Evidence-based Approach to the Contemporary Diagnosis and Management of CD and UC

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Learning Objectives

• Define the emerging and modified goals of IBD management.
• Review the available evidence supporting improved outcomes with objective goals of management.
• Develop a systematic approach to achieving the modified goals of IBD.
• Explore what the future may incorporate for IBD monitoring and prevention strategies.
We Have Made Great Progress in IBD....
But More Work to be Done

What are the Preferred Outcomes in IBD?

**Preferred Outcomes**
- Cure
- Stable Remission
- No surgery/repeat surgery
- No cancer
- Improved quality of life
- No hospitalization
- No infections
- Affordable care

**Surrogates of Outcomes**
- Symptom improvement (poor marker)
- Avoidance of steroids
- Healed mucosa
**Movement to Objective Measures of Control and Chronic Care Model of IBD: Improved Outcomes**

<table>
<thead>
<tr>
<th>Goal</th>
<th>Clinical parameters</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Improved symptoms</td>
<td>Improved QoL</td>
</tr>
<tr>
<td>Remission</td>
<td>No symptoms</td>
<td>Decreased hospitalization</td>
</tr>
<tr>
<td>Deep remission</td>
<td>Normal endoscopy</td>
<td>Avoidance of surgery</td>
</tr>
<tr>
<td></td>
<td>Mucosal healing</td>
<td>Minimal/no disability</td>
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**SUSTAINED DISEASE CONTROL**

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**Current Goals in IBD**

- **Make the diagnosis** quickly and accurately
  - include elements of prognosis

- **Achieve normal bowel function**
  - improve quality of life

- **Induce remission** rapidly

- **Maintain steroid-free remission** over time
  - Emphasis on mucosal healing, other biological markers ("deep remission")

- **Modify long-term outcomes** of the disease
  - Avoid hospitalization and surgery
  - Eliminate disability
  - Minimize exposure to steroids
  - Reduce costs of care
Why Might Outcomes be Improving in IBD?

- **Improvements in therapies**
  - Achieve more stable disease control, modify natural history
  - Achieve deeper levels of remission, i.e. mucosal healing

- **Improvements in goals of management**
  - More emphasis on steroid-free care
  - Movement to proactive management rather than reactive management (from “crisis care” to “chronic care”)
  - Inclusion of long-term improved outcomes in goals

- **Better evidence**
  - Are we just performing better research? Asking better questions?

- **Other interventions have improved**
  - i.e. surgery, surveillance colonoscopy

- **The diseases have changed.**
  - People with IBD now are less ill than those of the past.

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Treatments and Improved Outcomes
What we’ve learned about therapy and achieving preferred outcomes in IBD

- Ask the right questions....
- As therapies evolve, so does our ability to achieve preferred outcomes
- A personalized approach to management can optimize therapy
- Timing matters
- Individual pharmacokinetics matter
- Adherence to therapy matters

A Thoughtful Approach to Patients Losing Response to Anti-TNFs

The Use of Surrogate Markers to Assess Disease and Drug Response

The Possibility of De-escalating Therapy Safely in Some Patients

Incorporation of Quality Measures in Daily Practice
A Thoughtful Approach to Patients Losing Response to Anti-TNFs

- Loss of response is common
- Therapeutic drug monitoring is available
- Clinicians should evaluate carefully in order to make decisions about cycling or swapping therapies

The Use of Surrogate Markers to Assess Disease and Drug Response

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Biologic Therapies for Inflammatory Bowel Disease

Certolizumab pegol
Adalimumab
Golimumab
Infliximab

TNF receptor

CD

CD UC

UC

CD UC

(Fab')2

Fc region

Anti-integrins

Natalizumab
Vedolizumab

α4β1

α4β7

CD

CD

CD UC

UC

Challenges to Anti-TNF Therapy

- Not always effective
- Not always durable
- After primary response, may lose response
- Expensive
- Safety concerns

Approach to the IBD Patient Losing Response to Anti-TNF Therapy

Using Therapeutic Drug Monitoring

Measurement of anti-TNF level and anti-drug antibodies

- Undetectable or low anti-TNF level and (-) ADA
  - Increase anti-TNF dose or decrease dose interval
- High anti-TNF level and (-) or (+) ADA
  - Swap to another drug class
- Undetectable or low anti-TNF level and (+) ADA
  - Cycle anti-TNF or swap drug class
- High ADA level
- Low ADA level
  - Transient? Dose optimization and consider adding IMM
  - No response

What’s the Optimal Dose of Concomitant Therapy?

