Abdominal surgery in the era of biologic therapy: What are the guidelines?

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Disclosures:
None

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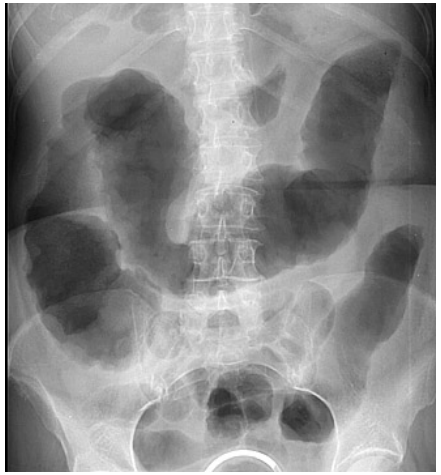
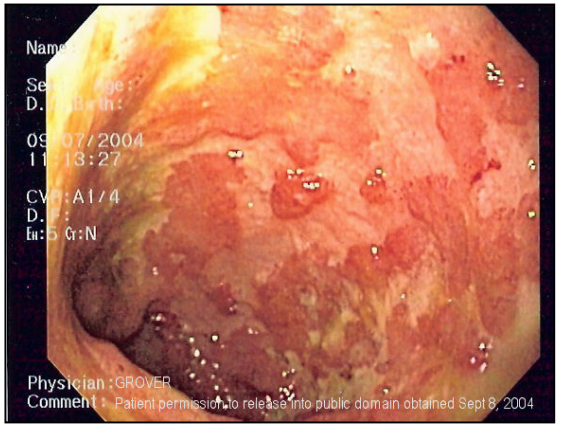
Surgery in Ulcerative Colitis

- Refractory colitis
- Clinical deterioration
- Medication intolerability
- Dysplasia
- Emergency

