THE UNIVERSITY OF CHICAGO MEDICINE
Digestive Diseases Center

Medical Treatment Options for Mild, Moderate, and Severe Inflammatory Bowel Disease

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WOCN Annual Education Day
October 11, 2017

OBJECTIVES

- To understand the difference between Crohn's Disease and Ulcerative Colitis.
- Understand current treatment strategies in Ulcerative colitis and Crohn's disease.
- To be able to differentiate extra intestinal manifestations of IBD including eye, skin, and musculoskeletal, as well as treatment options.

Disclosures

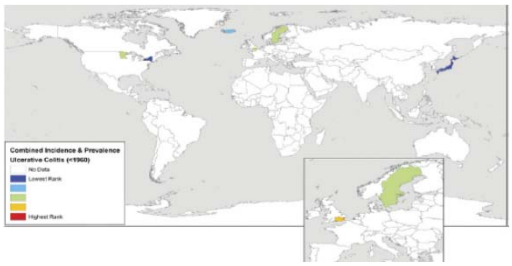
- None

What Is IBD?

- More than 1.6 million cases estimated in the United States
  - Ulcerative colitis (UC): 50%
  - Crohn's disease (CD): 50%
  - NOT IBS (Irritable Bowel Syndrome)
- Frequently young at diagnosis (ages 15 to 30)
- **Chronic** inflammation of the bowel
  - Slowly progressive OR
  - Remission and relapses
- Most IBD patients do not have a family history
- Affects all ethnicities (most commonly Ashkenazi Jews)
- Bowel **surgery** may be necessary

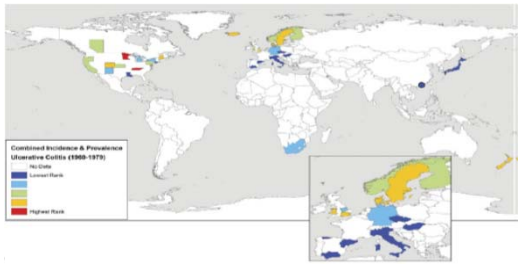
  50-80% for CD
  30% for UC
- Increased risk of **depression** or **anxiety**

IBD's Emergence as a Global Disease: Combined Incidence and Prevalence of UC - < 1960



Molodecky NA, et al. *Gastroenterology.* 2012;142:46-54.

IBD's Emergence as a Global Disease: Combined Incidence and Prevalence of UC – 1960- 1979



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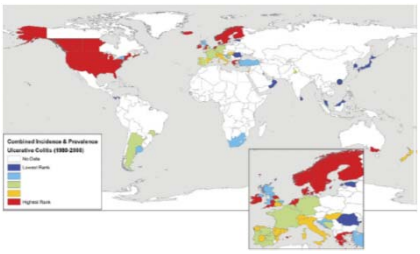
IBD's Emergence as a Global Disease: Combined Incidence and Prevalence of UC – 1980-2008

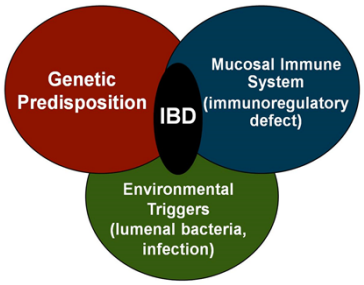


Molodecky NA, et al. *Gastroenterology.* 2012;142:46-54.

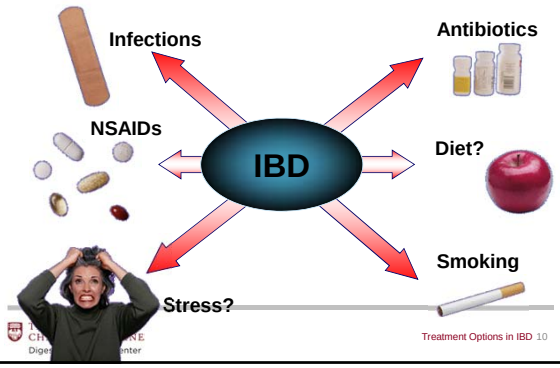
Why is IBD incidence rising?

- Change in Diet
- Rise in Antibiotic use
- "Hygiene"
- Infection
- We have better ways to find it

Etiologic Theories in IBD



Environmental Triggers of IBD

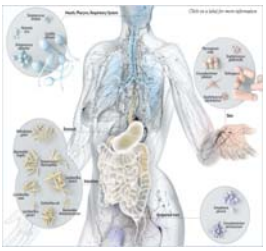


"You are more bacteria than human"

Microbiota of the Bowel

Outnumber human cells 10:1
Adults >500g of microbes
~80% are uncultured

Genetically engineered mice don't get colitis if they are raised in a germ-free environment!

