Optimal Management of Mild-Moderate Crohn’s Disease

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Goals of Therapy for CD

- Inducing remission
- Maintaining remission
- Restoring and maintaining nutrition
- Minimize disease/therapy complications
- Maintaining patient’s quality of life
- Selection of optimal time for surgery
CD Therapy

Induction

Maintenance
Management of Crohn’s Disease in Adults

Gary R. Lichtenstein, MD1-4, Stephen B. Hanauer, MD1-4, William J. Sandborn, MD1-3 and The Practice Parameters Committee of the American College of Gastroenterology


- Mild-Moderate
- Moderate-Severe
- Severe-Fulminant
- Remission
  - Asymptomatic; without inflammatory sequelae
  - Can be medical or surgically-induced
  - steroid-dependant if needed to keep well

Lichtenstein AJG 2009;104:465
Disease severity

- **Severe-Fulminant**
  - Failed Rx
    - high fever, cachexia
    - peritoneal signs
    - persistent vomiting
    - obstruction, abscess

- **Moderate-Severe**
  - Failed treatment for Mild-moderate
    - fevers, anemia,
    - abdominal pain/tenderness
    - intermittent N/V (without obstruction)
    - “significant” weight loss

- **Mild-Moderate**
  - Ambulatory, tolerating oral without:
    - dehydration
    - toxicity (high fevers, rigors, severe fatigue),
    - abdominal tenderness, painful mass,
    - obstruction or >10% weight loss
Aminosalicylates

Sulfasalazine

Mesalamine
NCCDS: Response to Therapy for Active Crohn’s Disease

Patients (%)

Weeks after Randomization

Sulfasalazine 1 g/15 kg (5 g)

Placebo

13%

NCCDS, National Cooperative Crohn’s Disease Study.
Summers RW et al. Gastroenterology 1979;77:847-869
Controlled-Release Mesalamine for Induction of Remission in Active Crohn’s Disease

Pentasa® vs Placebo After 16 Weeks

- Placebo: 18% Response, 18% Remission
- Pentasa 1 g/d: 36% Response, 23% Remission
- Pentasa 2 g/d: 39% Response, 24% Remission
- Pentasa 4 g/d: 43% Response, 64% Remission

* = NS

P values are Pentasa vs placebo; Singleton et al. *Gastroenterology.* 1993;104(5):1293
Meta-Analysis of Pentasa® (4g/day) in Active Crohn’s Disease


Change from baseline in CDAI score

- Pentasa® 4 g
- Placebo

Crohn's I: n=155 P=0.005
Crohn's II: n=150 P=0.7
Crohn's III: n=310 P=0.04
Overall: n=615

Crohn's I: n=155
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Overall: n=615
SASP/Mesalamine maintenance

- 3 RCT suggested benefit
  - GETAID, Italian IBD, International Mesalamine
    - Many were surgical remitters
- 8 RCT negative
- 5 meta-analyses performed
  - 2 of the early 3 suggested benefit
  - More recently, no clear benefit seen

Mesalamine Maintenance of Remission in Crohn’s Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cases</th>
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<tbody>
<tr>
<td>IMSG</td>
<td>1990</td>
<td>248</td>
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<tr>
<td>Prantera</td>
<td>1992</td>
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<td>Brignola</td>
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<td>Gendre</td>
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<td>Bresci</td>
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<td>66</td>
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<td>Thomson</td>
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<td>Arber</td>
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<td>59</td>
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<td>Modigliani</td>
<td>1996</td>
<td>129</td>
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<tr>
<td>Sutherland</td>
<td>1997</td>
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<tr>
<td>De Franchis</td>
<td>1997</td>
<td>117</td>
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<tr>
<td><strong>Overall</strong></td>
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<td>1,371</td>
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</table>

Risk Difference 95% CI

-0.5 -0.4 -0.3 -0.2 -0.1 -0.0 0.0 0.1 0.2 0.3 0.4 0.5

Camma C. Gastro 1997;113:1465-73.
Antibiotics

- Bacterial flora implicated in pathogenesis
- Metronidazole/ciprofloxacin most studied
- 0.8-1g/d, 10-20mg/kg/d:
  - no benefit in inducing remission over placebo
- ABX maintenance:
  - Long-term abx no data, resistance concerns

