IBD Survival Guide (CD, UC) – updated 02/09/23

	Crohn's Disease	Ulcerative Colitis
Epidemiology	Can occur at any age, incidence peaks at age 15-30 and age 50-80	
Presentation	- More likely to have chronic diarrhea - Perianal fissures, fistula or abscess	- More likely to have rectal bleeding/tenesmus
Pathology	- Affects any part of the GI tract - **Transmural inflammation** → fibrosis, strictures, fistula, obstruction - Discontinuous inflammatory changes - **Non-caseating granulomas** ~3% develop PSC	- Disease extends proximally from the rectum - Lesions affect predominantly the mucosa and submucosa in a circumferential and uninterrupted distribution - Often see islands of regenerating mucosa (pseudopolyps) - **Crypt abscesses** **~5% develop PSC**
Active Smoking	Risk factor	Protective
Severity Classification	**Mild-moderate disease**: able to tolerate oral intake without signs of systemic toxicity **Moderate- severe disease:** Patients have failed therapy for mild-moderate disease or have abdominal pain, n/v, fevers, dehydration, anemia or weight loss or > 10% **Severe-fulminant disease**: Persistent symptoms after corticosteroid therapy, or the presence of high fevers, obstruction, cachexia, surgical abdomen or abscess formation	**Mild UC:** ≤4 loose stools a day (may be bloody) and no signs of systemic toxicity. **Normal ESR** **Moderate UC**: > 4 stools per day and minimal signs of systemic toxicity **Severe UC:** ≥6 loose stools per day, with blood, HR >90, T ≥37.5F, Hgb <10.5, **ESR >30** • Fulminant colitis is along the continuum with severe colitis
Extraintestinal manifestations	Erythema nodosum, pyoderma gangrenosum, peripheral arthropathy, episcleritis or scleritis, uveitis, spondyloarthropathy, osteoporosis, **primary sclerosing cholangitis**, nephrolithiasis, cholelithiasis, **venous/arterial thromboembolism**	
Health Care Maintenance		
CRC Screening	- Initial colonoscopy = min 8 years of disease + ≥30% colonic involvement - Surveillance = 1-3 years * No screening needed for small bowel CD	- Initial colonoscopy = 8-10 years from onset of symptoms - Surveillance = 1-3 years after *No screening needed for ulcerative proctitis
	- If diagnosed with concurrently with PSC, undergo screening colonoscopy at time of diagnosis and annually after - If patient has an ileal pouch – perform flex sig + biopsies every other year	
Colectomy indications	- Evidence of carcinoma, high grade dysplasia or multifocal low-grade dysplasia on pathology	
Osteoporosis	- DEXA Scan Indications = previous fragility fracture, postmenopausal, male >50 years, hypogonadism or > 3 months of steroids) Normal Scan = repeat in 2-3 years Initial low bone mass w/u = CBC, BMP, phos, hepatic panel, 25-hydroxyvitamin D, testosterone (men), and PTH Supplement: **Vit D (800 to 1000 IU/day [20-25 µg /day]) and calcium (1200 mg/day)** Candidates for therapy: • Men > 50 and postmenopausal women with osteoporosis • Men >50 and postmenopausal w/o osteoporosis but a FRAX score with a 10-year prob of hip or combined major osteoporotic fracture of ≥3 and 20 percent, respectively. Treatment = alendronate/risedronate (oral once a week) or IV zoledronic acid Repeat scan = no more than once every 2 years	
Vit Def	- Vit B12, Vit A, Vit D, Ca, K, Iron, Zinc	Folate, Vit D, Iron, Vit B12
	Vitamin D (**Check every 6-12 months**) – target goal is between 20 and 40 ng/mL • <12, treat with 50,000IU (1250µg) of D2 or D3 qweek for 6-8 wks followed by 800IU of D2 or D3 after • 12-20, treat with 800-1000IU (20-25µg) • 20-30, treat with 600-800IU (20-25µg) to maintain levels	
	Vitamin B12 • PO 1000 mcg qday Folic acid daily • PO 1mg qday *Duration of depends on whether the initial cause of the deficiency persists. If cause reversible, discontinue after deficiency is corrected	
Vaccinations	- Hep A/B, yearly influenza, meningococcus, zoster (if age >50, or starting tofacitinib), TDAP, HPV (≤26) - Pneumococcal vaccine • All patients with IBD should be vaccinated once with the PCV13 followed by the PPSV23 (first dose after 8 weeks if immunocompromised, or after ≥1 year if immunocompetent; second dose after 5 years; and third dose after 65 years of age). • If previously vaccinated with the PPSV23, then the PCV13 should be administered at least 1 year after the PPSV23 in both immunocompromised and immunocompetent adults	
Pap smear	Annual – if on systemic immunosuppression (women on thiopurine at increased risk for abnormal pap)	
Skin Cancer	Annual skin exam - immunomodulators (including thiopurines) and biologics increase risk for skin cancer	
Parkland specific*	If patient is on a biologic – check a T-SPOT and Hep B surface antigen every year	

