Team Medicine

Inflammatory Bowel Disease

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Inflammatory Bowel Disease

Introduction:

Inflammatory bowel disease consists of two major diseases: Crohn's Disease & Ulcerative Colitis. These diseases could be similar in some aspects but are two distinct diseases.

Epidemiology:

IBD is more common in the West, but it is increasing in developing countries including Saudi Arabia **due to the westernization of lifestyle and diet.**
IBD occurs at any age but usually it peaks in two age groups: 15-30 years and a second peak at the age of 50. However because it is considerably a new disease to our environment we only see the first peak in Saudi Arabia.

Risk Factors:

Genetics: NOD2/CARD15.It was thought this genetic mutation was only found in Ashkenazi Jews, however this has been proven wrong. Even patients in KSA have the same genetic mutation.
Environment:

- Smoking**: is considered a risk factor for Crohn's Disease, and it is also proven that it worsens the prognosis if the patient persists on smoking after being diagnosed. However, smoking is protective in Ulcerative Colitis, it decreases the symptoms (many patients didn't know they had UC until they stopped smoking and the symptoms started showing up).**
- Appendectomy in young age is protective for Ulcerative Colitis.
- **Diet in the first 10 years of life is a major factor for developing IBD.**

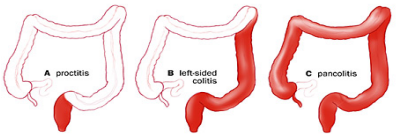
Etiology:

IBD is a disease that is still not well understood, many studies has been done to determine the pathophysiology of the disease. Some studies suggest that it has an infective origin (mycobacteria, helicobacter) but it is unlikely. Dysbiosis, which is an imbalance of the microbial colonies in the GIT, was thought to be a reason in the development of IBD. **However it is most likely due to deregulated immune response in which the immunity in the GIT is decreased when triggered by certain allergies.**

Ulcerative Colitis (UC)

- **Ulcerative colitis is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon.**
- **Usually starts in the rectum then extend proximally.**
- **Site of inflammation:**
  - **Ulcerative proctitis: Rectum only**
  - **Ulcerative proctosigmoiditis: rectum & sigmoid colon.**
  - **Left-sided colitis: extends beyond the rectum up to the splenic flexure.**
  - **Extensive colitis: beyond the splenic flexure.**
  - **Pancolitis: whole colon.**

50% of patients with UC have ulcerative proctitis or proctosigmoiditis, while 30% of the patients the disease extends beyond the sigmoid colon. Leaving only 20% of the patients with Pancolitis.



Clinical Manifestations

Patients with UC develop symptoms much earlier than patients with Crohn's disease because the disease starts in the rectum.

The common symptoms are: urgency (1st sign), diarrhea, rectal bleeding, tenesmus (painful defecation), passage of mucus and crampy abdominal pain. Systematic symptoms usually appear when the disease extends to the colon.

Patients with proctitis pass fresh blood (with or without mucus) either mixed with stool, or strained on the surface of normal or hard stool.

If the disease extends to the colon, the patient will pass stool, which is mixed with blood (grossly bloody diarrhea).

Symptoms that accompany moderate to severe disease are: anorexia, nausea and vomiting, fever, weight loss and liquid stool that contains blood, pus and fecal matter (in severe cases).

Diagnosis

One modality is NEVER enough to diagnose UC. Combination of clinical picture, radiographic imaging, labs, endoscopy and histopathology is required.

Imaging is used in Crohn's disease more than UC because UC is a disease of the colon (making colonoscopy a better choice) unlike Crohn's disease which can be anywhere in the GIT.

For the same reason stated above, colonoscopy is essential to diagnose UC. In colonoscopy it is important to appreciate that there are **NO skipped lesions** unlike Crohn's disease. Another important finding is the **loss of the characteristic vascular markings of the colon.** Petechiae, exudates, touch friability, and frank hemorrhage may be present.

Pathology: crypt abscesses, branching of crypts, atrophy of glands, loss of mucin in goblet cells and an increase in inflammatory cells is seen.

Serology: Antineutrophil cytoplasmic antibodies (pANCA) is positive in UC.

Complications & Management

Complications: Hemorrhage, perforation and toxic megacolon (transverse colon with a diameter of more than 5,0 cm to 6,0 cm with loss of haustration).