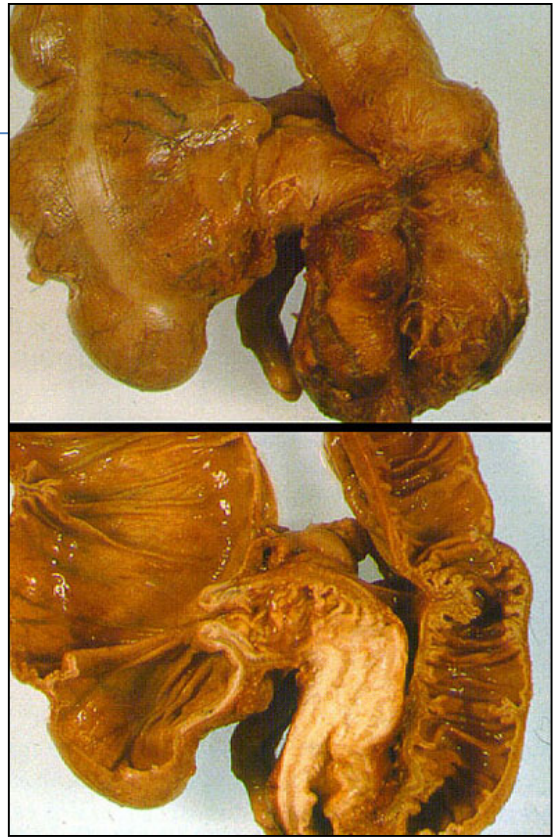


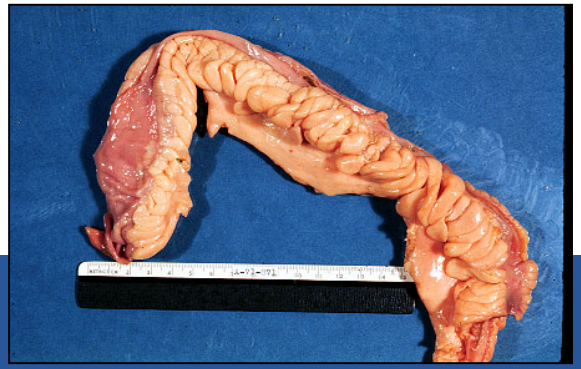


Surgery in Crohn's disease

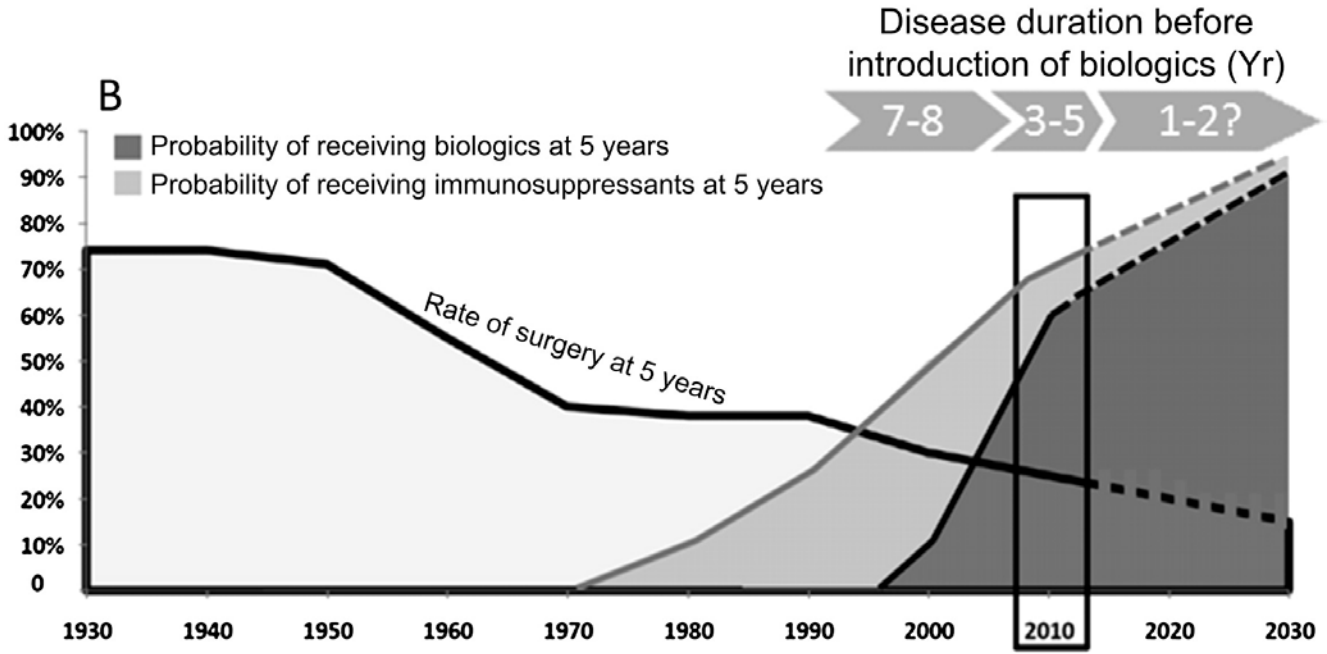
Commonly for complications

- Stricture
- Fistula
- Perforation and abscess





Surgery trends in the era of biologic therapy



1. Bouguen G, Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? *Gut* 2011;**60:**1178-1181.

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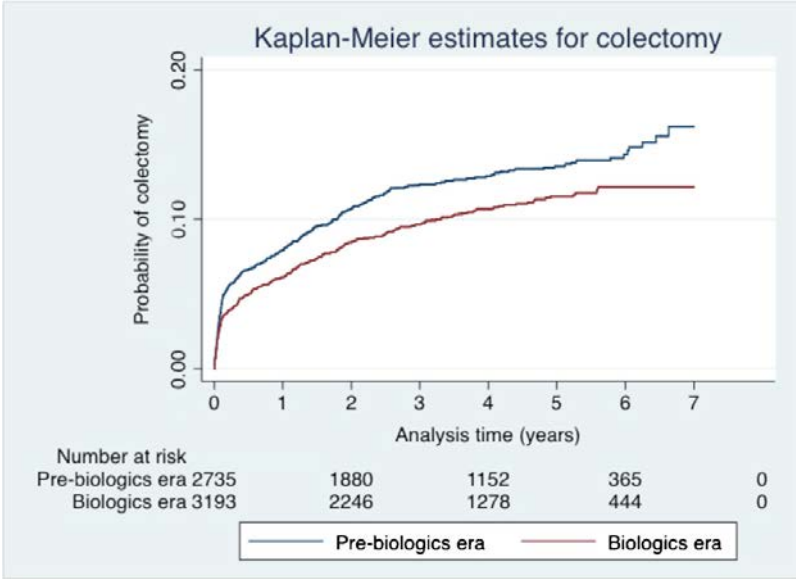
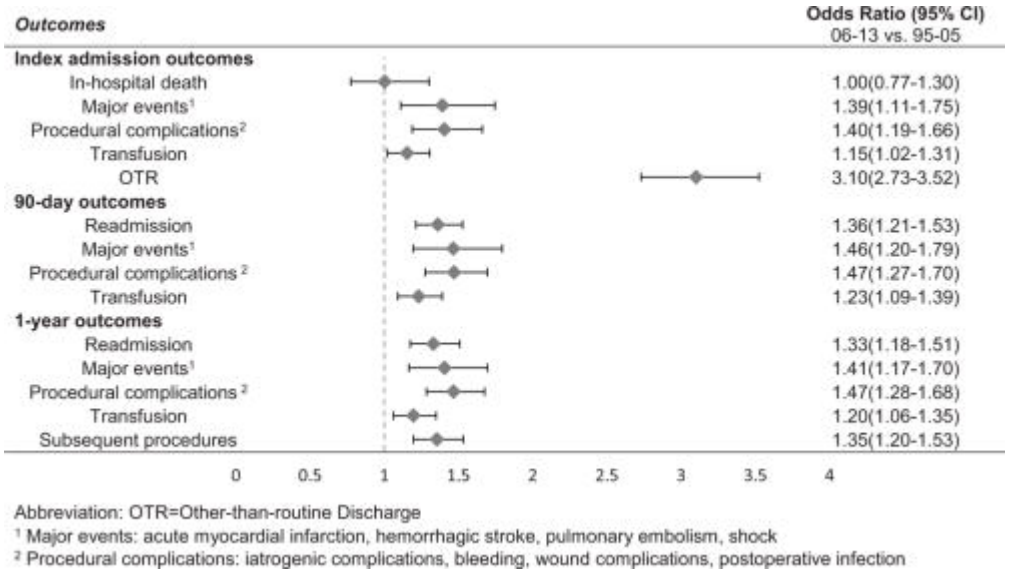
Surgery trends in the era of biologic therapy





Abbreviation: OTR=Other-than-routine Discharge

[1] Major events: acute myocardial infarction, hemorrhagic stroke, pulmonary embolism, shock

[2] Procedural complications: iatrogenic complications, bleeding, wound complications, postoperative infection

1. Abou Khalil, M., Boutros, M., Nedjar, H. et al. Incidence Rates and Predictors of Colectomy for Ulcerative Colitis in the Era of Biologics: Results from a Provincial Database. J Gastrointest Surg (2018) 22: 124.
2. 2. Abelson JS, Michelassi F, Mao J, Sedrakyan A, Yeo H. Higher Surgical Morbidity for Ulcerative Colitis Patients in the Era of Biologics. Ann Surg. 2018 Aug;268(2):311-317.

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Surgery on biologics

- We are still operating on many patients with IBD
- These patients are increasingly on biologic therapy
- These medications are immunosuppressive
- How do we address biologic therapy perioperatively

Surgery on biologics

- Does it affect our postoperative outcomes?
- If yes, does it impact our patient management?
- What data is available?
- UC vs Crohn’s disease

Can we blame the medications?