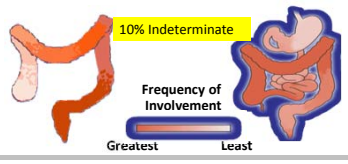


Key role of bacteria in the intestine

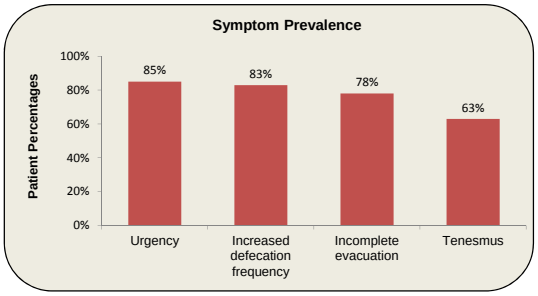
- Bacterial cells in the intestine outnumber our own human cells
- Bacteria perform many important functions:
  - Extract calories and nutrients from indigestible food
  - Synthesize vitamins and short-chain fatty acids
  - Protect against injury to the cells lining the colon
  - Instruct our immune system
- Most intestinal bacteria can't be grown in the lab, and we can only study them with more recent DNA sequencing technology

Clinical Features of UC and CD

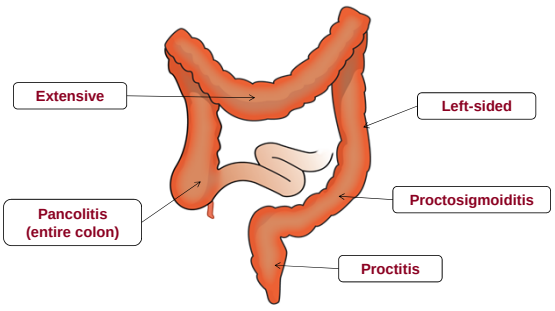
Ulcerative Colitis	Crohn's Disease
• Continuous inflammation	• Patchy inflammation
• Colon only	• Mouth to anus involvement
• Superficial inflammation	• Full-thickness inflammation
• Variable extent	• Fistulas and strictures
• Risk of cancer	• Risk of cancer
• Extra-intestinal manifestations	• Extra-intestinal manifestations



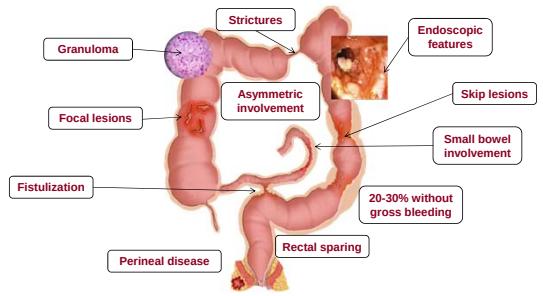
Clinical Presentation of Ulcerative Colitis



UC – Extent of Disease



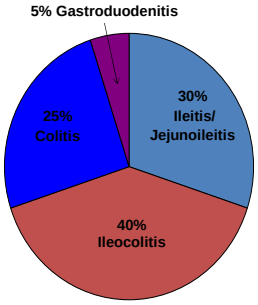
Crohn's Distinguishing Features



Lennard-Jones JE, Lockhart-Mummery HE, Morson BC. *Gastroenterology*. 1968;64:1162-1170.

Clinical Features of Crohn's Disease Depends on Location

- **Ileocecal disease**: abd pain, diarrhea, fever
- **Colonic disease**: bloody diarrhea, weight loss, fever
- **Perianal disease**: pain, fistulae, edematous hemorrhoids, fissures
- **Rectal-vaginal fistulae**: 10% of women with rectal involvement
- **Enterovesical fistulae**: Recurrent UTI's, pneumaturia



Smoking in IBD: A Tale of Two Diseases

- **Crohn's disease**
  - Two-fold increased risk of CD in current smokers
  - Smokers are less responsive to treatment
  - Smokers are more likely to develop recurrence of disease after surgery

- **Ulcerative Colitis**
  - Ex-smokers are more likely to develop UC

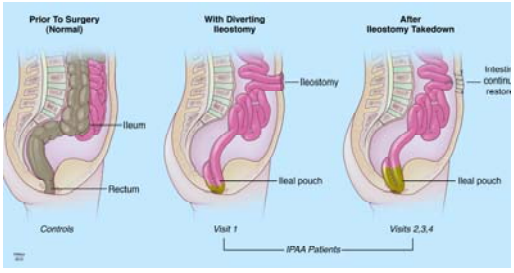
SURGICAL OPTIONS

DO NOT LEAVE AS "LAST RESORT DISCUSSION"

