Complex IBD: A Case Based Approach

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Treatment Goals for IBD in 2013

• Early accurate diagnosis
• Rapid effective induction of remission
• Sustained steroid-free maintenance of remission
• Prevention of complications
  – Disease related
  – Therapy related
  – Appreciation of the importance of a healed mucosa
• Improved quality of life
Why Do Patients With IBD Not Respond To Their Medications?

<table>
<thead>
<tr>
<th>Primary Nonresponse</th>
<th>Secondary Nonresponse</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug/mechanism just doesn’t work</td>
<td></td>
</tr>
<tr>
<td>• Wrong diagnosis</td>
<td></td>
</tr>
<tr>
<td>— Infection</td>
<td></td>
</tr>
<tr>
<td>— Ischemia</td>
<td></td>
</tr>
<tr>
<td>— Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>• Wrong dose</td>
<td></td>
</tr>
<tr>
<td>— Not enough</td>
<td></td>
</tr>
<tr>
<td>— Too much?</td>
<td></td>
</tr>
<tr>
<td>• Wrong delivery</td>
<td></td>
</tr>
<tr>
<td>— Rationale</td>
<td></td>
</tr>
<tr>
<td>• Allergy/intolerance</td>
<td></td>
</tr>
<tr>
<td>• Change in dose (by you)</td>
<td></td>
</tr>
<tr>
<td>• Change in delivery</td>
<td></td>
</tr>
<tr>
<td>• Change in physiology</td>
<td></td>
</tr>
<tr>
<td>— Does disease change over time?</td>
<td></td>
</tr>
<tr>
<td>• Intentional nonadherence</td>
<td></td>
</tr>
<tr>
<td>— Episodic dosing strategy</td>
<td></td>
</tr>
<tr>
<td>— Denial</td>
<td></td>
</tr>
<tr>
<td>— Fear of therapy</td>
<td></td>
</tr>
<tr>
<td>• Unintentional nonadherence</td>
<td></td>
</tr>
<tr>
<td>— Can’t afford medication</td>
<td></td>
</tr>
<tr>
<td>— Inconvenient dosing regimen</td>
<td></td>
</tr>
</tbody>
</table>

Pearls from the Clinic

• Overlapping IBS
• Bacterial overgrowth
• Not using combination therapy, especially when moving to second anti-TNF
• Waiting for surgery too long
• Confusing joint pain from steroids use/withdrawal and true disease-related arthropathy
• Patient resistance to recommendations
  — [www.youandibd.com]
Use Checklists!

www.cornerstoneshealth.org

The Patient Failing Thiopurine Therapy
The Patient not Responding to Thiopurine

- Confirm adherence, consider metabolites:

<table>
<thead>
<tr>
<th>6-TG</th>
<th>6-MMP</th>
<th>Possible cause</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>undetectable</td>
<td>undetectable</td>
<td>Non-adherent or underdosed</td>
<td>Understand why pt not taking med or increase dose</td>
</tr>
<tr>
<td>Low (&lt;230)</td>
<td>Low or undetectable</td>
<td>Non-adherent or underdosed</td>
<td>Discuss adherence, increase dose</td>
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<tr>
<td>Low (&lt;230)</td>
<td>High (&gt;5700)</td>
<td>6-MMP shunter</td>
<td>1. Increase thiopurine, or 2. Consider allopurinol, or 3. Switch agents</td>
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<tr>
<td>“Therapeutic” (&gt;230-&lt;400) or High (&gt;400)</td>
<td>Normal range or high</td>
<td>Primary non-responder</td>
<td>1. Assess disease 2. Switch to different mechanism</td>
</tr>
</tbody>
</table>

### 6-MP monotherapy

<table>
<thead>
<tr>
<th>Pt</th>
<th>TPMT</th>
<th>6-TGN</th>
<th>6-MMP</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23.0</td>
<td>137</td>
<td>13,477</td>
<td>114</td>
</tr>
<tr>
<td>2</td>
<td>19.7</td>
<td>301</td>
<td>12,796</td>
<td>141</td>
</tr>
</tbody>
</table>

#### The Patient not Responding to Thiopurine

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Practical Approach to Allopurinol and Thiopurine Combination Therapy

