Common mistakes in the management of Chron’s disease

Dr Eduan Deetlefs
Gastroenterologist
Common mistakes in the management of Crohn’s disease

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Gastroenterologist
ACG Clinical Guideline: Management of Crohn’s Disease in Adults

Gary R. Lichtenstein, MD, FACP, Edward V. Loftus Jr, MD, FACP, Kim L. Isaacs, MD, PhD, FACP, Miguel D. Regueiro, MD, FACP, Lauren B. Gerson, MD, MSc, MACG (GRADE Methodologist) and Bruce E. Sands, MD, MS, FACP
AGA key quality indicators

1. Document disease activity and severity
2. Recommend steroid-sparing therapy after 60 days
3. Assess bone health if steroid-exposed
4. Recommend influenza vaccine
5. Recommend pneumococcal vaccine
6. Document recommendation for cessation of smoking
7. Assess for Hepatitis B virus status pre-anti-TNF
8. Assess for latent Tuberculosis pre-anti-TNF
Common mistakes to be discussed

• Not reviewing the diagnosis
• Not documenting disease activity and severity
• Not having a goal of therapy
  • GI and non GI symptoms
  • Objective measurement of mucosal healing: SES-CD and faecal biomarkers
  • QOL
• Using Mesalazine / 5ASAs
• Excessive steroid use
• Not discussed: Many mistakes made in use of immunomodulators, biologics (and newer drugs), suboptimal co-management with surgeon, IBD nurse and rest of the MDT
Not reviewing the diagnosis
Not reviewing the diagnosis

• New patient with a previous diagnosis of Crohn’s or old patient refractory to therapy

• Especially important in SA private sector?
  • Patient “migration”
  • Fragmentation of care
  • Escalated workup for acute / sub-acute illness GI symptoms
  • Non-GI specialists
  • Over diagnosis is a problem

• Wrong diagnoses typical scenarios
  • Acute ileo-colitis: infective, drugs etc
  • “Over-interpretation” of subtle abnormalities on investigations (usually driven by a lot symptoms)
Case: Mrs M

- 50 year old female
  - IBS diagnosed during childhood
  - Multiple gastroscopies and ileocolonoscopies later in life all normal
  - At age 43 right hemicolecctiony for diverticulitis with perforation: ++ surgical complications
  - Further abdominal symptoms and repeated investigations at age 48
    - Some calprotectins a bit raised (NSAID use history)
    - Mild non-specific ileocolitis at one of the endoscopies
    - MRE: Mid to distal ileum short segment mural thickening
    - Capsule endoscopy
Case: Mrs M

- Diagnosed with isolated mid-small bowel Crohn’s disease
  - Steroids followed by Azathioprine

- Ongoing symptoms despite normal calprotectin

- Biological was going to be considered

- Moved down to Cape Town
Case: Mrs M

• Investigations with me:
  • Retrograde double balloon enteroscopy
  • Repeat capsule endoscopy
Case: Mrs M

- Revised diagnosis
  - IBS with NSAID induced small bowel ulcer: resolved
  - Stop NSAIDs
  - Stop Azathioprine and follow-up
  - So far unchanged symptoms and normal faecal calprotectin
Detailed history

Review all the investigations

Labs

Endoscopy (pictures NB)

Histology: Discuss with pathologist

Imaging: Discuss with...
Not documenting disease activity and severity
CD severity

• Only 20-30% of CD patients will have indolent course

• The rest will have typical pattern: “CD is a chronic destructive progressive disease”
  • 80% will require hospitalisation
  • 10 year risk of surgery ± 50% (decreasing to 30% in biologic era)

• Therefore important to identify factors predictive of progressive disease
Old definitions

- Old definition of severity
  - Symptoms: CDAI and others: Remission < 150, Severe > 450

<table>
<thead>
<tr>
<th>Clinical or laboratory variable</th>
<th>Weighting factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of liquid or soft stools each day for seven days</td>
<td>x 2</td>
</tr>
<tr>
<td>Abdominal pain (graded from 0-3 on severity) each day for seven days</td>
<td>x 5</td>
</tr>
<tr>
<td>General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days</td>
<td>x 7</td>
</tr>
<tr>
<td>Presence of complications*</td>
<td>x 20</td>
</tr>
<tr>
<td>Taking Lomotil or opiates for diarrhea</td>
<td>x 30</td>
</tr>
<tr>
<td>Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)</td>
<td>x 10</td>
</tr>
<tr>
<td>Hematocrit of &lt;0.47 in men and &lt;0.42 in women</td>
<td>x 6</td>
</tr>
<tr>
<td>Percentage deviation from standard weight</td>
<td>x 1</td>
</tr>
</tbody>
</table>

