

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 Day 1	Comp, pre-albumin, CBCPD, ESR, CRP, Total Cholesterol, TPMT enzyme activity*, Quantiferon*, Abdominal film, Stool Culture, C diff, CMV PCR, GI PCR, iron saturation, Schedule Flex sig for d2 Record: # stools, # with stool blood, urgency time, signs of toxicity. Get GI Consult service involved. Call Surgery (ACS) if patient was on OP Steroids or IV Steroids 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.	Lovenox 40q24 or SQ heparin5000 U tid IV fluid to produce clear urine output >50cc/hr x ≥8 h: goal ≥5L in 1 st 24hr NPO Bedside commode IV Steroids if no infection consider Rectal Rx
Day 2	Basic, CBCPD, Flex Sig, CRP Record: # stools, # with stool blood, urgency time, signs of toxicity	Lovenox 40q24 Titrate IV fluid to UOP NPO continue IV steroids consider Rectal Rx
Day 3	Basic, CBCPD, ESR, CRP, PT/PTT, Review Quantiferon, Review Bx results, Abd film, consider SB imaging*, Check <i>C diff</i> result Record: # stools, # with stool blood, urgency time, signs of toxicity Calculate risk indices, DOCUMENT IN NOTE Call surgery if ANY of the three risk indices are positive. IBD School 400s.	Lovenox 40q24 Titrate IV fluid to UOP Consider NPO if not improving. Continue IV steroids consider Rectal Rx if INR up, consider Vit K Consider clear liquid diet if hungry
Infliximab Rescue	Follow detailed protocol on p. 15	
Cyclosporine Rescue	Follow detailed protocol on p. 10	
Day 4 If no rescue	Comp, Mg, CBCPD, CRP Record: # stools, # with stool blood, urgency time, signs of toxicity	Lovenox 40q24 Titrate IV fluid to UOP Rectal Rx Consider soft diet if hungry
Day 5 If no rescue	Basic, CBCPD, ESR, CRP, PT/PTT, Abd film if sick Record: # stools, # with stool blood, urgency time, signs of toxicity Calculate predictive scores Call surgery if CRP still > 1 mg/dL and/or ≥ 5 BM's a day	Lovenox 40q24 Titrate IV fluid to UOP Rectal Rx, Consider soft diet if hungry Decide on taper – consider oral steroids. If not improving, not eating – consider NPO, revisit with surgery

Key Points for Surgical Team

1. On **day 3**, if the patient is not responsive to IV steroids (risk indices positive 72 h after starting 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.
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 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 total colectomy or proctocolectomy.
8. At follow-up outpatient surgery appointment, consider initiating maintenance therapy for rectal stump with Canasa 1g PR qhs or 2g Rowasa 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 (negative result) and C diff PCR (positive result) 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 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, but generally will not return results for 7-10 days. These are usually not useful for inpatient care, but may be helpful for future outpatient dose adjustment. Clear with GI fellow before ordering.

<p><u>Definition of Severe Colitis</u></p> <p><i>per Truelove and Witts</i>(1-4) includes all of:</p> <ul style="list-style-type: none"> • ≥ 6 BM's a day • Temp > 37.5 • Pulse > 90 • Hgb < 10.5 • ESR > 30 • Weight Loss 	<p><u>Concern for Toxic Megacolon:</u>(5)</p> <p>Colonic distension ≥ 5.5 cm on supine abdominal film PLUS <i>at least</i> three of the following:</p> <ul style="list-style-type: none"> • Fever $> 38^{\circ}\text{C}$ • Heart rate > 120 beats/min • Neutrophilic leukocytosis $> 10,500/\text{microL}$ • Anemia • Dehydration • Altered sensorium • Electrolyte disturbances • Hypotension
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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 $> 20\text{K}$ 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 $> 40\%$

Risk Indices: Prediction of Colectomy on DAY 3 (after 72h IV steroids):

Travis Index (3)	<p>> 8 BM's a day OR (> 2 BM's and CRP > 4.5 mg/dL) at day 3 (3)</p> <p style="text-align: center;">PPV of 85%</p>
Ho Index (7) (Point System)	<p>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)]</p> <p style="text-align: center;">total of ≥ 4 Ho Index points on day 3 predicts 85% probability of failing iv steroids.</p>
Lindgren Score (8)	<p>=stool frequency/d + $0.14 \times$ CRP (mg/dL)</p> <p style="text-align: center;">Lindgren Score > 8 at day 3 PPV of 72 %</p>

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 (or PPD if available) 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 15mg IV Q6 (9) or 60mg q 24 or 2.5 mg/h continuous drip (goal – approx. 1mg /kg per day). (5, 10)
 - If urgency a major component, can add Canasa 1 g PR bid-tid.
 - Infuse 0.9 NS– goal urine SG < 1.005 and urine output >50cc/hr. Usually 4-8 L requirement in first 24h.
 - SQ heparin 5000 U tid or Lovenox 40 mg q 24h 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 (earlier than usual) to evaluate patient if high risk:

- 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), tachycardic, febrile.

Day 2:

Medical

- Assess Clinical Factors:
 - # bloody stools
 - # stools/24h
 - Urgency time
 - Presence of toxic megacolon
- Assess Lab Factors
 - Basic
 - CBCPD
 - ESR
 - CRP
- Studies:
 - Flex Sig
 - Tap Water Enema or Unprepped.
 - Bx: confirm UC, r/o C diff/CMV/HSV. Take biopsies from edge and center of ulcers and 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 15mg IV Q6(9) or 60 mg q 24 or 2.5 mg/h continuous drip (Goal – approximately 1 mg/kg per day).
 - Diet as tolerated.
 - IVF to keep urine > 800 cc/d.
 - NO narcotics.
 - If rectal urgency a major component, can add Canasa 1 g PR tid.