- Not for everyone! Be aware of safety concerns.
- Choose patient (and MD) wisely:
  - Active disease
  - Adherence with thiopurines
  - Subtherapeutic 6-TGN, supratherapeutic 6-MMP
  - Elevated LFTs or nausea may be present but not necessary to consider this approach
- Drop thiopurine to 25 mg (6-MP) or 50 mg (Aza)
- Allopurinol 100 mg
- Notify pharmacist!
- CBC weekly for one month, then monthly...
- Metabolites at week 3
- Dose adjustment if necessary but in small increments


Brothers with Shunting

<table>
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<th>6-MP monotherapy</th>
<th>6-MP/allopurinol</th>
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<tr>
<td>2</td>
<td>19.7 301 12,796 141</td>
<td>351 -- 25</td>
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Both patients responded quickly (within 2-3 weeks), have been in stable steroid-free remission for >2 years.
The Patient Failing TNF-inhibitor Therapy

25 yo woman with Crohn’s disease of ileum and colon and E. nodosum

- 6 years ago, at age19 yo, severe ileocolitis and E. nodosum of legs
- Had presented 3 months earlier with diarrhea, hematochezia
- Steroid resistant
- Infliximab 5 mg/kg IV administered (0,2, 6) with prompt remission of bowel symptoms and healing of skin
25 yo woman with Crohn’s disease of ileum and colon and E. nodosum - 2

- Over the next 5 years, feeling well
- Occasionally late receiving infliximab
- Social smoker
- Presents to GI clinic with diarrhea, 5 pound weight loss

25 yo woman with Crohn’s disease of ileum and colon and E. nodosum - 3

- Labs after loss of response to infliximab (week 6):
  
  Infliximab level at 6 weeks: 3.1
  Antibodies to infliximab: positive titer
Switching to Another Biologic Therapy
What to choose and when to choose it?

- Evidence only exists in one direction (infliximab first), assumption is the opposite is true
- **Primary non-responder**: anti-TNFα loading dose with no response:
  - Where is the drug going?
  - 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 reasonable\(^1\):\(^3\)
  - If not immunogenicity, consider a different mechanism of treatment
    - Methotrexate?
    - Natalizumab?
    - Surgery?
    - Clinical trial

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Switching Between TNF Inhibitors: Rheumatoid Arthritis Experience

- Response to a second inhibitor is lower relative to first \(^1\)
- Response to a second inhibitor will be comparable if initial discontinuation was due to adverse events \(^1\), \(^2\)
- Patients who do not respond to 2 TNF inhibitors are not likely to respond to a third \(^2\)

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\(^2\) Panaccione R, et al. DDW 2008: #920
\(^3\) Rutgeerts PJ, et al. DDW 2008: #494

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Secondary Loss of Response to anti-TNF: Attenuation

Secondary Loss of Response to anti-TNF: Relapse/Other Causes
Case: Severe Crohn’s colitis failing TNF

- 32 yo woman, 16 year history Crohn’s ileocolitis
  - Prior therapy with 5-ASA, corticosteroids, azathioprine, methotrexate, infliximab, adalimumab, cyclosporine
  - Limited response but not remission on all prior therapies, some in combination
- Surveillance exam in April 2008: moderate to severe activity
- PMH:
  - Factor V Leiden deficiency, recurrent thromoses, PE (chronic anti-coagulation)
  - chronic iron deficiency
  - hypoalbuminemia

Case: Severe Crohn’s colitis failing TNF - 2

- Discussed natalizumab vs. surgery (proctocolectomy and end ileostomy)
- Initiated TOUCH program (patient lives in Michigan)
- Discontinued azathioprine (4 week washout)
- Not on steroids
- First natalizumab infusion July
Case: Severe Crohn’s colitis failing TNF - 2

- Clinical follow-up in October
- Feels “best since diagnosis”
- Hemoglobin 14 g
- Albumin 4.1
What happens to the patients who receive natalizumab in the current post-TNF paradigm?

Sakuraba et al. IBDJ 2013.