Crohns Disease

- Limited resection
  - Ileocectomy
  - Ileocolectomy (revision)
  - Ileo-anal/ileo-rectal anastomosis
  - stricturoplasty
- Flagyl 250mg po TID x 90 day course
- Therapy to prevent post-operative recurrence
- Re-assessment 6 months post-op to ensure therapy is effective

Ulcerative Colitis



Primary Clinical Endpoints in Ulcerative Colitis and Crohn's: Symptoms

- Formed stool
- No bleeding
- No urgency
- No nocturnal symptoms
- Able to pass gas without fear of leaking

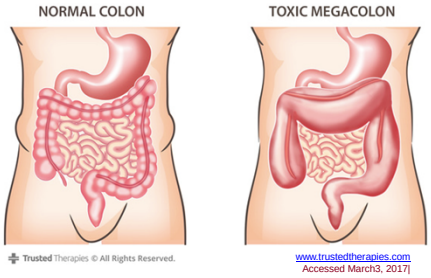
Secondary Clinical Endpoints in Ulcerative Colitis

- Normalized laboratory values
- Restored nutrition and development
- Improved quality of life
- Healed mucosa
- No dysplasia or cancer (increased w/diagnosis > 10 years)

Complications of Crohn's Disease

- Intra-abdominal abscess/phlegmon
- Sepsis (intra-abdominal or perianal
- Obstruction (surgical emergency if high-grade/complete
- Intestinal perforation
- Severe malnutrition (anastomotic leaks, healing issues)
- Short gut syndrome (if multiple SBRs)

Complications of ulcerative colitis



www.trustedtherapies.com
Accessed March3, 2017|

Medical options in IBD

New Management Goals for IBD

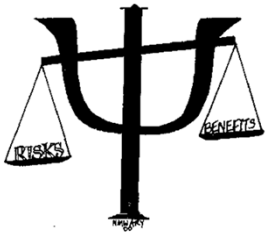
- Induce clinical remission – shift from just symptoms control
- Maintain remission
  - Steroid Free
  - Monitoring drug levels/titrating
- Enhance quality of life
  - Personalized therapy
  - Change in focus from clinical disease indices to objective markers of inflammation (CRP, fecal calpro)
- Modify natural history and long term outcomes of the disease
  - Reduce hospitalization (failure of po steroid trial and negative stool studies)
  - Avoid surgery or repeat surgery (Follow-up essential)
  - Early endosopy post resection
  - Eliminate disability

Medical Therapy in IBD

- Currently there is no cure for Crohn's
- The only cure for Ulcerative Colitis is taking out the colon
- All but the patients with the mildest of the disease will need to be on chronic lifelong therapy

Reaming questions in Anti-TNF Therapy

❖How do we choose who gets which medication?



Compliance is Key

Reaming questions in Anti-TNF Therapy

❖How do we dose adjust for best response, or if someone loses response?

Low Albumin	Increases clearance Worse outcomes
High baseline CRP	Increases clearance
Body size	High BMI may increase clearance
Gender	Males have higher clearance

Reaming questions in Anti-TNF Therapy

- Can we de-escalate therapy when a patient has healed?
  - Steroid de-escalation – yes
  - Stopping therapy altogether- no
- How will biosimilars affect drug choice?
  - Renflexis (Merck)
  - Inflectra (Pfizer)
  - Amjevita (Amgen)
    - Similar drugs, NOT GENERICS
    - Needed to test within same parameters, or else would have been different drug altogether

Medications

Class	Agents
5-ASA Agents	• Balsalazide • Mesalamine formulations – Delayed release tablets (Lialda®, Asacol®, Asacol HD®) – Controlled release tablets (Pentasa®) – Extended release capsules (Apriso™) – Rectal suspension (Rowasa®) – Rectal suppository (Canasa®) • Olsalazine; Sulfasalazine
Corticosteroids	• Adrenocorticotropic hormone • Budesonide • Hydrocortisone • Methylprednisolone • Prednisone
Antibiotics	• Ciprofloxacin • Metronidazole • Rifaximin

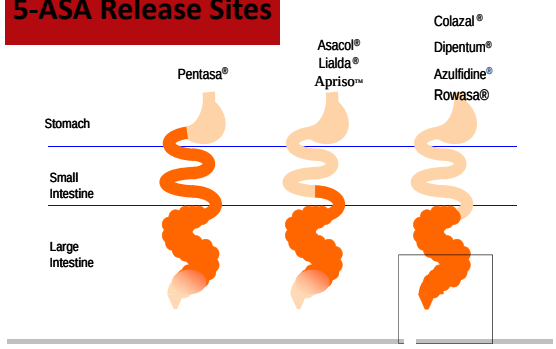
Medications (cont.)

