Latest Treatment Updates for Crohn’s Disease: Tailoring Therapy

David G. Binion, M.D.
Co-Director, IBD Center
Director, Nutrition Support Service
UPMC Presbyterian Hospital
Division of Gastroenterology, Hepatology and Nutrition
Professor of Medicine, Clinical and Translational Science
University of Pittsburgh School of Medicine
Pittsburgh, PA
Tailor (verb)

“make or adapt for a particular purpose or person”
What Tailoring CD Treatment Can Achieve

- Personalized approach – each patient will achieve goals of controlling inflammation, maximizing quality of life, limiting disease complications
- Improve quality of CD care
- Cost effective IBD care
How Can We Tailor CD Treatment?

• Maximize existing treatment approaches for gut inflammation
• Personalize care – define the issues driving patient symptoms (cumulative damage due to inflammation)
  – Abdominal pain
  – Co-morbidities - anxiety and depression in setting of chronic illness
• Identify and characterize refractory inflammation – develop new agents to achieve and maintain remission
Tailoring Treatments in CD

I. Defining success (and failure) in CD care

II. Changing spectrum of IBD admissions

III. Optimizing medical treatment - CD

IV. Identifying the “at risk” IBD population – development of personalized care

V. Summary
I. Defining Success (and Failure) in CD Care

- Avoid corticosteroid use (long-term)
- Achieve mucosal healing
- Ameliorate abdominal pain
- Maximize quality of life
- Prevent hospitalization
Tailoring Treatments in CD

I. Defining success (and failure) in CD care

II. Changing spectrum of IBD admissions

III. Optimizing medical treatment - CD

IV. Identifying the “at risk” IBD population – development of personalized care

V. Summary
II. Changing Spectrum of IBD Admissions

• More effective IBD drugs are available at this time than ever before

• IBD patients are being admitted in higher numbers than ever before
  – 1990 – 2003 annual hospitalization rates for IBD (Nationwide inpatient sample – pooled data from 1000 US Hospitals)
    – Crohn’s disease rose from 9.3 to 17.1 / 100,000 (p=0.0002)
    – UC rose from 8.2 to 12.4 / 100,000 (p=0.06)

• Why?

• What is underlying increase in IBD hospitalizations?

Changing Spectrum of IBD Admissions at UPMC: 1998 and 2008

- Evaluation of electronic medical record database at UPMC Presbyterian Hospital 1998 and 2008. No increase in bed capacity
- Search admissions with ICD9 codes for CD and UC
- Evaluation for repeat admissions
- Evaluation for chronic pain/anxiety/depression
- Evaluation for infectious complications
- Evaluation of mortality

<table>
<thead>
<tr>
<th>Primary IBD: IBD diagnosis is principle ICD 9 diagnosis</th>
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<tbody>
<tr>
<td>All IBD: IBD diagnosis is any of 25 possible ICD 9 diagnoses</td>
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* $p < 0.05$ – statistically significant

IBD Admissions as a Fraction of All Hospital Admissions

Type of Primary IBD Admissions (CD vs. UC)

IBD Admissions That are Repeat Admissions

- 1998: 14.1%
- 2008: 33.3%

IBD Admissions with Chronic Abdominal Pain and Anxiety/Depression

IBD Admissions Requiring IBD-related Surgery

Percentage of IBD admissions

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>1998</td>
<td>69.7</td>
</tr>
<tr>
<td>2008</td>
<td>43.8</td>
</tr>
</tbody>
</table>

IBD Admissions with *Clostridium difficile* (*C. difficile*) Enteritis

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage of IBD admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0.8</td>
</tr>
<tr>
<td>2008</td>
<td>5.9</td>
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IBD Admissions Which Ended in Death

II. Changing Spectrum of IBD

Admissions Summary

• More IBD hospitalizations at this time
• Crohn’s disease admissions are majority
  – Rehospitalization plays a major role - up to 1/3 of admissions
• Chronic pain/anxiety depression contributes to IBD admissions
• Refractory inflammation despite anti-TNF therapy?
Tailoring Treatments in CD

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V. Summary
Crohn’s Disease: 1960s Historical Perspective

- Treatment: Prednisone and sulfasalazine
- Goals of Surgery:
  - Relieve obstruction (and penetrating complications)
  - Discontinue medical therapy (chronic steroids)
- Results:
  - High rates of surgery – 92% of ileocolic disease were resected
  - High rates of work disability – 27%
### Probability of Surgery for Crohn’s Disease: Heterogeneous Natural Histories

<table>
<thead>
<tr>
<th>Years After Diagnosis</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td></td>
<td>1 Surgery</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
</tr>
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</table>

