University of Michigan
Severe Ulcerative Colitis Protocol

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UNIVERSITY OF MICHIGAN

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Daily Checklist for Medical Team Orders

Day	Studies	Rx
Admission/D1	Comp, pre-albumin, CBCPD, ESR, CRP, Total Cholesterol, TPMT enzyme activity*, Quantiferon**, Abdominal film, C diff, CMV PCR, GI PCR, Hepatitis serologies for Hep A, Hep BsAb, BsAg, Bcore, Hep C, iron saturation, Schedule Flex sig for d2 Record: # stools, # with stool blood, urgency time, signs of toxicity. Get GI Consult service involved. Call Surgery if patient has already been on OP Steroids or IV Steroids at OSH for 5 days. Please note that there is **no need** for CT or MRI in established ulcerative colitis. Please clear with GI fellow if considered.	SQ heparin5000 U tid or Lovenox 40q24 IV LR or NS to keep urine output >50cc/hr - usually 5-10L in 1st 24hr – start 1L/hr*5h, then 500cc/hr until urine clear and frequent. Less volume if documented CHF, CKD Bedside commode IV Steroids (do **not** hold for infection testing results unless a very strong suspicion of infection) consider Rectal Rx for urgency: start with mesalamine 1g PR suppository bid. Switch to 4g mesalamine enema bid when urgency mild, able to hold enema for at least 30 min. Usually NPO, but can have clear liquids if very hungry (rare on day 1). if INR up, consider Vit K. Also consider zinc & vit C supplementation if poor nutritional status.
Day 2	Basic, CBCPD, Flex Sig, CRP Record: # stools, # with stool blood, urgency time, signs of toxicity	SQ heparin/Lovenox 40q24 Titrate IV NS to UOP NPO or clear liquids, depending on appetite continue IV steroids consider Rectal Rx Consider clear liquid diet if hungry
Day 3	Basic, CBCPD, ESR, CRP, PT/PTT, Read PPD, Review Bx results, Abd film, consider SB imaging*, Check *C diff* result Record: # stools, # with stool blood, urgency time, signs of toxicity Calculate predictive scores at 72h after 1st dose IV steroids, DOCUMENT IN NOTE Call surgery if needed	SQ heparin/Lovenox 40q24 Titrate IV NS to UOP Advance diet if improving, appetite present. Continue IV steroids consider Rectal Rx

Day 4	Comp, Mg, CBCPD, CRP Record: # stools, # with stool blood, urgency time, signs of toxicity	SQ heparin/Lovenox 40q24 Titrate IV NS to UOP Rectal Rx Advance diet if hungry
Day 5	Basic, CBCPD, ESR, CRP, PT/PTT, Abd film if sick Record: # stools, # with stool blood, urgency time, signs of toxicity Calculate predictive scores If CRP < 1.5, convert to oral prednisone Call surgery if needed	SQ heparin/Lovenox 40q24 Titrate IV NS to UOP Rectal Rx Advance diet if hungry Decide on taper – consider oral steroids vs. Medication Rescue vs. surgery Not improving, not eating well – consider NPO
Tapering Prednisone for outpatients	Keep in hospital for 24 hours on full diet off of all IV medications, on prednisone. CRP should **not** rise. Consider 40 mg only for patients who have responded very rapidly. Use 60 mg for patients who had failed outpatient prednisone, received IV steroids prior to transfer, or had high peak CRP and low albumin. PJP prophylaxis is appropriate when discharging on cyclosporine plus prednisone plus azathioprine. It is not indicated for prednisone plus a single IM.	Taper by 5 mg per week as an outpatient. Prescribe a **complete** taper to zero prednisone for all discharged patients. This is 546 5mg tablets from 60mg, 252 5mg tablets from 40mg. Do not push them off a cliff at 20 mg prednisone. Do not schedule an outpatient visit before the patient is at 20 mg of prednisone or less (they will be doing fine).
Accelerated Tofa/Upa	Consider **at admission** for severe UC with prior biologic failure, and/or high CRP with low albumin	Follow detailed protocol on p. 16/18
Infliximab Rescue	Consider if IV steroids failing by criteria at 72h, and IFX naïve, especially if Albumin > 3.	Follow detailed protocol on p. 20
Cyclosporine Rescue	Consider if IV steroids failing by criteria at 72h, and there is an exit strategy (thiopurines, vedolizumab, ustekinumab)	Follow detailed protocol on p. 22

*Obtain TPMT enzyme activity, not genotype, if considering thiopurines as therapy. Do not re-order if already measured when outpatient.
** Do not repeat Quantiferon TB if negative in past 6 months

Key Points for Surgical Team

1. On **day 3**, if the patient is not responsive to IV steroids, the surgical team will be called to:

a. Describe a three stage colectomy to the patient.
b. Explain the details of a subtotal colectomy to the patient.
c. Explain the difference between an abdominal colectomy with end ileostomy leaving the rectal stump in place with potential for future IPAA/IPRA, and a total proctocolectomy with end ileostomy.
d. Counsel the patient on the risks and benefits of an urgent surgery vs. an emergent (post-perforation, toxic megacolon) surgery.
e. Help the patient make an informed decision between surgery and rescue therapy (cyclosporine or infliximab) which will start at the end of day 3 if surgery is not the course of action chosen by the patient.
f. IBD School videos (on YouTube, videos 401-406) can help patients retain information on surgical options.

2. Patients transferred in to UMHS unresponsive to IV steroids be considered already at **day 3**, and will require urgent surgical consultation as in point 1.

3. Stop cyclosporine or infliximab or tofacitinib as soon as a decision is made to undertake surgery.

4. Watch for secondary adrenal insufficiency – stress dose at the time of surgery may be needed for patients with > 1 month of steroid exposure.

