Crohn’s Disease: Can We Apply Algorithms to Our Individual Patients? When Should I Start More Aggressively?

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Sequential Therapies for Crohn’s Disease

Disease Severity at Presentation

- Severe
- Moderate
- Mild

- Aminosalicylate
- Corticosteroid
- Anti-TNF
- Natalizumab

Step-Up according to severity at presentation or failure at prior step

- Aminosalicylate (UC)/Thiopurine/MTX (CD)
- Anti-TNF (UC)/Thiopurine/MTX (CD)

Induction
Maintenance
Inflammatory Activity and Progression of Damage in a Theoretical Patient with CD

Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression


Cosnes J et al. Inflamm Bowel Dis. 2002;8:244-250.
Clinical Predictors of Risk of Progressive/Aggressive Crohn’s Disease at Diagnosis

- Young age
- Fistulae
- Need for steroids
- Deep ulcerations
- High serologic titers
- Smoking

Predictors of Disabling Disease 5-Years after Diagnosis

- Age at onset
  - <40 years vs. ≥40 years; \( P=0.0004 \)
- Location of disease
  - small bowel + colon vs. small bowel only; \( P=0.002 \)
- Smoking status
  - smoker vs. ex- or non-smoker; \( P=0.09 \)
- Perianal lesion at diagnosis
  - yes vs. no; \( P=0.01 \)
- Required steroids for first flare
  - yes vs. no; \( P=0.0001 \)

Beaugerie L et al. Gastroenterology. 2006;130:650-656
Predictors of Rapid Progression to Surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>3.09 (1.47–6.51)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.82 (1.05–3.18)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2.07 (1.04–4.10)</td>
</tr>
<tr>
<td>Ileal localization only</td>
<td>2.22 (1.30–3.81)</td>
</tr>
<tr>
<td>Oral steroid use in 1st 6mos</td>
<td>3.79 (1.90–7.55)</td>
</tr>
</tbody>
</table>


Prognosis of Crohn's Disease Patients with Severe Ulcerations (Colectomy)

- SELs defined as deep ulcerations >10% of mucosal area with at least one colonic segment
- Risk of colectomy associated with severe endoscopic lesions, high CDAI, absence of immunosuppression

Antibody Sum and Surgery Risk in Children

Efficacy of Conventional Agents
Immediate and Long-Term Outcomes of Corticosteroid Therapy in Adult CD

1 Month
- Complete Response: 58%
- Partial Response: 26%
- No Response: 16%

1 Year
- Prolonged Response: 32%
- Steroid-Dependent: 28%
- Surgery: 38%
- Lost to FU: 1%

Cumulative Incidence of Surgical Resection Over 1 Year in CD Patients Starting Corticosteroids

The CDAI

- Developed for NCCDS Study
- Logistic regression analysis: independent predictors of physician global ratings
- Scores 0 - ~ 600
- Validated extensively (reliable, responsive)
- Gold Standard for clinical trials
- 70-100 point change is meaningful
- <150 = remission
Development of CDAI

• “In defining a limit between active and quiescent disease, one might select cutoff values in the range of 100-200, so that most “very well” patients would fall below and most others would fall above. We have chosen the midpoint of this range, 150, as a reasonable compromise”

Best et al. Gastro 70:439;1976

Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone (GETAID).

… a number of basic data concerning CD endoscopic lesions are not known:

• Relationship between clinical and endoscopic pictures
• Ability of endoscopic findings to predict response to treatment
• Frequency of endoscopic remission with a drug-induced clinical remission

Gastroenterology, 1990. 98(4): 811-18
Relationship Between Clinical Symptoms and Endoscopic Indices at Presentation of Acute CD


Relationship Between Clinical Symptoms and CRP at Presentation of Acute CD

Gastroenterology, 1990. 98(4): 811-18
Clinical Remission Rates (CDAI <150) after 3-7 Weeks of Prednisolone

<table>
<thead>
<tr>
<th>Week</th>
<th>Clinical Remission Rate (%)</th>
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<tbody>
<tr>
<td>4</td>
<td>63%</td>
</tr>
<tr>
<td>5</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>88%</td>
</tr>
<tr>
<td>7</td>
<td>92%</td>
</tr>
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</table>

Endoscopic Remission Rates 27%

Endoscopic Monitoring of Crohn's Disease Treatment: A Prospective, Randomized Clinical Trial

Prospective randomized trial to assess:
- Effects of prolongation of prednisolone therapy in patients with clinical but not endoscopic remission and
- Determine prognostic value of colonoscopy in patients achieving clinical remission after a course of high-dose steroid therapy.

