Inflammatory Bowel Disease Management
Therapeutic Goals in IBD c. 2009

- Normal bowel function and improved quality of life (QOL)
- Induce remission rapidly
- Maintain steroid-free remission over time (deep remission)
- Modify long-term outcomes of the disease
  - Avoid hospitalization and surgery
  - Eliminate disability
  - Minimize exposure to steroids
Medical Management of IBD

- **The Basics**
  - Disease activity?
  - Extent of disease?
  - Treatment is safe?

- **The Specifics**
  - What drugs do we use?
  - How effective are they?
  - What are the limitations and side effects?

- **The Alternatives**
  - Are there non-drug treatments?
Classification of Disease

Crohn’s disease

- Quiescent
- Moderate
- Moderate to severe
- Severe

Ulcerative colitis

- Quiescent
- Mild to moderate
- Moderate to severe
- Severe
<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate “in between mild and severe”</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody stools/day</td>
<td>&lt;4</td>
<td>4 or more if</td>
<td>≥6 and</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;90 bpm</td>
<td>≤ 90 bpm</td>
<td>&gt;90 bpm or</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt;37.5°C</td>
<td>≤ 37.8°C</td>
<td>&gt;37.8°C or</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&gt;11.5 g/dl</td>
<td>≥10.5 g/dl</td>
<td>&lt;10.5 g/dl or</td>
</tr>
<tr>
<td>ESR</td>
<td>&lt;20 mm/h</td>
<td>≤ 30 mm/h</td>
<td>&gt;30 mm/h or</td>
</tr>
<tr>
<td>or CRP</td>
<td>normal</td>
<td>≤ 30 mg/l</td>
<td>&gt;30 mg/l</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Crohn’s Disease Activity Index

CDAI >450 - critically ill
CDAI <150 - inactive disease, remission

- Number of liquid or very soft stools during the previous week (*predominant component*)
- Severity of abdominal pain / cramping
- General well-being
- Extra-intestinal manifestations
- Presence of abdominal mass
- Use of antidiarrheal drug therapy
- Hematocrit
- Body weight
Clinical criteria for Crohn’s disease activity
(American College of Gastroenterology Practice Guidelines)

- **Mild-to-moderate:** Ambulatory, no abdominal tenderness, painful mass, or obstruction
- **Moderate-to-severe:** Unresponsive to treatment for mild-to-moderate stage or with prominent fever, weight loss, anemia, abdominal pain and tenderness, or intermittent nausea or vomiting
- **Severe-to-fulminant:** Persistent symptoms on corticosteroids or with high fever, rebound tenderness, cachexia, or abscess
- **Remission:** Asymptomatic, no inflammatory sequelae, not requiring systemic corticosteroids

*Hanauer et al, Am J Gastroenterol 2001; 96: 635*
Medical management of IBD.

Distal UC:
- IV cyclosporine or infliximab
- 6-Mercaptopurine or azathioprine
- Glucocorticoid intravenous
- Glucocorticoid oral
- Glucocorticoid rectal
- 5-ASA PR or PO

Extensive UC:
- IV cyclosporine or infliximab
- 6-Mercaptopurine or azathioprine
- Glucocorticoid intravenous
- Glucocorticoid oral
- Glucocorticoid rectal
- 5-ASA rectal or oral

Inflammatory CD:
- IV cyclosporine or tacrolimus
- Infliximab/adalimumab
- Methotrexate
- 6-Mercaptopurine or azathioprine
- Glucocorticoid intravenous
- Prednisone
- Budesonide (ileal and R colon)
- Sulfasalazine antibiotics

Fistulizing CD:
- Total parenteral nutrition
- Intravenous cyclosporine or tacrolimus
- Infliximab/adalimumab
- Methotrexate
- 6-Mercaptopurine or azathioprine
- Antibiotics

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Predictors of risk of progressive / aggressive Crohn’s disease

- Young age of onset
- Fistulizing disease
- Early need for steroids
- Deep ulcerations
- High serologic titers
- Smoking
Drug therapy for Crohn’s disease - 2008

First line therapy
- 5-ASA
- balsalazide
- budesonide
- antibiotics (metronidazole, Cipro, rifaximin, amoxicillin, minocycline, tetracycline)