Class	Agents
Immunologic/Thiopurine Agents	• Azathioprine • Cyclosporine • 6-Mercaptopurine • Methotrexate • Tacrolimus
Biologic Agents	• Adalimumab • Certolizumab pegol • Golimumab • Infliximab

Medications (cont.)

Class	Agents
Anti-cytokines (anti-TNF, Anti-IL12/23)	•Ustekinumab
Anti-integrin (adhesion molecule inhibitors)	• Natalizumab •Vedolizumab

5-ASA Release Sites



Corticosteroid Therapies

- Oral, Parenteral, Topical (rectal)
- Effective in INDUCING REMISSION
- Ineffective in MAINTAINING REMISSION
- Prohibitive Side Effect Profile

Prednisone

- Outpatient trial of 40mg po daily for 7 days
  - If fails trial with negative stool studies, then
    - Solu-medrol IV 20mg IV BID
      - Expected response should take effect 3-5 days
      - If cannot induce with IV steroids, consider Remicade or Cyclosporine/Tacrolimus salvage therapy
      - If response, consider as ONLY a bridge to maintenace therapy, with planned taper at discharge

Steroids are associated with worst outcomes in IBD, are used short-term only!

Budesonide

- High Potency (without steroid effects)
- Targeted Delivery To Bowel
- Fewer Steroid-Related Side Effects
  - Two current bowel formulations
    - Entocort (TI and right colon)
    - Uceris (colon)

The Purine Analogues

6-MP

Azathioprine

- **Thiopurine Therapy is More Effective Than 5-ASA in the Treatment of Steroid-Dependent UC**
  - **Maintenance of corticosteroid induced remission**
  - **Combination therapy with biologics for optimiztion of TNF as well as antibody prevention**

Thiopurine dosing 2017

- Personalized dosing
  - TPMT enzyme activity measurement prior to treatment
  - 2mg/kg escalation
  - Monitoring of 6TG and 6MMP metabolites
  - **Lab work need every 2 weeks until therapuetic dose acheieved, follow by every 3 month CBC, CMP**

Methotrexate

Crohn's: Active Disease

Crohn's: Maintenance

*nausea-take Zofran prior for better compliance (injectable and po)

- Usually IM initially then may switch to PO when stable
- Liver biopsy rec after 2-3 years of continuous therapy
- Not to be used in pregnancy
- Pregnancy category X

Current Anti-TNF's

Infliximab (Remicade®)

Adalimumab (Humira®)

Certolizumab (Cimzia®)

Golimumab (Simponi®)

Anti-TNF Agents: Safety

Common

- Same rates as placebo:
  - Headaches
  - Sinus / URI
  - Injection Site Reactions
  - Rash

Uncommon

- Lupus-like reaction
- Infusion reaction
- Hypersensitivity

Extremely Rare

- Serious Infections
  - TB reactivation
  - Hep B reactivation
- Neoplasms
- Neurological Events
- Hepatitis
- Cardiovascular Events
- Hematological Events

Prior to All Biologics

- Blood testing:
  - Quantiferon gold (or PPD) for TB
  - Hepatitis B
- Vaccination review - HPV, pneumococcus, influenza, etc
  - No LIVE vaccines (No Chicken pox, Shingles, MMR, Yellow Fever)

Anti-TNF Therapies (cont.)