5. After surgery - standard steroid taper:
- For patients with less than 1 month of continuous steroid therapy before surgery, 10% decrease per day once stable after surgery. Can switch to oral once taking po.
- For patients with more than 1 month of continuous steroid therapy before surgery, taper by 5 mg of prednisone equivalent per week.

6. Warn patients about ongoing risk of adrenal insufficiency for up to 1 year.

7. No immunosuppressive maintenance therapy is needed after proctocolectomy.

8. At follow-up outpatient surgery appointment, consider initiating maintenance therapy for rectal stump with Canasa 1g PR qhs or 2g Rowasa (half-volume) PR qhs, to optimize tissue integrity if a future J pouch is being considered.

Infection Concerns

1. Do not over-react to a few CMV inclusions, or a low level positive CMV PCR. This is most often colonization unless it is very dramatic (hundreds of inclusions). A low level positive is usually a marker of disease severity and immunosuppression.

2. If Clostridium difficile toxin and C diff PCR are discordant, this could simply be colonization (occurs in 5-10% of IBD). If clinical suspicion is high, it is reasonable to treat for C diff.

3. **Do not delay** IV steroids while waiting for a C diff or GI PCR result in a very sick patient

Trough level Drug Measurements (TDM – Therapeutic Drug Monitoring)

1. Measurement of trough levels of biologic therapies can be useful when outpatients are failing biologic therapy, but will generally not return results for 7-10 days. These are generally **not** useful for inpatient care. On highly selected occasions, trough levels may be helpful for future outpatient dose adjustment. Clear with GI fellow or outpatient IBD specialist before ordering.

Fecal Calprotectin Measurements

Fecal calprotectin is a protein correlated with inflammation in the GI tract, but it can vary a lot from one bowel movement to the next. While it is a noisy biomarker, it is helpful for tracking steady outpatient changes and responses to therapy, but is can be slower to respond to therapy when compared to CRP. For this reason, FCP is not frequently measured in inpatients with ASUC, beyond a single value during a flare. FCP is currently run in batches on Mondays, Wednesdays, and Fridays at Michigan Medicine, so a sample collected on Friday noon will not produce a result until Monday afternoon. FCP may be helpful when a second extra-intestinal source of inflammation is present, and may confound CRP measurements, but standard daily response thresholds in the treatment of ASUC are not established. FCP can be used in relation to prior values, but the high variance of this biomarker must be considered when interpreting changing results over a short period of time.

Definition of Severe Colitis	**Concern for Toxic Megacolon**:(5)
per Truelove and Witts(1–4) includes all of: • ≥6 BM's a day • Temp>37.5 • Pulse >90 • Hgb<10.5 • ESR>30 • Weight Loss	Colonic distension ≥ 5.5 cm on supine abdominal film PLUS *at least* three of the following: • Fever >38ºC • Heart rate >120 beats/min • Neutrophilic leukocytosis >10,500/microL • Anemia • Dehydration • Altered sensorium • Electrolyte disturbances • Hypotension

Predictors of Colectomy

General Predictors of Colectomy(6)
Temp>37.5
Pulse >90
CRP>2.5, or >4.5 mg/dL on day 3 of IV steroids
Severe endoscopic findings
Hypoalbuminemia
Colonic dilation
Non-response to prior steroids
Clostridium difficile infection (suspect, retest if WBC rises to >20K during treatment)

Prediction of Colectomy on admission *(Truelove and Witts' criteria)*:
≥6 bloody stools/day and one or more of
Temp>37.5, Pulse >90, Hgb<10.5, ESR>30). If +1 additional criterion,
Risk of colectomy = 9%; if +2, risk = 31%; if +3 or 4, risk >40%

Scores for Prediction of Colectomy on DAY 3 (after 72h IV steroids):

Travis Index(3)	>8 BM's a day OR (>2 BM's and CRP>4.5 mg/dL) at day 3 **PPV of 85%**
Ho Index (7) *(Point System)*	colonic dilation > 5.5 cm = 4 points albumin< 3.0 on admission = 1 point average daily # stools over 1st 3d = [<4 (0pts), 4-6 (1pt) 6-9 (2pts) ≥9 (4pts)] **total of ≥ 4 Ho Index points on day 3 predicts 85% probability of failing iv steroids.**
Lindgren Score(8)	=stool frequency/d + 0.14 × CRP (mg/dL) **Lindgren Score>8 at day 3 PPV of 72 %**

Protocol Detail

Admission Day:

Medical:

- Assess Clinical Factors:
  - # bloody stools
  - # stools/24h
  - Urgency time
  - Presence of toxic megacolon
- Assess Lab Factors:
  - Comp, pre-albumin
  - CBCPD
  - ESR
  - CRP
  - Total Cholesterol
  - TPMT enzyme activity if not already obtained, or not already on azathioprine
  - Quantiferon TB test (or PPD) if none in the past year
  - Pregnancy test if female
- Record the number of Truelove & Witts' criteria, since this helps predict colectomy
- Studies:
  - Acute abdominal series to r/o toxic megacolon
  - Stool Culture
  - *Clostridium difficile* testing
  - GI PCR
  - Schedule flexible sigmoidoscopy for day 2
- Treatment:
  - Solumedrol 30mg IV Q12 (9) or 60mg q 24 (goal – approx. 1mg /kg per day). (5,10)
  - If urgency a major component, can add Canasa (mesalamine) 1 g PR bid-tid. When urgency is more mild (able to hold enemas for at least 30 min), switch to Rowasa (mesalamine) enemas 4 g PR bid.
  - Infuse 0.9 NS– goal urine SG < 1.005 and urine output >50cc/hr. Usually 5-10 L requirement in first 24h.
  - Lovenox 40 mg q 24h or SQ heparin 5000 U tid for risk of DVT while active inflammation and iv steroids. (11)
  - No TPN or PPN – high risk of catheter infection and UE DVT.
  - NO narcotics.
  - If urgency a major component, and no 5-ASA allergy, can add Canasa 1 g PR bid-tid.
  - Note: There is NO convincing prospective data to support the use of prophylactic antibiotics in severe ulcerative colitis.

