Management of The Hospitalized IBD Colitis Patient failing IV Steroids

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The Mount Sinai Medical Center

UC Severity: Definitions

Truelove and Witts Severity Index*

<table>
<thead>
<tr>
<th>Blood in stool</th>
<th>Mild</th>
<th>Severe</th>
<th>Fulminant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>&lt;4</td>
<td>&gt;6</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Frequent</td>
<td>&gt;6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>&gt;10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Normal</th>
<th>&gt;37.5</th>
<th>&gt;37.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;37.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulse</th>
<th>Normal</th>
<th>&gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;90</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Normal</th>
<th>&lt;70% of normal</th>
<th>Transfusion required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;70% of normal</td>
<td>Transfusion required</td>
<td></td>
</tr>
<tr>
<td>&gt;70% of normal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESR</th>
<th>&lt;30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Who should NOT be offered medical therapy?

- Indications for surgery:
  - Massive unrelenting hemorrhage
  - Toxic megacolon with impending or frank perforation
  - Coexistent CRC or dysplasia
  - Longstanding colitis with “intractability”

- Medical noncompliance (especially for cyclosporine)

Current Therapeutic Options for Hospitalized Severe Colitis (UC, CD) Patients

- IV Corticosteroids
- IV Steroid Failures
- Medical Therapies
  - Cyclosporine
  - Infliximab
- Surgery
Differential diagnosis and superimposed dx

- C. difficile
- CMV
- NSAIDs

IBD: Differential Diagnosis

Cytomegalovirus Colitis

- Mild chronic inflammation with cryptitis and crypt cell apoptosis
- Viral intranuclear inclusions (confirmed by immunohistochemistry)
- May rarely be an important complication of ulcerative colitis
C. difficile in IBD

- Increasing prevalence in out-patient and hospitalized patients

Present in 16% of all hospitalized IBD pts.

76% of infected hospitalized pts. acquired C. diff as outpts.

40% had NO antibiotic exposure

Issa, et al. CGH 2007

“Cobblestoning” in UC

[Images of “Cobblestoning” in UC]
Relook in Severe UC: Do you really need to go that far? Couldn’t you pull out in time?

- Flex sig with severe inflammation to 30 cm w/o transition
- Uniform severe inflammation
- Is more proximal visualization necessary?
“Creeping Fat in UC”: An Endoscopic View

(“Well, the patient needed surgery someday anyway”)

Current Therapeutic Options for Hospitalized UC Patients

- IV Corticosteroids
- Cyclosporine
- Infliximab
- Surgery
Was corticosteroid treatment optimized?

- Optimal oral dose?
  - 1 dose/response trial to date
  - 40 mg nearly as good as 60 mg
    - Fewer side effects with 40 mg dose

- Optimal IV route?
  - Continuous vs. bolus
  - Bolus is as effective

- Optimal duration prior to surgery?
  - 5 days vs 7-10 days


How long to wait before calling steroids a failure?: Predictors of failure in UC

- Steroid failure at Day 3:
  - Sustained fever
  - Persistence of diarrhea (>4 BM/d)
  - CRP elevation

- In multivariate analysis:
  - Blood in stools
  - >6 BM/d

Consider earlier alternative medical or surgical therapy

### RCTs Severe Ulcerative Colitis: Acute Response to CSA

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CSA 4mg/kg</th>
<th>CSA + Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichtiger (1994)</td>
<td>20 (stopped after interim analysis)</td>
<td>-</td>
<td>87%</td>
</tr>
<tr>
<td>D’Haens (2001)</td>
<td>30</td>
<td>64%</td>
<td>-</td>
</tr>
<tr>
<td>Svanoni (1998)</td>
<td>30</td>
<td>67%</td>
<td>93%</td>
</tr>
<tr>
<td>VanAssche (2003)</td>
<td>73</td>
<td>84%</td>
<td>-</td>
</tr>
</tbody>
</table>

### Short-term efficacy of cyclosporine: relationship to blood levels

- Jewell 1998
- Actis 1998
- Targan 2000
- Lichtiger 1995
- Kornbluth 1998
- Arts 2001
- Cohen 1999
- D’Haens 2001
Cyclosporine: A User’s Guide

- Continuous iv infusion: 2-4 mg/kg/ day
- Daily or q2 day blood cyclosporine level
  - Goal level: 150-400 ng/mL during IV therapy
  - If pt is a responder:
    - Transition to oral CsA 8 mg/kg: Target levels of 100-250 ng/mL
- PCP prophylaxis
- Other antibiotics only if signs of toxicity are present, or if C. diff is suspected (and even consider empiric C. diff treatment?)