There is also an increased risk of developing Colon Cancer (even more than Crohn's). A healthy 70 year old has a 6% risk of developing colon cancer. In UC, after 8 years of being diagnosed with UC the risk will be 6%, and after 20 years, the risk will be 20%.
Management: The doctor emphasized that we should return to the pharmacology lecture, which we took in GIT so we have attached a table for treatment of IBD with this file.
-The most important point in management is to rule out infection every time the patient presents with symptoms, because some of the medications decrease the immunity.
-5 ASA therapy: Oral/ Rectal
-Corticosteroids: Systemic: Prednisolone. Local acting: enema.
-Immunomodulators : Azithyoprine/ Methotrexate
-Anti TNF therapy

Surgery is indicated in four cases (remove the whole colon in UC)

1. **Disease not responding to medications**
2. **Complications of a severe attack (perforation, toxic megacolon or acute dilatation)**
3. **Chronic continuous disease with an impaired quality of life**
4. **Dysplasia or Carcinoma**

Crohn's Disease (CD)

It is a disease with uncertain etiology, which can affect any area of the GIT. It is a transmural inflammation, which is characterized by skipped lesions.

Majority of the patients will have ileocecal involvement.
The small bowel alone will be affected in 80% and the colon alone in 20%. Upper GI tract involvement is very rare and is usually associated with ileocolitis.

Clinical Manifestations

Patients with Crohn's disease usually present late, because the disease is much more proximal than UC. Some of the non-specific symptoms are: fatigue, diarrhea, abdominal pain, weight loss and fever.

Because of the transmural involvement (all the layers not just the superficial like in UC) patients with Crohn's disease have a great risk of developing:

1. Abscesses
2. Phlegmons: walled off inflammatory mass without bacterial infection.
3. Fistulas: communication between two epithelial lined organs
    - Enterovesical: small bowel and bladder
    - Enterocutaneous: small bowel and skin
    - Enteroenteric: small bowel and small bowel
    - Enterovaginal: small bowel and vagina

Other manifestations:
Perianal disease.

Oral involvement: aphthous ulcers.
Esophageal involvement: dysphagia & odynophagia (painful swallowing).
Gall stones due to the malabsorption of bile in the ileum.
Gastroduodenal involvement : the patient will present with upper abdominal pain and symptoms of gastric outlet obstruction.
Granulomas.

Diagnosis

Colonoscopy: Transmural inflammation with skipped lesions (ulceration adjacent to normal mucosa) with polypoid mucosal changes that give cobblestone appearance.

Wireless capsule endoscopy is a new method of endoscopy, which is non-invasive, the patient swallows a pill, which has a camera and will take images of the GIT.

Imaging: CT, MRI, small bowel follow through (to assess the small intestine).

Serology: ESR, CRP (Inflammatory markers) are elevated in IBD but not in Irritable Bowel Syndrome.
Anti-Saccharomyces cerevisiae antibodies (ASCA) is positive in Crohn's.
Stool markers — fecal calprotectin.

Management

Again: most importantly is to rule out infection at every time the symptoms occur.
5 ASA therapy: Oral/ Rectal
-Corticosteroids: Systemic: Prednisolone. Local acting: **Budesonide (which is a corticosteroid) is used more in Crohn's disease than UC. That is because it works on the iliac and the proximal colon (which are the areas usually affected in Crohn's disease). Thus, making it very effective and with much less side effects.**
-Immunomodulators : Azithyoprine/ Methotrexate
-Anti TNF therapy

Surgery: Obstruction, severe perianal disease unresponsive to medical therapy, difficult fistulas, major bleeding, severe disability.

Usually we remove the affected area only in Crohn's disease.

Extraintestinal Manifestations for both UC & CD

Arthritis: Primarily involving large joints in approximately 20 percent of patients without synovial destruction, arthritis is the most common extraintestinal manifestation.
Bone loss and osteoporosis: may result related to glucocorticoid use and impaired vitamin D and calcium absorption.
Eye involvement: uveitis, iritis, and episcleritis.

Skin Disorders: erythema nodosum and pyoderma gangrenosum.
Renal stones. The Male Doctor said you should read about the cause; click here to read an article regarding the formation of renal stones in IBD and some other useful Extraintestinal manifestations.
Vitamin b12 deficiency: A clinical picture of pernicious anemia can result from severe ileal disease since vitamin B12 is absorbed in the distal 50 to 60 cm of ileum.
Thromboembolism.
Primary Sclerosing Cholangitis. The majority of patients with primary sclerosing cholangitis have UC.

Management for both UC & CD

The goals of therapy in both CD & UC are the same, which are:

- Induce and maintain remission.
- Ameliorate symptoms
- Improve patients quality of life
- Adequate nutrition
- Prevent complication of both the disease and medications.