Terminology:

Ulcerative proctitis – refers to disease within 18 cm of the anal verge, distal to the rectosigmoid junction

Ulcerative proctosigmoiditis – refers to disease limited to the rectum and sigmoid colon and not involving the descending colon

Left-sided colitis – refers to disease that extends beyond the sigmoid colon and as far proximally as the splenic flexure

Extensive colitis – refers to disease extending proximal to the splenic flexure

Hospital Flare:

- Check C. diff, stool culture or stool GI pathogen panel, stool O&P, and stool giardia/crypto antigen (though speaking with Dr Fudman, do not need to obtain stool O&P and giardia/crypto antigen unless there are risk factors).
- Get a KUB do ensure that there is no megacolon (>6cm)/ severe dilation.
- IV Methylpred 20mg q8 (q4 in severe disease) x3-5 days. Followed by prednisone 40, taper by 5mg a week. Some attendings prefer 40mg x2 week, 30mg x1 week and then 20mg indefinitely until patient is seen in clinic (If patient doing well in clinic then can go down by 5mg weekly). Note: IV methylpred 60mg = PO pred 75mg.
- If patients don't have **zero** response to methyl pred after 24 hours, consider salvage therapy with infliximab (renflexis 10mg/kg can give up to 3 doses Q72 hours). If zero response after 2-3 doses of salvage therapy – generally will need to consult CRS for surgical management.
- Tofacitinib may be considered for the management of severe acute UC after infliximab failure

* Bactrim 1DS tablet daily if patient receiving ≥20 mg of prednisone daily for one month or longer (above regimen ~ 1 month) → note this is ONLY if patient is immunosuppressed (outside of their IBD) or have some underlying pulmonary condition that puts them at risk of PCP (ex, interstitial pulmonary fibrosis). Otherwise IBD patients have a low incidence of developing PCP, even on long-term steroids

Antibiotics :

CD (simple perianal fistulas): PO Metronidazole 500mg BID x 4 weeks; if clinical response - continue at 250mg TID for additional 4 weeks

UC (Fulminant colitis) : IV Metronidazole 500mg q8 +/- PO ciprofloxacin 500mg BID for 10-14 days to reduce bacterial gut translocation

* Flagyl- monitor for irreversible peripheral neuropathy. Cipro – tendon inflammation/rupture in patients on steroids, age >60 or organ transplant

5-ASA compounds, Mesalamine: Watery diarrhea, abdominal pain, headache, nausea. Sulfasalazine: nausea/headache, rash, **male infertility**, headache

**CAG recommends against routine use of mesalamine in CD.

Medication	MOA	Indication	Induction Dosing	Maintenance dosing	Notes
Mesalamine (Pentasa)	Diffusion dependent	Proximal disease (UC or CD**), severe diarrhea, strictures, pouchitis, post-operative anastomosis	1g QID for 4-8 wks	1.5 to 4 g/day in 3-4 divided doses	- Release not affected by rapid transit)
Mesalamine (Asacol)	pH Dependent	Ileocolonic disease (UC)	1.6g TID for 4-8 wks	1.6-2.4g daily in 1-3 divided doses	Asacol HD comes in 800mg tablets
Mesalamine (Lialda)			2.4-4.8g qday	2.4-3.6g qday	
Mesalamine (Apriso)			1.5-4.5g qAM	1.5-g qAM	
Sulfasalazine (Azulfidine)	Colonic Bacterial dependent	Colonic disease (UC or CD)	1g QID	1g TID-QID	- Preferred in patients with peripheral arthropathy - a competitive inhibitor of folate absorption; therefore, folic acid should be supplemented while taking this medication. - Associated with reversible sperm dysfunction that can cause male infertility.
Balsalazide (Colazal)		Universal and distal UC	2.25g TID for 8 to 12 wks	1.5-3g BID for 6 to 12 months	
Mesalamine Suppository (Canasa)	Directly Acting (Topical)	Left-sided colitis and proctitis (UC)	1g (one suppository) qhs	1g (one suppository) qhs	- Suppositories are effective only for disease limited to the rectum
Mesalamine Enema (Rowasa)			4g qHS or 4g BID	1-4g qHS	- Enemas reach the proximal sigmoid colon and splenic flexure in most patients who are able to retain them

