

# University of Michigan Severe Ulcerative Colitis Protocol

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UNIVERSITY OF MICHIGAN

**Contributors:**

Peter D.R. Higgins  
Akbar K. Waljee  
Leslie Aldrich  
Timothy T. Nostrant  
Grace Elta  
Sam Hendren  
Scott Regenbogen  
Karin Hardiman  
Arden Morris  
Ryan W. Stidham  
Ellen M. Zimmermann

**Consultants:**

Simon P.L. Travis

**Daily Checklist for Orders**

Day	Studies	Rx
Admission/D1	Comp, pre-albumin, CBCPD, ESR, CRP, Total Cholesterol, TPMT enzyme activity*, PPD*, Abdominal film, Stool Cx, C diff, CMV 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 (NTE) if patient was on OP Steroids or IV Steroids for 5 days.	SQ heparin IV NS to urine out >50cc/hr - usually $\geq$ 5L in 1 <sup>st</sup> 24hr NPO iv Steroids if no infection consider Rectal Rx
Day 2	Basic, CBCPD, Flex Sig Record: # stools, # with stool blood, urgency time, signs of toxicity	SQ heparin Titrate IV NS to UOP NPO continue iv steroids consider Rectal Rx
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, DOCUMENT IN NOTE Call surgery if needed	SQ heparin Titrate IV NS to UOP Consider NPO if not improving. Continue iv steroids consider Rectal Rx if INR up, consider Vit K Consider clear liq if hungry
Day 4 Steroids	Comp, Mg, CBCPD Record: # stools, # with stool blood, urgency time, signs of toxicity	SQ heparin Titrate IV NS to UOP Rectal Rx Consider soft diet if hungry
Day 5 Steroids	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 needed	SQ heparin Titrate IV NS to UOP Rectal Rx Consider soft diet if hungry Decide on taper – consider oral steroids vs. cyclo vs. surgery Not improving, not eating – consider NPO

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

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#### **General Predictors of Colectomy<sup>(6)</sup>**

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

#### **Prediction of Colectomy on admission (Truelove and Witts' criteria):**

$\geq 6$  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  $> 40\%$

#### **Prediction of Colectomy on DAY 3:**

<b>Travis Index</b>	$> 8$ BM's a day OR ( $> 2$ BM's and CRP $> 4.5$ mg/dL) at day 3 (3)  <p style="text-align: center;"><b>PPV of 85%</b></p>
<b>Ho Index</b> (Point System)	colonic dil $> 5.5$ cm = 4 points alb $< 3.0$ on admission = 1 pt avg daily # stools over 1 <sup>st</sup> 3d = [ $< 4$ (0pts), 4-6 (1pt) 6-9 (2pts) $\geq 9$ (4pts)]  <p style="text-align: center;"><b>total of <math>\geq 4</math> Ho Index points on day 3  predicts 85% probability of failing iv steroids.</b></p>
<b>Lindgren Score<sup>(7, 8)</sup></b>	=stool frequency/d + $0.14 \times$ CRP (mg/dL)  <p style="text-align: center;"><b>Lindgren Score <math>&gt; 8</math> at day 3 PPV of 72 %</b></p>

## Protocol Detail

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### 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
  - PPD or 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 x 3
  - Schedule flexible sigmoidoscopy for day 2
- Treatment:
  - Solumedrol 15mg IV Q6(9) or 60mg q 24 [Need Reference] 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 or Lovenox 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

#### 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
  - 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 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 – approx 1 mg/kg per day)
  - NPO
  - 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
- AND blood in stools (suspect C diff if nonbloody or WBC >20)

## Day 3:

### Medical

- Assess Clinical Factors:
  - # bloody stools
  - # stools/24h
  - urgency time
  - presence of toxic megacolon
- Assess Lab Factors
  - Basic
  - CBCPD
  - PT, PTT

- Pregnancy test if female
- Studies:
  - Read PPD – in case infliximab used later
  - Review Bx Results.
  - AAS r/o toxic megacolon
  - If not turning around, consider imaging evaluation for SB inflammation, r/o Crohn's if not done previously (SBFT, CTE)
  - Confirm 3 *Clostridium difficile* sent
- 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 – approx 1 mg/kg per day)
  - NPO
  - 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
  - If hungry, and negative score – BM <8, CRP < 4.5, alb >3, etc., discuss stress testing colon on day 4 with clear liquids.
- 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. 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 patient goes to surgery within 2 weeks of anti-TNF (12-15)
  - If child-bearing age female, discuss 50% risk of infertility (though IVF works) after J pouch(16).
  - Discuss surgical options:
    - (1) Abdominal colectomy with end ileostomy leaving rectal stump with potential future IPAA in place for future resection,
    - (2) Total proctocolectomy with end ileostomy

### Surgical

- Calculate Predictive Scores: 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 scores 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.