As stated earlier, the Doctor said it is very important to return to the pharmacology lecture in GIT because we will be asked about them; attached is a table done by 430 pharmacology team work for this lecture.

Comparisons between CD & UC

Distinguishing characteristics

Feature	CD	UC
Location	SB or colon	colon
Anatomic distribution	Skip lesions	Continuous
Rectal involvement	Rectal spare	Involved in >90%
Gross bleeding	Only 25%	Universal
Peri-anal disease	1/3	Rare
Fistulization	Yes	No
Granulomas	30%	No

Endoscopic features

Feature	CD	UC
Mucosal involvement	Discontinuous	Continuous
Aphthous ulcers	Common	Rare
Surrounding mucosa	Relatively normal	Abnormal
Longitudinal ulcer	Common	Rare
Cobble stoning	In severe cases	No

Mucosal friability	Uncommon	Common
Vascular pattern	Normal	distorted

Pathologic features

Feature	CD	UC
Transmural inflammation	Yes	Uncommon
Granulomas	30%	No
Fissures	Common	Rare
Fibrosis	Common	No
Submucosal inflammation	Common	Uncommon

Summary

- **IBD consists of two diseases, which are similar, Ulcerative colitis and Crohn's disease.**
- **Both of the diseases are not understood fully, but are probably autoimmune disorders.**
- **Ulcerative colitis usually affects the rectum and extends proximally; it can affect the entire colon.**
- **Crohn's disease can affect any area of the GIT, but most commonly the ileum and cecum.**
- **Ulcerative colitis is characterized by a superficial inflammation that has NO skipped lesions.**
- **Crohn's disease is characterized by transmural inflammation with skipped lesions "cobblestone appearance".**
- **Mutations NOD2/CARD15 are associated with IBD.**
- **Diet in the first 10 years of life is important in developing IBD.**
- **Smoking is a risk factor for developing Crohn's but is protective from Ulcerative colitis.**
- **Patients with UC present much earlier than Crohn's because the disease is distal in the GI tract.**
- **Always use multiple modalities when diagnosing IBD; colonoscopy, imaging, histopathology.**
- **Imaging is more important in Crohn's disease.**
- **p-ANCA is positive in Ulcerative Colitis**
- **ASCA is positive in Crohn's disease.**
- **ESR & CRP are used to distinguish between IBD and IBS.**
- **Colon cancer is more common in Ulcerative Colitis than Crohn's disease.**
- **Toxic megacolon is a severe complication that accompanies UC more than Crohn's.**
- **Abscesses, fistulas and Phlegmons are common in Crohn's because of the transmural involvement.**

- **It is important to rule out infection each time the patient presents with symptoms of IBD.**
- **Budesonide is used more in Crohn's disease.**
- **Surgery is indicated in severe disease in IBD, however; in UC the entire colon is usually removed while in Crohn's only the effected are is removed.**

Questions

1- A 23 years old women have been seen her family doctor complaining from a crampy abdominal pain and constant diarrhea , which is occasionally bloody . she says that the pain is mostly in her right lower quadrant .she's lost about 15 pounds over the past year. upon reviewing her labs in follow up visit, the doctor noticed that her ESR and CRP are elevated .

-What would be your top diagnosis?

A. ulcerative colitis.
B. Ischemic colitis.
C. Crohn's disease.
D. Celiac disease.

2- A 25 years old female presented with 4 weeks of bloody diarrhea associated with lower crampy abdominal pain , weight loss , urgency and tenesmus . She also gave a history of arthralgia affecting the hand and back.

-what is the most likely diagnosis?

A. Ulcerative colitis.
B. viral gastroenteritis.
C. colon cancer.
D. yersinia entrocolitis.

Answers:

1- C / 2- A

Good Luck

Drugs used in IBD

Drug	MOA	Pharmacokinetics and Uses	ADRs
5-aminosalicylic acid compounds: Topical anti-inflammatory drugs. 5-ASA itself is absorbed from small intestine. Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine Uses: Induction and maintenance of remission in mild to moderate ulcerative colitis & Crohn's disease (First line of treatment). Are NOT USEFUL in actual attack or severe forms of IBD. ▪ Rheumatoid arthritis, psoriasis *(Sulfasalazine only)* ▪ Rectal formulations are used in *ulcerative* proctitis and proctosigmoiditis.			
Azo compounds : Sulfasalazine	5-ASA has anti-inflammatory action due to: ▪ inhibition of prostaglandins and leukotrienes. ▪ decrease neutrophil chemotaxis. ▪ Antioxidant activity (scavenging free radical production).	▪ Pro-drug ▪ A combination of 5-ASA and sulfapyridine ▪ Is given orally (enteric coated tablets). ▪ Little amount is absorbed (10%), secreted in the bile ▪ *In the terminal ileum and colon*, sulfasalazine is broken by azoreductase into: 5-ASA (not absorbed, active moiety) and Sulphapyridine (absorbed, side effects)	▪ Muscular pain 29% caused by sulpha. N/V(nausea or vomiting), Diarrhea ▪ Crystalluria and interstitial nephritis. ▪ Hypersensitivity reactions as: skin rash, fever, aplastic anemia. caused by sulpha. ▪ Inhibit absorption of folic acid (megaloplastic anemia) ▪ Infertility in man (decrease sperm counts). However, it is save in pregnancy . ▪ Bone marrow depression
Mesalamine compounds: Well tolerated, less side effects (sulfa free), useful in patient sensitive to sulfa drugs.	▪ Treat and maintain remission in mild to moderate ulcerative colitis .	• Formulations that have been designed to deliver 5-ASA in terminal small bowel & large colon. • Oral formulations -Asacol: 5-ASA coated in pH-sensitive resin that dissolved at pH 7 (*controlled release*). -pentasa: time-release microgranules that release 5-ASA throughout the small intestine (*delayed release*). • Rectal formulations Canasa (suppositories), Rowasa (enema)	
Glucocorticoids	▪ Inhibits phospholipase A2 ▪ Inhibits gene transcription of NO synthase, cyclooxygenase -2 (COX-2) ▪ Inhibit production of inflammatory cytokines	• Treat moderate – severe ulcerative colitis. (Prednisone P.O. 40-60 mg/day for 2 weeks). • Less effective as prophylactic (maintaining remission). • Budesonide as controlled release oral (9 mg/day) formulation (Entocort). • Oral glucocorticoids is commonly used in active condition. • Hydrocortisone enema or suppository for rectum or sigmiod colon. • Used also for extracolonic manifestations such as ocular lesion, skin disease, peripheral arthritis. Asthma, immunosuppressive drug for organ transplants , and antiemetics during cancer chemotherapy	

Immunomodulators

Uses: Are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients.

Purine analogs (azathioprine & 6-mercaptopurine)	Inhibit purine synthesis	Azathioprine is pro-drug of 6-mercaptopurine Used in Induction and maintenance of remission in IBD	▪ Bone marrow depression: leucopenia, thrombocytopenia. ▪ Gastrointestinal toxicity. ▪ Hepatic dysfunction. ▪ Hypersensitivity reaction Complete blood count & liver function tests are required in all patients
Methotrexate	▪ a folic acid antagonist ▪ Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate)	▪ Orally, S.C., I.M. Uses: ▪ Used to induce and maintain remission. ▪ Inflammatory bowel disease ▪ Rheumatoid arthritis ▪ Cancer	▪ Megaloblastic anemia ▪ Bone marrow depression

Monoclonal antibodies used in IBD (TNF-α inhibitors)

Infliximab	▪ TNF-α inhibitors ▪ Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes and	▪ a chimeric mouse-human monoclonal antibody ▪ 25% murine – 75% human. ▪ Given intravenously as infusion (5-10 mg/kg). ▪ has long half life (8-10 days) ▪ 2 weeks to give clinical response Uses ▪ In moderate to severe active Crohn's disease and ulcerative colitis ▪ Patients not responding to immunomodulators or glucocorticoids. ▪ Treatment of rheumatoid arthritis ▪ Psoriasis	▪ Acute or early adverse infusion reactions (Allergic reactions or anaphylaxis in 10% of patients), this reaction can be reduced by pretreatment with diphenhydramine, acetaminophen, corticosteroids. ▪ Delayed infusion reaction (serum sickness-like reaction, in 5% of patients).Infection complication (Latent tuberculosis, sepsis, hepatitis B ▪ Loss of response to infliximab over time due to the development of antibodies to infliximabSevere hepatic failure. ▪ Rare risk of lymphoma.

Adalimumab (Humira)

- Fully humanized IgG antibody to TNF-α.
- Adalimumab is TNFα inhibitor.
- It binds to TNFα, preventing it from activating TNF receptors.
- Has an advantage that it is given by subcutaneous injection.
- It is approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis.

Certolizumab pegol (Cimzia)

- Fab fragment of a humanized antibody directed against TNF-α .
- Certolizumab is attached to polyethylene glycol to increase its half-life in circulation.
- Given subcutaneously for the treatment of Crohn's disease & rheumatoid arthritis.