Surgical Decision-Making:

Call surgery on day 1 to evaluate if:

- No response to prior OSH iv steroids or oral steroids for more than 5 days.
- AND blood in stools (suspect *Clostridium difficile* if nonbloody or WBC >20).
- OR evidence of megacolon (diameter $\geq$ 5.5cm).

Day 2:

Medical

- Assess Clinical Factors:
    - # bloody stools
    - # stools/24h
    - Urgency time (15 sec? 5-10 min?)
    - Clear urine output (goal clear and 50+ cc/hr)
    - Presence of toxic megacolon – call surgery if present
- Assess Lab Factors
    - Basic
    - CBCPD
    - ESR
    - CRP – **note that CRP will often go UP** from admission levels at 12-24 hours if a dehydrated patient with ASUC is volume repleted (often 5-10L) – as more cytokines (especially IL6) will travel from the colon to the liver, which will make more CRP in response.
- Studies:
    - Flex Sig
        - Tap Water Enema or Unprepped.
        - Bx: confirm UC, r/o C diff/CMV/HSV. Take edge (HSV) and center (CMV) of ulcers and also nearby non-ulcerated tissue. Send STAT to path.
- Treatment
    - SQ heparin or Lovenox for risk of DVT while active inflammation and iv steroids.
    - No TPN or PPN – high risk of catheter infection and UE DVT.
    - Solumedrol 30mg IV Q12 or 60 mg q 24 (Goal – approximately 1 mg/kg per day).
    - Diet as tolerated.
    - IVF to keep urine > 800 cc/d.
    - NO narcotics.
    - If urgency a major component, can add Canasa 1 g PR tid.

Surgical

Call surgery on day 2 if:

- Evidence of toxic megacolon.

Day 3:

Medical

- Assess Clinical Factors:

    - # bloody stools
    - # stools/24h
    - Urgency time
    - Presence of toxic megacolon
- Assess Lab Factors
    - Basic
    - CBCPD
    - CRP
    - PT, PTT
    - Pregnancy test if female.
- Studies:
    - QFTB results – in case infliximab used later.
    - Review Bx Results.
    - Abd film r/o Toxic Megacolon.
    - If not turning around, consider imaging evaluation for SB inflammation, r/o Crohn's if not done previously (SBFT, CTE).
- Treatment
    - SQ heparin or Lovenox for risk of DVT while active inflammation and iv steroids.
    - Keep NPO, No TPN or PPN – high risk of catheter infection and UE DVT
    - Solumedrol 30mg IV Q12 or 60 mg q 24 (Goal – approximately 1 mg/kg per day).
    - IVF to keep urine > 800 cc/d.
    - NO narcotics.
    - If INR elevated, correct vitamin K in case surgery needed.
    - If urgency a major component, can consider Canasa 1 g PR tid or try switching to Rowasa 4g bid.
    - Diet as tolerated.
- Day 3 Discussions
    - Discuss use of Cyclosporine if has NOT previously failed a good (adequate dose, at least 8 weeks) trial of azathioprine. If previously failed azathioprine, discuss infliximab vs. surgery.
    - Infliximab success rates are comparable to cyclosporine success rates in an UC European RCT of infliximab vs. cyclosporine out to 98 days. (12) This is important for patients who have failed previous adequate trials of thiopurines.
    - Discuss 2-3 fold higher risk of infections and surgical complications if infliximab fails surgery within 2 weeks of anti-TNF.(13–15)
    - If child-bearing age female, discuss 50% risk of infertility (though IVF works) after J pouch.(16)
    - Discuss surgical options:
        - Abdominal colectomy with end ileostomy leaving rectal stump in place with potential for future IPAA.
        - Total proctocolectomy with end ileostomy.

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Choosing a Medication Rescue Therapy	
Factors Favoring The Use of Cyclosporine	***Factors Favoring the Use of Infliximab***
Has never tried thiopurines or MTX Has not failed vedolizumab TPMT <15 Previous anti-TNF failure At risk for TB or Hepatitis B No insurance coverage for IFX Total cholesterol > 100	Has failed thiopurines at good doses for at least 12 weeks, or completely intolerant of thiopurines Never tried anti-TNF therapy TPMT >25 No latent TB or HBV Good insurance coverage for IFX Total cholesterol < 100

Please note: Vedolizumab (Entyvio) is an effective but slow-acting therapy for ulcerative colitis, and is NOT recommended as a rescue therapy. Vedolizumab can be very effective maintenance therapy <u>after</u> a patient has had rescue therapy with steroids, cyclosporine, or anti-TNF therapy.

<u>Surgical Decisions</u>

- Calculate Predictive Scores at 72 h of IV steroids: If any score Positive - Travis Rule (>8 BM's a day OR [>2 BM's and CRP>4.5 mg/dL] at day 3), or Ho Index points ≥4, or Lindgren SCORE >8, call surgery to evaluate.
- If evidence of toxic megacolon, call surgery.
- If predictive scores positive, discuss with patient and family that steroid treatment is failing, discuss cyclosporine, infliximab, AND plans for surgery as reasonable options, one of which must be started on day 4.
- Discuss with an experienced IBD specialist and a colorectal surgeon, and make a decision and have a clear plan BEFORE day 4.