Nutritional therapy
- elemental diet
- TPN

Immunomodulators/Second line therapy
- corticosteroids
- budesonide
- azathioprine/6-MP
- methotrexate

Bioologic Therapy
- infliximab
- adalimumab
- certolizumab pegol
- natalizumab

Biologics - in development
- mesenchymal stem cells
- abatacept
- thalidomide
- anti IL-12 (ABT-874)
- Trichuris suis
- probiotic therapy
- visilizumab (anti-CD3)
- Adacolumn (leukocytopharesis)
- golimumab
- fontalizumab

Investigational Immunomodulators
- mycophenolate mofetil
- leflunamide
- FK 506
- thioguanine
- stem cell transplant
5-ASA Delivery Systems

- **Stomach**
- **Jejunum**
- **Ileum**
- **Colon**

**Sulfasalazine**
- pro-drug; azo bond of 5-ASA + sulfapyridine

**Dipentum® (olsalazine)**
- pro-drug; azo bond of 2 5-ASAs

**Colazal™ (balsalazide)**
- pro-drug; diazo bond of 5-ASA + 4ABA carrier

**Asacol® (mesalamine) Delayed-Release Tablets**
- coated to release at pH ≥ 7

**Lialda (MMX)**

**Pentasa® (mesalamine) Controlled-Release Capsules**
- coated to release over time
5-ASA in UC

- Topical 5-ASA is effective in treatment of left sided UC

- Combination of oral and topical therapy is more effective than single therapy in left sided colitis

- The optimal induction dose is not established (higher dose is better than lower dose – 4.8 vs 2.4 of Asacol)

- It is not clear whether switching formulation improves response rate

- Effective in inducing remission (mild-moderate) OR: 0.39 vs placebo
5-ASA in UC

- Effective in maintaining remission

- All formulation are equally effective
  - Azulfidine more effective (OR: 1.29)
  - Colazal for left sided UC

- May decrease the risk of colon cancer (OR: 0.25 [0.13-0.48])

- In patients with ulcerative proctitis; maintenance therapy is not recommended in patients with a first episode that has responded promptly to treatment

Hanauer S. Gastroenterology 2004;126:1582
Carter MJ. Gut 2004 (supplv) v1-v16
5-ASA for Crohn’s; Questions to be Answered

- Should we use 5-ASA products in active CD?
  - Yes, sometimes

- Should we use 5-ASA products for inactive CD?
  - Yes, sometimes

- Should we use 5-ASA products in Crohn’s patients and colonic involvements?
  - Yes, always to try
5-ASA in Crohn’s

- High dose mesalamine (Pentasa) has modest effects in active CD (therapeutic effects of 20%)

- High dose mesalamine has modest effects in maintenance of remission in CD

- 5-ASA does not appear to have steroid sparing effects

Camma Gastroenterology 1997;113:146
Carter, MJ. Gut 2004 (supplv)
5-ASA in IBD  Therapeutic Failure

- Incorrect indication
  - Disease severity
  - Incorrect diagnosis

- Incorrect dose; inappropriate formulation

- Compliance

- Side-effects
  - Diarrhea
  - Allergic colitis

Kane, S. AM. J. Med 2003;114:39
5-ASA in IBD Side Effects

- Headache
- Hair loss
- GI upset
- Diarrhea
- Skin rash
- Fever
- Pancreatitis
- Alveolitis
- Bone marrow suppression
- Hepatitis
- Interstitial nephritis/salt-losing nephritis
Steroid in IBD

- Provide rapid symptomatic relief

- Highly effective for the induction of remission in patients with active disease of UC and CD

- Short-term response rates (12–16 weeks) range from 70–90%

Not recommended in maintenance of remission

Corticosteroids: Short- and long-term efficacy in Crohn’s disease

30-day responses (n=74)
- Complete 58% (n=43)
- Partial 26% (n=19)
- None 16% (n=12)

1-year responses (n=74)*
- Prolonged response 28% (n=21)
- Steroid dependent 32% (n=24)
- Surgery 38% (n=28)

*One patient lost to follow-up

Faubion et al, Gastroenterology 2001; 121: 255
Budesonide in CD

- Budesonide releases in the distal ileum and right colon and thus cannot be used in patients with CD involving the left colon.