Corticosteroids
Immunomodulators
Disease severity
Malnutrition
Anemia
Emergency surgery
Sepsis
Time since last administration
Varied provider practice

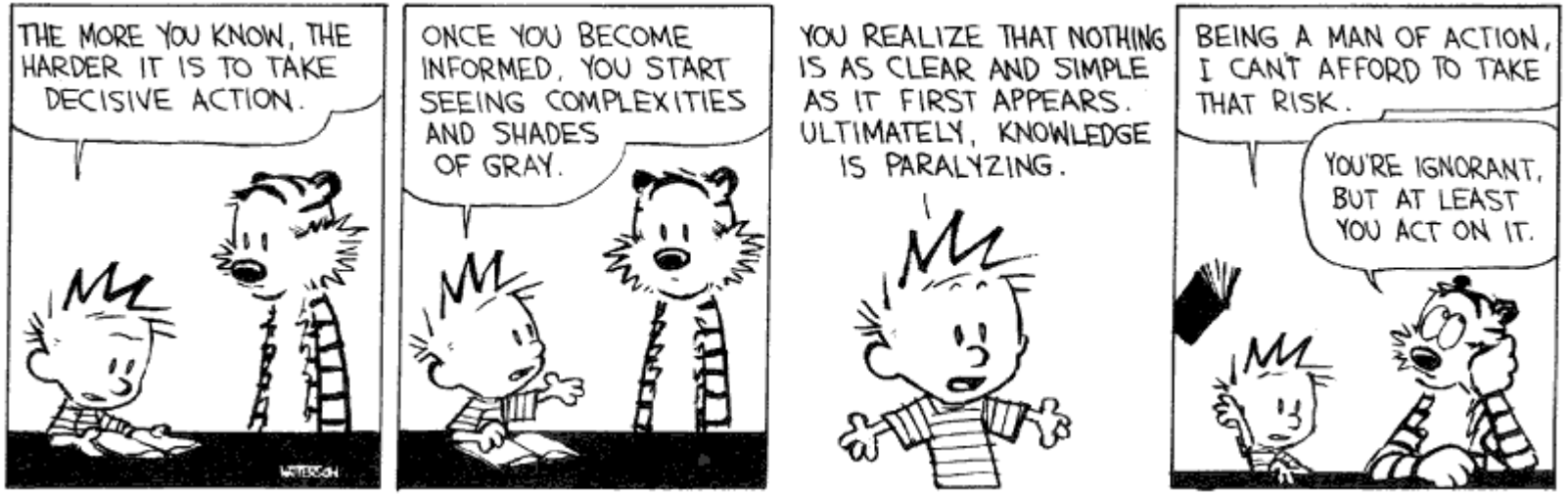
Anti-TNF

Majority of the literature is focused on infliximab

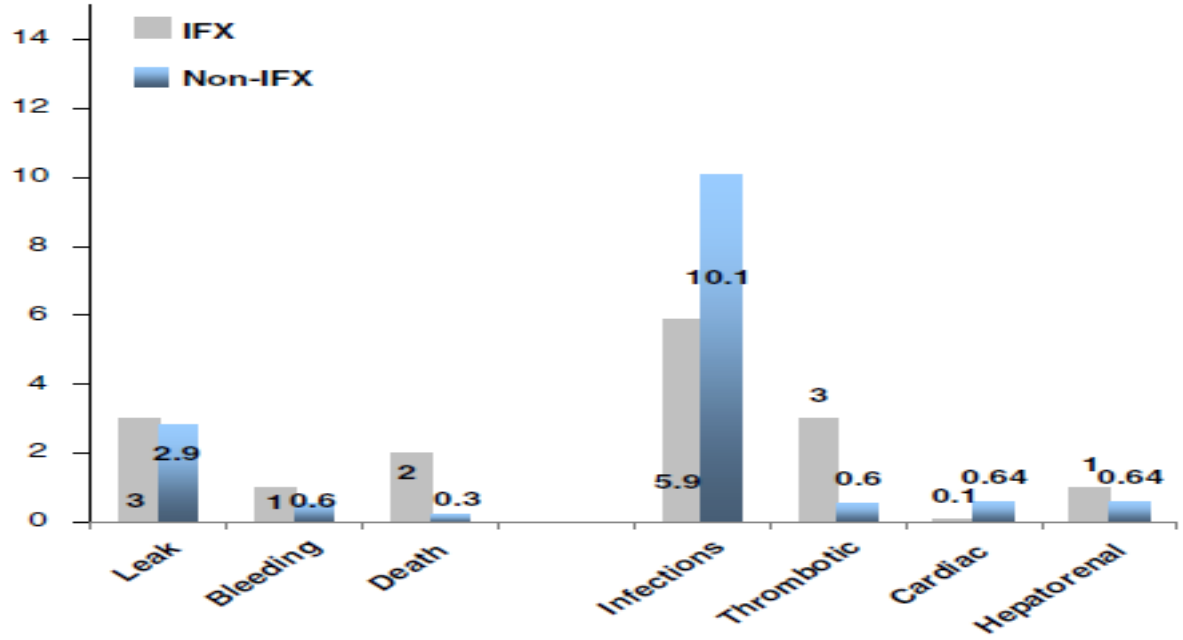
- FDA approved for Crohn's disease in 1998
- FDA approved for UC in 2005

Anti-TNF and postoperative outcomes

Data is mixed and controversial



Anti-TNF and IBD surgery



Kunitake, H., Hodin, R., Shellito, P.C. et al. J Gastrointest Surg (2008) 12: 1730

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Anti-TNF and IBD surgery

Table 5 Post Operative Outcomes

	Complication	Non IFX group (1998–2007) n=329 (%)	IFX group n=60 (%)	Pre-IFX group (1991 to 1997) n=69 (%)	Odd's ratio (95%CI)	p-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[a] 0.007[b]
	Sepsis	9.7	20.0	5.8	2.32(1.12, 4.82)* 4.06(1.23,13.37)†	0.024[a] 0.021[b]
	Intraabdominal abscess	4.3	10.0	4.3	2.50(0.92, 6.79)* 2.44(0.58,10.23)†	0.10[a] 0.30[b]
	Anastomotic leak	4.3	10.0	1.4		0.09[a] 0.049[b]
	Reoperation	3.0	8.3	0.0	2.9(0.95,8.81)*	0.06[a] 0.02[b]