Day 4:

<u>Medical</u>

- Assess Clinical Factors:
    - # bloody stools
    - # stools/24h
    - Urgency time
    - Presence of toxic megacolon
- Assess Lab Factors
    - Cholesterol
    - Magnesium
    - Comprehensive panel
    - CBCPD
    - CRP
- Studies:
    - Abd film r/o Toxic Megacolon if still sick.
- Treatment

- Start cyclosporine or infliximab OR go to surgery – discuss with experienced IBD specialist and colorectal surgery – do not delay this decision!
- SQ heparin or lovenox for risk of DVT while active inflammation and iv steroids.
- No TPN or PPN – high risk of catheter infection and UE DVT.
- Solumedrol 30mg IV Q12 or 60 mg q 24 (Goal – approximately 1 mg/kg per day).
- If urgency a major component, can consider Canasa 1 g PR tid or try switching to rowasa 4g bid.
- NPO.
- IVF to keep urine > 800 cc/d.
- NO narcotics.
- Diet as tolerated.
- If tolerated diet, and stools <4, little or no blood, ESR<30 and CRP <1.0, convert to oral prednisone.
- If improving, make a decision about maintenance therapy –return to azathioprine, or start azathioprine, or start biologic therapy.

<u>Surgical Decision-making</u>

Call surgery on day 4 if:

- Evidence of toxic megacolon
- AND blood in stools (suspect *Clostridium difficile* if nonbloody or WBC >20)
- If toxic megacolon, take to OR

- If not improving, plan to make OR decision on day 5, possible OR on day 6 or 7.

Day 5:

<u>Medical</u>

- Assess Clinical Factors:
  - # bloody stools
  - # stools/24h
  - Urgency time
  - Presence of toxic megacolon
- Assess Lab Factors
  - Basic
  - CBCPD
  - ESR
  - CRP
  - PT, PTT
- Studies:
  - Abd film rule out toxic megacolon if still sick
  - Evaluate predictive Score: If Travis Rule (>8 BM's a day OR [>2 BM's and CRP>4.5 mg/dL] at day 3), Ho Index points ≥4, or Lindgren SCORE >8 proceed with surgery vs. choose cyclosporine – Note success rate of cyclosporine changes with Ho index points.

- Criteria for Predicting Cyclosporine response after steroid failure:
  1. Ho Index points at day 5 of IV steroids: Ho index score <6 after at least 5d IV steroids, success with cyclosporine is ~ 95%, while if Ho index ≥ 6, then colectomy-free success is ~58%.(18) (prospective validation).
  2. Cacheaux Criteria: peak HR > 90, peak Temp > 37.5, CRP > 4.5. 6 month colectomy rates 22% if 0 criteria, 47% if 1, 55% if 2, 90% if all 3 present.(6) For 1 or 2 criteria – absence or presence of severe endoscopic lesions can predict cyclosporine response. (Retrospective study)

- Treatment
  - SQ heparin or lovenox for risk of DVT while active inflammation and iv steroids.
  - No TPN or PPN – high risk of catheter infection and UE DVT.
  - Solumedrol 30mg IV Q12 or 60 mg q 24 (Goal – approximately 1 mg/kg per day).
  - IVF to keep urine > 800 cc/d
  - NO narcotics.
  - If urgency a major component, can consider Canasa 1 g PR tid or try switching to rowasa 4g bid.
  - Choose add Cyclosporine (if can bridge to azathioprine) vs. Surgery – note that if Ho index score <6 after at least 5d IV steroids, success with cyclosporine is ~ 95%, while if Ho index ≥ 6, then colectomy-free success is ~58%.(17)
  - If surgery looks likely, get pre-op EKG if > 50 of age and CXR if the patient has any pulmonary complaints.
  - If tolerated diet, tolerated oral prednisone without worsening, stools still <4/d and no blood, plan steroid taper, start maintenance medication (azathioprine or biologic), and prepare for discharge.
  - If improving, start maintenance therapy if a change is to be made.
- Surgical Decision-making
  - IF failing intravenous steroids (score >8, Ho Index points ≥4, etc.), and not choosing cyclosporine, proceed with surgical option as detailed by surgeon on day 6 or 7.
  - IF failing intravenous steroids (score >8, Ho Index points ≥4, etc.), and previous failure of a good trial of azathioprine or 6MP, revisit the pros and cons of infliximab vs. colectomy.
  - Watch for secondary adrenal insufficiency – may need to taper steroids slowly.

Preparing for Discharge

1. A patient approaching safe discharge will have a low CRP, generally < 5 mg/L (0.5 mg/dL), is able to take a full diet, has fewer than 5 BM/24 hours with some form, and has minimal if any blood in the stool.
2. Patients with significant iron deficiency anemia can receive IV iron therapy during their admission, and be set up for continued repletion as outpatients.
3. Patients should be transitioned to oral prednisone for 24 hours prior to discharge. As 60 mg of solumedrol is roughly equivalent to 80 mg of prednisone, very few patients should go directly from IV solumedrol to 40 mg of prednisone (only those who responded very rapidly). Most should transition to 60 mg of daily prednisone. They should be able to tolerate a full diet, not need IV fluids, be able to walk the floor (not restricted to room by urgency) and be prepared to function at home on prednisone to minimize readmissions.
4. The standard prednisone taper is 5 mg per week. Patients should be sent home with a **complete** steroid taper to zero mg prednisone. This requires 546 5mg tablets from a 60 mg starting dose, or 252 5mg tablets from a 40 mg starting dose. Do not push them off a cliff at 20 mg prednisone by ending their prescription early.
5. Refer all post-ASUC patients to the IBD Transitions of Care program. Make sure all patients have access to the Epic patient portal. Let the patient know that a nurse practitioner will contact them about their medications and symptoms. This program will monitor outpatient CRP and FCP and patient symptoms during the steroid taper.
6. Schedule an outpatient visit with the IBD PA or their outpatient GI for when the patient is at 20 mg of prednisone or less.
7. Recommend DEXA at outpatient visit if patient has been on corticosteroids for more than 3 months (lifetime) without a prior DEXA evaluation.
8. Patients who have not received Prevnar or pneumovax in the past 5 years should be recommended for these at their follow up when off prednisone.