- Budesonide 9 mg q.d. is more effective than Pentasa 4 g q.d. for inducing remission.

- Budesonide 9 mg q.d. is slightly less effective than prednisolone 40 mg q.d. but causes substantially fewer corticosteroid side effects.
Oral budesonide vs prednisolone in active Crohn’s disease

Remission* (%)

<table>
<thead>
<tr>
<th>Weeks of treatment</th>
<th>Budesonide 9 mg/day tapered (n=88)</th>
<th>Prednisolone 40 mg/day tapered (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>45</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>66</td>
</tr>
</tbody>
</table>

*p=0.22
p<0.001
p=0.12
p=0.12

*CDAI score ≤150

Adapted from Rutgeerts et al, N Engl J Med 1994; 331: 842
Summary: Steroids in the treatment of Crohn’s disease

- Only short-term efficacy
- No maintenance of response / remission
- Only deaths in controlled trials related to steroids and abscess
- Toxicity profile unacceptable for long-term use
- More recent evidence suggests that exposure to steroids may alter course of disease toward surgery or worse outcomes
  - this remains theoretical but steroid-sparing or steroid-avoiding strategies are favored and being studied
Evidence-based treatment for mild-to-moderate Crohn’s disease

Mild-to-moderate Crohn’s disease

Left-sided disease restricted to colon
- Sulfasalazine 16 weeks
  - Sulfa-allergic / failed treatment

Disease involving the ileum and/or ascending colon
- Budesonide 8-16 weeks
  - Failed treatment

Conventional steroids

Steroid refractory

- Steroid-responsive disease
- Steroid-dependent disease
- Steroid-refractory disease:
  1. Are symptoms caused by ulcerative colitis or concomitant IBS?
  2. Could the patient have Crohn's disease?
  3. Could dietary factors such as lactose intolerance be contributing to symptoms?
  4. Are conventional drugs (such as oral or topical 5-ASA agents) being used appropriately in maximal doses?
  5. Are patients compliant with medications?
  6. Is there a superimposed bacterial (e.g., Clostridium difficile) or viral (e.g., cytomegalovirus (CMV)) infection?
- Only 15 to 20% of patients with UC will ever experience an attack of fulminant colitis

- Patients with pancolitis appear to be predisposed to severe flares

- If patients fail 3 to 5d of IV corticosteroids, they should be considered for any of three options:
  - IV cyclosporine (2 mg/kg for 7 d)
  - Infliximab (5 mg/kg IV, 0-2-6 wk)
  - or total colectomy
Between 65 and 85% of patients will initially respond to cyclosporine and avoid colectomy on the short term.

Therefore, patients not responding to these agents within 5-7 d should be considered for colectomy.

Responders should be closely monitored for infections.
CMV colitis:

- Prevalence of CMV infection in patients hospitalized for IBD at 0.5–3.4%.
- CMV sero-status be determined before starting systemic steroids in patients with severe UC.
- Only those seropositive patients who are steroid refractory would need biopsies to look for CMV.
- Sero-prevalence increases with increasing age.
- Most CMV infection in immunocompetent individuals is likely asymptomatic.

Dig Dis Sci; 29 January 2010
Diagnostic tests for CMV include:

- Detection of the antigen in the blood (pp65 antigenemia assay)

- Detection of CMV-DNA by PCR in blood can quantify viral load

- GI disease is diagnosed by detection of CMV in biopsy

- IHC can increase the yield in biopsies to 93%
Immunosuppressants in IBD

- Drugs include:
  - Azathioprine
  - 6-mercaptopurine
  - Methotrexate
- Interfere with inflammatory pathway
- Effective
  - Up to 75% of patients brought into remission
- Slow
  - Optimal effect often not seen until after 12 weeks of treatment
- Need close monitoring for toxicity
- Safety
  - Methotrexate not to be used in pregnancy
When to use immunosuppressants

- Maintenance of steroid-induced remission
- Perianal fistula, abscess, fissure
- Induction agents in mild / moderate inflammatory CD
- Steroid refractory disease
- Combination with biologics to reduce immunogenicity
- 3–6 months to be effective
TPMT is the key enzyme in AZA/6-MP metabolism

AZA → 6-MP

6-MMP

TPMT

Hepatotoxicity

IMMUNO SUPPRESSION

? 6-thio-GTP

Myelosuppression

6-TGN
Lower TPMT Correlates with Higher 6-TGN Production and Higher Clinical response

