Overview

- Review the clinical features and epidemiology of microscopic colitis
- Discuss drug-induced MC
- Review treatment options
- Propose a treatment algorithm
Clinical Features

- Chronic watery diarrhea
- 50% with abdominal pain, mild weight loss
- Arthralgias, autoimmunity common, sprue
- Overlap with IBS
  - 50-70% in Olmsted County\(^1\)
  - 28-65% in analysis of RCTs\(^2\)
- Association with NSAIDs and other meds

1) Limsui IBD 2007  2) Madish World J Gastro 2005
Clinical Features

- Two subtypes
  - Collagenous and Lymphocytic colitis
- Very similar clinically and histologically
- Unclear if distinct or parts of a spectrum

Celiac sprue

- 1/3 of patients with sprue have MC-like changes on colon biopsies\(^1,2\)
- In largest studies, sprue-like small bowel changes in 2-9% of MC\(^3,5\)
- Serologies may be less sensitive in MC\(^6\)
- Consider sprue if steatorrhea, IDA, non-response to MC medications

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Epidemiology

- 7-15% of chronic watery diarrhea
- Incidence ~5-10/100,000 each
- Typically 6th-7th decade
  - e.g. in Calgary, age >65 RR = 5.6
- Female predominance (CC>LC in most)
Age- and Gender-specific Incidence Rates
Olmsted County, MN

Incidence of Microscopic colitis,
Olmsted County 1985-2001

Updated Olmsted County Incidence Data

Incidence of Microscopic Colitis

Incidence

Total MC
Collagenous Colitis
Lymphocytic

Years

2002-2004
2005-2007
2008-2010

0
5
10
15
20
25

Incidence of Microscopic colitis,
Olmsted County 1985-2011

MC
LC
CC
Pathophysiology

• NSAIDs and other drugs
  • Abnormal fluid/salt secretion/absorption
  • Bile acid malabsorption
  • Abnormal collagen synthesis/degradation
  • Infection
  • Autoimmunity
  • Reaction to luminal antigen

Drug-induced Microscopic colitis

• High level evidence
  • acarbose, aspirin, NSAIDs, PPI, SSRI, ticlopidine

• Intermediate level evidence
  • carbamazepine, flutamide, lisinopril, simvastatin

Beaugerie and Pardi APT 2005
Drug-induced Microscopic colitis

- Collagenous colitis
  - Associated with NSAID, SSRI

- Lymphocytic colitis
  - B-blockers, SSRI, statins, bisphosphonates
  - not NSAID

- Watery diarrhea
  - SSRI, statins

Fernandez-Banares Am J Gastro 2007

Treatment
Bismuth Subsalicylate: Open-Label Study

- 13 patients newly dx (7 CC, 6 LC)
- BiSS 262 mg tablets, 8 daily, for 8 weeks
- Response 92%
- Mean time to response 2 weeks
- 75% maintained remission for 7-28 months

Fine and Lee, Gastroenterology 1998;114:29-36
Open-Label Bismuth: Clinical Results

Stool Frequency
5.3/day to 1.6/day

Stool Consistency

Fecal Weight
557 g/d to 274 g/d

Fine and Lee, Gastroenterology 1998;114:29-36

Open-Label Bismuth: Histology Results

Histopathology Score (0-10)
8.3 to 3.1

Before

After

Fine and Lee, Gastroenterology 1998;114:29-36
**Bismuth Subsalicylate: RCT**

- N=14, 9 tabs/d x 8 weeks vs. placebo
- Clinical response 100% vs. 0%
- Stool freq: 7.5/d to 2/d in BSS; no Δ placebo
- Stool wt: 550 g/d to 150 g/d in BSS; no Δ pbo
- Histology: improved/nl in 6/7 BSS, 1/6 placebo
- Relapse 25%, all retreated
- Placebo patients received BSS: 5/6 improved
- No statistics given in abstract

*Fine et al, DDW abstract 1999 (Gastro 1999;116:A880)*

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**Open Label Treatment Responses**

Complete and Partial Response

<table>
<thead>
<tr>
<th>Colitis type (N)</th>
<th>¹LC (170)</th>
<th>²LC (199)</th>
<th>³CC (163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiarrheals</td>
<td>73%</td>
<td>70%</td>
<td>71%</td>
</tr>
<tr>
<td>Bismuth</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>65</td>
<td>57</td>
<td>59</td>
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<tr>
<td>5-ASA</td>
<td>42</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>Steroids</td>
<td>87</td>
<td>88</td>
<td>82</td>
</tr>
</tbody>
</table>

1) Pardi Am J Gastro 2002
2) Olesen Gut 2004
3) Bohr Gut 1996
Mesalamine

Mesalamine +/- cholestyramine

• N=64, randomized but unblinded
• 2.4 gm/d +/- cholestyramine
• Remission 85% in LC (+ or – cholestyramine)
• CC: 73% w/o vs. 100% with cholestyramine