Preparing for Surgery

- Stop cyclosporine or infliximab or tofacitinib as soon as a surgical decision is made.
- Watch for secondary adrenal insufficiency – stress dose at time of surgery may be needed for patients with > 1 month of steroid exposure.
- Standard steroid taper after surgery:
  - For patients with less than 1 month of continuous steroid therapy before surgery, 10% decrease per day once stable after surgery
  - For patients with more than 1 month of continuous steroid therapy before surgery, taper by 5 mg of prednisone equivalent per week.
- No immunosuppressive maintenance therapy is needed after proctocolectomy.
- In 2 weeks at surgery appointment, consider maintenance therapy with Canasa 1g PR qhs or 2g Rowasa PR qhs after subtotal colectomy, to optimize tissue for future J pouch.
- Warn patients about ongoing risk of adrenal insufficiency for up to 1 year.

Why Not to Consider a Second Rescue Medication

Occasionally, after failure of steroids and failure of a 1st rescue medication, the patient would like to try a 2nd rescue medication rather than surgery. When this combines cyclosporine with infliximab, this carries increased risk of serious infection (20-40%) and a risk of death, often by pneumonia or pulmonary embolism (18–20). These risks must be discussed with the patient, and considered relative to the risk of urgent (rather than emergent) colectomy. Remember that infliximab often stays in the system for 8 weeks or more after use. "Switching" from infliximab to cyclosporine is not truly a switch – it is a combination.

The combination of infliximab and tofacitinib (or the sequential use of tofacitinib after infliximab) is associated with significantly increased infectious risks, and is **not** recommended.

The combination of cyclosporine and tofacitinib is not well studied, and given the many infections associated with the combinaton of cyclosporine and infliximab, is **not** recommended. While in theory, these drugs have short measurable serum half-lives, they do have extended biologic activity (they work intracellularly), and may interact in unexpected ways.

Only after extensive consultation with both an IBD specialist and the surgical team should a second rescue medication be considered. These discussions of significantly increased risk must be documented carefully in the medical chart.

If switching from cyclosporine to infliximab:

- Stop cyclosporine for at least 48 hours before infliximab is begun
- Continue iv steroids
- Continue prophylaxis with trimethoprim/sulfamethoxazole.
- The duration of the biologic effects of cyclosporine is not well known, though the half-life is short.

If switching from infliximab to cyclosporine:

- Last dose of infliximab should be at least 72 hours prior to cyclosporine initiation.
- Continue iv steroids

- Continue prophylaxis with trimethoprim/sulfamethoxazole.
- Be aware that the biologic effects of infliximab will continue for at least 8 weeks.

Accelerated Tofacitinib Protocol

Recent case series (21) and case-control data (22) have suggested that high-risk patients likely to fail 72 hours of IV solumedrol could benefit from initiation of accelerated tofacitinib dosing with the initiation of IV corticosteroids. This is **NOT** a rescue therapy, but an initial co-therapy with corticosteroids. While the case-control study showed an association between tofacitinib 10 mg tid with reduced 90-day colectomy rates by 85%, there was no measurable association with tofacitinib 10 mg bid.

This approach has not been supported by a randomized controlled trial, and tofacitinib is not FDA-approved for use in inpatients. This approach should only be undertaken in consultation with an IBD specialist.

Patient Selection

Patients who are most likely to benefit from accelerated tofacitinib plus IV corticosteroids are

- Those who have previously failed biologics, especially infliximab
- Those who have recently failed outpatient prednisone at 40 mg daily or more
- Those who have recently failed IV corticosteroids at another hospital before transfer
- Those with a high CRP to Albumin ratio on admission (CRP in mg/dL divided by Albumin in g/dL > 2, or (SI units) CRP in mg/L divided by Albumin in g/L > 200)

Patients who should be considered to have a relative contraindication to tofacitinib include

- Patients with strong personal history of VTE/PE who are **not** on effective anticoagulation
- Pregnant patients
- Toxic megacolon
- Use of strong CYP3A4 inducing medications
- Recent history of incompletely treated malignancy
- Neutropenia with baseline ANC < 100 cells/mm3, Lymphopenia with baseline ALC < 500 cells/mm3
- Severe hepatic or renal impairment

Use of Accelerated Tofacitinib

Stop any other immunomodulators, including thiopurines (azathioprine, mercaptopurine), methotrexate, and tacrolimus, before initiating tofacitinib. Contact the Specialty Pharmacy to begin the process of prior authorization and/or patient assistance programs for the planned outpatient dose of 10 mg po bid x 8 weeks after discharge.

Along with the initiation of IV corticosteroids, begin tofacitinib at 10 mg tid – with the first dose when IV steroids begin. Vigorously hydrate patients as per the standard protocol, with 5-10L IVF in the first 24 hours, until clear urine with a UOP > 50 cc/hr is

sustained. Continue at 10 mg tid until a goal CRP of less than 5 mg/L (0.5 mg/dL) is reached.

Monitor CRP and document clinical symptoms every 24 hours. Expect that CRP will fall at least 20% on each of the first 3 days. Note that there may be an initial rise in CRP in the first 12 hours when vigorous hydration is achieved. The fall in CRP may slow to a decay curve after the first 3 days, but should keep falling each day on tofacitinib 10 mg tid plus IV corticosteroids.

Anticoagulation with daily enoxaparin should begin with IV corticosteroids, and continue until discharge. We have no evidence that this is cost-effective to continue after discharge, and have not documented any VTE/PE in 40 previous patients treated with this protocol.