TPMT

AZA → 6-MP

→ 6-MMP

→ 6-TGN

↑ CLINICAL RESPONSE
~70%
Higher TPMT Correlates with Lower 6-TGN Production and Lower Clinical response

AZA → 6-MP

TPMT → 6-MMP

6-TGN → CLINICAL RESPONSE

Hepatotoxicity

Myelosuppression

~20-40%
Immunosuppressants: Safety and tolerability

- Most common side-effects
  - flu-like symptoms occurring after 2–3 weeks and resolve on discontinuation (~20%)
  - hepatotoxicity and pancreatitis (<5%)
  - leukopenia (~3%)

- Long-term tolerance is good if initial 3 weeks treatment shows no adverse effects

- Can be given during pregnancy

- No evidence of increased risk of neoplasm

Travis, Gut 2006; 55(Suppl. 1): i16
Are we giving azathioprine too much time?
World J Gastroenterol 2008 September 28; 14(36): 5519-5522

- When; no symptoms or signs of disease activity, both clinicians and patients often arise:
  - should I withdraw the drug, when it’s time?

- Two reasons could actually lead to the withdrawal:
  - a loss of efficacy over time
  - or adverse events that exceed the benefits of the drug
- CD and UC patients, show that maintenance with AZA is clearly useful for up to 5 years.

- AZA can be safely stopped after 3–4 years of therapy in those patients who have been in complete remission.

Dig Dis Sci 2006; 51:1516-1524
Cyclosporine

- 20 patients with severe UC not responding to 7 days of IV corticosteroids
- Randomized to 4 mg/kg/24hrs IV cyclosporine vs placebo
- 82% (9/11) responded (CSA) vs 0% (0/9) in placebo group (p < 0.01)
  - Mean response time: 7 days
- Clinical activity score 13 ➔ 6 (CyA) vs 14 ➔ 13 (continued corticosteroids)
Cyclosporine: Practical Considerations

- Not for use in toxic megacolon
  - Some experts recommend checking KUB before initiating, and repeat daily or qod
- Total cholesterol < 120 ng/ml: high seizure risk
- Older patients or if renal impairment: check creatinine clearance
- Flexible sigmoidoscopy before initiating CyA

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Cyclosporine: Practical Considerations

- Monitor electrolytes daily:
  - magnesium in particular

- Monitor CyA levels:
  - target trough 150-250 ng/ml

- If response: longer plan
  - Oral cyclosporine (3 to 6 months)
  - Start 6-MP/AZA
  - Taper steroids
Cyclosporine: Safety

- First 111 consecutive IBD pts (64 UC, 47 CD) at Mt. Sinai treated with CyA 4 mg/kg/d IV then 8 mg/kg/d po, mean duration 9.3 mo (range 1 wk – 34 mo)
- Major adverse events in 15.3%
  - Nephrotoxicity* sufficiently severe to warrant discontinuation of therapy (5.4%)
  - Serious infections (6.3%)
  - Seizures (3.6%)
  - Anaphylaxis (0.9%)
  - Death (1.8%)

*Serum creatinine ≥1.4 mg/dL [123 μmol/L] or a rise by at least 33% over baseline not responding to dose adjustment
Efficacy of cyclosporine for refractory fistula of Crohn’s disease

- Intravenous cyclosporine is effective in treating fistula
  - response $24/28 = 86\%$
  - closure $17/28 = 61\%$
  - mean response time = 4–7 days

- Relapse occurs frequently on oral cyclosporine
  - $10/24 = 42\%$

- Toxicity potential is uncertain

- Requires long-term maintenance with 6MP / AZA and / or combinations of medications with avoidance of steroids
Antibiotic and IBD

- Metronidazole
  - Severe UC
  - Active CD
  - Maintenance of CD (post-surgical)
  - Perianal disease
- Cipro
Efficacy of antibiotic combination therapy in patients with active ulcerative colitis, including refractory or steroid-dependent cases

- Infections usually start with adherence of the microorganism to host cells
- Role of *Bacteroides vulgatus* or *Fusobacterium varium* in experimental UC has been suggested
- Decreases in *Lactobacillus* and *Bifidobacteria* concentrations in colonic biopsy specimens from patients with active UC