**Thiopurine:** $6\text{-TGN} \geq 125 \text{ pmol}/8 \times 10^8 \text{ RBCs}

- Correlation Between 6-TGN and IFX Concentrations

- Maintenance of Remission by MTX Dose

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Adding an Immunomodulator Overcomes ATIs

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# Vedolizumab Single Center “Real World” Experiences: Response Rates Similar Across Institutions

<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>CD %</th>
<th>Measure of Response</th>
<th>Week 6</th>
<th>Week 14</th>
<th>Week 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Chicago</td>
<td>177</td>
<td>70</td>
<td>SCCAI and HBI at week 14 and 30</td>
<td>50% CD</td>
<td>48% UC</td>
<td>60% CD</td>
</tr>
<tr>
<td>Cedars-Sinai Medical Center</td>
<td>109</td>
<td>67</td>
<td>50% decrease CRP at week 14 and 30</td>
<td>30% IBD</td>
<td>38% IBD</td>
<td>33% IBD</td>
</tr>
<tr>
<td>Swedish IBD Registry Eriksson C et al.</td>
<td>100</td>
<td>64</td>
<td>Partial Mayo and HBI at week 12</td>
<td>57% CD</td>
<td>65% UC (Week 12)</td>
<td></td>
</tr>
<tr>
<td>Massachusetts General Hospital Stevens B et al.</td>
<td>86</td>
<td>53</td>
<td>SCCAI and HBI at week 6 and 14</td>
<td>51.4% CD</td>
<td>46.2% UC</td>
<td>42.3% CD</td>
</tr>
<tr>
<td>Brigham &amp; Women’s Hospital Lucci M et al.</td>
<td>62</td>
<td>71</td>
<td>Physician impression at week 14</td>
<td>68% CD</td>
<td>83% UC</td>
<td></td>
</tr>
<tr>
<td>Washington University Vivo E et al.</td>
<td>33</td>
<td>55</td>
<td>Partial Mayo, HBI, CDAI and SIBDQ at week 6</td>
<td>27% CD</td>
<td>47% UC</td>
<td>23% CD</td>
</tr>
<tr>
<td>Boston University Oppenheim S. et al.</td>
<td>46</td>
<td>67</td>
<td>SCCAI and HBI at follow-up after week 6 infusion</td>
<td>47% IBD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cedar-Sinai Medical Center (Pediatrics) Singh N. et al.</td>
<td>23</td>
<td>65</td>
<td>PCDAI and PUCAI at week 6 and 14</td>
<td>40% CD Remission</td>
<td>88% UC Remission</td>
<td>36% CD Remission</td>
</tr>
</tbody>
</table>

Lessons Learned #1

- Careful assessment of reasons for loss of response
- Thoughtful cycling or swapping based on perception of disease activity and potential mechanisms
- Increased use of combination therapies, especially in switching

How Do We Incorporate This Into Practice?

- Improve fund of knowledge
- “Algorithmatize” management to achieve goals
- Knowledge of limits to our therapeutic success (when do you stop?)
- Shared decision making
A Proposed Algorithm for Achieving and Maintaining Targets of Control in IBD

1. Baseline assessment of disease activity by endoscopy paired with surrogate marker (Fecal Calprotectin, CRP)
2. Choice of initial therapy based on severity and prognosis of patient
3. 3-6 months: Re-assessment of disease activity directly or with surrogate marker
4. If target is achieved: "Disease Monitoring"; otherwise, proceed to "Treat to Target"
5. Clinical follow-up that includes assessment of disease stability
6. Clinical follow-up: if no other treatment options left
7. If no other treatment options left: "Treat to Target"
8. Choice of initial therapy based on severity and prognosis of patient
9. Decision: Is patient willing to proceed with your recommendations?
10. Target Achieved: Yes or No
11. Discussion with patient treatment options
12. Adjust therapy

STRIDE: Selecting Therapeutic TaRgets in Inflammatory Bowel Disease Endpoints

- **Methods**: 28 IBD specialists developed recommendations based on a systematic literature review and expert opinion.
- **Results**: 12 recommendations for UC and CD.
- **UC TARGET**:
  - PRO: resolution of rectal bleeding and diarrhea/altered bowel habit and endoscopic remission: Mayo endoscopic subscore of 0-1. Histological remission is an adjunctive goal.
- **CD TARGET**:
  - PRO: resolution of abdominal pain and diarrhea/altered bowel habit; and endoscopic remission:
    - resolution of ulceration at ileocolonoscopy, or
    - resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy.
- **Biomarker remission (normal CRP and calprotectin) was considered an adjunctive target.**

‘Silent’ Crohn’s Patients Have 6-Fold Higher Risk of Hospitalizations
Why we should be PROACTIVE!

