dose**
  - **Emergent v elective surgery**
  - **Different Surgeons and procedures**



# Emergency Setting

- **Can't turn off the medications so no choice but to operate**
- **Counsel patients on higher risks**





# Literature

- **Confusing data**
- **Variable study designs and heterogeneous data**
- **Differing endpoints**
- **Meta-analyses not clear**



# Surgery in IBD with Anti-TNF

Table III. Post-operative side effects in patients with IBD who took IFX before operation and those who did not

Side effects	OR/RR combined meta-analysis	CI	Value of <i>p</i> for OR/RR	Value of <i>p</i> for heterogeneity	Publication bias
Anastomotic leak	OR: 1.71	1.02-2.87	0.05	0.07	No
Pelvic abscess	OR: 1.09	0.17-6.93	0.93	0.15	NA
Pouch-related complication	OR: 2.06	1.16-3.66	0.023	0.054	NA
Wound infection	OR: 1.96	0.84-4.62	0.19	0.29	NA
Other infections	OR: 1.53	0.41-5.67	0.53	0.005	No
	RR: 1.06	0.16-6.87	0.95	0.48	NA
Small intestinal obstruction	OR: 0.44	0.12-1.64	0.22	0.83	NA
GI complications	RR: 4.17	0.48-35.94	0.19	0.96	NA
Sepsis	OR: 1.85	1.15-2.97	0.02	0.054	No
Postoperative haemorrhage	OR: 2.24	0.42-11.85	0.34	0.67	NA
Thrombotic event	4.56	1.12-18.53	0.03	0.94	NA
Ileus	OR: 0.95	0.19-4.68	0.95	0.42	NA
Wound failure	1.27	0.15-10.55	0.82	0.78	NA
Intra-abdominal abscess	1.85	0.79-4.3	0.16	0.5	NA

NA – not applicable

Ehteshami-Afshar, et al., *Arch Med Sci*, 2011



# Perioperative Anti-TNF for CD

First Author	Type of surgery	N	Postoperative complications	Increased postop complications
<b>Tay</b>	Segmental resection with primary anastomosis or strictureplasty	100	11%	<b>No</b>
<b>Marchal</b>	Intestinal resection (symptomatic stenosis or refractory fistulas and/or abscesses, or intractable disease)	79	24%	<b>No</b>
<b>Colombel</b>	Abdominal surgery	270	23%	<b>No</b>
<b>Appau</b>	ileocolonic resection	389	71.7%	<b>Yes</b>
<b>Indar</b>	Intestinal surgy (Ileocecal resection and small intestine resection++)	112	33%	<b>No</b>
<b>Nasir</b>	surgery which included a suture or staple line	370	29%	<b>No</b>
<b>Canedo</b>	Abdominal surgery	225	ND	<b>No</b>
<b>Kasperek</b>	Abdominal surgery	96	59%	<b>No</b>

After Kopylov et al. IBD 2012 Slide from Dr. Regueiro, Pittsburgh



# Perioperative Anti-TNF for UC

Author	Type of Surgery	N	Postoperative Complications	Increased Postop Complications
Selvasekar	IPAA	301 47 IFX	62%	Yes
Schluender	IPAA	134 17 IFX	28% 37%IFX v 27%	No
Mor	IPAA	523 85 IFX	OR IFX 3.5 total OR IFX 13.8 infxn	Yes
Ferrante	IPAA	141 22 IFX ↑	22% overall Steroids/1 step J	No
Norgard	Most stoma	1226 199 IFX	OR IFX 0.5	No
Yang	Most IPAA	5 studies	OR IFX 1.8	Yes

Slide from Dr. Regueiro, Pittsburgh



# Meta-analysis for UC

- **5 Studies and 706 patients**
- **Infliximab use preoperatively increases the risk of short-term post operative complications**

