Overlapping IBD and IBS

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Defining IBD/IBS

**IBD:**
- Immune mediated inflammation of the GI tract
- Two major types:
  - Crohn’s disease
  - Ulcerative colitis
- Diagnosis based on clinical, endoscopic, histologic features

**IBS:**
- Functional GI disorder
- Abdominal pain & altered bowel habits
- Fulfills Rome III criteria:
  - Recurrent abdominal pain/discomfort ≥3 days/month in the last 3 months with ≥2 of the following:
    - Change in frequency of stool
    - Change in stool form
    - Improvement with defecation
Defining IBD/IBS

Two separate entities?

Continuum of one disease spectrum?
IBD/IBS Differentiation

• IBS: “Diagnosis of Exclusion”

• Typical IBS symptoms w/o alarm features
  – Overt GI bleeding
  – Unexplained IDA
  – Unintentional weight loss
  – Symptoms onset after age 50
  – Nocturnal diarrhea
  – Family history IBD/colorectal cancer/celiac disease
  – Should not require exhaustive testing prior to IBS diagnosis

• ACG recommendation
  – Celiac screening
  – Colonoscopy with biopsies for microscopic colitis

• Despite these recommendations → multiple diagnostic tests to rule out other organic diseases
IBD/IBS: Biomarkers

**ESR:**
Elevated when proteins produced by hepatocytes/immune cells lead to RBC aggregation

**CRP:**
Produced by hepatocytes in response to pro-inflammatory cytokines (i.e. IL-1, IL-6)

**Calprotectin:**
Calcium/Zinc protein
Present in neutrophils/monocytes
Cell disruption/death → Elevation in stool

**Lactoferrin:**
Iron-binding glycoprotein
Secreted by mucosal membranes
Major component of neutrophil secondary granules

**Screen for inflammation**

**Biomarkers**

Serologic markers

Stool-based markers

Am J Gastroenterol 2015; 110:444-454
• Meta-analysis evaluating the diagnostic ability of fecal lactoferrin to distinguish IBD from IBS

• Seven studies involving 1012 patients included

Pooled sensitivity 0.78
(95% CI 0.75-0.82)

Pooled specificity 0.94
(95% CI 0.91-0.96)
Meta-analysis evaluating the diagnostic ability of fecal lactoferrin to distinguish IBD from IBS

Seven studies involving 1012 patients included

Conclusions: Fecal lactoferrin, as a non-invasive and simple marker, is useful in differentiating between IBD and IBS
Aim of study: Discriminating IBD from IBS

Evaluating accuracy
- Fecal markers (calprotectin/lactoferrin)
- CRP
- Blood leukocytes
- Antibody panels (ASCA/pANCA)

Define a “Best test”

136 study patients
- 64 IBD (36 Crohn’s, 28 UC)
- 30 IBS
- 42 Healthy controls

**IBS Diagnosis:**
- Excluded infection, celiac, IBD, diverticular disease, microscopic colitis
- Fulfilled Rome II criteria
- No alarm symptoms
- Normal endoscopy/histology
Conclusions:

- Fecal Calprotectin (PhiCal) and Fecal Lactoferrin (IBD-SCAN) are highly accurate for discriminating IBD from IBS.
- Combining these two tests with ASCA and pANCA lead to a marginal additional diagnostic accuracy.

**TABLE 5. Overall Accuracy of the Different Tests for Discriminating CD, UC, and IBD from IBS**

<table>
<thead>
<tr>
<th>Single Tests</th>
<th>CD vs. IBS</th>
<th>UC vs. IBS</th>
<th>IBD vs. IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhiCal-Test</td>
<td>91%</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>IBD-SCAN</td>
<td>89%</td>
<td>94%</td>
<td>90%</td>
</tr>
<tr>
<td>LEUKO-TEST</td>
<td>80%</td>
<td>85%</td>
<td>78%</td>
</tr>
<tr>
<td>Hexagon-OBTI</td>
<td>75%</td>
<td>85%</td>
<td>74%</td>
</tr>
<tr>
<td>CRP</td>
<td>82%</td>
<td>73%</td>
<td>73%</td>
</tr>
<tr>
<td>Blood leukocytes</td>
<td>65%</td>
<td>73%</td>
<td>63%</td>
</tr>
<tr>
<td>CD markers</td>
<td>78%</td>
<td>50%</td>
<td>55%</td>
</tr>
<tr>
<td>UC markers</td>
<td>49%</td>
<td>75%</td>
<td>49%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined Tests</th>
<th>CD vs. IBS</th>
<th>UC vs. IBS</th>
<th>IBD vs. IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhiCal-Test and CD-markers</td>
<td>95%</td>
<td>90%</td>
<td>91%</td>
</tr>
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CD markers: ASCA+/pANCA− or ASCA+/pANCA+; UC markers: pANCA+/ASCA−. CRP, C-reactive protein; CD, Crohn’s disease; UC, ulcerative colitis; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease.
A Meta-Analysis of the Utility of C-Reactive Protein, Erythrocyte Sedimentation Rate, Fecal Calprotectin, and Fecal Lactoferrin to Exclude Inflammatory Bowel Disease in Adults With IBS

Stacy B. Menees, MD, MS\textsuperscript{1}, Corey Powell, PhD\textsuperscript{2}, Jacob Kurlander, MD\textsuperscript{1}, Akash Goel, MD\textsuperscript{3} and William D Chey, MD, AGAF, FACP\textsuperscript{1}