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Colectomy Rate in hospitalized Ulcerative Colitis Patients Undergoing Therapy with Cyclosporine


The Dr. Henry D. Janowitz Division of Gastroenterology
The Mount Sinai School of Medicine, New York, NY
CRIB
### Patient Characteristics: Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Median or n</th>
<th>% or IQR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>287</td>
<td></td>
</tr>
<tr>
<td>Admission Hgb g/dl</td>
<td>10.7</td>
<td>9.2-12.4</td>
</tr>
<tr>
<td>Admission ESR mm/hr</td>
<td>35</td>
<td>18-60</td>
</tr>
<tr>
<td>Admission Albumin (g/dl)</td>
<td>3.0</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>C. difficile toxin assay +</td>
<td>69</td>
<td>26.4%</td>
</tr>
</tbody>
</table>

*Values calculated for available data only

### Adverse Events: Acute hospitalization phase

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>4</td>
<td>1.4%</td>
</tr>
<tr>
<td>LFT Elevation</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Headaches</td>
<td>3</td>
<td>1.0%</td>
</tr>
<tr>
<td>Paresthesias/Orofacial Numbness</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>3.8%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Infections</td>
<td>2</td>
<td>0.6%</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>Worsening renal failure (Cr &gt;25%)</td>
<td>16</td>
<td>5.6%</td>
</tr>
</tbody>
</table>
Summary

- 84.7% of hospitalized UC patients treated with IV CsA were able to avoid colectomy during hospitalization

- Albumin $\geq 3.3$ and prior thiopurine exposure were associated with greater colectomy avoidance

Predictive factors for failure to respond to cyclosporin

- Persistent fevers
- Tachycardia
- Elevated CRP
- Hypoalbuminemia
- Deep colonic ulcerations

Long term response

Moskovitz, Clin Gast Hep, 2006

Symptom-free

Long term response

Moskovitz, Van Assche, Rutgeerts; Clin Gast Hep, 2006

Colectomy
The rate of colectomy in those already on azathioprine compared with those starting azathioprine concurrently with CSA was 59% vs 31%, respectively ($P < .05$).

CSA: Avoiding Colectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Colectomy-Free Rate</th>
<th>Mean study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kornbluth (1994)</td>
<td>9</td>
<td>64%</td>
<td>6 months</td>
</tr>
<tr>
<td>Cohen (1999)</td>
<td>42</td>
<td>62%</td>
<td>5.5 years</td>
</tr>
<tr>
<td>Arts (2004)</td>
<td>86</td>
<td>55%</td>
<td>5 years</td>
</tr>
<tr>
<td>Campbell (2005)</td>
<td>76</td>
<td>58%</td>
<td>7 years</td>
</tr>
<tr>
<td>Moskovitz (2006)</td>
<td>142</td>
<td>12%</td>
<td>7 years</td>
</tr>
<tr>
<td>Actis (2007)</td>
<td>61</td>
<td>35%</td>
<td>7 years</td>
</tr>
<tr>
<td>Cacheux (2008)</td>
<td>135</td>
<td>44%</td>
<td>5 years</td>
</tr>
</tbody>
</table>

**Cyclosporine: The Bottom Line**

- Effective short term bridge to definitive therapy
  - Long term immunomodulator (especially if naïve)
  - Elective colectomy

- Variable long term colectomy-free and symptom-free rates

- Rates of serious complications are lower with lower dose, and SAEs probably due in large part to concomitant steroids

**Current Therapeutic Options for Hospitalized UC Patients**

- IV Corticosteroids
- Cyclosporine
- Infliximab
- Surgery
Infliximab for *Moderate or Severe* Refractory UC:
Excluded hospitalized patients

<table>
<thead>
<tr>
<th>% of Patients Achieving Endpoint</th>
<th>ACT 1(^1) (N=364)</th>
<th>ACT 2(^2) (N=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Infliximab 5 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg/kg</td>
</tr>
<tr>
<td><strong>Clinical response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 week</td>
<td>37.2</td>
<td>69.4*</td>
</tr>
<tr>
<td>30 week</td>
<td>29.8</td>
<td>52.1*</td>
</tr>
<tr>
<td><strong>Clinical remission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 week</td>
<td>14.9</td>
<td>38.8*</td>
</tr>
<tr>
<td>30 week</td>
<td>15.7</td>
<td>33.9**</td>
</tr>
<tr>
<td><strong>Mucosal healing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 week</td>
<td>33.9</td>
<td>62.0*</td>
</tr>
<tr>
<td>30 week</td>
<td>24.8</td>
<td>50.4*</td>
</tr>
<tr>
<td><strong>Discontinued steroids</strong> (30 week)</td>
<td>10.1</td>
<td>21.7 (combined groups, (P = 0.039))</td>
</tr>
</tbody>
</table>

Infliximab for Severe Colitis: Randomized Open Label Placebo Controlled trial

- Patients failing IV steroids with:
- **FULMINANT** disease at day 4, or
- **SEVERE** at day 6-8
- Treated with single infusion 5mg/kg infliximab or placebo

Jarnerot, Gastroenterology 2006
Clinical Endpoint at day 90:
- The avoidance of death or colectomy

Infliximab for Severe Colitis: Jarnerot 2005
- Colectomy in 29% of all infliximab patients
- Colectomy in 67% of placebo patients, p=0.017

- In fulminant patients treated with infliximab, 47% of patients required colectomy
2 yr follow up of colectomy rate: Järnerot trial