*Journal of Gastroenterology and Hepatology* 25 (2010) Suppl. 1; S62–S66
long term follow up study suggests 2 week antibiotic combination therapy to be effective and safe in patients with active UC including those with steroid refractory or dependent disease

Journal of Gastroenterology and Hepatology 25 (2010) Suppl. 1; S62–S66
Antibiotics for active Crohn’s disease

- Ciprofloxacin vs mesalamine – moderately active disease
- 40 patients – randomized, controlled, 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin 1 gm</th>
<th>Mesalamine 4 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>10/18 (56%)</td>
<td>12/22 (55%)</td>
</tr>
</tbody>
</table>

- CRP statistically decreased in ciprofloxacin group, but not in mesalamine group
- Ciprofloxacin and mesalamine demonstrated similar efficacy

*Colombel et al, Gut 1996; 39: 69*
Overview: Biologic Therapy in IBD c 2009-2010

• Why: to achieve steroid-free remission and change outcomes

• What: currently includes 3 anti-TNF therapies and one anti-integrin therapy

• Who: positioning has been for patients with moderately to severely active IBD who have “failed conventional therapies”; we are moving to a model of prognosis to choose therapy

• When: we have learned that treating earlier increases benefit and decreases risks; waiting for failure of all other therapies is often too late to use these

• How: minimize risk, maximize responsiveness, maintain remission

• Where: infusion suites, your office, at home
Indications for biologics

Crohn’s disease
- refractory disease
  - failure to induce remissions…
    - despite steroids
  - failure to maintain remissions…
    - despite optimized immune suppressants
- early for bad prognosis

Ulcerative colitis
- refractory disease
  - failure to induce remissions
    - despite steroids
  - failure to maintain remissions
    - despite aminosalicylates or immune suppressants
Conventional approach to induction therapy: Step-up

- Clinical approach to use “mildest” form of drug therapy to treat patients first
- Move to next step in non-responders
# Dosing of Anti-TNFα Agents in IBD

Chart does not imply comparable safety or efficacy

<table>
<thead>
<tr>
<th>Agent</th>
<th>U.S. Approval</th>
<th>Induction Dosing</th>
<th>Adult Maintenance Dose</th>
<th>Interval Between Maintenance Injections (weeks)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab¹</td>
<td>CD lumen</td>
<td>5 mg/kg at 0, 2, and 6 weeks</td>
<td>5 mg/kg (10 mg/kg in responders who lose response)</td>
<td>8</td>
<td>IV</td>
</tr>
<tr>
<td>Adalimumab²</td>
<td>CD lumen</td>
<td>160 mg at week 0 followed by 80 mg at week 2</td>
<td>40 mg</td>
<td>2</td>
<td>SC</td>
</tr>
<tr>
<td>Certolizumab pegol³</td>
<td>CD lumen</td>
<td>400 mg at 0, 2, and 4 weeks</td>
<td>400 mg</td>
<td>4</td>
<td>SC</td>
</tr>
</tbody>
</table>

¹ REMICADE (infliximab) Prescribing Information, August 2008, Centocor, Inc., Malvern, PA.
² HUMIRA (adalimumab) Prescribing Information, February 2008, Abbott Laboratories, North Chicago, IL.
³ CIMZIA (certolizumab pegol) Prescribing Information, April 2008, UCB, Inc., Smyrna, GA.
The Challenge of Immunogenicity

- All biologic therapies, regardless of humanization, induce immunogenicity
- Immunogenicity results in hypersensitivity reactions and loss of response to therapy
- Methods to reduce immunogenicity:
  - Maintenance therapy with drug
  - Loading dose of drug
  - Concomitant immune-modulatory therapy
10% of patients with “refractory” or newly diagnosed CD seem not to respond to anti-TNF treatment.

Outcome of prolonged infliximab therapy in patients with CD revealed that after a median follow-up time of 55 months:
- 63% of patients had sustained benefit
- 22% loss of response despite increases in dose and shortening of dosing intervals

The annual dropout rates averaged 11%
The loss of response to infliximab is:
- development of antibodies against the chimera that bind and inactivate the compound
- and lead to a reduction in the biologically active infliximab levels

Antibodies to infliximab;
- human antichimeric antibodies or HACAs

Pretreatment with hydrocortisone before infusions has also been effective in reducing antibody formation.
Switching to Another Biologic Therapy
What to choose and when to choose it?