[a] p: No IFX vs. IFX
[b] p: Pre-IFX vs. IFX

Appau, et al. J Gastrointest Surgery, 2008

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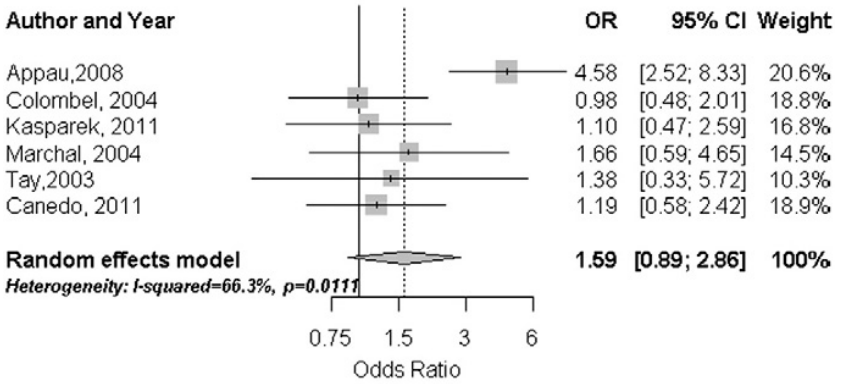
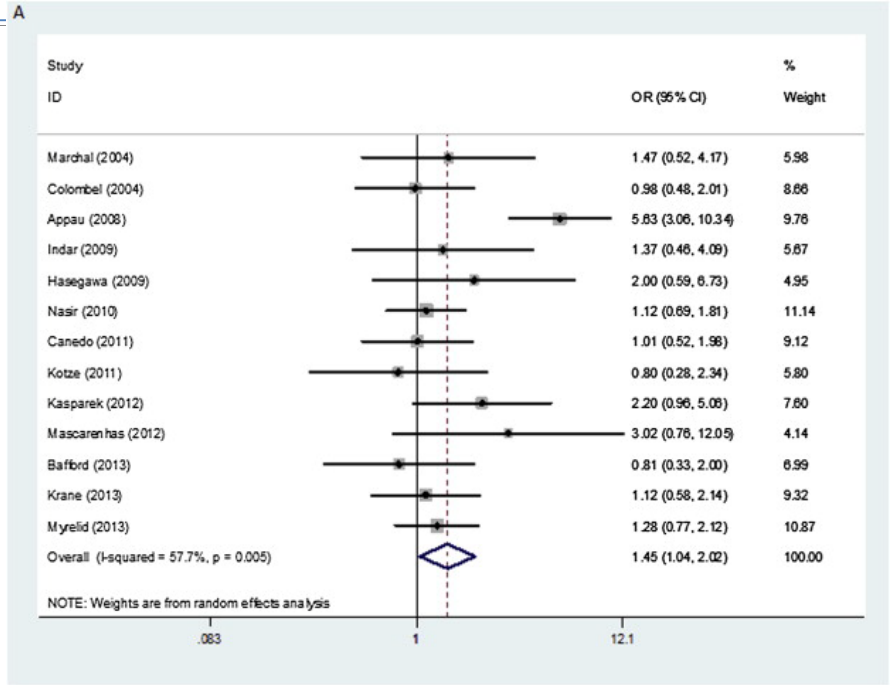
Anti-TNF and Crohn's disease

Authors	Journal	Year	Pts with Crohn's	anti-TNF	Outcome
Lau et al.	Ann Surg	2014	123	All	Increasing drug levels associated with adverse outcomes
de Buck van Overstraeten et al	Br J Surg	2017	538	111	Increased risk of AL in subset analysis
Brouquet	Ann Surg	2018	592	143	Increased risk of adverse outcome with anti-TNF < 3month
Fumery et al.	Am J Gastro	2016	209	137	No effect regardless of drug level or interval from last dose; worse outcomes with corticosteroids
Yamamoto et al.	UEG	2016	231	79	No effect of anti TNF; blood transfusion, perforating disease, and previous resection were risk factors for complication

Anti-TNF and Crohn's meta-analyses





1. Greg Rosenfeld, Hong Qian, Brian Bressler; The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: A systematic review and meta-analysis, *Journal of Crohn's and Colitis*, Volume 7, Issue 11, 1 December 2013, Pages 868–877
2. Yang ZP, Hong L, Wu Q, et al. Preoperative infliximab use and postoperative complicationsin Crohn's disease: a systematic review and meta-analysis. Int J Surg 2014;12(3):224–30.

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Surgery for Crohn's and anti-TNF