- Systematic review/meta-analysis
- Evaluate the utility of four biomarkers:
  - CRP
  - ESR
  - Fecal calprotectin
  - Fecal lactoferrin
- Distinguish between IBS, IBD, Healthy controls
- Included studies:
  - Prospective, adult, diagnostic cohort studies
- 12 studies with 2,145 patients included
  - 1,059 IBD, 595 IBS, 491 healthy controls

Regarding inclusion criteria:

- Only included studies that utilized ELISA fecal calprotectin assay, not point of care testing
- Only included studies that used Manning or Rome Criteria for IBS diagnosis
Results: CRP

- CRP ≤0.5 → <1% likelihood of IBD
- CRP >2.7 → >90% likelihood of IBD

Figure 2. CRP predictive probability of being a healthy control, or having IBS or IBD. The line graph is a graphical representation of the table. The dotted line represents the following: at a CRP level of 0.2 mg/dl, a person has a 0.3% probability of IBD, a 9.9% probability of IBS, and 89.9% probability of being a healthy control. CRP, C-reactive protein; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.
Results: ESR

↑ESR not predictive of IBD

ESR does not differentiate IBD from IBS or healthy controls
Results: Calprotectin

Fecal calprotectin 40μg/g:
- 1% IBD
- 14.9% IBS
- 84.1% Control

Figure 3. Fecal calprotectin predictive probability of being a healthy control, or having IBS or IBD. The line graph is a graphical representation of the table. The dotted line represents the following: at a fecal calprotectin level of 40μg/g, a person has a 1% probability of IBD, a 14.9% probability of IBS, and 84.1% probability of being a healthy control. IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.
Results: Lactoferrin

- Significant overlap between IBD & IBS
- Highest predictability of IBS at 2,660 (74%)

Conclusions:
- CRP of ≤0.5 and calprotectin of 40 μg/g essentially excludes IBD in patients with IBS symptoms
- The addition of CRP and calprotectin to symptom based criteria may improve the confident diagnosis of IBS

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IBD/IBS Overlap

- IBS-like “pro-drome” prior to IBD diagnosis
- IBD patients may report GI symptoms without objective evidence of ongoing disease activity

Patient/Physician dilemma:
Step-up IBD treatment, which may involve potent immunomodulating agents with potential adverse effects?
Prevalence of Symptoms Meeting Criteria for Irritable Bowel Syndrome in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis

Stephen J. Halpin, MBChB and Alexander C. Ford, MBChB, MD, MRCP

• Systematic review and meta-analysis
• Examine the prevalence of IBS symptoms in patients with IBD compared with normal individuals
• 13 studies including 1,703 IBD patients
• Pooled prevalence for IBS in all IBD patients was 39.0% (95% CI 30.0-48.0%)
• IBS symptoms
  – Crohn’s disease > Ulcerative colitis
Prevalence IBS symptoms in IBD pts: 39%

More pts with Crohn’s vs UC had IBS symptoms
Prevalence of IBS symptoms in IBD patients is as high as 40% compared with non-IBD controls. IBS-symptoms significantly more common in Crohn’s than in UC patients.

Conclusions:

Although prevalence of IBS-type symptoms were higher in patients with active disease, up to 1/3 of patients in “remission” also reported similar symptoms.

Figure 3. Odds ratio for symptoms meeting criteria for irritable bowel syndrome in Crohn’s disease patients vs. ulcerative colitis patients.
IBD-IBS Disease

Inflammatory Bowel Disease-Irritable Bowel Syndrome
IBD-IBS Syndrome

- IBD patients
  - Bloating
  - Diarrhea
  - Ano-rectal pain
  - Fecal incontinence

- No observable inflammation

- Symptoms attributed to active IBD

- However…may be related to mechanisms similar to those that occur in a functional GI disorder

IBD-IBS Syndrome

• Why would IBD patients develop IBS symptoms?

• Post-infectious IBS symptoms may occur in IBD patients producing visceral hypersensitivity

• Epidemiologic standpoint:
  – IBS occurs in 10-20% of the population
  – >10-20% of IBD patients may also have IBS

• Functional GI symptoms in IBD patients
  – Before disease onset
  – During active disease with symptoms out of proportion to inflammation
  – Remission

**IBD-IBS Syndrome**

**Abnormal motility**

- **UC patients:**
  - Higher prevalence of functional constipation due to reduced basal contractile activity in distal colon

- **Crohn’s patients:**
  - More prone to functional diarrhea due to persistently increased SB motility beyond period of active disease

**Visceral hypersensitivity**

- **Crohn’s patients in remission:**
  - May have persistently increased levels of colonic tryptophan hydroxylase → leads to ↑serotonin levels
  - Serotonin known to play a key role in visceral hypersensitivity in IBS

**Psychosocial factors**

- IBS-like symptoms in IBD patients can be predicted by the degree of anxiety, depression, and general well-being
- Crohn’s patients have greater psychologic disturbances than those with UC

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IBD-IBS Unifying Model

Life Stress (HPA dysfunction) → Psychosocial distress

Genetic predisposition → Immune dysfunction/Mucosal inflammation

Infection → CNS disinhibition

Altered bacterial flora → Pain Diarrhea

Conclusions

- IBD and IBS are both diseases that are commonly diagnosed and managed by gastroenterologists.

- Several biomarker combinations can be used to attempt at differentiating between the two diagnoses.

- A biopsychosocial model combining IBD and IBS can be used to provide a better understanding of the interactions between the two diseases.