178 CD patients with clinical remission defined by SIBDQ scores in a prospective registry


SIBDQ, short inflammatory bowel disease questionnaire

Fecal Calprotectin Can Predict Relapse in CD Patients on Maintenance Adalimumab

• 4-month prospective study of 30 CD patients with clinical remission >6 months on adalimumab

• Optimal cut-off of fecal calprotectin to predict remission was 204 µg/g
  – Associated with sensitivity 100%, specificity 85.7%, PPV 74.1% and NPV 100%

HBI, Harvey-Bradshaw index

Lessons Learned #2

• Don’t wait for failure

• Early reassessment of drug and disease response can be predictive and improve outcomes

• After achieving a goal, MONITOR for stability

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The Possibility of De-escalating Therapy Safely in Some Patients

Incorporation of Quality Measures in Daily Practice

• Patients ask about stopping their meds all the time!
• Payers want us to stop (or prove that they should re-authorize) therapies
• De-escalation can be in the form of stopping one or more therapies or dose reducing
• Monitoring before and after such approaches is absolutely necessary!
Therapy Adjustments Over Time the Concept of Disease Burden

Induction therapy continues at same dose as maintenance

Maintenance therapy decreased/de-escalated

How long?

Examples of De-escalation of Therapy

• 5-ASA?
  – MOMENTUM study shows 4.8 g/d → 2.4 g/d IF complete response

• Steroid induction → steroid-sparing maintenance therapy
  – Steroids withdrawn

• Concomitant IMM + anti-TNF therapy
  – Maintained on combo therapy
  – Possibility of withdrawing IMM (IMM experienced)
  – Possibility of withdrawing anti-TNF (Crohn’s disease)

• Withdrawal of thiopurine monotherapy

Withdrawal of Therapy in IBD Patients on Thiopurine Monotherapy

**CD** (n=129)  
**UC** (n=108)

Discontinuation of Infliximab in Patients in Clinical Remission who Remain on IMM: The STORI Trial

**Baseline Predictors of Relapse:**
1. Elevated CRP
2. Elevated fecal calprotectin
3. Lack of healing on baseline colonoscopy
4. Males
5. Detectable infliximab levels at trough


## Studies of Infliximab/Adalimumab Restarts after Drug Holidays

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Clinical Setting</th>
<th>Premedication when restarting therapy</th>
<th>Results (remission by 12 mo)</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louis et al, 2012</td>
<td>Prospective</td>
<td>Multi center cohort study</td>
<td>Yes</td>
<td>CD: 38/43</td>
<td>None</td>
</tr>
<tr>
<td>Steenholtz et al, 2012</td>
<td>Retrospective</td>
<td>Single Center</td>
<td>Yes</td>
<td>UC: 5/7 CD: 24/25</td>
<td>Ifn Rxn: 1</td>
</tr>
<tr>
<td>Farkas et al, 2013</td>
<td>Prospective</td>
<td>Multi center</td>
<td>No</td>
<td>UC: 17/18</td>
<td>Ifn Rxn: 4</td>
</tr>
<tr>
<td>Baert et al, 2014</td>
<td>Prospective</td>
<td>Single Center IBD Biobank</td>
<td>Yes</td>
<td>IBD: 76/98</td>
<td>Ifn Rxn: 15 DHR: 10</td>
</tr>
<tr>
<td>Molander et al, 2014</td>
<td>Prospective</td>
<td>Multicenter</td>
<td>No</td>
<td>UC: 9/10 CD: 4/4</td>
<td>DHR: 0 Ifn Rxn: 0</td>
</tr>
</tbody>
</table>

## Chicago Algorithm for Restarting IFX

**Modified from Baert, et al. 2014**

1. **Initial IFX Treatment**
2. Loss of Response
   - Intentional D/C
   - Unintentional discontinuity of therapy
3. **≥ 6 Month Drug Holiday**
4. **IFX Restart (with premeds)**
5. **Check: IFX / ATIs (7-14 days after 1st Dose)**
   - ATIs (-) IFX Present
     - Short-term + long term-response likely
   - ATIs (+) Infusion reaction likely
   - ATI (+) Infusion reaction likely

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Lessons Learned #3

• De-escalation does NOT mean no treatment!

• Any plan to dose reduce or discontinue therapy for any reason should come with the following:
  – Confirmation of disease stability (the “deeper” the better)
  – A monitoring strategy
  – A rescue strategy
CCFA “Top Ten” Process Measures for Quality by RAND panel determination

- Test for TB before anti-TNFa therapy
- Test for *C. difficile* in flares
- Flex sig. for CMV in steroid-refractory hospitalized UC
- Check TPMT before starting thiopurines
- Recommend steroid-sparing agents if >4m steroids
- Recommend colectomy or close surveillance for low-grade dysplasia in colitis
- Recommend smoking cessation if smoker with CD
- Educate patients regarding vaccinations

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CCFA “Top Ten” Outcome Measures

- Steroid-free clinical remission
- Days lost from work/school
- Days hospitalized
- ED visits
- Malnutrition
- Anemia
- Narcotic use
- Incontinence
- Normal health related QOL
- Nighttime BMs or leakage

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Process Measures: Checklists

http://cornerstoneshealth.org/checklist/

Lessons Learned #4

• Delivery of complex care in IBD results in tremendous heterogeneity

• Development of process and outcome measures can provide basic minimum requirements

• Study of access to healthcare resources allows for targeted interventions
  – Patients frequently delay care or medications in part due to cost
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