Note: 2.4g Mesalamine = 6g Sulfasalazine = 6.75g Balsalazide

Immunomodulators (Thiopurines) → **Check TPMT activity –** Avoid med in pts with low activity. Starting dose should be lowered in those with intermediate activity. **Check NUDT15 mutations in Asians** → affects thiopurine metabolism as well

- Monotherapy is more effective in UC > CD
- Azathioprine and methotrexate may be used for **maintenance of remission** but **NOT** for induction or remission for CD**. (**Budesonide on the other hand can be used for induction, but not for maintenance)

Medication	Dosing			Side effects	Note
Azathioprine	**Weeks 1-4**:	50mg daily	Weekly CBC, hepatic panel, Tbili and amylase	Dose-dependent side effects: - Bone marrow suppression - Hepatotoxicity Dose-independent side effects - Nausea - Pancreatitis (if patient develops this, thiopurine rechallenge is contraindicated) - Infection - Malignancy (risk of **lymphoma** is <1 case per 1000 person years)	- Max dose = 2.5 mg/kg (lean body weight).
	Weeks 5-8:	100mg daily	Q2 week CBC, hepatic panel, Tbili and amylase		
	Weeks 9 to 12:	150mg daily			
	Weeks 12	150mg daily	Q3 month CBC, hepatic panel, Tbili and amylase - Consider checking metabolites – 6TG (therapeutic) and 6 MMP (hepatotoxic). Goal 6TG > 235-240 for treatment effect, >125 for immunogenicity		
6-MP	**Weeks 1-4**:	50mg daily	Weekly CBC, hepatic panel, Tbili and amylase		- Max dose = 1.5 mg/kg (lean body weight).
	Weeks 5-8:	75mg daily	Q2 week CBC, hepatic panel, Tbili and amylase		
	Weeks 9 to 12:	100mg daily			
	Weeks 12	100mg daily	Q3 month CBC, hepatic panel, Tbili and amylase		

- In patients with **severe UC/Crohn's** often use combination therapy with a TNF inhibitor and Azathioprine. Starting at 50mg per day. Can be gradually increased to a maximum of 2.5 mg/kg per day. Reason is to reduce immunogenicity against biologic therapy which is highest when the biologic agent is first started and to improve the pharmacokinetics of biologic therapy.
- If WBC ≤4 or platelet count <150 during therapy, discontinue the drug or reduce by 50%. Repeat a CBC within 2 weeks. If a 50% reduction in the dose is associated with persistent cytopenia, then permanently discontinue
- If ALT or AST > 2x the ULM, discontinue med until hepatic panel normalizes, after which AZA/6-MP can be reintroduced at a lower dose.
- Stop medication if Tbili is elevated
- Azathioprine can cause hepatosplenic T-cell lymphoma in young males
- Stable, mild macrocytosis in the absence of vitamin deficiency is a potential side effect that is well-tolerated and does not require discontinuation of medication
- Note thiopurines are safe during pregnancy/for breastfeeding