Legend:
- **Mild**
- **Moderate**
- **Severe**

Severe CD and Permanent Work Disability

Estimate of work capacity: 10 years following diagnosis

Crohn’s Disease - Medical Management Algorithm:
No Partial Obstruction, Abscess Or Infection Detected

**Mild**
- 5-ASA, budesonide or antibiotics

**Moderate**
- Corticosteroid taper
- AZA/6MP/MTX to induce/maintain remission

**Severe**
- Unable to taper corticosteroids
- Inadequate response to AZA/6MP/MTX
  - infliximab
  - adalimumab
  - certolizumab
  - natalizumab
  - vedolizumab

**Surgical patients**
Mesalamine as CD Maintenance Therapy: Ineffective for the Majority of CD Patients

Prednisone 1 mg/kg for 3–7 weeks
Mesalamine 4 g added after induction of remission (during weaning)

Placebo: 19% steroid dependent
Mesalamine: 6% steroid dependent

Efficacy of AZA as Maintenance Therapy in Patients with Active Crohn’s Disease

*Remission induced by prednisolone tapered over 12 wk
Azathioprine Intolerance in CD:
Rates of Early Adverse Reactions

- Autoimmune Hepatitis: 5%
- Crohn’s Disease: 29%

P = .008

10%: Severe adverse reactions to azathioprine/6MP, including fevers, headache, pancreatitis, respiratory failure, blistering skin lesions within 4 weeks of initiation

Moderate to Severe CD: Induction of Remission With Methotrexate

Moderate to Severe CD: Maintenance of Remission With Methotrexate

70% of MTX treated CD patients fail to achieve long-term remission with monotherapy

Benefits of Chemotherapy Based Immunosuppression in CD Management

- Relatively inexpensive
- Familiarity in IBD care (1980 purine analogs, 1995 methotrexate)
- Long-term track record of safety (RA experience with methotrexate)
- Purine analogs can be used during pregnancy
Limitations of Chemotherapy Based Immunosuppression in CD Management

• Majority fail to achieve remission with purine analog or methotrexate monotherapy

• High rates of adverse reactions – subgroup of patients will not tolerate these agents – both idiosyncratic and dose related side effects

• Consider switch to alternate purine analog for upset stomach/abdominal pain (tolerated in 50%; no pancreatitis detected)

• Methotrexate disqualified for patients anticipating pregnancy in near future (discontinue 3 months prior to planned attempt for pregnancy)

• Methotrexate hepatotoxicity increased in diabetics, regular alcohol intake and obese (>60% of IBD are overweight/obese at this time)
The First-line Biologic Agents for the Treatment of CD

**Infliximab**
- Chimeric monoclonal antibody (75% human IgG\(_1\) isotype)

**Adalimumab**
- Human recombinant antibody (100% human IgG\(_1\) isotype)

**Certolizumab Pegol**
- Humanized Fab’ fragment (95% human IgG\(_1\) isotype)

PEG, polyethylene glycol.
Biologic Era in CD Management: Healing of Refractory Ulceration/Fistula With Anti-TNF Agents

Durability of Infliximab for CD

- 50% of CD patients have discontinued infliximab by 6 years of maintenance therapy (n=153)
- 82% of these patients were on combination immunosuppression

Avoid episodic dosing
Effect of Prior Episodic Dosing on Performance of Infliximab Maintenance: Hospitalizations and Surgeries at 3 years

- 40 patients with prior irregular dosing
- 61 patients with scheduled maintenance
- Total excess cost in the PI exposure cohort of $11,464 during the third year of infliximab maintenance therapy per patient

Adalimumab: Induction Only/Reinitiated vs Continuous Maintenance Therapy at Week 56

$^{a}P<.05$, 40 mg EOW vs IO/R

$^{b}P<.05$, 40 mg EW vs IO/R

How Can We Maximize the Utility of Biologic Therapy for CD?

Concomitant immunosuppression improves efficacy and pharmacokinetics of infliximab
Corticosteroid-Free Clinical Remission at Week 26 in the SONIC Study

Primary Endpoint

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>AZA + placebo</th>
<th>IFX + placebo</th>
<th>IFX + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52/170</td>
<td>75/169</td>
<td>96/169</td>
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- **30.6** (P < .001)
- **44.4** (P = .009)
- **56.8** (P = .022)

43% do not achieve remission

Mucosal Healing at Week 26 in the SONIC Study

SONIC: IFX Trough Levels at Week 30* are Higher with Concomitant AZA

*Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.