Yang, et al., *Aliment Pharmacol Ther*, 2010



# Infliximab and Surgery for UC

- **151 patients**
  - 112 IPAA
- **Overall complications 28%**
  - 37% Infliximab v 27% without (NS)
- **But, for 5 patients with infliximab and cyclosporin, 80% complications**

Schluender, et al. Dis Colon Rectum 2007





# Infliximab and Surgery for UC

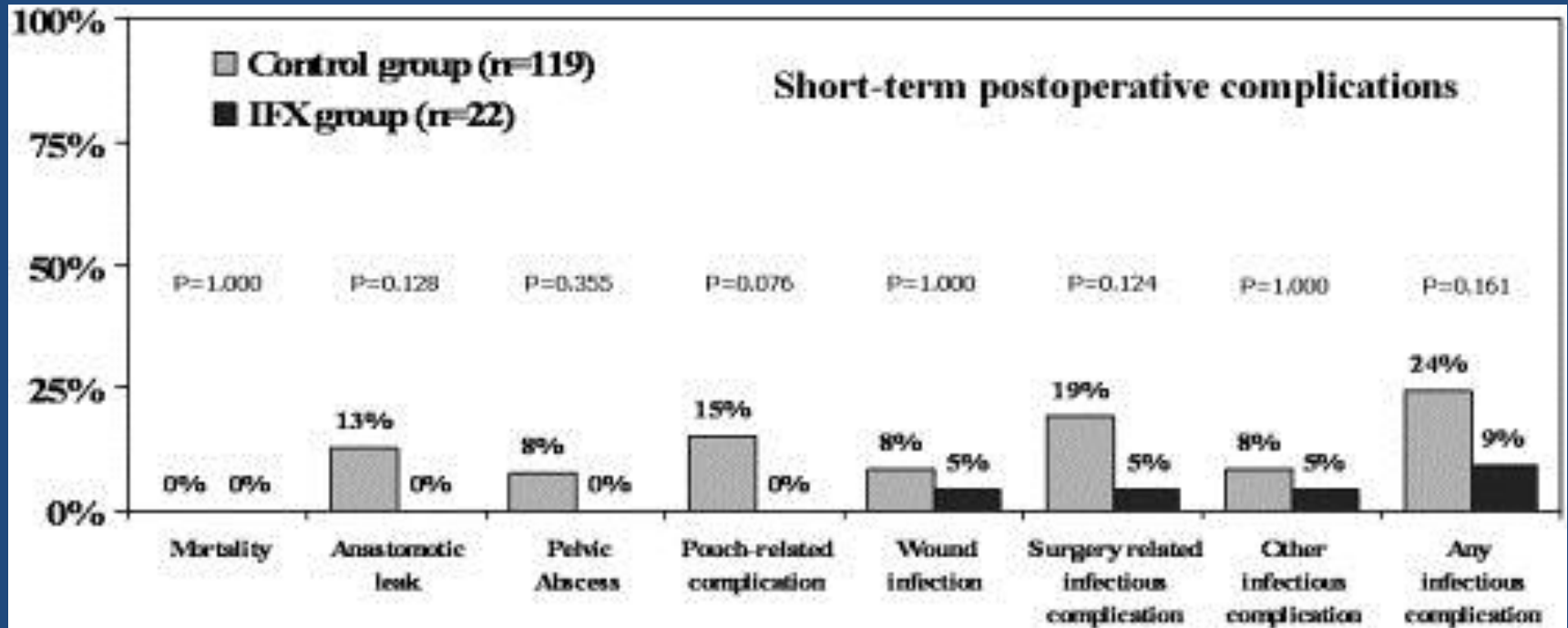
- **523 patients**
  - All underwent IPAA
- **Odds ratios for complications higher in infliximab group:**
  - OR 3.54 for early complication
  - OR 13.8 for sepsis
  - OR 2.19 for late complication
  - OR 2.07 for requiring 3-stage operation