Biologics

Medication	Target	Route	Dosing	CD	UC	Notes
Infliximab (Remicade/Renflxis)	TNF-α	IV	5-10mg/kg over 2 hours at wks 0, 2, 6 and then q8 wks' **Can titrate to q4 week max**	✓	✓	* Effective in fistulizing CD * Use in combo with AZA for max effectiveness. (If patient cannot tolerate thiopurines, use MTX) - salvage dosing of renflexis is 10mg/kg can give up to 3 doses Q72 hours.
Adalimumab (Humira)	TNF-α	SubQ	160mg →80mg →40mg (wks 0, 2 then q2 wks) **Can titrate to 80mg qweek max**	✓	✓	
Certolizumab (Cimzia)	TNF-α	SubQ	400mg at wks 0,2, and 4 then q4 wks	✓		Note this is not a very good medication. Rarely used *Does NOT cross the placenta
Golimumab (Simponi)	TNF-α	SubQ	200mg at wks 0, 100mg at wk 2, then 100mg q4 wks.		✓	This is an "okay" medication. Rarely used
Vedolizumab (Entyvio)	α4β7 (anti-integrin)	IV	300mg at 0, 2, and 6 wks then q8 wks **Can titrate to q4 week dosing max**	✓	✓	*Preferred in patients ≥ 65 years old or history of recent infection in the past 3 months (given lower risk of serious infection) ***VARSITY TRIAL (2019)** demonstrated that vedolizumab is superior to adalimumab for the induction and maintenance of patients with **moderate to severe UC.** * The clinical response with vedolizumab is slow in comparison with anti-TNF therapies. While the clinical response in relation to placebo is reported to be significantly different at week 6, the peak effect may not be expected till weeks 10–14
Ustekinumab (Stelara)	IL-12/23	IV→ SubQ	Weight based IV infusion: -260mg (0-55kg), 390mg (55-85kg), 520mg (>85kg) -Then 90mg subQ q8 wks **Can titrate to q4 week max** **Can re-induce patient as much as needed**	✓	✓	*may be effective for achieving fistula closure and maintaining fistula closure in CD.
Natalizumab (Tysabri)	α4-integrin	IV	300mg q4 wks	✓		*Associated with PML. Rarely Used

Biologics are unique in that the immune system may recognize the biologic medicine as nonself and cause a humoral or cell-mediated immune response with the formation of anti-drug antibodies.
*Anti-TNF agents are associated with a small risk of lymphoma
* In primary non-responders → check a **drug trough level** and **anti-drug antibody levels**. Low trough levels + high antidrug antibodies suggest need for an alternative biologic agent
Anti-Diarrheal Agents
* Primary nonresponse with anti-tumor necrosis factor agents is clinically diagnosed as having no change in symptoms **after completion of induction.**

Synthetic Small molecules → not prone to immunogenicity

Medication	Target	Route	Dosing	CD	UC	Notes
Tofacitinib (Xeljanz)	JAK1 &3	PO	Induction: 10 mg BID x 8 weeks, can extend to 16 weeks. Discontinue if inadequate response after 16 weeks. Then transition to 5mg BID, can increase back to 10mg BID if inadequate response.		✓	*Increased risk of thrombosis. Avoid being on hormonal contraceptives/therapy. On formulary at Parkland. Adverse reactions: Lipid abnormalities (check lipid panel 4-8 weeks after therapy initiation and periodically), cytopenias, liver function abnormalities and infectious complications (herpes zoster)

Favorable characteristics of small molecules (Tofacitinib [Xeljanz]**, Upadacitinib** [Rinvoq], **Ozanimod** [Zeposia]**)**: Targeted synthetic molecules, oral delivery, predictable pharmacokinetics, FAST on FAST off.

Loperamide: 4 mg, followed by 2 mg after each loose stool; maximum: 16 mg/day
Lomotil: 5 mg 4 times daily until control achieved. Once control is achieve, reduce dose as needed. If no improvement within 10 days, discontinue use
*Do not give in severe active disease given risk of toxic megacolon

Methotrexate (CD specific immunomodulator)
Induction: IM or SubQ 25 mg once weekly + daily folate 1mg daily
Maintenance: 15 mg once weekly if steroid-free remission maintained for 4 months + daily folate 1mg daily
Typical combo/immunogenicity prevention dose: 12.5-15mg oral/SC weekly plus daily folate
Side effects: erythema multiforme, SJS. TEN, abdominal distress, diarrhea, nausea/vomiting, elevated hepatic panel, headache, AKI, bone marrow suppression

Therapeutic drug Monitoring (for TNF-inhibitors)
This is especially important during the induction phase – should check levels at 6-14 weeks depending on drug/dosing. When patient is on maintenance dose of a TNF-inhibitor should check levels 1-2x a year. Strongly consider combo therapy with a TNG-inhibitor to prevent immunogenicity if not doing proactive TDM due to high rates of secondary loss of response. (**This is particularly true for infliximab** – upwards of 2/3rds of patients develop immunogenicity**)** Role of TDM is less clear **after induction** for VDZ and USK.