Gastroenterology. 1992 May;102(5):1647-53
No difference with immediate tapering vs. additional 5 weeks of steroids

Figure 2. Maintenance of clinical remission after steroid discontinuation in groups A and B. Group A, immediate tapering of prednisolone; group B, prolongation of prednisolone therapy for 5 weeks; n, number of patients at risk of clinical relapse.
No difference +/- endoscopic healing

After steroid therapy there is no advantage of prolonging therapy beyond clinical remission....

Yet....

With Biologic therapy Mucosal Healing is Associated with Improved Long-term outcomes.
ACCENT I & SONIC

- 18-36% of patients entered with endoscopies had NO mucosal lesions at baseline despite CDAI scores >220-400

- Patients entered without active CD!

Colombel et al. NEJM 362:1383-1395, 2010

SONIC: Corticosteroid-Free Clinical Remission at Week 26 by Baseline Endoscopy Status

Absence of mucosal ulceration predicts non-response!

Sandborn WJ et al. Presented at: 73rd Annual Scientific Meeting of the American College of Gastroenterology; October 3-8, 2008; Orlando, Florida. Abstract 1117
Infliximab: Endoscopic Healing and Reduced Hospitalization and/or Surgeries


Mucosal Healing with Infliximab Predicts Sustained Clinical Remission in Early CD

EXTEND: Patients Who Achieved Deep Remission* with Adalimumab at Week 12 and Hospitalization Rates

All-cause hospitalization through Week 52

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<th>Remission Status</th>
<th>Week 52 (%)</th>
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<td>Deep remission* (Week 12)</td>
<td>0/11 (0%)</td>
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<tr>
<td>Non-deep remission* (Week 12)</td>
<td>9/53 (17%)</td>
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CD-related hospitalization through Week 52

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<td>5/53 (9%)</td>
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* Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND
CD: Crohn’s disease; CDAI: Crohn’s disease activity index


Earlier Treatment with anti-TNFs has better results:
Clinical Remission at Weeks 26 by Disease Duration in Adalimumab CHARM study

<table>
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<tr>
<th>Disease Duration</th>
<th>Placebo</th>
<th>Adalimumab</th>
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<tr>
<td>&lt;2 years</td>
<td>17/23</td>
<td>29/39</td>
</tr>
<tr>
<td>2 to &lt;5 years</td>
<td>28/36</td>
<td>48/57</td>
</tr>
<tr>
<td>≥5 years</td>
<td>14/111</td>
<td>47/233</td>
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*p=0.002, **p<0.001, †p=0.014, ‡p=0.001 all vs placebo

Week 26 Remission with certolizumab by Duration Of Crohn’s Disease In PRECiSE 2

Can therapy alter the natural history of Crohn’s disease?

- Induce and maintain gastrointestinal healing
- Prevent need for steroids
- Prevent strictures and penetrating complications
- Prevent extra-intestinal complications
- Decrease hospitalization / surgery
- Decrease long-term cost of care
>2012 Crohn’s Disease Treatment will be towards Disease Modification

Mucosal Healing
• Prevention of Structural Damage
• Prevention of Surgery

Indications for Anti-TNF Biologics in Crohn’s Disease

• Refractory disease
  – Failure to induce remissions…
    • Despite steroids
  – Failure to maintain remissions…
    • Despite optimized immune suppressants
• Early for bad prognosis
• Post-operative prevention of recurrence in patients with poor prognosis
“Proposed” Algorithm for Moderate-Severe Crohn’s Disease Treatment

Assess Risk for Rapid Progression
(Early Onset, SB or Extensive Disease, Perianal or other Fistulae, Deep Ulcerations, Prior Resections)

+ Risk Factors
Top Down
ImmuneRX + Anti-TNF

-Risk Factors
Accelerated Step-up
Steroid + ImmuneRx

Fail
Balancing Risks and Benefits of Different Treatment Strategies

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<th>Early Top-Down</th>
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<td><strong>Benefits</strong></td>
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</tr>
<tr>
<td>Lower costs</td>
<td>Higher efficacy</td>
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<tr>
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<td>Improved MH</td>
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<tr>
<td>Disease Progression</td>
<td>Reduced Disease</td>
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<tr>
<td>&amp; Surgeries (steroids)</td>
<td>Progression</td>
</tr>
<tr>
<td>Infections (steroids)</td>
<td>Decreased surgeries &amp;</td>
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<td>Lymphomas with ImmuneRx</td>
<td>Hospitalizations</td>
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Crohn’s Disease Therapy in the Future

- Will treat both the *Patient* (accprdomg to presentation & symptoms) and
- *Disease* (according to risk profiles).....
- Until eventual Causes, Cures and Prevention Strategies are Identified