Sutherland, Gut 1991;32:1071-5
Allan, Gut 1977;10:A422
Blichfeldt San J Gastro 1978;13:123-7
Lichtenstein, IBD 2004;10:S2-10
Metronidazole for Active Crohn’s

No difference in clinical remission rates

Sutherland, Gut 1991;32:1071-5
Antibiotics in Active CD

Antibiotics in Addition to Entocort

Anti-mpTB

- Ruminants get a TI illness (Johne’s dz)
  - Caused by mpTB
- Cochrane review of 7 RCT
  - No induction benefits
  - Maintenance benefit in steroid-induced remission
    - OR 1.36 (95% CI 0.87-2.13).
    - Subgroup analysis of 2 small studies
- RCT of anti-mpTB vs placebo in 213 pts.
  - Steroid-induced remission
  - Benefit at 16 wk for abx + steroids (nonspecific)
  - No prolonged advantage during/after abx

Corticosteroids


≈ 50%
COPING WITH Prednisone

IT MAY WORK MIRACLES, BUT HOW DO YOU HANDLE THE SIDE EFFECTS?

(*and other cortisone-related medicines)

Eugenia Zukerman and Julie R. Ingelfinger, M.D.
Corticosteroids in CD: Induction of Remission

Clinical Remission

- NCCDS: 17 weeks
  - 60% of patients responded
- ECCDS: 18 weeks
  - 82% of patients responded
- GETAID: 7 weeks
  - 92% of patients responded

References:

Benchimol Cochrane Database Syst Rev. 2008:CD006792
Corticosteroid Therapy for Crohn’s Disease

Immediate Outcome* (n=74)

- Complete Remission 58% (n=43)
- Partial Remission 26% (n=19)
- No Response 16% (n=12)

1-Year Outcome (n=74)

- Prolonged Response 32% (n=24)
- Steroid Dependent 28% (n=21)
- Surgery 38% (n=28)

*30 days after initiating corticosteroid therapy

Faubion W et al. *Gastro* 2001;121:225
Corticosteroids: Maintenance of Remission

- **Smith** 36 months: n=59; p=NS
  - Steroid: 55%
  - Placebo: 58%

- **Summers** 12 months: n=274; p=NS
  - Steroid: 75%
  - Placebo: 76%

- **Malchow** 24 months: n=237; p=NS
  - Steroid: 23%
  - Placebo: 30%

Sources:
- Steinhart Cochrane Database Syst Rev 2003 CD000301
“Fancy” Prednisone

• Controlled-release EC Budesonide (Entocort)
  – Locally-acting, slowly-released steroid
  – Absorbed by gut, 80-90% cleared by liver
    • 10-20% of drug enters circulation
  – For Crohn’s in the ileum/upper colon
  – All the potential for prednisone side effects
    • Much less frequent
    • Much less severe
Budesonide for Active Crohn’s

Greenberg, et al. NEJM 1994;331:836
Thompson, et al. NEJM 1998;339:370
Rutgeerts P, et al. NEJM 1994;331:842
Budesonide EC for active CD

Corticosteroid-related adverse events

Summary RR: 0.65; 95% CI: 0.53 - 0.80

Rutgeerts (13)
Gross (14)
Campieri (15)
Bar-Meir (16)

CD Maintenance Therapy with Budesonide

Proportion of patients relapsing

- 6mg/day
- 3mg/day
- placebo

CD Maintenance Therapy with Budesonide

ACG 2009

• Mesalamine 3.2-4g po/d for I, IC, C dz
  – Minimally effective vs. placebo
  – Less effective than budesonide/CS
• SASP 3-6g/d for IC or C dz
• Metro 10-20mg/kg in SASP non-resp.
• Budesonide EC 9mg/d in I +/- RC
• Anti-TB not effective
Ileum +/- R colon

Budesonide EC
9mg/d
8-16 wks

Budesonide EC
6mg/d for 6mo, Taper off

Isolated colonic
(? ileocolonic)

Metronidazole
10-20mg/kg
8-16 wks

SASP
3-6g/d for 16 weeks

SASP
Mesalazine
Nothing