Mor, et al. Dis Colon Rectum 2008



# Infliximab and Surgery for UC

Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis



Inflammatory Bowel Diseases

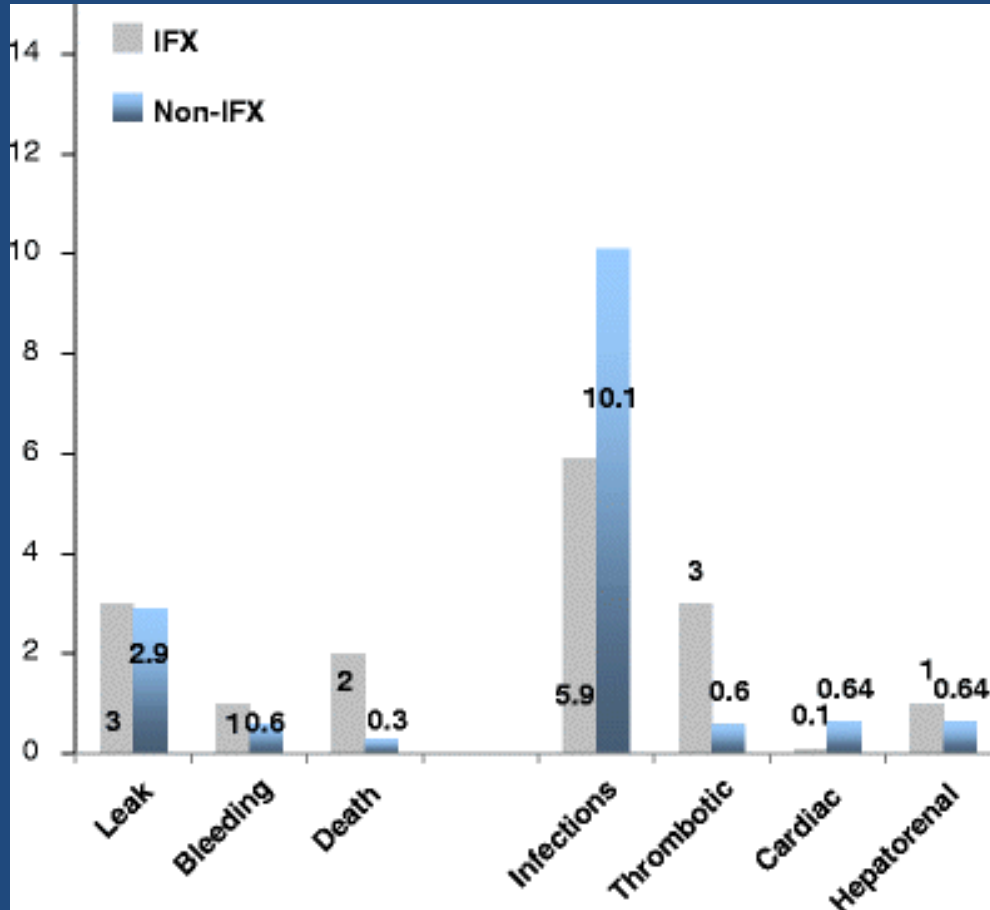
Volume 15, Issue 7, pages 1062-1070, 22 JAN 2009 DOI: 10.1002/ibd.20863

