Functional Medicine Approach to Inflammatory Bowel Disease
- An Overview -

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Inflammatory Bowel Disease

A chronic inflammatory disease that causes progressive functional and structural damage to the GI tract.

IBD Types
- Ulcerative Colitis (UC)
- Crohn’s Disease (CD)
- UC-like Crohn’s
- Indeterminate colitis
- Milialy Crohn’s
- Microscopic / Collagenous colitis

Serologic testing
Differentiating UC and Crohn’s from each other, as well as from non-IBD.
**IBD Severity Assessment Checklist**

- No. of daily BM's.
- Anorectal symptoms
- Mucosal lesions
- Anemia.
- Weight loss.
- Bleeding
- Pain control required.
- Medication response.
- Hospitalizations.
- Surgery and signs of complicated disease.
- Anatomical extent of disease.

**Bad Tissue Loss**

**IBD Severity**

- Mild
- Moderate
- Severe

Differentiation based on severity

**Traditional Approach**

Pharmaceuticals target inflammation at different levels:

- 5ASA's
- Corticosteroids.
- Immunomodulators.
- TNF alpha blockers.

**5-aminosalicylic acid – (5ASA)**

**Sulfasalazine | Mesalamine**

- 5ASAs reduce inflammation of intestine lining.
- More effective in UC
- Known to induce and maintain remission in mild to moderate UC.

**Mesalamines**

| Asacol | Pentasa | Lialda | Apriso | Delzicol |

These drugs differ in terms of their coating, which determine where in gut drug delivery occurs and how many times a day meds needs to be taken.

**Corticosteroids**

Prednisone | Prednisolone | Hydrocortisone | Budesonide

Used for moderate to severe flare ups of IBD.

**Mechanism of Action**

- Suppresses interleukin transcription
- Suppresses arachidonic acid metabolism
- Stimulates apoptosis of lymphocytes within the lamina propria of the gut.
**Budesonide | UCERIS**

A steroid which targets the small intestine and colon. Considered to be mainly “locally acting” because the majority of the drug is metabolized through the first pass – liver.

**Immunomodulators**

- **Azathioprine** *(Imuran, Azasan)*
  Antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins.

- **6-mercaptopurine** *(6-MP, Purinethol)*
  Inhibits purine nucleotide synthesis and metabolism.

**TNF blockers**

**Anti-TNF agents:**
- **Infliximab** *(Remicade)*
- **Adalimumab** *(Humira)*
- **Certolizumab pegol** *(Cimzia)*
- **Golimumab** *(Simponi, Simponi Aria)*

*Mechanism of Action - Unclear*

TNF-α inhibitors promote rapid reduction in the number of cells at the inflammation site.

**Anti-Integrin Biologics: (IBD)**

- **Natalizumab** *(Tysabri)*
- **Vedolizumab** *(Entyvio)*

**Cytokine IL 12 and IL 23: (CD)**

- **Ustekinumab** *(Stelara)*

**Vedolizumab - Entyvio**

**Mechanism:**
- Blocks migration of leukocytes into gut via blockade of alpha-4-beta-7 integrin.

**Key points:**
- Gut selective.
- Can be considered first line agent.
- Recommended for older patients, immunosuppressed, those with Hx of malignancy.

**Ustekinumab - Stelara**

**Mechanism:**
- Blocks inflammation produced through IL 12 and IL 23.

**Key points:**
- Can be considered a first line agent, particularly for older patients, the immunosuppressed, those with Hx of malignancy.
- Used in those who failed or intolerant to immunomodulators, corticosteroids or TNF blockers.
Tofacitinib - Xeljanz

Mechanism:
– Selective Janus Kinase (JAK) inhibitor.

Key points:
– The first oral medication approved for treatment of moderate to severe UC.

What is considered healing?

1. Control of symptoms
   – Diarrhea, bleeding etc.
2. Overall improvement in QOL.
3. Mucosal healing.

Treat-to-Target approach

Many experts are advocating paradigm shifts that emphasize mucosal healing, rather than clinical remission as the primary objective.

Functional Medicine Approach

Target patients that are in mild to possibly moderate activity.

• Lifestyle
• Diet
• Food Sensitivities
• Stress
• Environmental Toxicity (Mold, Heavy metals)
• Gut Dysbiosis (SIBO, SIFO)
• Altered microbiome
• Increased Intestinal permeability.
• Targeting the inflammation.

Considerations in IBD management

– Stress
– Use of ABX
– Dietary factors
– The anatomical description.
– OCP
– Smoking.
– Alcohol.

IBD Etiology

It is postulated that IBD arises due to a dysregulated immune response to a dysbiotic gut microbiome on a background of genetic predisposition.
The gut microbiome plays an important role in the development of IBD. Research suggests that patients with IBD exhibit a decrease in diversity of the gut microbiota and have an average of 25% fewer microbial genes than healthy persons.