### **Day 4:**

## Medical

- Assess Clinical Factors:
  - # bloody stools
  - # stools/24h
  - urgency time
  - presence of toxic megacolon
- Assess Lab Factors
  - Cholesterol
  - Magnesium
  - Comprehensive panel
  - CBCPD
  - Review *Clostridium difficile* results
- Studies:
  - AAS r/o toxic megacolon if still sick
- Treatment
  - Start cyclosporine or infliximab OR go to surgery – discuss with experienced IBD specialist and colo-rectal 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 – approx 1 mg/kg per day)
  - If urgency a major component, can consider Canasa 1 g PR tid or try switching to Rowasa 4g PR bid
  - NPO
  - IVF to keep urine > 800 cc/d
  - NO narcotics
  - If hungry, and did well on clears, advance to soft diet
  - If tolerated clears, and stools <4, little or no blood, ESR<30 and CRP <4, convert to oral prednisone
  - If improving, make a decision about maintenance therapy – return to 5ASA, 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 C diff 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:**

## Medical

- Assess Clinical Factors:
  - # bloody stools
  - # stools/24h
  - urgency time

- presence of toxic megacolon
- Assess Lab Factors
  - Basic
  - CBCPD
  - ESR
  - CRP
  - PT, PTT
- Studies:
  - AAS 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  $\geq 4$ , 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  $\geq 6$ , then colectomy-free success is ~58%.(17) (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 15mg IV Q6(9) or 60 mg q 24 or 2.5 mg/h continuous drip (Goal – approx 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 PR 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  $\geq 6$ , then colectomy-free success is ~58%.(17)
  - If surgery looks likely, get pre-op EKG and CXR
  - If tolerated soft diet, tolerated oral prednisone without worsening, stools still <4/d and no blood, plan steroid taper, start maintenance medication (5ASA vs. azathioprine), 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  $\geq 4$ , 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  $\geq 4$ , 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

### **Cyclosporin (18-21) Protocol**

Labs before use:

- Creatinine
- Cholesterol >120 mg/dl
- Magnesium > 1.5 mg/dl
- Pregnancy test. Women should be on birth control if doing therapy

**Inpatient use of cyclosporine IV(22)**

**Induction**

- Surgical discussions, and detailed discussion of colectomy option, should always occur before cyclosporine is initiated.
- Start at 2 mg/kg/day (20) of intravenous cyclosporine as a continuous infusion.
- For example, for a 72-kg patient, the order is written as follows: "Infuse cyclosporine 100 mg in 250 cc D5W in a glass bottle at 15 cc per hour as a continuous infusion."
- Continue IV steroids
- Continue DVT prophylaxis
- No TPN or PPN – high risk of catheter infection and UE DVT
- 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 vs. infliximab.

**Monitoring on Therapy**

Review for adverse effects	Daily
Blood pressure	Q4h while awake
Cyclosporine level	start on 2 <sup>nd</sup> 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 120-140 mg/dl
Liver function tests	Every 2nd day *

ESR and CRP	Every 2 <sup>nd</sup> 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 50 (range 200-300) 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 rate by 50%
100-150	Increase rate by 33%
150-200	Increase rate by 20%
200-400	No change
400-500	Decrease rate by 20%
500-600	Decrease rate by 33%
Over 600	Decrease rate by 50%

- Reduce cyclosporine infusion rate 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 2<sup>nd</sup> day, and < 200 ng/mL after the 3<sup>rd</sup> day.
- If hungry, and negative markers – BM <8, CRP < 4.5, alb >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.(23)

### 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(24)
- 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 approx 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 DS on Mon, Wed, & Fri for PCP prophylaxis due to risk of infection.(21)

### **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 MgSO<sub>4</sub> 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 wk
Cyclosporine level serum chemistries magnesium, CBC, ESR	With each visit as above and within 1 wk 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.
- A flexible sigmoidoscopy is generally performed after 6-8 wk of therapy.
- Consider discontinuing cyclosporine at 3 months or after colonoscopy.
- Discontinue cyclosporine by reducing the dose by 50% for 2 wk, followed by complete cyclosporine withdrawal.
- 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.**

## Infliximab 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) Dose at 5 mg/kg intravenous infliximab, round dose up to nearest 100 (no waste); continue iv steroids
- 3) 60-66 h after 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  $\geq 0.7$  mg/dL, repeat steps 2 and 3, with next dose 72 h after previous dose.
  - c. If CRP reduced to  $< 0.7$  mg/dL, schedule next infusion for 2 weeks later, then 6 weeks later, then q 8 weeks.
- 4) Notify outpatient nurses immediately when it is determined that infliximab is working. It can take 7-14 days to get insurance issues ironed out and also to get infusion scheduled at busy EAA infusion center.

- 5) When CRP <0.7, convert to oral steroids 40 mg prednisone daily, advance diet. Ready for discharge when next infusion scheduled, on oral prednisone for 24h, and eating full diet without relapse. Discharge on prednisone taper by 5 mg per week.
- 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 Dx (in 1<sup>st</sup> 2 years), high CRP (SONIC-like) patients.

### **Surgery Protocol**

- stop cyclosporine or infliximab as soon as a surgical decision is made
- No maintenance therapy for proctocolectomy
- At surgery outpatient appointment 2 weeks after discharge, 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.
- Watch for secondary adrenal insufficiency – stress dose at time of surgery. If acute steroid use (<2 weeks), standard taper is 10% per day once stable after surgery.
- After surgery, if reason to suspect steroid dependent (months of steroids in past), taper down slowly by 10mg per week till at 20mg daily, and then individualize (some chronic steroid users may require a taper as slow as 2.5 mg per week after that).

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