Infliximab Levels in Patients Taking Concomitant Immunosuppressives

Increased infliximab blood levels in patients who take immunosuppressives

<table>
<thead>
<tr>
<th></th>
<th>No immunosuppressives</th>
<th>Immunosuppressives</th>
<th>Immunosuppressives</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX levels (median + IQR) Max IFX</td>
<td>2.42 µg/mL (1–10.8) 21 µg/mL</td>
<td>6.45 µg/mL† (3–11.6) 33.4 µg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZA</td>
<td>MTX</td>
</tr>
<tr>
<td>IFX levels (median + IQR) Max IFX</td>
<td></td>
<td>6.15 µg/mL (3–11.6) 33.4 µg/mL</td>
<td>5.65 µg/mL† (2.87–10.8) 31 µg/mL</td>
</tr>
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</table>

†P=0.065
Infliximab Serum Levels are Related to Mucosal Healing

- **Methods** - Analysis of serial serum samples
- **Patients** - Crohn’s disease on infliximab (N=215)

Mucosal Healing After Treatment Predicts Subsequent Disease Course in Crohn’s Disease

Frøslie et al, Gastroenterology 2007; 133: 412–22
## Immunogenicity of Biologics for IBD

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Episodic</th>
<th>Scheduled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM- (%)</td>
<td>IM+ (%)</td>
</tr>
<tr>
<td>Infliximab¹ (CD 5 mg/kg)</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>Infliximab² (UC all doses)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Certolizumab³,⁴ (CD all doses)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Adalimumab⁵,⁶ (RA all doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab⁷ (Classic II only)</td>
<td></td>
<td></td>
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*30% patients on episodic
**36–37% patients on AZA/6-MP
***30% patients on IM³

Practical Advice: If a Patient Loses Response and/or Develops Immunogenic Complications....

• Combination therapy is mandatory with the second TNF inhibitor because:
  – We are exhausting limited options
  – Response to the second TNF inhibitor may not be as good as the first
  – Patients may be genetically predisposed to developing antibodies to biologics
Biologic Agents With Alternate Mechanisms of Action: Natalizumab Maintenance in Crohn’s Disease

- Blockage of leukocyte trafficking into the gut (non-selective alpha4 blocker)
- FDA approved – MS, CD
- Effective at longterm maintenance in CD
- Reactivation of JC virus leading to PML, in setting of longterm maintenance

<table>
<thead>
<tr>
<th>Estimated PML Risk on NAT (in multiple sclerosis)</th>
<th>Anti-JCV Antibody (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natalizumab Exposure</strong></td>
<td><strong>No Prior Immunosuppression</strong></td>
</tr>
<tr>
<td>1-24 mo</td>
<td>0.35/1000</td>
</tr>
<tr>
<td>25-48 mo</td>
<td>4/1000</td>
</tr>
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Vedolizumab: Selective alpha4-beta7 integrin Inhibition for IBD Therapy

- Selective blocker of the alpha4-beta7 integrin (ligand for MAdCAM-1) which mediates leukocyte traffic into the mucosa in IBD
- Safety profile: No evidence of JC virus reactivation and PML
- Slow acting in CD – requires 10 weeks to achieve significant therapeutic response with durable maintenance of remission
- Choice for CD anti-TNF failure patients but best efficacy in anti-TNF naïve population
- Approved by FDA for UC and CD May 2014
Crohn’s Disease - Medical Management Algorithm: No Partial Obstruction, Abscess Or Infection Detected

**Mild**
- 5-ASA, budesonide or antibiotics

**Moderate**
- Corticosteroid taper
- AZA/6MP/MTX to induce/maintain remission
  - Yes
  - breakthrough
  - AZA/6MP/MTX maintenance
- No

**Severe**
- Unable to taper corticosteroids
- Inadequate response to AZA/6MP/MTX
  - infliximab
  - adalimumab
  - certolizumab
  - natalizumab
  - vedolizumab

**Surgical patients**
When to Operate or Start/Switch Biologics?
Biologics Decrease Surgery Due to “Low-Risk” Strictures in Patients with CD

- Historical cohort study of 226 patients with stricturing CD that had CTE or MRE
- 49% surgery within median of 1 year

Development Simplified Stricture Severity (SSS) Score

<table>
<thead>
<tr>
<th>Internal Fistula</th>
<th>Small Bowel Obstruction (SBO)</th>
<th>Prox. Dilation ≥ 3cm</th>
<th>Abdominal mass/abscess</th>
<th>Mesenteric stranding</th>
</tr>
</thead>
</table>

AUC = 0.7 for predicting surgery at 1 year

Biologics may reduce the risk of surgery by up to 44% in stricturing CD. This benefit may be more pronounced in patients with a “low-risk” (SSS=0) enterographic findings.

CTE, computed tomography enterography
MRE, magnetic resonance enterography
When to Switch Biologics in CD?