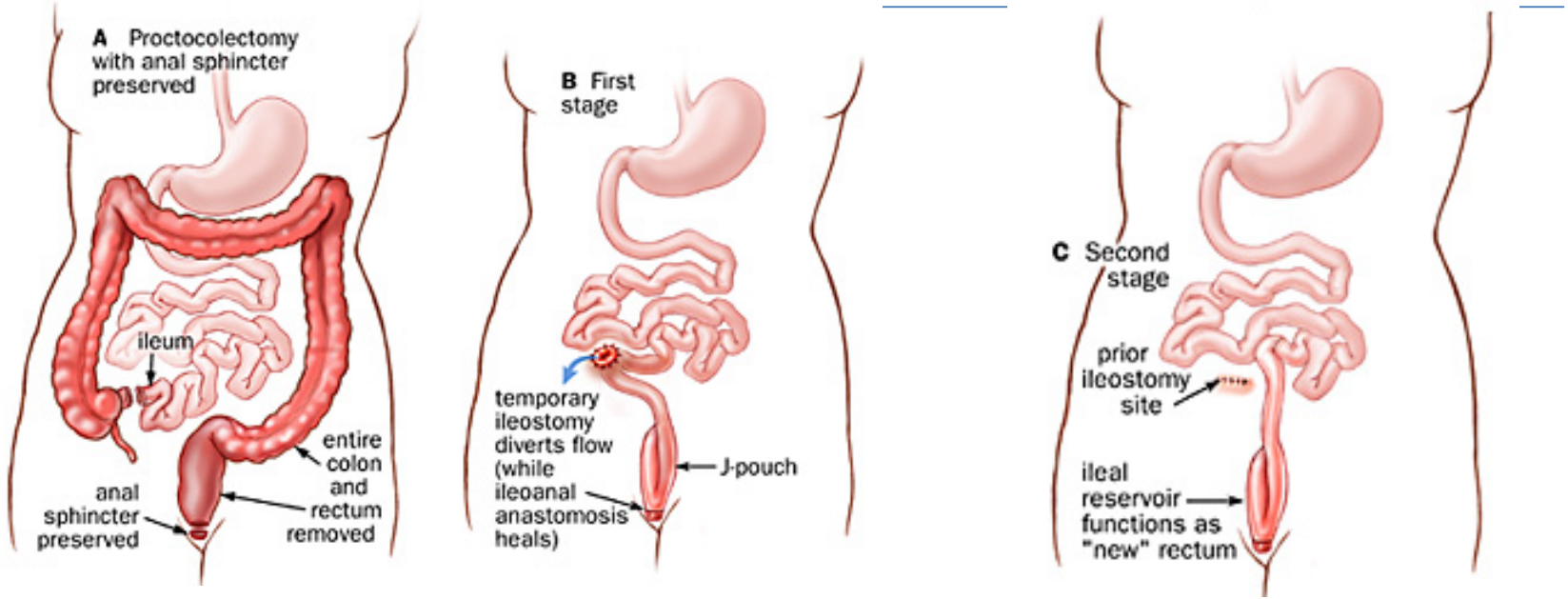
- Likely safe to operate with anti-TNF
- Reasonable to hold anti-TNF approaching surgery when possible
- Restart once all postoperative infectious complications resolved

Anti-TNF and Ulcerative colitis

Do outcomes differ from Crohn’s disease?

Are implications different in Crohn’s disease?

Two stage restorative proctocolectomy



1st Stage

2nd Stage

https://www.halstedsurgery.org/

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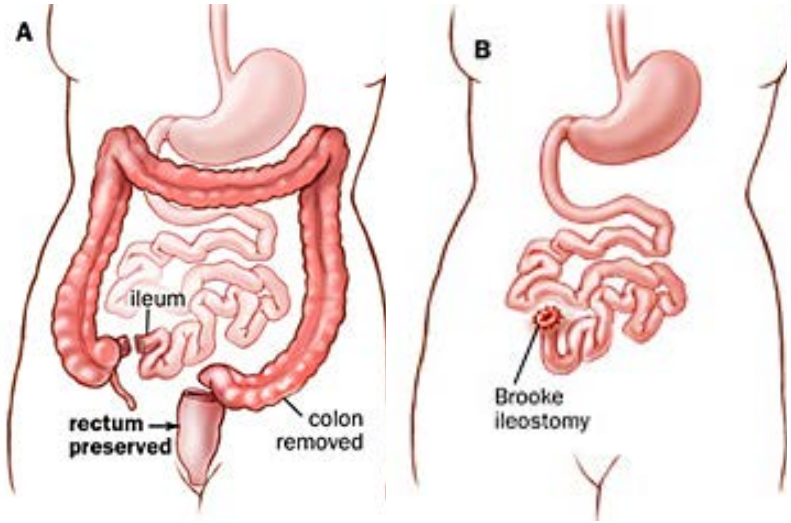
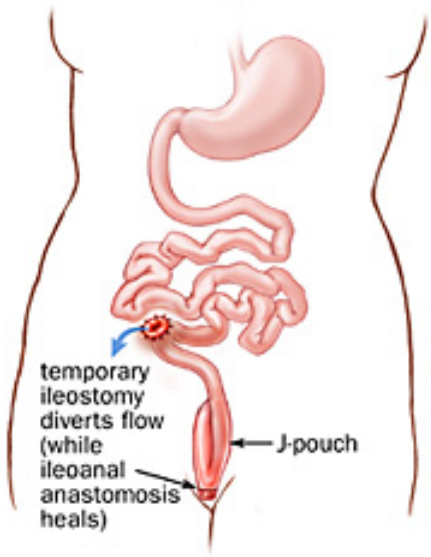
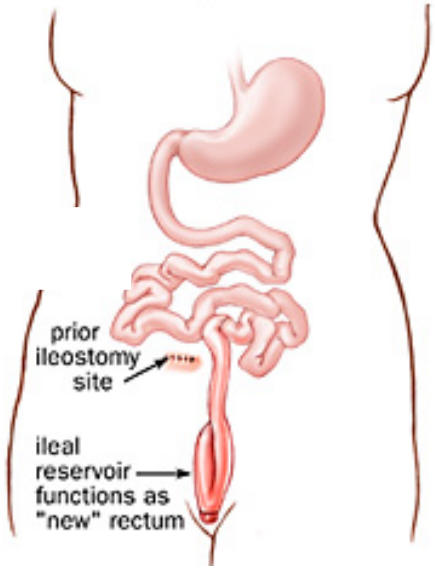
Three stage restorative proctocolectomy



1st Stage



2nd Stage



3rd Stage

https://www.halstedsurgery.org/

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Anti-TNF and UC: Ileal pouch anal anastomosis

Complication	IFX (n=29)	Non-IFX (n=52)	p value
Overall	13 (44.8%)	23 (44.2%)	0.96
Infectious	5 (17.2%)	14 (26.9%)	0.32
Pelvic/intraabdominal abscess	4 (13.8%)	7 (13.5%)	1.00
Wound infection	1 (3.5%)	10 (19.2%)	0.09
Non-infectious	12 (41.4%)	16 (30.8%)	0.34
Pouch/anastomotic leak	1 (3.5%)	5 (9.6%)	0.41
Pouch-related	0 (0.0%)	2 (3.9%)	0.53
Other	12 (41.4%)	13 (25.0%)	0.13

Gainsbury, M.L., Chu, D.I., Howard, L.A. et al. J Gastrointest Surg (2011) 15: 397.