Updated Utilization and Safety Results of Natalizumab in CD and MS
(TOUCH, CD INFORM, TYGRIS & Pregnancy Registry Studies)

- 75,500 patients treated as of 09/30/2010 (post-marketing)
  - 48,400 treated >1 year
  - 37,000 treated >18 months
  - 29,400 treated >24 months
  - Predominantly MS patients

- PML (Progressive Multifocal Leukoencephalopathy)
  - 85 cases as of 07-Jan-2011; 16 of the 85 (19%) have died
  - No known post-marketing cases amongst CD patients
  - Longer duration and prior immunosuppressant use increases risk
  - Risk:
    - 0 within first year of treatment
    - 0.4/1000 after 12-24 months of treatment
    - 1/1000 after >24 months of treatment
  - Only 56% of CD patients positive for JC!

Recommendations for JCV Antibody Testing

• Testing prior to treatment with natalizumab
  • If positive, consider retesting.
    – If confirmed, option is treatment with natalizumab for 9-12 months

• If negative, may treat with natalizumab, retest every 6 months
  – If converts to positive, stop therapy

• The benefit and safety of a drug holiday and restarting after “resetting” the exposure has not been tested in Crohn’s disease
• Vedolizumab (expected approval Q2 2014) does not have PML associated with it.

Can we assess loss of response to anti-TNF more accurately?

Update on Therapeutic Monitoring
Clinical utility of measuring IFX and ATI levels in patients with IBD

Clinical outcomes in patients with detectable ATI (n=35)*

Complete / partial response (%)

Anti-TNF changed (11/12) | Infliximab increased (1/6) | P<0.004

92 | 17

Clinical outcomes in patients with sub-therapeutic concentrations (n=69)*

Complete / partial response (%)

Anti-TNF changed (2/6) | Infliximab increased (25/29) | P<0.016

40 | 86

* 6 discontinued IFX, 3 continued same dose, 3 proceeded to surgery, 5 patients could not be assessed
* 10 continued same dose, 9 discontinued IFX, 8 proceeded to surgery and 7 patients could not be assessed


Interpretation of Infliximab Levels and Antibodies to Infliximab

<table>
<thead>
<tr>
<th>Infliximab Level</th>
<th>Antibodies to Infliximab</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated</td>
<td>Absent</td>
<td>Switch treatment mechanism</td>
</tr>
<tr>
<td>Elevated</td>
<td>Present</td>
<td>Unclear, consider switching to another TNF-inhibitor</td>
</tr>
<tr>
<td>Not elevated</td>
<td>Absent</td>
<td>Adjust dose, interval of infliximab</td>
</tr>
<tr>
<td>Not elevated</td>
<td>Present</td>
<td>Switch to another TNF-inhibitor</td>
</tr>
</tbody>
</table>
Factors contributing to primary non-response or loss of response to TNF inhibitors

- No inflammation (IBS)
- Wrong endpoint
  - Structural damage, i.e. stricture
  - Bile-salt diarrhea, bacterial overgrowth, B12 deficient
  - Celiac disease
- Mechanism of inflammation not TNF dependent
  - Normal CRP (1)
  - pANCA positive? (2,3)
- Polymorphism in IgG Fc receptor IIIa (4)
- Smoking (5)


Poor Correlation Between Symptoms and Objective Markers of Inflammation

- Prospective follow-up of 188 patients enrolled in SONIC trial, with assessment of endoscopic activity at baseline and 26 weeks

<table>
<thead>
<tr>
<th></th>
<th>‘Clinical Remission’ (CDAI &lt;150, n=136)</th>
<th>‘Moderate-Severely Active CD’ (CDAI ≥220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Mucosal Healing</td>
<td>56.9%</td>
<td>29.6%</td>
</tr>
<tr>
<td>CRP Normalization</td>
<td>64.7%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Both, Complete Mucosal Healing and CRP Normalization</td>
<td>39.7%</td>
<td>22.9%</td>
</tr>
</tbody>
</table>

(asymptomatic) have active endoscopic disease

- Almost a third of patients believed to have symptoms due to CD, are in endoscopic remission

‘Silent’ Crohn’s Patients (Asymptomatic With Elevated CRP) Have a 6-Fold Higher Risk of Hospitalizations

- 178 CD patients with clinical remission defined by SIBDQ scores in a prospective registry
- Silent (asymptomatic) Crohn’s disease (CD) patients feel well but have an elevated CRP
  - Represent up to 24% of CD patients that feel well (clinical remission)
  - May benefit from further evaluation or closer monitoring to prevent disease related complications and hospitalization
- Hospitalizations tend to be for surgical intervention for ileal disease