IFX/placebo in IV steroid refractory colitis

- IFX group 13/15 initial responders started on AZA vs 3/7 in placebo group
- Only 4/24 received more than one IFX infusion

Gustavsson A, et al. DDW 2007: #983

3 m colectomy rates

IFX
Placebo

p=0.0038 (logrank test)

Pts at risk, n
IFX 24
Placebo 21
17
7
17
7
17
7

Probability not operated
0.0
0.2
0.4
0.6
0.8
1.0

Time (days)
0
30
60
90

2 y colectomy rates

IFX n=24
Placebo n=21

46%
76%

Probability not operated
0.0
0.2
0.4
0.6
0.8
1.0

Time (months)
0
3
6
9
12
15
18
21
24

Pts at risk, n
IFX 24
Placebo 21
17
7
17
7
14
6
5

Infliximab in Severe UC

- Effective in moderately active disease and severe disease in outpatients
- Limited data to date to support its use in severe IV-steroid refractory hospitalized UC patients
- Exercise extreme caution if using soon after a course of cyclosporin (and vice versa)
Is it Effective to use Cyclosporine after Failing Infliximab (IFX) and Vice Versa?

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Other immune suppression</th>
<th>Drug Sequence</th>
<th>Medication Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death - gram negative sepsis</td>
<td>Azathioprine</td>
<td>IFX-Salvage</td>
<td>1 day</td>
</tr>
<tr>
<td>Pancreatitis - Enterococcus, and klebsiella bacteremia</td>
<td>Azathioprine</td>
<td>CSA-Salvage</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Herpes Esophagitis</td>
<td>Prednisone taper</td>
<td>CSA-Salvage</td>
<td>5 days</td>
</tr>
</tbody>
</table>

Serious Adverse Event Total = 16% (3/19)
Acute Salvage Therapy - Conclusion

In patients with severe steroid refractory UC who fail treatment with either CSA or IFX, the likelihood of achieving a steroid free remission, using salvage therapy with the other drug, is low and similar despite which drug is used first.

The incidence of a serious adverse event of 16%, including 1 fatality, suggesting that the risks may outweigh the benefit of acute salvage therapy.

Severe Colitis: CSA or Infliximab
Dec 6, 2009

- CSA longer short term and long TERM track record
- Prompter response with CSA suggested
- CSA: Exit strategy known
- Infliximab: Avoids hospitalization in the pre IV steroid phase
**Infliximab in UC: Relevant Questions**

- Should it always be used with 6-MP/ AZA?
- For how long should patients be treated?
  - Inpatient?
  - Outpatient?
- IV Steroid Refractory UC: Infliximab vs. Cyclosporin?
  - Await results from multicenter European CSA vs. infliximab trial

**Venous thromboemolism (VTE) in severe UC**

- Increased risk with acute, extensive colitis
- May be arterial or venous, atypical sites (CNS, portal vein, retinal veins)
- Mortality in pt. with recurrent VTE may be as high as 8-25%.
- Relative risk for mortality in hospitalized IBD patients with VTE = 2.1
- Risk of VTE after UC surgery = 4%
- SQ Heparin prophylaxis should be considered in all hospitalized pts.

Nguyen, et al AJG 2008
ICU admissions for patients with Severe UC

- Mt. Sinai cohort of 1582 patients UC 2004-2008
- 40 pts admitted to medical or surgical ICU (2.5%)
- Fatality rate of 0.5% for all pts—all related to fulminant UC pts presenting with shock
- Fatality rates associated with
  - Renal failure
  - Respiratory failure
  - Multidrug resistant bacteremia
  - Hypoalbuminemia
  - Prior history of liver transplant
Risk-Benefit Ratio of Surgery in UC

**Benefit**
- Probably reduces rate of mortality in the sickest patients
- Considered “cure” for UC
- Subtotal colectomy during acute phase
  - IPAA
  - Permanent ileostomy

**Risk**
- Post-surgical complications
  - Infection
  - Small bowel obstruction
  - Sepsis
  - Leak
  - Pouch dysfunction
  - Irritable pouch
- Pouchitis/Cuffitis
- Reduced female fertility
- Risk male erectile dysfunction

Top 10 Pearls and Pitfalls in Managing Severe UC

10. Waiting too long for oral prednisone to work—consider infliximab if hospitalization not required.
9. Consider the Ddx and superimposed factors—especially C. difficile
8. Recognize outpatient medical failure
7. Maintain extreme vigilance in the “sick” patient—older, hypoalbuminemic, febrile.
Top 10 Pearls and Pitfalls in Managing Severe UC

6. Remember in long standing UC, enough is enough
5. If considering inpatient cyclosporin or infliximab, think about it early (day 3-5)
4. And get the surgeon in to chat with the patient now (if not sooner)
3. Fulminant colitis mandates even prompter response

Top 10 Pearls and Pitfalls in Managing Severe UC

2. It’s a reasonable goal to avoid surgery to avoid pouch problems, female infertility, and male impotence, but in the sick unresponsive patient

1. The ultimate goal is not saving colons but saving lives and quality of these lives