*One point each is added for each set of complications:
- the presence of joint pains (arthralgia) or frank arthritis
- inflammation of the iris or uveitis
- presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
- anal fissures, fistulae or abscesses
- other fistulae
- fever during the previous week.
New definitions

- Symptoms
- Endoscopy
  - Deep ulcerations
  - SES-CD
- Prognostic factors
  - Young age
  - Extensive bowel involvement
  - Perianal disease
  - Penetrating and stenosing phenotype
Simple endoscopic score (SES-CD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of ulcers (cm)</td>
<td>None</td>
<td>Aphthous ulcers (diameter 0.1-0.5)</td>
<td>Large ulcers (diameter 0.5-2)</td>
<td>Very large ulcers (diameter &gt; 2)</td>
</tr>
<tr>
<td>Ulcerated surface</td>
<td>None</td>
<td>&lt;10%</td>
<td>10-30%</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>Affected surface</td>
<td>Unaffected segment</td>
<td>&lt;50%</td>
<td>50-75%</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Presence of narrowings</td>
<td>None</td>
<td>Single, can be passed</td>
<td>Multiple, can be passed</td>
<td>Cannot be passed</td>
</tr>
</tbody>
</table>

SES-CD = sum of all variables for the 5 bowel segments. Values are given to each variable for every examined bowel segment.

Segments:
- Rectum
- Left colon
- Transverse
- Right colon
- Ileum

Scoring:
- Inactive
- Up to 6: mild
- 7-15 moderate
- ≥16 severe

Daperno, M et al. Gastrointestin Endosc. 2004
The application CALCULATORS IN GASTROENTEROLOGY has been implemented with the scientific contribution of IBD
the Italian Group for the study of Inflammatory Bowel Disease.

Supported by an unrestricted grant from abbvie &

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**CLINICAL SCORES**

- **CDAI**
  Crohn’s Disease Activity Index
- **HBI**
  Harvey-Bradshaw Index
- **MAYO**
  Partial
- **MAYO**
  Full

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**ENDOSCOPIC SCORES**

- **CDEIS**
  Crohn’s Disease of Severity
- **SES-CD**
  Simple Endoscopic Score for Crohn’s Disease
- **CDEIS ⊕ SES-CD**
- **MAYO**
  Endoscopic
- **RUTGEERTS**

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**SCORE DECODING TABLE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Decoding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 2</td>
<td>remission</td>
</tr>
<tr>
<td>3 - 6</td>
<td>mild endoscopic activity</td>
</tr>
<tr>
<td>7 - 15</td>
<td>moderate endoscopic activity</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>severe endoscopic activity</td>
</tr>
</tbody>
</table>

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Not having a management goal
What should the goals be?

• **Symptoms**
  • Use of IBD Disk

• **Mucosal healing**
  • Monitor endoscopic response with endoscopic scores: SES-CD
  • Within 1 year of surgery for POR
  • Faecal biomarkers: calprotectin, lactoferrin

• **QOL**
  • Attention to management of stress, anxiety and depression
Symptoms correlate very poorly with inflammation and disease activity.

Relationship Between Clinical Symptoms and Endoscopic Indices at Presentation of Acute CD

IBD Disk. S Ghosh. Inflammatory bowel diseases 2017
IBD Disk

Initial assessment
High scores
High disease burden

Therapeutic goal
Low scores
Low disease burden
IBD Disk

• “Ms L’s symptoms seem to be in remission and she will continue on her chronic medication”

…… but that is not the full story
SCORE EACH STATEMENT ON A SCALE OF 0 TO 10 AND CIRCLE YOUR SCORE ON THE COLORED DISK

TOTAL SCORE: 54

Add the scores here for all 10 categories
What should the goals be?