Ulcerative colitis (mild/moderate disease)
Ulcerative proctitis

- Mesalamine suppository 1g daily → if no relief after 2 weeks, increase to 1g BID for 4 weeks → then reduce dose to 1g daily
  - If no improvement after 4 weeks, add 5-ASA agent (refer below)
  - If no response to oral 5-ASA and topical mesalamine, **add oral budesonide** to existing regimen
    → 9 mg daily for eight weeks and then **stop** without a taper
    → patients who develop symptoms of relapse (eg, diarrhea, rectal bleeding) at ≥8 weeks, give another 8-wk course of budesonide

Remission: For those responsive to only topical therapy , 1 mesalamine suppository qhs

- If unable to tolerate topical medications, induce the patient with high dose mesalamine (>3g total daily) or start Sulfasalazine
  - After remission is achieved (typically within eight weeks), decrease mesalamine to 2-3 grams per day

Ulcerative proctosigmoiditis

1. Mesalamine enema qday
    - For patients with fecal urgency/tenesmus also begin mesalamine suppository 1g daily
2. If no relief after 2 wks, increase enema to BID or add suppository 1g daily (if not previously added already)
    - Symptoms should improve within 1 wk. Clinical remission can take up to 4-6+ weeks

* Topical mesalamine is more effective than oral 5-ASA therapy

Remission: 1 mesalamine enema qhs

Left-sided or extensive colitis

- High dose mesalamine (>3g total daily) or Sulfasalazine + mesalamine enema qdaily
    - Symptoms should improve within 2-4 weeks
    - Keep the enema for 2 months then after remission is achieved, can continued based on pt pref

Remission: can continue high dose mesalamine or decrease to 2-3g daily

Subsequent therapy

- If no response to oral 5-ASA and topical mesalamine add budesonide to your existing regimen
  → 9 mg daily for 8 wks and then stop without a taper
  → For patients who develop symptoms of relapse at ≥8 weeks, can give another 8-week course of budesonide
- If unable to stop budesonide given symptom recurrence, **stop** budesonide or and start steroids or a biologic
    - Start prednisone 40. Taper by 5-10mg qweek
    - Patients has steroid-dependent UC if prednisone cannot be tapered to <10mg daily → these patients require escalation to biologics

Monitoring during remission: Colonoscopy in 6-12 months after clinical remission. Obtain CRP and fecal calprotectin at time of colonoscopy to correlate tests with degree of mucosal healing.

Ulcerative colitis (moderate/severe disease)

Peri-hospitalized/hospitalized: infliximab (typically with immunomodulator at least to start). Can also consider tofacitinib in someone who is TNF-experienced

Moderate disease: vedolizumab (or ustekinumab), though all biologics except for tofacitinib is reasonable as 1st line. Adalimumab is also likely less effective compared to other biologics

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Crohn's Disease (Low risk with mild symptoms)

Low risk = normal or mild elevation in CRP/fecal calprotectin, diagnosis at age >30, superficial or no ulceration on colonoscopy, lack of perianal complications, no prior intestinal resections, absence of penetrating or stricturing disease

* The use of 5-aminosalicylates (5-ASA) for Crohn disease is controversial → limit use to mild Crohn disease with limited ileocolonic involvement who prefer to avoid glucocorticoids. For such patients, consider mesalamine (eg, Pentasa). Note: 5-aminosalicylate is not indicated for induction of remission for CD.

Disease limited to ileum and/or proximal colon

- Start oral budesonide 9mg daily for 4-8 weeks (this is ~ to about 30-40mg of pred)
    - If responds to treatment, taper budesonide by 3mg q2-q4 weeks until off
        - If no relapse, repeat colonoscopy in 6-12 months
        - If relapse in symptom, restart budesonide 9mg daily for 8 weeks and then taper by 3mg q4 weeks. Start thiopurine at the same time.
    - If no response to treatment, start biologic

Diffuse colonic/distal colonic involvement

- Begin prednisone 40mg for 1 week
    - If responds to treatment, taper prednisone by 5mg per week until off
        - If no relapse, repeat colonoscopy in 6-12 months
        - If relapse, restart prednisone 40mg per day and taper by 5mg per week until off. Start thiopurine at the same time.