- Primary non-responder: anti-TNFα loading dose with no response: try a different mechanism (not a different anti-TNFα therapy!)
- Primary responder now relapsing
  - Assess for inflammation
  - If suspect immunogenicity, switching to second anti-TNF is reasonable¹-³
  - If not immunogenicity, consider a different mechanism of treatment
    - Methotrexate?
    - Natalizumab?
    - Surgery?

<table>
<thead>
<tr>
<th>Current Medication</th>
<th>Serious Infections* (95% CI)</th>
<th>Mortality* (95% CI)</th>
<th>All Cancer (95% CI)</th>
<th>Lymphoma (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>1.28 (0.87-1.90)</td>
<td>0.93 (0.59-1.45)</td>
<td>0.74 (0.49-1.12)</td>
<td>0.8 (0.22-2.99)</td>
</tr>
<tr>
<td>6-MP/AZA/MTX</td>
<td>0.91 (0.63-1.31)</td>
<td>0.75 (0.49-1.14)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2.04 (1.42-2.93**)</td>
<td>1.96 (1.28-3.00+)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>2.17 (1.51-3.14**)</td>
<td>2.06 (1.33-3.21**)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported.
*Multivariate; **P<0.001; †P=0.002.
Safety of anti-TNF antagonists in Crohn’s disease: Meta-analysis of placebo-controlled trials

- MEDLINE, Cochrane Library, EMBASE: 21 studies; n=5356
- Overall and individual efficacy and safety of infliximab, adalimumab, certolizumab pegol, etanercept, onercept and CDP571

<table>
<thead>
<tr>
<th>Overall analysis</th>
<th>Anti-TNF group (n=3341) (%)</th>
<th>Control group (n=2015) (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infections</td>
<td>2.09</td>
<td>2.13</td>
<td>-0.45 – 0.65</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0.24</td>
<td>0.39</td>
<td>-0.45 – 0.18</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.21</td>
<td>0.05</td>
<td>-0.21 – 0.29</td>
</tr>
</tbody>
</table>

- Anti-TNF therapy is safe and effective in patients with CD refractory to standard medical therapy

Which Patients are at Risk for Worst Outcomes?
Targeting patients based on prognosis

- >2 surgeries
- >2 hospitalizations
- Need for rapid induction (e.g. hospitalized)
- Intolerance to standard IMM
- Significant perianal disease
- At risk of ostomy
- Significant duodenal disease
- Pyoderma gangrenosum
- Deep ulcers
- Young age of diagnosis
- Smokers

1 Allez et al. Am J Gastroenterol. 2002; 97:947-953
2 Beaugerie et al. Gastroenterology. 2006; 130:650-6
3 Seksik et al. Gastroenterology. 2007; 132 4(Suppl 2):A-17
Pregnancy

- Study presented during this year's ACG meeting examined the safety of natalizumab in pregnancy
  
  *Am J Gastroenterol. 2008;103:P295*

- Recommendation: to avoid pregnancy during and 6 months after infliximab administration until further data are available
  
  *CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2008;6:1212–1217*
## Infliximab: Safety

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity reactions</td>
<td>Largely treatable; sometimes dose limiting; rarely life-threatening anaphylactoid</td>
</tr>
<tr>
<td>Infections</td>
<td>Including serious and opportunistic infections; all patients must be screened for TB</td>
</tr>
<tr>
<td>Autoimmune phenomena</td>
<td>High rate of new ANA positivity and other autoimmune antibodies; lupus-like reactions rare</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Contraindicated at doses above 5 mg/kg in mod to severe CHF; rare cases new onset heart failure</td>
</tr>
<tr>
<td>Demyelinating disorders</td>
<td>Temporal association with treatment; exacerbation of pre-existing; may reverse on stopping</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>Rare serious hepatitis; many reports of severe HBV exacerbation</td>
</tr>
<tr>
<td>Lymphoma, other cancers</td>
<td>Absolute risk appears to be small</td>
</tr>
<tr>
<td>Definite</td>
<td>Relative</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Active Abscess</td>
<td>Inefficacy</td>
</tr>
<tr>
<td></td>
<td>● First</td>
</tr>
<tr>
<td></td>
<td>● Subsequent</td>
</tr>
<tr>
<td>Suspected active T.B</td>
<td>Absc of Active inflam.</td>
</tr>
<tr>
<td>Intestinal Obstruction</td>
<td>Refractory Pouchitis</td>
</tr>
<tr>
<td>M.S or Optic Neuritis</td>
<td>PSC</td>
</tr>
<tr>
<td>Class III/IV CHF</td>
<td></td>
</tr>
<tr>
<td>Previous Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Uncontr. Infusion Reaction</td>
<td></td>
</tr>
<tr>
<td>● ATI related</td>
<td></td>
</tr>
<tr>
<td>● IG E mediated</td>
<td></td>
</tr>
<tr>
<td>Metastatic CD</td>
<td></td>
</tr>
</tbody>
</table>
Probiotic Characteristics