<http://onlinelibrary.wiley.com/doi/10.1002/ibd.20863/full#fig1>

Ferrante, et al. Inflamm Bowel Dis, 2009



# Infliximab and Surgery for UC/CD

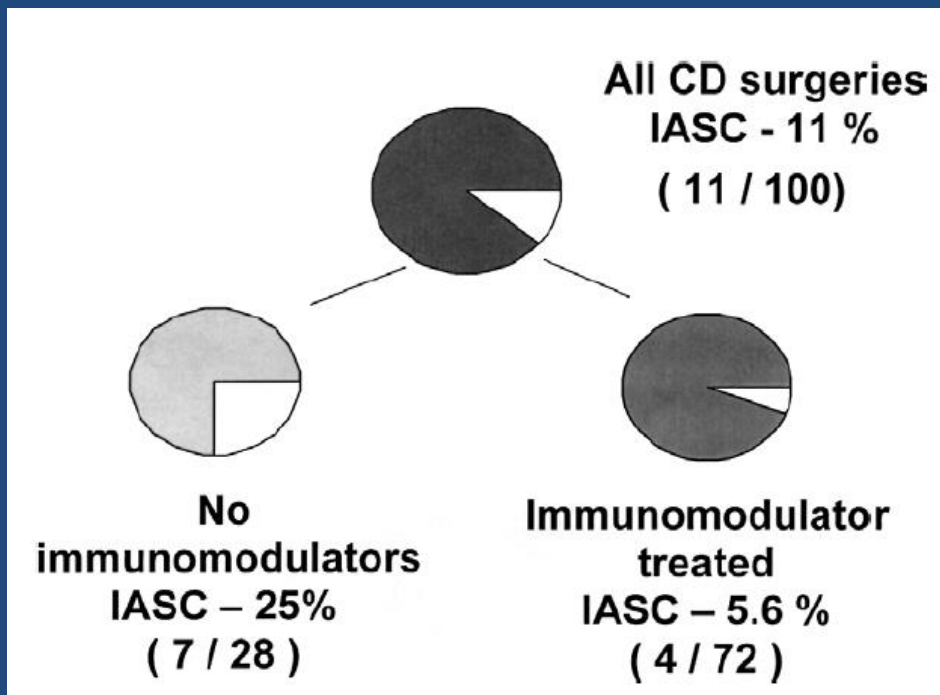


- Perioperative infliximab in patients with UC/CD is NOT associated with increased rate of postoperative complications

Kunitake, et al. J Gastrointest Surg, 2008



# Immunomodulators and Surgery for Crohn's Disease



Tay, et al. Surgery, 2003

Improved perioperative outcomes in Crohn's Disease for patients receiving immunomodulators

- 11% complications
  - 5% on IMM
  - 25% not on IMM



# Infliximab within 3 Months of Surgery for Crohn's

**Table 5** Post Operative Outcomes

	Complication	Non IFX group (1998–2007) <i>n</i> =329 (%)	IFX group <i>n</i> =60 (%)	Pre-IFX group (1991 to 1997) <i>n</i> =69 (%)	Odd's ratio (95%CI)	<i>p</i> -Value
30-Day complications	Readmission rate	9.4	20.0	2.9	2.40(1.15,5)* 8.37(1.79,39.15)†	0.019 <sup>a</sup> 0.007 <sup>b</sup>
	Sepsis	9.7	20.0	5.8	2.32(1.12, 4.82)* 4.06(1.23,13.37)†	0.024 <sup>a</sup> 0.021 <sup>b</sup>
	Intraabdominal abscess	4.3	10.0	4.3	2.50(0.92, 6.79)* 2.44(0.58,10.23)†	0.10 <sup>a</sup> 0.30 <sup>b</sup>
	Anastomotic leak	4.3	10.0	1.4		0.09 <sup>a</sup> 0.049 <sup>b</sup>
	Reoperation	3.0	8.3	0.0	2.9(0.95,8.81)*	0.06 <sup>a</sup> 0.02 <sup>b</sup>

<sup>a</sup>*p*: No IFX vs. IFX

<sup>b</sup>*p*: Pre-IFX vs. IFX

After Appau, et al. J Gastrointest Surgery, 2008



# Infliximab within 3 Months of Surgery for Crohn's

**Table 8** Multivariable Logistic Regression Model Results for 30-day Intraabdominal Abscess

Variable	Odds ratio(95% CI)	<i>p</i> -Value
IFX	5.78 (1.69–19.7)	0.005
6MP/AZA/MTX	0.41 (0.11–1.52)	0.18
Steroids	2.94 (0.63–13.6)	0.17
Comorbidity	0.30 (0.03–2.73)	0.29
Penetrating abscess	1.40 (0.55–3.57)	0.48
Diverting stoma	0.16 (0.02–1.25)	0.08