- Confirm active inflammation (endoscopy, imaging)
- Assess for infection – *C difficile*, CMV (stool studies, endoscopy)
- Are symptoms related to obstruction? Imaging, patency capsule
- Consider checking drug levels, antibodies against the biologic. This allows for dose adjustment if trough is low (shortened interval/increased dose) and/or confirms immunogenicity/increased clearance of the drug
- Maximize initial biologic if possible
Poor Correlation Between Symptoms and Objective Evidence of Inflammation in CD

- Identify objective evidence of inflammation and use this to guide treatment – serologic markers, fecal markers, colonoscopy
- What is driving symptoms in CD?

*Number per 100 patients
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V. Summary
What Should We Measure to Assess IBD Patients Status and the Impact of Disease on Their Lives?

- Hospitalizations and surgery are infrequent and too late (goal is to prevent these issues)
- Work disability – too late and limited numbers
- Mortality is low – also way too late
- No ideal biomarker (at this time)
- No genetic prediction (at this time).
- Impact of IBD extends beyond mucosal inflammation – post-surgical anatomy/physiology, nerve damage, chronic pain
- Patient telephone calls
Association Between Telephone Activity and Features of Patients With Inflammatory Bowel Disease

Claudia Ramos-Rivers,* Miguel Regueiro,* Eric J. Vargas,* Eva Szigethy,‖ Robert E. Schoen,* Michael Dunn,* Andrew R. Watson,§ Marc Schwartz,* Jason Swoger,* Leonard Baidoo,* Arthur Barrie,* Anwar Dudekula,† Ada O. Youk,‖ and David G. Binion*

*Division of Gastroenterology, Hepatology and Nutrition, ‡Department of Psychiatry, §Division of Colorectal Surgery, ‖Division of General Internal Medicine, University of Pittsburgh School of Medicine; †Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania
Telephone Encounters Across IBD Patients

**Distribution of IBD registry patient population**

- **2009**
  - 0-1 (LTE): 27%
  - 2-5: 31%
  - 6-10: 36%
  - >10 (HTE): 34%

- **2010**
  - 0-1 (LTE): 22%
  - 2-5: 20%
  - 6-10: 22%
  - >10 (HTE): 16%

**Distribution of telephone encounters recorded in EMR**

- **2009**
  - 0-1 (LTE): 2%
  - 2-5: 20%
  - 6-10: 29%
  - >10 (HTE): 51%

- **2010**
  - 0-1 (LTE): 2%
  - 2-5: 20%
  - 6-10: 27%
  - >10 (HTE): 51%
Creating an IBD Severity Index: Inflammation, Pain, Psych Co-morbidity
Creating an IBD Severity Index: Quality of Life and Healthcare Utilization

Graphs showing the proportion of patients with poor quality of life, who had an ED visit, and who had a hospital admission across different categories of annual number of telephone encounters.
Clusters of Telephone Encounters and Subsequent Healthcare Utilization

Chi2(3)=21.61; p=0.001
Crohn’s Disease and Pain

• Chronic (non-post-operative) narcotic use was identified in 13% of Crohn’s disease patients evaluated in a referral population
  – More likely to be female (72% vs 49%; p <0.01)
  – More permanent work disability
  – More neuropsychiatric drug use
  – Longer duration of disease
  – Worse disease activity
  – Worse quality of life

• Multifactorial causes: Inflammation, obstruction, neuropathic, vitamin deficiency (i.e. vitamin B12)
Management of IBD Pain

• Avoid NSAIDS and Cox 2 inhibitors
  – Interfere with small intestinal mucosal repair
  – May contribute to local tissue ischemia
• Correct nutritional deficiencies – vitamin B12
• Bile acid sequestrant agents for cholerhelic diarrhea (improvement in up to 83% of patients)
• Avoid chronic narcotics – disturbs gut physiology and increased mortality
• Assess for adrenal insufficiency
• Referral for supportive psychotherapy

Swoger JM et al., *Dig Dis* 2010; 28; 452-62.
Szigethy E et al., *Inflamm Bowel Dis* 2009; 34: 156-63.
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Summary and Conclusions - I

- Optimizing existing CD treatments is essential goal at this time
- Majority of CD patients seeking care have moderate to severe disease, implying need for long term immunomodulator and possibly biologic treatment to maintain remission
- Over half of CD patients will fail to maintain remission with immunomodulator monotherapy
- CD patients who are intolerant to or fail standard immunomodulators are candidates for long-term biologic treatment
- Durability of biologic therapy in CD is limited
  - Episodic dosing diminishes durability
- Efficacy and durability is improved with standard dosing and concomitant immunosuppression
Summary and Conclusions - II

- There is a significant increase in CD hospitalizations.
- Chronic pain and psychiatric comorbidity (anxiety/depression) may play a key role in rising IBD admissions.
- Increased telephone activity identifies a subgroup of IBD patients with poor clinical outcome and high health care utilization.
- Improved care and cost-effective care will need to develop a personalized approach which addresses inflammation, pain, co-morbid psychiatric illness in CD.