Majority of hospitalizations in asymptomatic patients with elevated CRP occur within the first 12 months of the clinic visit when CRP elevation was detected


Therapeutic Drug Monitoring of Infliximab (IFX) Predicts Mucosal Healing Following Dose Intensification in IBD

- Enrolled 52 IBD patients (34 CD and 18 UC) with secondary failure to IFX. Dose escalation to 10mg/kg in all.
- IFX trough, ATI, CRP, and calprotectin measured before dose optimization and at Week 8
- Endpoint – Mucosal healing at Week 8
- Conclusion: The change in infliximab trough levels after dose intensification (delta IFX) predicts mucosal healing in IBD patients.

Fecal Loss of Infliximab (IFX) As a Cause of Lack of Response in Severe Inflammatory Bowel

Aim:
- To determine if fecal loss of IFX contributes to failure of
  - response to induction therapy in severe colitis

Methods:
- Fecal samples collected within first 14 days following 1st IFX infusion (5mg/kg)
- Nonresponse: Cessation or intensification of therapy within 3 months

Results:
- 11 patients (8 UC, 3 CD); all with colonic disease
- Compared to responders, non-responders to IFX had:
  - Higher fecal IFX concentration at day 1 \( (P=0.02) \)
  - Lower serum IFX concentration at day 14 \( (P=0.03) \)

Conclusion: Fecal loss of infliximab may contribute to primary non-response in severe IBD colitis


Your Patient Stops their anti-TNF Therapy

Now what?
Close Monitoring of CRP and Fecal Calprotectin is Able to Predict Clinical Relapse in Patients with CD in Remission after Infliximab Withdrawal: A Sub-Analysis of the STORI Study

113 patients with luminal CD treated with > 1 year IFX/IS combination in stable steroid-free remission for > 6 months (STORI), with discontinuation of IFX

51 (45%) with relapse at median of 10 months

In relapsers, higher median CRP and calprotectin during follow-up but also a sudden and pronounced increase in CRP and calprotectin during 4 months prior to relapse

CRP of 6.1mg/L and calprotectin of 305mcg/g best for prediction of relapse


Trough Levels and Anti-drug Antibodies Predict Safety and Success of Restarting Infliximab After a Long Drug Holiday

- Consecutive cohort of patients (n=128); 105 CD, 23 UC where IFX was restarted after a median drug holiday of 15 months (at least >6 months).
- Success at Week 14, year, and end of follow-up (median 4 years); ATI and trough level (TL) assessed
- Results
  - Restarting IFX successful in 84.5% (short term), 70% (at 1 year) and in 61% (end of follow-up)
  - IFX discontinued in 12% due to infusion reaction. IMM at restart prevents infusion reactions.

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Short-term</th>
<th>Year 1</th>
<th>End of Follow-Up</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATI (at 2nd infusion) detectable N=31</td>
<td>71%</td>
<td>54.8%</td>
<td>38.7%</td>
<td>0.14 (0.026-0.74) P=0.021</td>
</tr>
<tr>
<td>IMM at restart N=84</td>
<td>91.6%</td>
<td>74.7%</td>
<td>66.6%</td>
<td>6 (1.3-2.7) P=0.019</td>
</tr>
<tr>
<td>Reason for discontinuation (remission &amp;/or pregnancy)</td>
<td>90%</td>
<td>77.5%</td>
<td>66.6%</td>
<td>2.70 (1.09-6.67) P=0.033</td>
</tr>
<tr>
<td>TL (at 2nd infusion) &gt; 2 μg/ml N=43</td>
<td>93%</td>
<td>74%</td>
<td>70%</td>
<td>2.94 (1.18-7.69) P=0.021</td>
</tr>
</tbody>
</table>

- Conclusion: Restarting IFX after a drug holiday is safe, with success predicted by absence of early ATI formation, IMM at recommencement, and not having had previous infusion reactions

A Proposed Algorithm for Disease Monitoring in IBD

Baseline assessment of disease activity by endoscopy paired with surrogate marker

Choice of initial therapy based on severity and prognosis of patient

3-6 months

Re-assessment of disease activity directly or with surrogate marker

Dz Monitoring

Healing Documented?