Anti-TNF and UC: Ileal pouch anal anastomosis

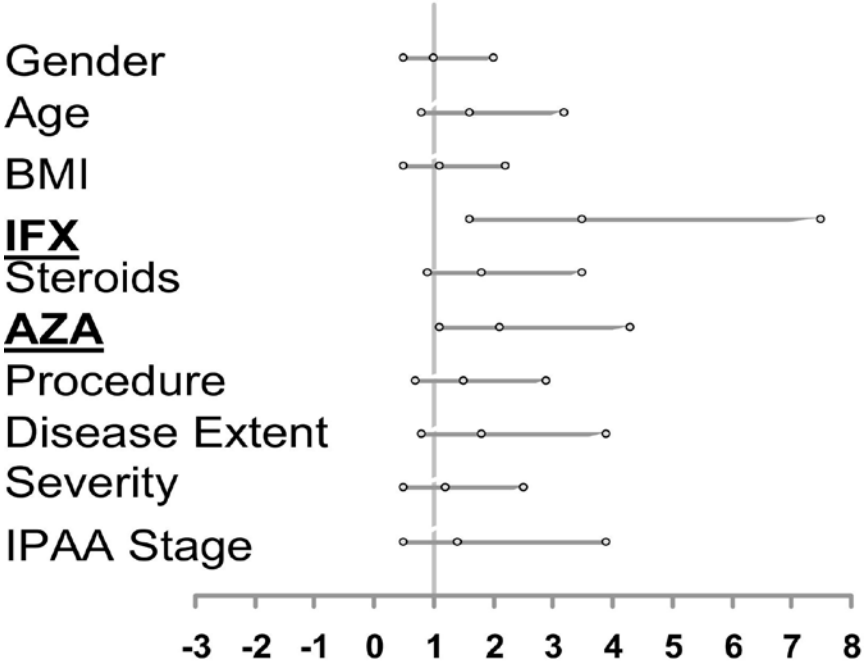

Table 3. Multiple Variable Logistic Regression Model Assessing Association of Infliximab Use and Infectious Complication in First 30 Days after Ileal Pouch Anal Anastomosis, Adjusting for Age, Colitis Severity, and Other Medication Use

Factor	Category	Odds ratio* (95% CI)
Age (y)	≤ 38	1.3 (0.6–2.7)
	> 38	1.0 (reference)
IFX	Yes	2.7 (1.1–6.7)
	No	1.0 (reference)
Steroid	High	1.3 (0.6–2.7)
	No/low/moderate	1.0 (reference)
AZA use	Yes	1.3 (0.6–2.9)
	No	1.0 (reference)
Colitis severity	Severe/fulminant	1.0 (0.4–2.1)
	Mild	1.0 (reference)

*Odds ratio using logistic regression model, infectious complication as the dependent variable.
AZA, azathioprine; IFX, infliximab.

Selvasekar CR, Cima RR, Larson DW, et al. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg*. 2007;204(5):956-962

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Anti-TNF and UC: Ileal pouch anal anastomosis

- 523 patients
  - All underwent IPAA
  - 46 underwent 2 stage IPAA with IFX

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

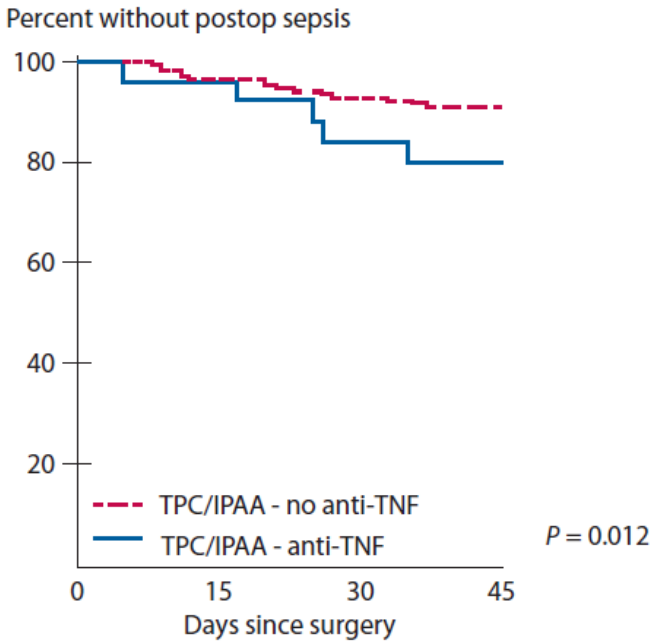
Table 2. Early and late postoperative complications, univariate analysis (n=46 matched pairs)