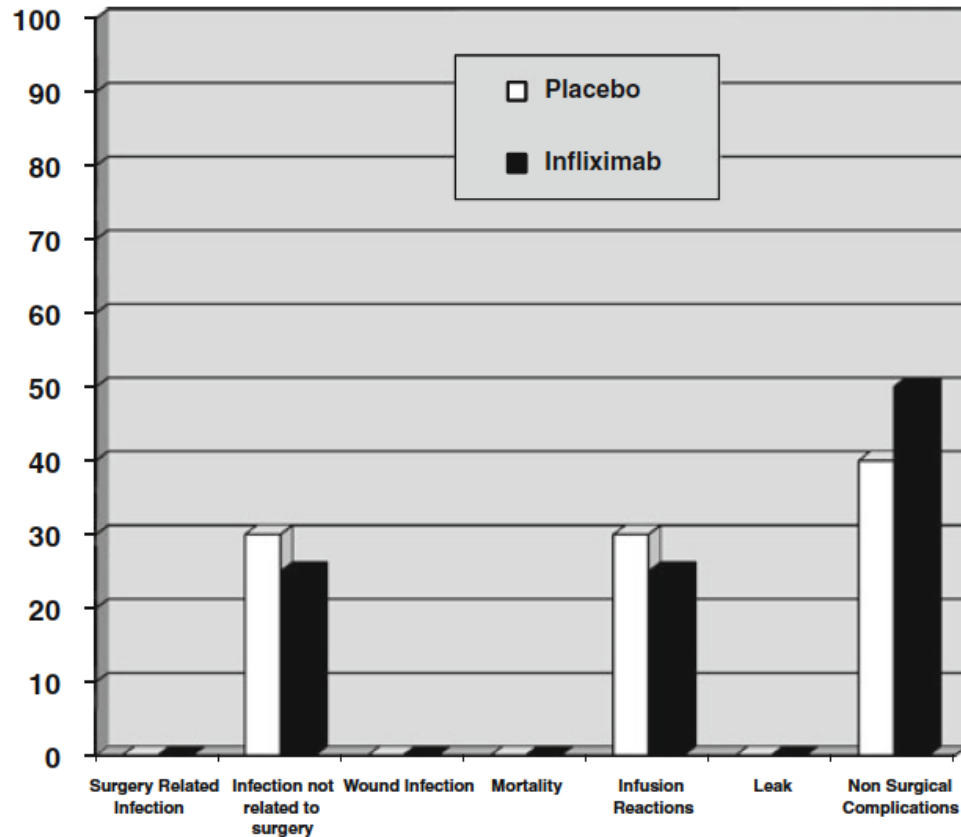
Parameter estimate and odds ratio relative to a 5-year difference.

Appau, et al. J Gastrointest Surgery, 2008





# Infliximab after Surgery for CD



**Fig. 1** Postoperative adverse events within 1 year of surgery. \*All comparisons nonsignificant with  $P > 0.05$

Postoperative  
infliximab is not  
associated with  
an increase in  
adverse events in  
Crohn's Disease

Regueiro, et al. Dig Dis Sci, 2011



# Perioperative Anti-TNF for IBD

## Is It Safe?

	Yes it is!	No way!
Anti-TNF before Crohn's surgery	7	1
Anti-TNF before Ulcerative Colitis surgery	3	2
Anti-TNF after Crohn's surgery	1	0



# My Conclusions

- **Perioperative anti-TNF probably safe in patients with UC and CD, though data mixed**
  - **Risks are likely related to severity of disease**
- **In essence, surgery should not be delayed due to medical management**
  - **Consider diversion or 3-stage operation**