• Symptoms
  • Use of IBD Disk

• Mucosal healing
  • Monitor endoscopic response with endoscopic scores: SES-CD
    • Within 1 year of surgery for post operative recurrence (POR)
  • Faecal biomarkers: calprotectin (lactoferrin)

• QOL
  • Attention to management of stress, anxiety and depression
Role of faecal biomarkers

• Calprotectin (and lactoferrin) correlated with SES-CD

• Specific defined uses
  • Differentiated IBS from IBD
  • Monitor post operative recurrence
    • > 100μg/g: show endoscopic recurrence with sensitivity 89%
  • In patients with anti-TNF-induced remission
    • > 160μg/g: sensitivity of 91.7% and specificity of 82.9% to predict relapse
What should the goals be?

- Symptoms
  - Use of IBD Disk

- Mucosal healing
  - Monitor endoscopic response with endoscopic scores: SES-CD
  - Within 1 year of surgery for POR
  - Faecal biomarkers: calprotectin, lactoferrin

- QOL
  - Attention to management of stress, anxiety and depression
QOL

• Strong association between depression and flares of CD

• Pts with major depression and anxiety have a greater risk of surgery and higher degree of health-care utilisation

• “Assessment and management of stress, depression and anxiety should be included as part of the comprehensive care of the Crohn’s disease patient”

• Identify the go to person in your MDT for these issues
Using Mesalazine in CD
Case: Mrs K

- 47 year old female
- Many years of IBS-type symptoms and heartburn
- Investigated at age 39
  - GORD B
  - Normal ileo-colonoscopy
- Age 40: Gallstone pancreatitis and lap cholecystectomy
- Age 45
  - 3 week spell of diarrhoea an re-investigated
  - GORD C
  - Normal ileo-colonoscopy
  - However CT enterography: suggestive of a colitis of the ascending colon
  - Commenced on Pentasa for suspected Crohn’s and has remained on it ever since
Case: Mrs K

- Persistent symptoms and came to see me for enrolment into a drug trial
- Investigations with me
  - Faecal calprotectin: 664 (But a history of NSAID abuse)
  - Repeat ileocolonoscopy
Case: Mrs K

- Stopped her Pentasa and commenced treatment for IBS
- She was very happy .... has been paying her Pentasa out of pocket!
- I was pretty confident she won’t be worse off as Mesalazine doesn’t work in Crohn’s...
5 ASAs in Crohn's

- No role for Mesalazine in induction or maintenance of Crohn's

- Some evidence of Sulphasalazine for mild colonic Crohn's
# 5-ASA vs placebo

## Outcome: Relapse of CD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>5-ASA Events</th>
<th>Placebo Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anonymous 1990</td>
<td>49</td>
<td>125</td>
<td>9.7%</td>
<td>0.93 [0.69, 1.25]</td>
</tr>
<tr>
<td>Arber 1995</td>
<td>12</td>
<td>28</td>
<td>3.3%</td>
<td>0.70 [0.42, 1.17]</td>
</tr>
<tr>
<td>Bondesen 1991</td>
<td>29</td>
<td>101</td>
<td>5.4%</td>
<td>1.00 [0.65, 1.54]</td>
</tr>
<tr>
<td>De Franchis 1997</td>
<td>42</td>
<td>58</td>
<td>7.0%</td>
<td>1.12 [0.88, 1.44]</td>
</tr>
<tr>
<td>Gençre 1993</td>
<td>37</td>
<td>80</td>
<td>7.9%</td>
<td>0.87 [0.64, 1.19]</td>
</tr>
<tr>
<td>Mahmud 2001</td>
<td>110</td>
<td>167</td>
<td>16.3%</td>
<td>1.23 [1.03, 1.48]</td>
</tr>
<tr>
<td>Modigliani 1996</td>
<td>46</td>
<td>65</td>
<td>9.4%</td>
<td>0.91 [0.74, 1.11]</td>
</tr>
<tr>
<td>Prantera 1992</td>
<td>29</td>
<td>64</td>
<td>7.0%</td>
<td>0.75 [0.53, 1.05]</td>
</tr>
<tr>
<td>Sutherland 1997</td>
<td>77</td>
<td>141</td>
<td>16.4%</td>
<td>0.90 [0.74, 1.10]</td>
</tr>
<tr>
<td>Thomson 1995</td>
<td>85</td>
<td>138</td>
<td>15.1%</td>
<td>1.09 [0.90, 1.32]</td>
</tr>
<tr>
<td>Wellman 1988</td>
<td>10</td>
<td>31</td>
<td>2.4%</td>
<td>0.81 [0.42, 1.55]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>998</strong></td>
<td><strong>1016</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.98 [0.91, 1.07]</strong></td>
</tr>
</tbody>
</table>