A rise in CRP on this combination therapy is a very bad prognostic sign, and colectomy is nearly inevitable. Tofacitinib should be stopped as soon as a surgical decision is made, and should wash out for at least 18 hours prior to surgery unless emergent surgery is required for perforation or toxic megacolon.

At CRP goal of < 5 mg/L, tofacitinib can be reduced to 3 doses per day of 10/5/10 mg. If this goes well, without recurrence of symptoms or a rise in CRP, the patient can proceed to tofacitinib 10 mg bid the following day. Conversion from IV to oral steroids (see discharge recommendations above) generally occurs on this day. If the patient can tolerate a full diet on tofacitinib 10 mg bid with oral prednisone, and without IV fluids & without severe urgency for 24 hours, they are ready for discharge.

Plan for a standard steroid taper by 5 mg per week, with continuation of tofacitinib 10 mg bid for 90 days post-discharge while the steroid taper is ongoing. At this point, the outpatient GI physician and patient can decide whether to stay on tofacitinib as a maintenance therapy, or to use it as a bridge to another therapy. Biologic therapies can be overlapped with tofacitinib for a short time (usually the last 15-30 days of tofacitinib, when finishing prednisone), but extended combination therapy with tofacitinib is not recommended.

Accelerated Upadacitinib Protocol

Upadacitinib is an option for ASUC since the Michigan Medicine Inpatient Formulary added this for UC on June 17, 2022. Recent clinical trial data (23) and network meta-analyses (24) have suggested that upadacitinib is roughly 2.5x more effective for induction of clinical remission in outpatient moderate to severe ulcerative colitis than tofacitinib. This is **NOT** a rescue therapy, but an initial co-therapy with corticosteroids. While upadacitinib is provided as a sustained-release formulation, the majority of the drug is absorbed in the first 6 hours, and the serum levels after 6 hours are nearly the same as an immediate release formulation (25).

This approach has not been supported by a randomized controlled trial, and upadacitinib is not FDA-approved for use in inpatients. This approach should only be undertaken in consultation with an IBD specialist.

Patient Selection

Patients who are most likely to benefit from accelerated upadacitinib plus IV corticosteroids are

- Those who have previously failed biologics, especially infliximab
- Those who have recently failed outpatient prednisone at 40 mg daily or more
- Those who have recently failed IV corticosteroids at another hospital before transfer
- Those with a high CRP to Albumin ratio on admission (CRP in mg/dL divided by Albumin in g/dL > 2, or (SI units) CRP in mg/L divided by Albumin in g/L > 200)

Patients who should be considered to have a relative contraindication to upadacitinib include

- Patients with strong personal history of VTE/PE who are **not** on effective anticoagulation. Therapeutic anticoagulation mitigates risk.
- Pregnant patients
- Patients with toxic megacolon
- Use of strong CYP3A4 inducing medications (azoles, clarithromycin)
- Recent history of incompletely treated malignancy
- Neutropenia with baseline ANC < 100 cells/mm3, Lymphopenia with baseline ALC < 500 cells/mm3
- Severe hepatic or renal impairment

Use of Accelerated Upadacitinib

Stop any other small molecule immunomodulators, including thiopurines (azathioprine, mercaptopurine), methotrexate, cyclosporine, and tacrolimus, before initiating upadacitinib. Contact the Specialty Pharmacy to begin the process of prior authorization and/or patient assistance programs for the planned outpatient dose of 45 mg po qd x 8 weeks after discharge.

Along with the initiation of IV corticosteroids, begin upadacitinib at 30mg bid – with the first dose when IV steroids begin. Vigorously hydrate patients as per the standard protocol, with 5-10L IVF in the first 24 hours, until clear urine with a UOP > 50 cc/hr is sustained. Continue Upa at 30 mg bid until a goal CRP of less than 5 mg/L (0.5 mg/dL) is reached.

Monitor CRP and document clinical symptoms every 24 hours. Expect that CRP will fall at least 20% on each of the first 3 days. Note that there may be an initial rise in CRP in the first 12 hours when vigorous hydration is achieved. The fall in CRP may slow to a decay curve after the first 3 days, but should keep falling each day while on upadacitinib 30 mg bid plus IV corticosteroids. Expect to reach a CRP of 15 mg/L at later dates when starting with a higher peak CRP. Roughly, day 3 when peak CRP ~ 50-100, day 4 for 100-150, day 5 for 150-200, and day 6+ when peak CRP >200.

Anticoagulation with daily enoxaparin should begin with IV corticosteroids, and continue until discharge. We have no evidence that this is cost-effective to continue after discharge, and have not documented any VTE/PE in 40 previous patients treated with this protocol (with tofacitinib).

A rise in CRP on this combination therapy is a very bad prognostic sign, and colectomy is nearly inevitable. Upadacitinib should be stopped as soon as a surgical decision is made, and should wash out for at least 18 hours prior to surgery unless emergent surgery is required for perforation or toxic megacolon.

At a CRP level of 15 mg/L or less, switch IV corticosteroids to prednisone, usually at 60 mg daily. Plan to taper by 5 mg per week. At this point patients should thrive on a full diet and Upa 30 bid with prednisone for 24 hours before discharge. Taper Canasa or Rowasa to qhs at this point.

At CRP goal of < 5 mg/L, upadacitinib can be reduced to 45 mg once daily, generally making this change at the time of discharge from the hospital.

Plan for a standard steroid taper by 5 mg per week, with continuation of upadacitinib 45 mg qd for 8 weeks days post-discharge while the steroid taper is ongoing. At this point, the outpatient GI physician and patient can decide whether to stay on upadacitinib as a maintenance therapy at 30 mg po daqily, or to use it as a bridge to another therapy. Biologic therapies can be overlapped with upadacitinib for a short time (usually the last 15-30 days of upadacitinib), but extended combination therapy with upadacitinib has not been tested and is not recommended.