- Acceptable Safety
- Anti-infective
  - Inhibitory GI pathogens
  - Beneficial effects in children and adults by preventing GI infections
- Anti-inflammatory
- Nutritional enhancement
  - Facilitating digestion and absorption
Suggested Mechanisms of Action of Probiotics in IBD

Inhibition of pathogenic enteric bacteria growth by:

- Interference with bacterial adherence to the epithelium
- Decreasing luminal pH (Lactobacilli produce acetic and lactic acid)
- Secretion of bacterial proteins (bacteriocins) that act as local antibiotics
Treatment Algorithm for UC


UC

Mild

- Oral +/- Topical Mesalamine/Sulfasalazine

Moderate

- Prednisone
  - FAIL 2–4 wk

Severe

- Admit + IV Corticosteroids 3–5 days
- IFX 0, 2, 6
- Scheduled Maintenance +/- Immunomod.*
  
* Cyclosporine may be considered in some cases.

IFX, infliximab

* *immunomodulation.*
Moderate UC Algorithm

Am J Gastroenterol. 2004;99(7):1371-1385

Moderate

Prednisone

Corticosteroid Dependent

16–24 Weeks

Corticosteroid Refractory

2–4 Weeks

Respond and Taper Maint. 5-ASA

FAIL

IFX 0, 2, 6 Scheduled Maintenance +/- Immunomod.

AZA × 16 Weeks

IFX, infliximab
Panaccione R. Oral presentation presented at: United European Gastroenterology Week; 15-19 October 2005; Copenhagen, Denmark.
Moderate CD Algorithm: Time Bound


- **Moderate**
  - Prednisone
    - Corticosteroid Dependent
      - 16-24 Weeks
        - MTX × 12 Weeks
          - Or
            - AZA × 16 Weeks
        - Respond and Taper
      - IFX 0, 2, 6 Scheduled Maintenance + Immunosomod.
    - Corticosteroid Refractory
      - 2-4 Weeks

Panaccione R. Oral presentation presented at: United European Gastroenterology Week; 15-19 October 2005; Copenhagen, Denmark.
Fistulising CD Algorithm


**Fistulising CD**

**Simple**
- Trial of Antibiotics
- Fistulotomy

**Complex**
- IFX 0, 2, 6
- Scheduled Maintenance + Immunomod.

FAIL
Balloon Dilation of Strictures

- High success rate for anastamotic strictures
- Used for colonic and duodenal stenosis
- TTS balloons 15 to 18 mm for 1 minute
- Fluoroscopy only if needed
- Successful if scope passed post
- Medical treatment
- Complications

Aliment Pharmacol Ther; 2010 31, 634–639
Injection of Corticosteroids

- Post dilation
- Sclerotherapy needle
- Triamcinolone 40 mg/ml – 1 cc in 4 quadrants at site of maximal inflammation/stenosis
Intestinal Stents

- Limited data
- Migration is common
- Coated metal enteral stents / plastic stents may be of benefit
Go Home Messages

• Crohn’s disease incidence is rising

• We need to try to enter *terminal ileum and Bx* in every colonoscopy

• Genetic components are emerging

• *Serum ASCA & ANCA* could be a valuable *non-invasive good positive test* in pts with suspicious for IBD

• Disease anatomy + severity determine Rx

• Smoking is bad for Crohn’s disease patients