Total events: 526 vs 544
Heterogeneity: Chi² = 14.84, df = 10 (P = 0.14); I² = 33%
Test for overall effect: Z = 0.38 (P = 0.70)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Placebo Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.2 24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gençre 1993</td>
<td>54</td>
<td>80</td>
<td>100.0%</td>
<td>0.99 [0.80, 1.23]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>80</strong></td>
<td><strong>81</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.99 [0.80, 1.23]</strong></td>
</tr>
</tbody>
</table>

Total events: 54 vs 55
Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>5-ASA Events</th>
<th>Placebo Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.3 Pediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cezard 2009</td>
<td>50</td>
<td>68</td>
<td>100.0%</td>
<td>1.07 [0.86, 1.33]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>68</strong></td>
<td><strong>64</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.07 [0.86, 1.33]</strong></td>
</tr>
</tbody>
</table>

Total events: 50 vs 44
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.55)
5-ASAs for maintenance of medical remission in Crohn’s

• No RCT to show that these drugs are useful in this situation

• Cochrane meta-analysis: “No further evidence is needed”
  “Further RCT in this area might be unethical”

• We are however all still using it…..
> 50% exposed to 5ASA’s in the first year after dx
# How we rationalise using 5 ASAs

<table>
<thead>
<tr>
<th>Possible justification</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic disease</td>
<td>No evidence</td>
</tr>
<tr>
<td>Cheap</td>
<td>R1400/month for Asacol 2.4g daily</td>
</tr>
<tr>
<td>Few side effects</td>
<td>Not completely true – renal toxicity etc</td>
</tr>
<tr>
<td>No alternatives</td>
<td>Not true</td>
</tr>
<tr>
<td>Worth a try</td>
<td>Opportunity cost / delay in effective treatment</td>
</tr>
<tr>
<td>Personal experience</td>
<td>This is not evidence / placebo etc</td>
</tr>
</tbody>
</table>
Excessive steroid use
Quiz

How many courses of steroids in 12 months are excessive?

• 1
• 2
• 3
• Any amount
Quiz

How many courses of steroids in 12 months are excessive?

• 1
• 2
• 3
• Any amount
Steroids

- Effective for induction
- No evidence that steroids are effective maintenance therapies
Adverse effects

- Occur with prolonged use of high doses
- Cushing’s disease

**Psychiatric**
- Sleep disturbance/activation
- Mood disturbance
- Psychosis

**Skin/soft tissue**
- Cushingoid appearance
- Abdominal striae
- Acne
- Hirsutism
- Oedema

**Neurologic**
- Neuropathy
- Pseudomotor cerebri

**Cardiovascular**
- Hypertension

**MSK**
- Osteoporosis
- Aseptic necrosis of bone
- Myopathy

**Endocrine**
- Diabetes mellitus
- Adrenal cortex suppression

**Immunologic**
- Lymphocytopenia
- Immunosuppression
- False-negative skin test

**Ophthalmic**
- Cataract
- Narrow-angle glaucoma

**Developmental**
- Growth retardation
Definitions (ECCO)

Steroid refractory disease: active disease despite Prednisolone up to 1mg/kg/day for a period of 4 weeks

Steroid dependent disease:
- Unable to reduce steroids below 10mg/d (or Budesonide 3mg/d) within 3 months of starting steroids, without recurrent active disease
- or who have a relapse within 3 months of stopping steroids

“The aim should be to withdraw steroids completely…more than one full course of systemic steroids per year may be considered as the threshold for induction of steroid sparing agents”

Comillon et al JCC 2017
Summary

- Always consider reviewing the diagnosis

- Disease activity and severity definitions include symptoms, endoscopy and prognostic factors

- Goals of therapy are symptom and endoscopy based (mucosal healing) with role for biomarkers

- No role for the use of Mesalazine in CD

- Guard against excessive steroid use and delaying steroid sparing therapy
Thank you