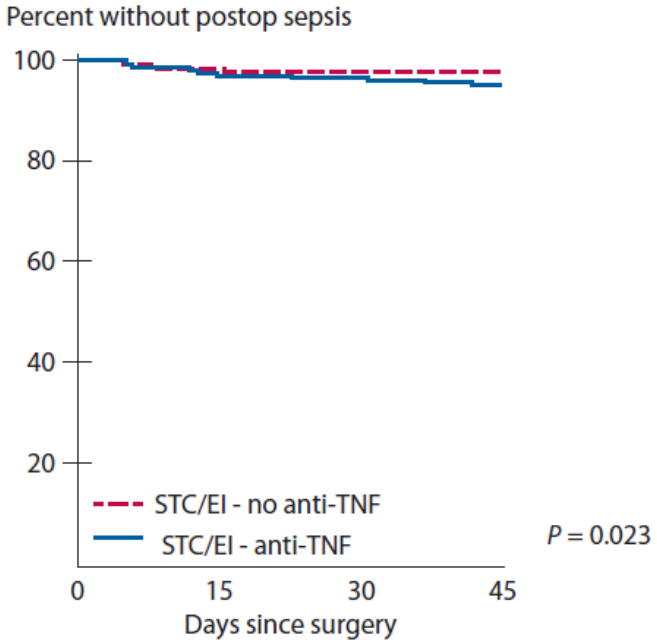
	Infliximab	*Noninfliximab*	*McNemar P value*
Sepsis	10 (21.7)	1 (2.2)	0.016
Leak	8 (17.4)	1* (2.2)	0.023
Postoperative hemorrhage	3 (6.5)	1 (2.2)	0.62
Thrombotic event	4 (8.7)	1 (2.2)	0.37
Ileus	2 (4.3)	3 (6.5)	1.00
Overall early postoperative complication	16 (34.8)	7 (15.2)	0.027
Pouchitis	18 (39.1)	7 (15.2)	0.037
Stricture	5 (10.9)	9 (19.6)	0.39
SBO	3 (6.5)	6 (13)	0.45
Overall late postoperative complication	24 (52.2)	17 (37)	0.23

SBO = small-bowel obstruction. • Data are numbers with percentages in parentheses unless otherwise indicated. • *Subclinical leak not associated with pelvic sepsis.

Mor, I.J., Vogel, J.D., da Luz Moreira, A. et al. Dis Colon Rectum (2008) 51: 1202.

Two stage vs. three stage approach





Anti-TNF and UC

Ulcerative colitis

- Strongly consider 3 stage procedure in patients with recent exposure to anti-TNF

Vedolizumab

Murine monoclonal antibody to α4β7 integrin

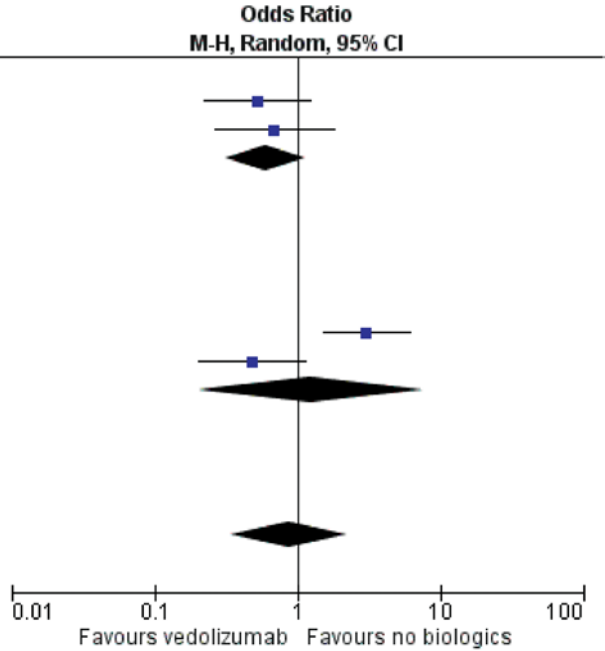
Half life of 22 days

2014 - Approved by FDA for moderate to severe UC and Crohn's disease

Again data is controversial

Vedolizumab vs. no biologic

Study or Subgroup	Vedolizumab Events	Total	No biologics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2.4.1 Ulcerative colitis						
Ferrante 2017	11	29	43	80	24.7%	0.53 [0.22, 1.25]
Yamada 2017	7	24	48	129	23.8%	0.69 [0.27, 1.80]
Subtotal (95% CI)		**53**		**209**	**48.5%**	**0.60 [0.31, 1.13]**
Total events	18		91			
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
2.4.2 Crohn's Disease						
Lightner 2017 (CD)	32	100	14	105	26.7%	3.06 [1.52, 6.17]
Yamada 2017	8	40	41	121	24.8%	0.49 [0.21, 1.15]
Subtotal (95% CI)		**140**		**226**	**51.5%**	**1.24 [0.21, 7.52]**
Total events	40		55			
Heterogeneity: Tau² = 1.53; Chi² = 10.50, df = 1 (P = 0.001); I² = 90%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**193**		**435**	**100.0%**	**0.88 [0.34, 2.26]**
Total events	58		146			
Heterogeneity: Tau² = 0.74; Chi² = 15.07, df = 3 (P = 0.002); I² = 80%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%						



1. Diana E Yung, et al; Systematic Review and Meta-analysis: Vedolizumab and Postoperative Complications in Inflammatory Bowel Disease, *Inflammatory Bowel Diseases*, Volume 24, Issue 11, 12 October 2018, Pages 2327–2338,
2. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. J Crohns Colitis. 2017;11:185–90.
3. Lightner AL et al. Postoperative Outcomes in Vedolizumab-Treated Patients Undergoing Major Abdominal Operations for Inflammatory Bowel Disease: Retrospective Multicenter Cohort Study, *Inflammatory Bowel Diseases*, Volume 24, Issue 4, 19 March 2018, Pages 871–876,

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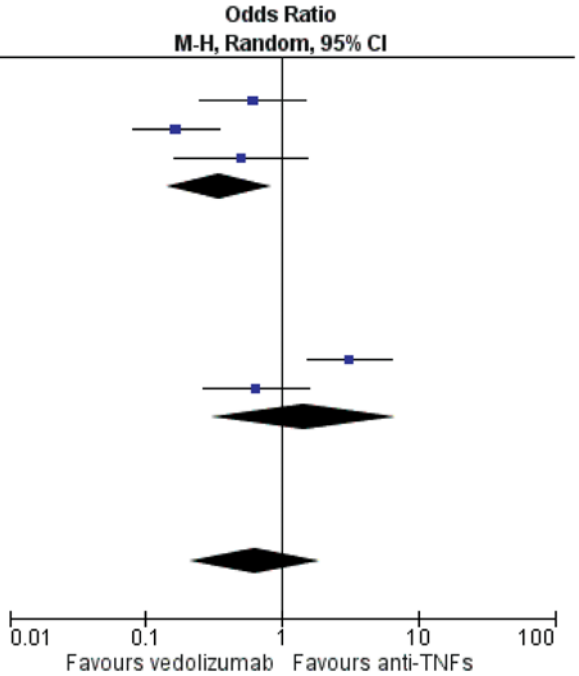
Vedolizumab vs. anti-TNF