Calabrese J Gastro Hep 2007
Mesalamine Open-label

- N=35
- ~3 gm/day
- Remission
  - 83.3% in LC
  - 35.3% in CC (p=0.005)

Fernandez-Banares, Am J Gastro 2003

Open Label Treatment Responses

Complete and Partial Response

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3) Bohr Gut 1996
Mesaline RCT

- Collagenous colitis, N = 92
- Budesonide 9 mg/d vs. mesalamine 3 g/d vs. placebo
- Mesalamine no better than placebo
  - Remission ($\leq$ 3 BM/d): 44% vs 60%
  - Remission (Hjortswang): 32% vs 38%
  - Histology 45% vs 50%

Miehlke DDW 2012

Budesonide
Budesonide Controlled Trials

- 3 RCTs in collagenous colitis, 2 in LC
- 9 mg/d x 6-8 weeks, +/- taper
- Response 57-100% (~85%) vs. 12-40%
- Relapse ~80%

1) Baert, Gastro 2002  
2) Miehlke, Gastro 2002  
3) Bonderup, Gut 2003  
4) Miehlke, Gastro 2009  
5) Pardi, Gastro 2009 (abstr)

Budesonide Induction in Collagenous Colitis: Cochrane Meta-Analysis

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Budesonide</th>
<th>Placebo</th>
<th>Peto OR 95% CI</th>
<th>Weight %</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baert 2002</td>
<td>8/11</td>
<td>3/12</td>
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<tr>
<td>Miehlke 2002</td>
<td>20/26</td>
<td>3/25</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bonderup 2003</td>
<td>10/10</td>
<td>2/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>47</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 38 (Budesonide), 8 (Placebo)
Test for heterogeneity: Chi² = 1.25, df = 2 (P = 0.54), P = 9%
Test for overall effect: Z = 6.14 (P < 0.00001)

Budesonide Induction in Lymphocytic Colitis

- N = 42
- 9 mg/day vs placebo


Budesonide in Lymphocytic colitis

- *p<0.02

Abboud, Pardi in preparation
Natural History of Steroid-treated MC

- 80 patients rx with steroids (37%)
  - 50% LC, 50% CC
  - Prednisone 21%, budesonide 79%
  - Remission 76%, response 20%
- Remission: 83% vs 53% (p = 0.02)
- Response: 14% vs 41%, NR: 3% vs 6%
- Recurrence: HR 0.38 (95% CI 0.18-0.85)

Budesonide Maintenance in Collagenous Colitis

- Two RCTs (N=82), 9 mg/d x 6 wks, remission 87-96%
- Budesonide 6 mg/d or placebo x 6 mo
- Relapse: 13-23% budesonide, 61-88% placebo
Budesonide Maintenance in Collagenous Colitis: Cochrane Meta-Analysis

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<th>Placebo</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boderup 2008</td>
<td>13/17</td>
<td>2/17</td>
<td>-</td>
<td>18.40</td>
<td>24.38 [3.82, 155.45]</td>
</tr>
<tr>
<td>Melleike 2008</td>
<td>17/23</td>
<td>8/23</td>
<td>-</td>
<td>81.60</td>
<td>5.31 [1.50, 18.84]</td>
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<tr>
<td>Total (95% CI)</td>
<td>40</td>
<td>40</td>
<td>8.82 (3.19 – 24.37)</td>
<td>100.00</td>
<td>8.82 [3.19, 24.37]</td>
</tr>
</tbody>
</table>


Azathioprine for Microscopic Colitis

- 9 patients (2.3%), 8 CC, 1 LC
- Steroid dependent, refractory, or intolerant
- Median dose 2 mg/kg/d, f/u 26 months
- 7 tapered off steroids, no-mild symptoms
- 1 intolerant to steroids responded
- 1 non-responder: colectomy

## Methotrexate in Collagenous Colitis

- N = 19, 5 mg/wk orally, increased by 2.5 mg increments
- Median dose 7.5-10 mg per week, range 5-25 mg/wk
- Response complete in 74%, partial in 11%

Riddell, J Gastro Hep 2007

## Anti-TNF in Microscopic Colitis

- N = 4 (of 372 pts, 1.1%) treated with infliximab
- Response after one dose
- 3 switched to adalimumab (2 allergic rxn, 1 loss of response)
- 3 maintained response thru 1 year
- 1 lost response to ADA → colectomy

Esteves J Crohns Colitis 2011
Recommended Treatment Approach

- **D/C NSAIDs, other drugs**
  - **mild**
  - **moderate**
  - **severe**

**Antidiarrheals**
- Bismuth subsalicylate

**Cholestyramine**
- Prednisone

**Anti-TNF**
- Surgery

**Azathioprine/6-MP/MTX**
- Budesonide

Summary

- Incidence of MC appears to have stabilized
- Consider celiac disease if suggestion of steatorrhea or significant weight loss
- Consider drug-induced MC
- Treat with bismuth or budesonide
  - Right dose and right duration
- Maintenance therapy with budesonide is often required
Thank you