Very severe UC patients with a high burden of inflammation are likely to need to continue on 30 mg upadacitinib daily for maintenance. Those with a lesser inflammatory burden (lower peak CRP, FCP, a shorter extent of colitis) may be able to titrate down to 15 mg upadacitinib daily after 90 days at 30 mg qd. If this down-titration is performed, close monitoring of FCP and CRP before and after dose reduction should be done, and dose re-escalation if inflammatory markers rise.

Infliximab (Remicade/Inflectra) Rescue Protocol

1) Eligible patients:
    a. Proven UC on severe UC protocol.
    b. Meets criteria for severe UC.
    c. QFTB (or PPD) negative.
    d. Active inflammation – CRP elevated, flex sig consistent with UC.
    e. No *C diff* (PCR), CMV (get final path read), other infections.
    f. Intravenous steroids for 72 h, with positive Travis index, Ho index, etc.
2) Initial dosing with 10 mg/kg, starting with 1st dose.
3) 60-66 h after 1st infliximab infusion, check CRP and HACA
    a. If CRP >80% of previous level (still high), go to surgery.
    b. If CRP reduced by 20% or more from previous level, but still ≥ 0.7 mg/dL, repeat steps 2 and 3, with next dose 72 h after previous dose. Second dose, if needed, should be 10 mg/kg (with dose rounded up to nearest 100 mg) and this should be discussed with surgery.
    c. If CRP reduced to < 0.7 mg/dL, schedule next infusion for 2 weeks later, then 6 weeks later, then q 8 weeks (notify outpatient nurses ASAP).
4) 60-66 h after 2nd infliximab infusion, check CRP
    a. If CRP > 0.5 (still high) and symptomatic, go to surgery.
    b. If CRP reduced to ≤ 0.5 mg/dL, schedule next infusion for 2 weeks later, then 6 weeks later, then q 8 weeks (notify outpatient nurses ASAP).
    c. Do not give a 3rd inpatient dose of infliximab. Our experience is that patients who do not respond to sequential doses of 5 and 10 mg/kg will not respond to additional doses.
5) When CRP ≤ 0.5 and symptomatically doing well, convert to oral steroids, 40 mg prednisone daily, advance diet.

    Discharge Criteria:

    - next outpatient infusion scheduled.
    - on oral prednisone for 24 h.
    - Eating a full diet.
    - discharge on prednisone taper by 5 mg per week.

Logistic Requirements for Discharge of Patients Starting Infliximab as an Inpatient at the University of Michigan
Identify nurse for outpatient GI who will follow up with patient
Send an email to nurse and outpatient GI, identifying: - Patient - Registration number - Date of first dose of IFX - Date on which next dose needed (14 days after last dose) - Dose 10 mg/kg for at least 14 weeks with trough at week1 - Patient weight in kg - Whether a previous infusion reaction to IFX occurred
Do not discharge until an appointment is confirmed for the next infusion.

Logistic Requirements for Discharge of Patients Starting Infliximab as an Inpatient at the AA VA
Consult attending to write orders for the inpatient use of Infliximab. At discharge, however, a COU order needs to be placed with the following information:
- Patient - Registration number - Date of first dose of IFX - Date on which next dose needed (14 days after last dose) - Dose (5 or 10 mg per kg) - Patient weight in kg - Whether a previous infusion reaction to IFX occurred - Identify follow-up GI provider. Email Bridgette.Flowers@va.gov

6) Notes for pregnant patients
    a. Plan on q 8 week infusions until ~ 24 weeks.
    b. Adjust interval to move last dose to ~ 32 weeks (earlier than q 8 weeks if needed).
    c. Plan on next dose the day after delivery, with 100 mg hydrocortisone premedication.
    d. Continue q 8 weeks, with hydrocortisone used as a premedication for the first 3 post-delivery infusions, then try to infuse without it.
7) Consider adding azathioprine for added effect, reduction of anti-infliximab antibodies, especially in new, high CRP (SONIC-like) patients.

Cyclosporine Rescue Protocol (8,26,27)

Labs before use:

- Creatinine.
- Cholesterol >80 mg/dl – if 80-120 and choose to proceed, use seizure protocol.
- Magnesium > 1.5 mg/dl.
- Pregnancy test. Women should be on birth control if doing therapy.

Inpatient use of cyclosporine IV (28)

Induction

- Surgical discussions, and detailed discussion of colectomy option, should always occur before cyclosporine is initiated.
- Start at 2 mg/kg/day (27) of intravenous cyclosporine as a continuous infusion. Always infuse in volume of 100cc, over 24 hours (rate 4.2 mL/hour). ONLY make changes in the number of milligrams to prevent confusion over the rate.
- For example, for a 72-kg patient, the order is written as follows: "Infuse cyclosporine 144 mg in 100 cc D5W in a glass bottle over 24 hours as a continuous infusion."
- Continue IV Steroids.
- Continue DVT prophylaxis.
- No TPN or PPN – high risk of catheter infection and UE DVT.
- While patients are on triple therapy (cyclo, Aza, steroids) patients should be maintained on DS Bactrim/Septra (MWF) for PCP prophylaxis due to risk of infection.{Citation}
- Monitoring the first hour of infusion:
  - monitor for signs of allergy or anaphylaxis (hypotension, hives, wheezing, laryngeal spasm) every 15 min. Discontinue the infusion if any such signs develop and treat with subcutaneous epinephrine and diphenhydramine, as necessary, as with any allergic reaction.
  - if unable to tolerate cyclosporine, need to re-address and discuss options of colectomy and infliximab.
- Monitoring at 18-24 hours: check cyclosporine level, if >300 (likely to overshoot goal), decrease rate by 25%.