Smoking modulates immune responses and diversity and composition of the gut microbiota through which it may exert its influence on disease risk. Chronic smoke exposure can alter composition and integrity of epithelial mucous membrane, causing intestinal inflammation.

Smoking & UC
• Current smoking appears to be protective.
• Smokers have a milder disease course, a better prognosis compared to nonsmokers, and have a lower risk of colectomy.
• Smoking cessation is frequently associated with relapse.

Smoking and CD
• Current and former smokers have elevated risk for CD.
• Current smokers have a worse prognosis with an increased need for corticosteroids, immunosuppressants, and IBD-related surgeries.

Appendectomy protects against UC. The increased CD4/CD8 ratio and infiltration of CD4+ and CD69+ T cells in the appendix of patients with UC may act as a priming site in the pathogenesis of UC.

Appendix & Intestinal Microbiome
The vermiform appendix directly interacts with the intestinal microbiome, which regulates the intestinal biofilm.

Smoking & Gut Integrity

Appendectomy

IBD and Diversity


### Diet

Plays a predominant role in the pathophysiology of IBD exerting its effects by:

- Modulating the intestinal microbiome
- Predisposing patients to proinflammatory substrate production.
- Disruption of mucus layer
- Increasing intestinal permeability.

### Fiber

- Higher intake of dietary fiber has been associated with decreased risk of CD.
- Fiber obtained from vegetables or fruits had the greatest reduction in risk compared to fiber from cereals and whole grains.


### Fish Oil & UC

- Higher intake of dietary n-3 PUFAs (fish oil), EPA/DHA was associated with lower incidence of UC in middle aged adults.
- Diets rich in n-6 PUFAs (which is metabolized to arachidonic acid) was associated with an increased risk of UC due to proinflammatory properties.


### Fish Oil & CD

- A higher ratio of omega 3/6 fatty acids has been found to be associated with a lower risk of CD.


### Animal Protein

- High intake of animal protein (meat or fish) has been associated with an increased incidence of IBD.
- Additional risks: non-grassfed, non-organic, charred and BBQ foods.


### Westernization of Diet

**Saturated fats | Processed meats | Refined sugars**

Associated with promoting dysbiosis, which may increase the proinflammatory state of the colon.

Childhood dietary influence

Increased incidence of CD among subjects who have a lower intake of fruits, vegetables, and fish during adolescence


Zinc Deficiency

Dietary Zinc intake is associated with reduced risk of CD.

Patients with IBD who are zinc deficient have worse IBD-related outcomes, which eventually improve with replacement.


Sulfur & Sulfate

| preserved meats | alcoholic beverages | milk | food additives – carrageenan |

Sulfur containing foods are associated with relapse in UC and are commonly found with the westernization of diet.


Curcumin

Effective in inhibition of TNF pathway, as well as CD4 T-cell proliferation.


Vitamin D Deficiency

Implicated as playing a role in the pathogenesis as well as the natural history of IBD.

Occurs more frequently in IBD patients than in the general population.

What's Best?

SCD  Low Fodmap  Gluten Free
Paleo  Ketogenic

SCD

Elaine Gottschall - Breaking the Vicious Cycle

A diet intended mainly for Crohn's disease, ulcerative colitis, celiac disease, diverticulitis, cystic fibrosis and chronic diarrhea.

- Monosaccharides – OK.
- Disaccharides and polysaccharides – Not OK.
- Nuts, aged cheeses, fish, beef, unsweetened juices - OK.
- Sugars, oats, pasta, potatoes, rice, sugar substitutes, and wheat – Not OK

Yeast & IBD

Mouse studies show that S. Cervevisiae aggravates the symptoms of IBD. That they had higher concentrations of Purines. S. Cervevisiae can not break down purines that accumulate in the GI tract, transitioning to Uric Acid – which Exacerbates inflammation.

University of Utah Health Sciences – Common yeast may worsen IBD symptoms in CD.

SIBO & IBD

Testing and Treating Small Intestinal Bacterial Overgrowth Reduces Symptoms in Patients with Inflammatory Bowel Disease.

A single randomized, controlled trial showed enteric release–formulated rifaximin to be superior to placebo in inducing clinical remission.


Sulfate reducing Bacteria

Sulfate reducing bacteria produce toxic hydrogen sulfide H2S as a result of oxidative metabolism.

ABX and IBD

Exposure to ABX in first year of life associated with an increased risk of IBD, particularly CD


ABX and IBD

A meta-analysis of 11 observational studies showed a marked increase in the risk of CD in children with exposure to most antibiotic groups.


FMT

In 4 separate studies FMT for inducing remission of active UC have shown promising results

(28% FMT group vs 9% placebo group)


Psychosocial Stress

Pathways through which stress may exert a role in the pathogenesis of CD and UC:

- Vagus nerve inhibition,
- Proinflammatory cytokine production,
- Modification of the gut microbiome,
- Increase in intestinal permeability.


Psychosocial Stress

High perceived stress has been associated with IBD flares.