Study or Subgroup	Vedolizumab Events	Total	anti-TNFs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 Ulcerative colitis						
Ferrante 2017	11	29	33	66	19.9%	0.61 [0.25, 1.49]
Lightner 2017 (UC)	30	88	47	62	20.8%	0.17 [0.08, 0.34]
Yamada 2017	7	24	15	33	18.5%	0.49 [0.16, 1.51]
Subtotal (95% CI)		**141**		**161**	**59.2%**	**0.35 [0.14, 0.85]**
Total events	48		95			
Heterogeneity: Tau² = 0.39; Chi² = 5.76, df = 2 (P = 0.06); I² = 65%						
Test for overall effect: Z = 2.33 (P = 0.02)						
1.7.2 Crohn's Disease						
Lightner 2017 (CD)	32	100	14	107	21.0%	3.13 [1.55, 6.31]
Yamada 2017	8	40	27	96	19.9%	0.64 [0.26, 1.56]
Subtotal (95% CI)		**140**		**203**	**40.8%**	**1.45 [0.31, 6.86]**
Total events	40		41			
Heterogeneity: Tau² = 1.09; Chi² = 7.51, df = 1 (P = 0.006); I² = 87%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**281**		**364**	**100.0%**	**0.64 [0.21, 1.88]**
Total events	88		136			
Heterogeneity: Tau² = 1.34; Chi² = 33.03, df = 4 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: Chi² = 2.43, df = 1 (P = 0.12), I² = 58.8%						



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Vedolizumab in UC

Table 3. Thirty-day post-operative complications.

	No biological therapy [*n*=172]	TNFα inhibitors [*n*=126]	Vedolizumab [*n*=94]	*p*-Value
Any postoperative complication	57 [33%]	35 [28%]	50 [53%]	<0.01
Non-SSI infections	10 [6%]	6 [5%]	7 [7%]	<0.71
UTI	5	2	4	<0.49
Pneumonia	2	1	3	<0.31
Non-abdominal sepsis	2	2	1	<0.92
C.diff colitis	0	1	1	<0.44
Cholangitis	1	0	0	<0.52
All SSIs	22 [13%]	13 [10%]	35 [37%]	<0.01
sSSIs	11 [6%]	5 [4%]	20 [21%]	<0.01
dSSIs	11 [6%]	6 [5%]	13 [14%]	<0.03
Anast leak	1 [1%]	4 [3%]	2 [2%]	<0.24
MCS	1 [1%]	1 [1%]	7 [7%]	<0.01
SBO/ileus	20 [12%]	12 [10%]	9 [10%]	<0.79
Readmission	17 [10%]	12 [10%]	15 [16%]	<0.24
ROR	8 [5%]	10 [8%]	8 [9%]	<0.37

SSI = surgical site infection [superficial, deep, anastomotic leak, mucocutaneous separation]. Non-SSI infections = pneumonia, *Clostridium difficile* [*C.diff*], urinary tract infection [UTI], cholangitis, sepsis. sSSI = superficial surgical site infection. dSSI = deep space surgical site infection. Anast leak = anastomotic leak. MCS = mucocutaneous separation. ROR = return to the operating room. SBO = small bowel obstruction.

1. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. J Crohns Colitis 2017;11:185–90.

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Vedolizumab:

Likely safe in the perioperative period

Similar approach as is used with anti-TNF is applicable

Ustekinumab

Human monoclonal antibody to interleukin -12 and -23

Biologic half life of 15-32 days

2016 - approved for moderate to severe Crohn’s disease

Ustekinumab

Table 4. Postoperative outcomes

	Ustekinumab cohort (n=20)	Anti-TNF cohort (n=40)	P value
Postoperative complications:			
Wound infection ≤ 30 days	1 (5%)	2 (5%)	1.00
Wound infection > 30 days	0	0	-
Anastomotic leakage ≤ 30 days	0	3 (7.5%)	0.54
Anastomotic leakage > 30 days	0	0	-
Abscess ≤ 30 days	0	4 (10%)	0.29
Abscess > 30 days	0	2 (5%)	0.54
Nonsurgical site infection ≤ 30 days	0	3 (7.5%)	0.54
Nonsurgical site infection > 30 days	0	0	-
Postoperative ileus /bowel obstruction	3 (15%)	4 (10%)	0.67
Delayed wound healing	0	5 (12.5%)	0.16
Need for reoperation/readmission	2 (10%)	6 (15%)	0.59
Median preoperative hospital stay (days, IQR)	0 (0–4)	0 (0–2)	0.59
Median total hospital stay (days, IQR)	7 (5–14)	7 (4–9)	0.45
Mortality at 6 months	0	0	-

1. Shim HH et al.; Preoperative Ustekinumab Treatment Is Not Associated With Increased Postoperative Complications in Crohn's Disease: A Canadian Multi-Centre Observational Cohort Study, *Journal of the Canadian Association of Gastroenterology*, Volume 1, Issue 3, 12 September 2018, Pages 115–123
2. Lightner AL et al., Postoperative Outcomes in Ustekinumab-Treated Patients Undergoing Abdominal Operations for Crohn's Disease, *Journal of Crohn's and Colitis*, Volume 12, Issue 4, 28 March 2018, Pages 402–407

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Ustekinumab

Likely safe perioperatively

Limited data available

Summary

Likely safe to operate in the setting of biologics

Holding biologic therapy approaching an operation is appropriate

Resumption of therapy once all infectious complications resolved safe