Monitoring on Therapy

Review for adverse effects	Daily
Blood pressure	Q4h while awake
Cyclosporine level	start on 2nd day - Daily until stabilizes, then q2d
Serum creatinine	Every 2nd day *
Serum potassium	Every 2nd day *
Serum magnesium	Every 2nd day *
Serum cholesterol	Daily if <140 mg/dl
Liver function tests	Every 2nd day *
ESR and CRP	Every 2nd day
Stool number and presence of blood	Daily

* Daily, if abnormal.

- Monoclonal radioimmunoassay should be used to obtain cyclosporine levels starting on day 2 of therapy, with the aim of achieving whole blood levels of 300 (range 200-400) ng/ml. This blood test is obtained in a lavender-top tube.
- The intravenous cyclosporine dosage is rarely raised above 4 mg/kg/day, in rare patients who are fast metabolizers.

Cyclosporine Dose adjustment table

Cyclosporine Level	Dose/rate adjustment
0-100	Increase mg by 50%
100-150	Increase mg by 33%
150-200	Increase mg by 20%
200-400	No change
400-500	Decrease mg by 20%
500-600	Decrease mg by 33%
Over 600	Decrease mg by 50%

- Reduce cyclosporine infusion mg if drug levels are greater than 400 ng/ml or if serum creatinine increases by 30% over baseline, serum liver enzymes double, diastolic blood pressure exceeds 90 mm Hg, or systolic blood pressure exceeds 150 mm Hg despite anti-hypertensive treatment.
- Increase cyclosporine infusion rate if drug levels are less than 100 ng/ml after the 2nd day, and < 200 ng/mL after the 3rd day.
- If hungry, and negative markers – BM <8, CRP < 4.5, albumin >3, etc., discuss stress testing colon on following day with clear liquids. Advance diet slowly only if tolerated.
- If unable to eat by day 9, and albumin <2.5, consider drip elemental feeds via Dobhoff or G tube at a rate of 5-20 cc/hr to nourish intestine.
- Evaluate stool, stool blood, ESR, and CRP response on day 10 (day 5 of cyclosporine). If not 50% response, plan expectantly for surgery ~ day 12.
- Evaluate stool, stool blood, ESR, and CRP response on day 12 (day 7 of cyclosporine). If not 90% response, plan for surgery ~ day 13.
- NOTE: case series of patients who have failed cyclosporine and tried salvage infliximab rather than colectomy have had little success and a high rate of serious adverse events.(29)

Maintenance

In patients who respond to 3-7 days of intravenous cyclosporine, the drug is changed to the oral formulation:

- Solumedrol is changed to oral Prednisone, 40-60 mg daily.(30) Consider 40 mg for patients who have responded rapidly. Use 60 mg for patients who had failed outpatient prednisone, received IV steroids prior to transfer, or had high peak CRP and low albumin.
- On that evening, intravenous cyclosporine is discontinued at 8 PM.
- The following morning, cyclosporine level is determined at 8 AM immediately preceding the first oral dose.

- The oral dose is calculated to be approximately twice the daily intravenous dose or approximately 5 mg/kg, rounded to nearest 25 mg, and is administered every 12 h (*i.e.*, a 70-kg patient treated with 2 mg/kg/day, intravenous cyclosporine, or 140 mg daily, is treated with 150 mg q 12 h of the oral cyclosporine capsules). Oral cyclosporine solution can be administered as Neoral gel capsules available in 25-, 50-, or 100-mg doses.
- The patient may be discharged home after 1-2 days of observation on oral cyclosporine with daily levels and is continued on Prednisone, 60 mg/day.
- Plan to taper prednisone by 10 mg q week until at 40 mg, then by 5 mg q week.
- Start azathioprine – 2-2.5 mg/kg if TPMT > 13, 1-1.5 mg/kg if TPMT <13.
- While patients are on triple therapy (cyclo, Aza, steroids) patients should be maintained on Bactrim/Septra daily for PCP prophylaxis due to risk of infection.(31)

Outpatient Monitoring on Therapy

- Patients are followed weekly for the first month and then bi-weekly for the second month and then at least monthly.
- At each visit, assess their clinical status, ask specifically for any drug-associated adverse effects.
- Check a complete blood count, serum chemistries, serum magnesium, and 12-h trough cyclosporine levels. Aim for trough cyclosporine levels of 150-300 ng/ml during the outpatient phase.
- Never increase the oral dose above 8 mg/kg/day.
- Oral MgSO4 or magnesium injections (magnesium sulfate 50% solution, 1-2 ml intramuscularly) are often required to correct hypomagnesemia.

Test Frequency

Office visit and review for adverse effects	Weekly x 4 then biweekly x 2 then Q3-4 weeks
Cyclosporine level, serum chemistries, magnesium, CBC, ESR	With each visit as above and within1 weeks after any dose change

Tapering prednisone and cyclosporine

- Lower the daily Prednisone dosage by 10-mg decrements each week until 40 mg is reached and then reduce the daily dose by 5 mg weekly or every other week, as tolerated.
- Patients who cannot be clinically maintained on 20 mg of Prednisone daily by week 8 are considered cyclosporine failures and are referred for surgery.
- After 15-20 mg of daily Prednisone, some patients will require even smaller dose reductions (2.5 mg q week).
- All patients should be entirely weaned off Prednisone within 6 months of hospital discharge.
- Discontinue cyclosporine at 3 months by reducing the dose by 50% for 2 weeks, followed by complete cyclosporine withdrawal.
- A flexible sigmoidoscopy is generally performed after 6-8 weeks of therapy and colonoscopy at 4-6 months, in anticipation of discontinuing cyclosporine.

- At 6 months, the patient who is in remission is then maintained on azathioprine or methotrexate, and (optionally) also a maintenance dose of a 5-ASA drug.
- **Refer to surgery early in this period so that surgeons are aware of patient.**

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