- Infliximab
  - Indicated for CD & UC
  - Loaded with 15mg/kg 0,2,6 weeks. Then q 8 weeks
- Adalimumab
  - Indicated for CD & UC
  - Loaded with 160mg, followed 80mg, then 40mg SQ injection every 2 weeks
- Certolizumab
  - Indicated for CD only
  - Loading followed by monthly SQ injection
- Golimumab
  - Indicated for UC only
  - Loading followed by monthly SQ injection

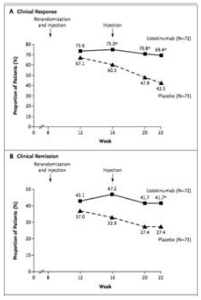
Natalizumab

- Humanized, Monoclonal Antibody (mAb) against α4 Integrins
- Affects intestine and blood brain barrier
- Used for CD and multiple sclerosis
- Risk of PML (progressive multifocal leukoencephalopathy) in the presence of JC virus
- Indicated for CD only
  - Given by infusion monthly 400mg

Vedolizumab (Entyvio)

- Monoclonal antibody targeting a4b7 integrin.
- GUT Specific Blockade
- Should Not Affect Central Nervous System Defenses.
- FDA approved May 2014
  - Indicated for both CD and UC
  - Given by infusion
    - Induction @ week 0,2,6
    - Maintenance @ every 8 weeks

Newest Crohn's therapy: ustekinumab



- Monoclonal antibody targeting IL-12 and IL-23
- Previously on market for psoriasis and psoriatic arthritis
- Approved for CD Sept 2016
- IV load followed by SQ injections q 8 weeks

Cyclosporine in Ulcerative Colitis

- Effective As Acute **INDUCTION** Therapy (IV) For Patients With Severe Colitis.
- Placebo-controlled Trial: 82% CSA response rate vs. 0% for placebo (all patients receiving IV and rectal steroids)
- Not effective long-term unless given in combination with 6-MP/Aza (approx 3 month bridge course)
- Typically bridge to 6MP/Imuran or Entyvio
- Bactrim qMWF as long as on treatment

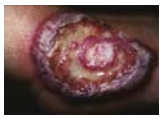
New targets under development

IL-6	Tocilizumab
JAK inhibitor	Tofacitinib
SMAD7 antisense	Mongersen

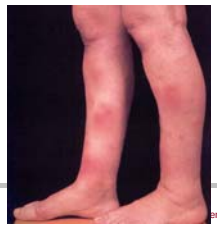
EXTRAINTESTINAL SYMPTOMS

IBD: Dermatologic

- Pyoderma gangrenosum



- Erythema nodosum

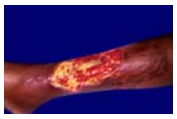


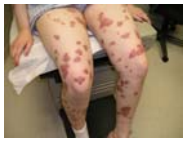
Pyoderma Gangrenosum in IBD *Presentation*

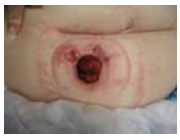
- Occurs in 1% to 10% of patients
- More common in UC than CD
- Typically on extensor surface of lower extremities, but also appears around ostomy sites (areas of trauma)
- Begins as erythematous pustule or nodule
- Becomes burrowing sterile ulcer with irregular edges
- Treatment: Steroids, Kenalog, Tacromilus

Su CG et al. *Gastroenterol Clin North Am.* 2002;31:307.

Pyoderma Gangrenosum in IBD







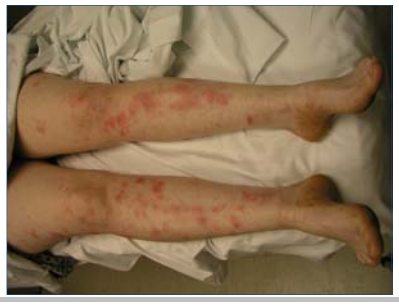
peristomal

Erythema Nodosum in IBD

- Occurs in 10% to 20% of patients
- Hot, red tender nodules usually on extensor surfaces of lower extremities
- Activity correlates with IBD activity
- Often occurs in conjunction with peripheral arthritis
- Treatment: control of IBD

Su CG et al. *Gastroenterol Clin North Am.* 2002;31:307.

Erythema Nodosum in IBD



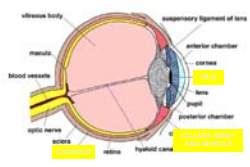
IBD Ocular Manifestations

- Occurrence in UC: 1% to 4%
- Occurrence in CD: 1% to 3%
- Most common ocular manifestations
- Uveitis
- Episcleritis
- Treatment-related complications
- Steroid-induced subcapsular cataracts

Jobling AI et al. *Curr Opin Ophthalmol.* 2002;13:61.
Su CG et al. *Gastroenterol Clin North Am.* 2002;31:307.