Yes

Clinical follow-up that includes assessment of disease stability

6-12 months

No

Discussion with patient treatment options

Clinical follow-up

Is patient willing to proceed with your recommendations?

No

Adjust therapy

3-6 months

3-6 months

If no other treatment options left

Treat to Target

Management of Pain in IBD
Causes of Pain in IBD

- Related to bowel disease
  - Transmural inflammation
  - Penetrating complication
  - Obstruction
  - Dysmotility
  - Abscess

- Related to extraintestinal manifestations
  - Arthritis/arthralgias
  - Eye
  - Skin (PG/EN)
  - Urologic

- Other
  - Drug withdrawal (steroids, narcotics)
  - IBS
  - Psychosomatic

Treating Pain in IBD

- Identify cause and treat it
  - NPO
  - Anti-inflammatory therapy: SASP, MTX if arthralgias
  - Drainage of abscess
  - Surgery

- Avoid narcotics
- Assess anxiety/depression
### Non-Bowel Analgesic Therapy for IBD

<table>
<thead>
<tr>
<th>Acceptable</th>
<th>Use with caution/avoid</th>
</tr>
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<tbody>
<tr>
<td>• Acetaminophen</td>
<td>• NSAIDs</td>
</tr>
<tr>
<td>• Celecoxib¹ (short-term)?</td>
<td>• Narcotics</td>
</tr>
</tbody>
</table>

**Possible**

- Tramadol (Ultram)
- Pregabalin (Lyrica)
- Gabapentin (Neurontin)


### Concerns about Narcotics in IBD

- Obscures penetrating complication
- Obscures severe colitis
- Contributes to megacolon
### Serious Infections and Mortality in the TREAT Registry

**Serious Infections (Multivariate)**

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Current use of IFX</td>
<td>1.4</td>
</tr>
<tr>
<td>Current use of 6-MP/AZA/MTX</td>
<td>0.9</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Current use narcotic analgesics</strong></td>
<td><strong>2.7</strong></td>
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†p < 0.0001

**Mortality (Multivariate)**

<table>
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<tbody>
<tr>
<td>Current use of IFX</td>
<td>1.1</td>
</tr>
<tr>
<td>Current use of 6-MP/AZA/MTX</td>
<td>0.8</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.2</td>
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<tr>
<td><strong>Current use of narcotic analgesics</strong></td>
<td><strong>2.6</strong></td>
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* p = 0.001; **p < 0.001


### Clinical Variables Associated with Narcotic Use in IBD

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<th>Independent variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Active disease*</td>
<td>4.12</td>
<td>1.75-9.71</td>
</tr>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.99-1.04</td>
</tr>
<tr>
<td>Disability</td>
<td>5.25</td>
<td>1.75-15.74</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>1.03</td>
<td>1.00-1.06</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.51</td>
<td>1.20-5.29</td>
</tr>
<tr>
<td>Polypharmacy*</td>
<td>5.4</td>
<td>2.29-12.72</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.39</td>
<td>1.12-5.11</td>
</tr>
</tbody>
</table>

*Active disease defined as a HBI ≥ 4

*Polypharmacy defined as on ≥ 5 drugs

Predictors of Narcotic Use in IBD

- Coexisting psychiatric disease (67% vs. 8%)
- Stricturing ileal disease
- Female gender
- Concomitant psychiatric medication (37% vs. 19%)
- Worse disease activity
- Smoking
- Polypharmacy


Risk of Hospitalization and NSAID Use in IBD

- Prospective case-control study
- 1989-1993
- N=319,465
  - 785 admitted with colitis
  - 200 due to IBD
  - 1198 controls from the community

Overall results:
- Current NSAID use
  - OR 1.77 (1.01-3.10)
- Recent NSAIDs
  - OR 1.93 (1.20-3.09)

Incident cases:
- Current NSAID use
  - OR 2.96 (1.21-6.64)
- Recent NSAIDs
  - OR 2.51 (1.13-5.55)

Summary: Tough Issues in IBD

• Clarify diagnosis and overlapping extra-intestinal problems
• Optimize/individualize and maximize existing therapies
  – This should include anti-integrin therapy
• Don’t mask inflammatory symptoms with analgesia
• Communicate risks of therapy in the context of the risks of disease
• Get a second opinion!