Surgical

Call surgery on day 2 if:

- Evidence of toxic megacolon.
- AND blood in stools (suspect *Clostridium difficile* if nonbloody or WBC >20).

Day 3 (Decision Day at 72 h on IV steroids):

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 to evaluate colon diameter for Ho index, and to r/o Toxic Megacolon.
 - If not turning around, consider imaging evaluation for SB inflammation, to 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 15mg IV Q6(9) or 60 mg q 24 or 2.5 mg/h continuous drip (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 rectal 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.
 - Criteria for Predicting Cyclosporine response after steroid failure:
 1. Ho Index points on IV steroids: Ho index score <6 after IV steroids, success with cyclosporine is ~ 95%, while if Ho index ≥ 6, then colectomy-free success is ~58%.(12) (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)
 - Infliximab success rates are comparable to cyclosporine success rates in an UC European RCT of infliximab vs. cyclosporine out to 98 days. (13) 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 and surgery is needed within 2 weeks of anti-TNF dosing.(14-17)
 - If child-bearing age female, discuss 50% risk of infertility (though IVF works) after J pouch.(18)
 - Discuss surgical options, recommend IBD School 400 series videos to patients: (<http://www.med.umich.edu/ibd/school/index.html>)
 - Abdominal colectomy with end ileostomy leaving rectal stump in place with potential for future IPAA.
 - Total proctocolectomy with end ileostomy.

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

Please note: Tacrolimus can be used in place of Cyclosporine as a rescue therapy

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 after a patient has had rescue therapy with steroids, cyclosporine, or anti-TNF therapy.

Surgical Decisions

- Calculate Predictive Risk Indices at 72 h of IV steroids: If Travis Rule Positive (>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, and blood in stool, call surgery to evaluate.
- If evidence of toxic megacolon, call surgery.
- If predictive risk indices positive, discuss with patient and family that steroid treatment is failing, discuss cyclosporine, infliximab, AND plans for surgery as reasonable options that must be started on day 4.
- Discuss with an experienced IBD specialist and a colorectal surgeon, and make a decision BEFORE day 4.

Medical Rescue Decisions

- If patient chooses medical rescue over surgery, proceed to infliximab (page 15) or cyclosporine (page 10) protocol
- For a low-risk patient (all indices negative after 72h of steroids), can proceed with IV steroid monotherapy on days 4 – 5 below.

Day 4 (if not rescued)

Medical

- Assess Clinical Factors:
 - # bloody stools
 - # stools/24h
 - Urgency time
 - Presence of toxic megacolon
- Assess Lab Factors
 - Magnesium
 - Comprehensive panel
 - CBCPD
 - CRP

- Studies:
 - Abd film r/o Toxic Megacolon if still sick.
- Treatment
 - Rescue pathway: 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 15mg IV Q6(9) or 60 mg q 24 or 2.5 mg/h continuous drip (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 infliximab.

Surgical Decision-making

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 or if CRP rising, take to OR

Day 5 (if not rescued):

Medical

- 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
- 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 15mg IV Q6(9) or 60 mg q 24 or 2.5 mg/h continuous drip (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.
- 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 plan on outpatient biologic initiation), and prepare for discharge.
- If improving, start maintenance therapy if a change is to be made.
- Surgical Decision-making
 - IF failing intravenous steroids at day 5 despite being low risk on Day 3, proceed with surgical option as detailed by surgeon on day 6.
 - Watch for secondary adrenal insufficiency – may need to taper steroids slowly.

Cyclosporine (19-22) Protocol

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 using cyclosporine therapy.

Inpatient use of cyclosporine IV(23)

Induction

- Surgical discussions, and detailed discussion of colectomy option, should always occur before cyclosporine is initiated.
- Start at 2 mg/kg/day (21) 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. Use a dedicated IV so that infusion is NOT interrupted.
- 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 and 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/Septa (MWF) for PCP prophylaxis due to risk of infection.(22)
- 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 2 nd 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 2 nd 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/kg/day by 50%
100-150	Increase mg/kg/day by 33%
150-200	Increase mg/kg/day by 20%
200-400	No change
400-500	Decrease mg/kg/day by 20%
500-600	Decrease mg/kg/day by 33%
Over 600	Decrease mg/kg/day 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 mg/kg/day 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.(24)

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.(25)
- 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.(22)

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 within 1 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 outpt surgery early in this period so that surgeons are aware of patient.**

Infliximab (Remicade/Inflectra) Protocol

- 1) Eligible patients:
 - a. Proven UC on severe UC protocol.
 - b. Meets criteria for severe UC.
 - c. QFTB 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
 - 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, consider surgery, or 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 2 sequential doses of 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
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Starting Infliximab as an Inpatient at the University of Michigan
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Identify nurse for outpatient GI who will follow up with patient
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Send an email to nurse and outpatient GI, identifying:
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- | |
|--|
| <ul style="list-style-type: none">- 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 week 2- 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 [10 recommended if IFX rescued])
- 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, and for reduction of anti-infliximab antibodies, especially in new, high CRP (SONIC-like) patients.

Surgery Protocol

- Stop cyclosporine or infliximab 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 total colectomy or 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.

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. This requires combining cyclosporine effects with infliximab effects, in addition to intravenous steroids. This carries increased risk of serious infection (20-40%) and a risk of death, often by pneumonia or pulmonary embolism (26-28). These risks must be discussed with the patient, and considered relative to the risk of urgent (rather than emergent) colectomy.

Only after extensive consultation with both medical and surgical teams should a second rescue medication even be considered. These discussions of 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.

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