Patients with low stress and good coping mechanisms had fewer relapses than those with avoidant coping and high perceived stress.

**Major Depressive Disorder**

Associated with failure of infliximab therapy and decreased time to retreatment.


**Sleep Disturbance**

Sleep disturbance at baseline during remission was associated with a 2-fold increase in the risk of active disease in patients with CD at 6 months (OR, 2.00; 95% CI, 1.45-2.76).


**Sleep Disturbance**

Having fewer than 6 hours of sleep per day and having more than 9 hours of sleep per day were associated with an increase in the risk of UC.


**Urban living**

A meta-analysis of 25 and 30 observational studies in UC and CD, respectively, demonstrated an association of urban environment or residence with a higher incidence of UC and CD, respectively.


**Air Pollution**

Prior to the implementation of environmental regulations, between 1940 and 1980, the increase in incidence of UC and CD paralleled growing air pollution.


**Exercise**

In a large prospective study of 1857 patients with UC or CD, an increase in the level of exercise was associated with a decrease in the risk of active disease by 32% in patients with CD and 24% in patients with UC at 6 months.

A case of Bartonella and IBD

**Bartonella henselae** and inflammatory bowel disease

Francesco Massel, Mauro Massimetti, Francesco Messina,

- Patient had increased thickness of the terminal ileum on ultrasonography - a sensitive and specific finding that suggests IBD.
- During treatment, Patient subsequently developed fevers, multiple hypoechoic lesions in the liver and spleen, suggestive of hepatosplenic granulomatosis, a well-known complication of B henselae infection.

- IgM antibodies to *B. henselae* were highly positive.
- The patient received ciprofloxacin for a week, then azithromycin for 5 days.
- Fever subsided 2 days after starting azithromycin.
- Thickening of the terminal ileum and hypoechoic lesions of liver and spleen normalized in 6 weeks.

Heavy Metal

Both Mercury and Nickel toxicity have been associated as contributors to intestinal permeability and IBD.

Consideration is required for any prosthesis, dental implants and piercings.


Lectins

- Naturally occurring carbohydrate-binding protein that sticks to cell membranes in the GI Tract.
- They exist in plant and animal food.
- Hold no nutritional value when consumed in foods.
- Found in the highest amounts in legumes, nightshade vegetables, dairy products, and grains.

Galectins in IBD

Galectin-1 and Galectin-2 contribute to the suppression of intestinal inflammation by the induction of apoptosis of activated T cells, Galectin-4 is involved in the exacerbation of inflammation by specifically stimulating intestinal CD4+ T cells to produce IL-6.

- Low dose Naltrexone for induction of remission in inflammatory bowel disease patients


Naltrexone has a direct effect on intestinal epithelial wound healing and Endoplasmic stress reduction.
**Antiulcer Peptide - BPC157**

- Shows no toxicity
- A lethal dose is not achieved.
- Stable in human gastric juice.

In comparison with other standard treatments it is more effective for ulcers and various wounds, and can be used without a carrier needed for other peptides, both locally and systemically.

**BPC157 – rat studies**

BPC 157 is a fundamental treatment that quickly restores blood supply to the ischemically injured area and rapidly activates collaterals.

BPC 157 has been shown to have a beneficial effect on ileoileal anastomosis healing.

**Dietary habits.**

- Eating too much, too fast, too late
- Grilled and charred foods
- Non organic, non GMO.
- Gyphosate

**What is the Approach**

Evaluate severity of IBD

Identify what is moderate to severe.

Work with a gastroenterologist.

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**Identify risk factors that drive inflammation**

<table>
<thead>
<tr>
<th>Heavy metals</th>
<th>Alcohol</th>
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<tbody>
<tr>
<td>Metal allergy</td>
<td>Lack of sleep</td>
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<tr>
<td>Mycotoxins</td>
<td>Smoking</td>
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<tr>
<td>Stress</td>
<td>Lack of exercise.</td>
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<tr>
<td>Red meat</td>
<td>High carbohydrate intake</td>
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<tr>
<td>Burned meat – charring</td>
<td>Dietary habits.</td>
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<tr>
<td>Food Allergies</td>
<td>Food sensitivities</td>
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Correct malnutrition or micronutrient deficiency to aid recovery

Identify and correct SIBO/SIFO

?? Parasites

Intestinal Permeability Issues

- Zinc
- Glutamine
- Omega3
- Antioxidants
- Amino Acids
- Colostrum
- BPC157

Interesting
Closing Points

Constipation and Colitis.

- Constipation is not a typical symptom of Crohn’s disease.
- Constipation can be a symptom of Crohn’s disease complications.
- It also can be a side effect of medications.

Constipation can be a symptom of ulcerative colitis, particularly in people with left-sided disease, where only the left side of the large intestine is inflamed.

Miliary Crohn’s Disease

Mycobacterium avium complex.

https://humanpara.org/dr-william-m-chamberlin/

Okotoka pathway – Australia.