Diffuse or extensive small bowel disease only

- Consider starting a biologic

Crohn's Disease (moderate/severe disease)

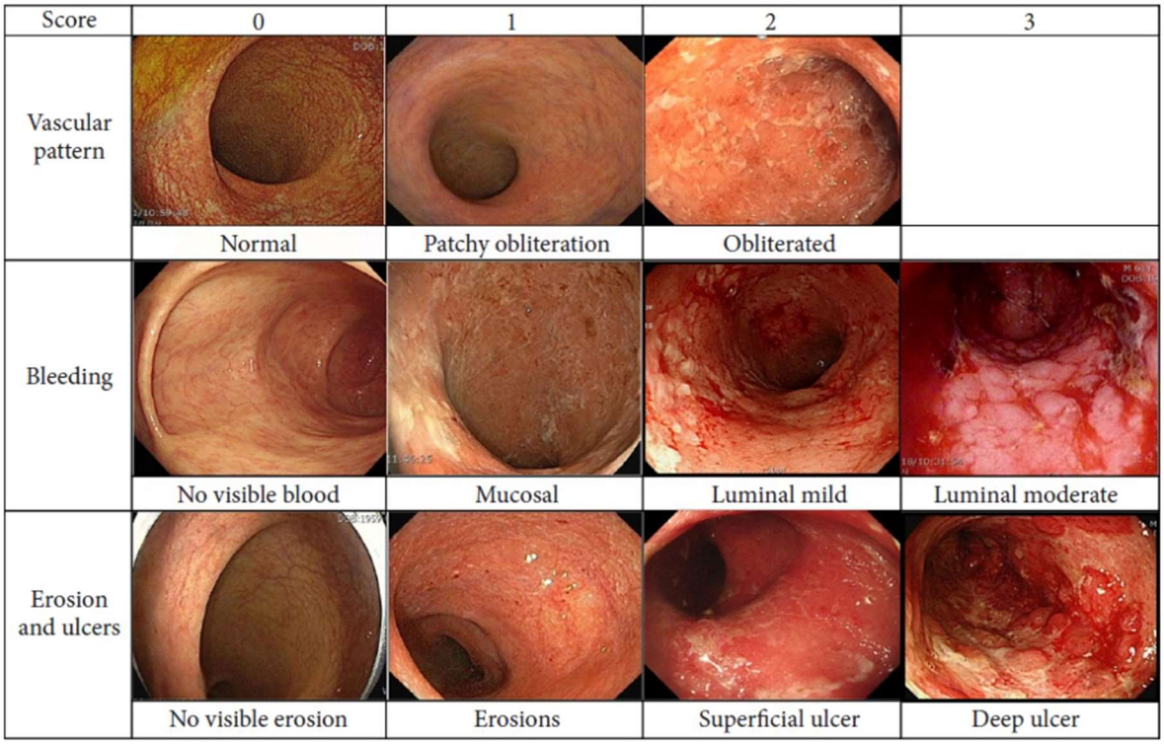
- Fistulizing or perianal or otherwise severe: 1st line is infliximab (almost always with immunomodulator to start), 2nd line = Ustekinumab or adalimumab

- **Inflammatory**: most options are reasonable (Ustekinumab > vedolizumab, for small bowel disease)

Endoscopic Activity Index Scoring Tools

Ulcerative Colitis

- The **Mayo endoscopic subscore is** commonly used as a target for treatment with a proposed remission score of 0 to 1
- The **Ulcerative Colitis Endoscopic Index of Severity (UCEIS)** is a validated endoscopic score → UCEIS has a proposed remission score of ≤1.



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Endoscopic features of each descriptor in ulcerative colitis endoscopic index of severity.

Crohn's Disease

- the Simple Endoscopic Score for Crohn Disease (SES-CD) has been used with a proposed remission score of ≤3

Post-operative Crohn's Disease

- **Rutgeerts Score** (used to evaluate endoscopic recurrence in the neoterminal ileum after ileocolic resection). Most studies adjust therapy for findings >i1