Overview of Uveitis

- Inflammation of the uveal tract, which includes the iris, ciliary body, and choroid
- 3rd leading cause of blindness in the U.S.
- Complications: cataracts, glaucoma, retinal detachment



Review of Ophthalmology. www.revophth.com

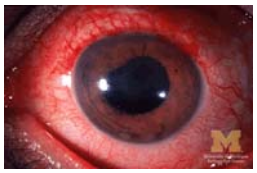
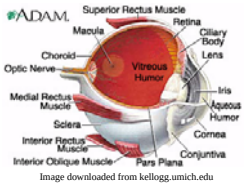


Image downloaded from kellogg.umich.edu

Overview of Episcleritis

- **Inflammation of tissue between the conjunctiva and sclera.**
- **Painless; No loss of vision**
- **Occurrence parallels IBD activity**
- **Usually responds to anti-inflammatories**



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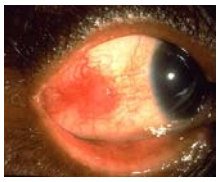
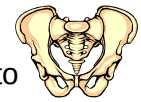


Image downloaded from eyemac.com

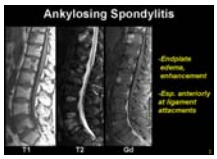
Su CG et al. *Gastroenterol Clin North Am.* 2002;31:307.

IBD: Bones and Joints

- 20-25% of patients
- Axial skeleton (disease independent)
  - Ankylosing spondylitis
  - Sacroileitis
- Peripheral arthritis (related to disease activity)
  - Type 1: asymmetric, limited
  - Type 2: chronic, symmetric



Ankylosing Spondylitis (AS) : *Images*



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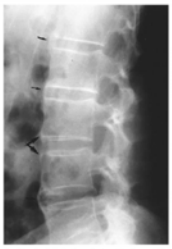

Image downloaded from Medservation.com

IBD: Biliary Disease
Primary Sclerosing Cholangitis

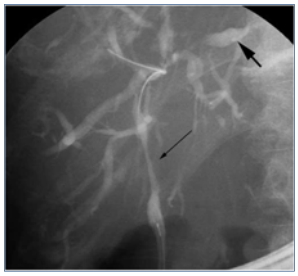

Image downloaded from: Georgios I et al. *Nature Clinical Practice Gastroenterology & Hepatology* (2004) **1**, 53-57.

Primary Sclerosing Cholangitis in IBD

- Unknown etiology
- Progressive inflammation, fibrosis,and destruction of intra- and extrahepatic bile ducts
- Results in cirrhosis and portal hypertension
- Prevalence in UC and in colonic CD: 2.4% to 7.5%
- Male:female ratio in UC is 2:1; this is reversed in CD

Ahmad J et al. *Gastroenterol Clin North Am.* 2002;31:329.

Health Maintenance for IBD

- Vaccinations
  - –Immunosuppression (No live vaccines)
  - –Disease risk from preventable infections
  - –Travel, college considerations
- Cancer screening
  - –Longstanding Colitis → colon cancer risk
  - –Non-melanoma skin cancer
  - –Cervical cancer screening
- Bone health
  - –Steroids → DEXA

Moscandrew et al. IBD 2009

Increased Need for Women's Health Screening

- ❑Female IBD patients are at higher risk of cervical dysplasia
  - *annual cervical cancer screening recommended
- ❑HPV vaccination if indicated
- ❑Pre-conception counseling improves pregnancy outcomes

Diet and IBD

- ❖ No foods will make the disease worse, but foods can make the symptoms worse (greasy/heart healthy diet)
- ❖ Risk for obstruction with high fiber, not easily digestible foods
  - ❖ Corn, nuts, seeds, popcorn
- ❖ Interest by patient in many diets (FODMAP, gluten free)
- ❖ May change microbiome (fast food)?

Summary

- ✓ IBD is a global problem with increasing incidence
- ✓ IBD is likely caused by a combination of factors:
  - ✓ an abnormal immune response to environmental triggers
  - ✓ genetically susceptibility
  - ✓ Overall-what affects the microbiome
- ✓ Location of disease dictates type of symptoms
- ✓ Aims of treatment are to be well and treat symptoms, but also heal the intestine and prevent complications (DON'T JUST LOOK AT LABS)
- ✓ Therapy options are increasing, and we are using therapy in more personalized and targeted ways

References

- About the epidemiology of IBD. Available at: www.ccfa.org/about/press/epidemiologyfacts. Accessed April 7, 2010.
- Jostins, L. et al, Nature. 2012; 491: 119-124
- Turnbaugh, et al. *Sci Transl Med*. 2009 November 11; 1(6): 6ra14
- Lennard-Jones JE, Lockhart-Mummery HE, Morson BC. *Gastroenterology*. 1968;64:1162-1170.

Thank you