Inflammatory Bowel Disease Update for Primary Care Providers

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Prisma Health Gastroenterology and Liver Center
Financial Disclosure Statement

- No relevant financial relationships to disclose.
Learning Objectives

- Historical Background & Epidemiology
- Etiology & Clinical presentation
- Goals of care in the IBD patient
- PCP Role in IBD Care
Historical Background of UC - 1859

Sir Samuel Wilks
Landmark Article
Oct 15, 1932
(JAMA 1932;99:1325-1329)

Regional Ileitis
A Pathologic and Clinical Entity

Burrill B. Crohn, M.D.
Leon Ginzburg, M.D.
and
Gordon D. Oppenheimer, M.D.

New York

We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and exudative inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

Such, in essence, is the definition of a disease, the description of which is based on the study, to date, of fourteen cases. These cases have been carefully observed and studied in their clinical course; the pathologic details have resulted from a close inspection of resected specimens from thirteen of fourteen patients operated on by Dr. A. A. Berg.

Burrill Crohn, MD

Crohn B, Ginzburg L, Oppenheimer GD, JAMA 1932
“Mr. President, we need to go to the OR”

Dwight Eisenhower – 34th President of the United States

New York Times, June 1956
Mulder DJ et al, J Crohns Colitis 2014
Increasing IBD trend in industrialized countries

Kaplan G, Gastroenterology, 2017
Global prevalence of IBD - 2015 snapshot

0.5%

1.5 million patients

Incidence of IBD

- Overall Incidence 6-12/100K
- Peaks at 2\textsuperscript{nd} and 4\textsuperscript{th} decade*
- 30,000 new cases each year

Herrinton et al, Am J Gastroenterol, 2008
Health Care Costs

- Estimated at 14 billion
- Direct
  - Hospitalizations
  - Outpatient Visits
  - Surgery
  - Medications **
- Indirect – Missed work and school
- Mean cost per patient $18,095
IBD costs by service

- Inpatient, 23.1%
- Outpatient hospital procedures, 15.7%
- MD office, 8.2%
- Other, 3.2%
- Emergency room, 2.6%
- Home, 1.4%
- Pharmacy (includes injectable drugs and drugs billed by hospitals using revenue codes), 45.5%

Park KT et al, Am J Gastroenterol, 2016
Proposed Etiologies of IBD
Genetics of Inflammatory Bowel Disease

➢ Twin Studies Crohn’s disease
   • 50% monozygotic, 10% dizygotics

➢ Genes
   • NOD2/CARD 15 identified in 2001

➢ Since then more than 200 IBD risk loci identified

Kaplan G, Gastroenterology, 2017
The Hygiene Hypothesis

Early life exposures
- Diet (breast milk vs formula)
- Birth mode (vaginal vs Caesarean section)
- Infection
- Antibiotic exposure
- Household size and number of siblings
- Furred pet exposure

Normal intestinal microbiota
Intestinal homeostasis and immune tolerance

Dysbiotic intestinal microbiota
Immune dysregulation (atopic disease, T1D, and IBD)
The Intestinal Microbiome

- Decrease: Roseburia hominis, Clades IV, XIVa Clostridia, Faecalibacterium, Prausnitzii, Firmicutes, Bifidobacterium
- Increase: Enterobacteriaceae, Escherichia coli, Fusobacterium adherent-invasive, E. coli (AIEC), Proteus

Healthy to IBD transition

Kaplan G, Gastroenterology, 2017
Question 1

When compared to IBS (Irritable Bowel Syndrome), which of the following symptoms has a stronger association with inflammatory bowel disease?

- A. Mucus in stools
- B. Blood in stools
- C. Diarrhea
- D. Bloating
- E. Abdominal Pain
IBD Clinical Presentation

- Abdominal Pain
- Nausea and Vomiting
- Diarrhea
- Rectal Bleeding
- Weight Loss
Take home point: IBD and IBS symptoms may overlap

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IBD</th>
<th>IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bloating</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Constipation</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Mucus in stools</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Rectal bleeding/urgency</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Elevated inflammatory markers</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

Schoepfer AM et al, Am J Gastroenterol. 2013
Question 2

Which of the following conditions is not associated with inflammatory bowel disease?

A. Ankylosing Spondylitis
B. Pyoderma Gangrenosum
C. Deep Vein Thrombosis
D. Osteoarthritis
E. Osteoporosis
Extraintestinal Manifestations

- Up to 50% of patients may have at least one EIM
- Mechanism: shared epitopes/molecular mimicry?
- Associated with HLA B-27: Ankylosing Spondylitis
- May parallel luminal disease activity
- Joints, skin, eyes, hepatobiliary system commonly affected

Vavricka S et al, Inflamm Bowel Dis, 2015
Aphthous Stomatitis & Erythema Nodosum

Vavricka S et al, Inflamm Bowel Dis, 2015
Pyoderma Gangrenosum

Vavricka S et al, Inflamm Bowel Dis, 2015
Scleritis, Uveitis, Axial Arthropathy (SI/AS)

Vavricka S et al, Inflamm Bowel Dis, 2015
Primary Sclerosing Cholangitis

Vavricka S et al, Inflamm Bowel Dis, 2015
Extraintestinal Manifestations

- 3-fold higher risk of DVT/PE with active disease

- Poorly implemented due to concerns about safety and lack of awareness

- Prophylactic AC is safe in patients with flare

Papa A, World J Gastroenterol, 2015
## Take home point 2: Think outside the gut!

<table>
<thead>
<tr>
<th>Extraintestinal Manifestation</th>
<th>Parallel Course of IBD</th>
<th>Independent Course of IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing Spondylitis</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Erythema Nodosum</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pyoderma Gangrenosum</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Aphthous Stomatitis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Primary Sclerosing Cholangitis</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
IBD Diagnostic Components

- History
- Physical Examination
- CBC, CMP, CRP, Iron Studies
- Stool Studies – *C diff*, cultures, fecal calprotectin
- Imaging – CT or MR enterography
- Endoscopy, Colonoscopy, Capsule endoscopy
- Pathology
Ulcerative Colitis – Mayo Score
Crohn’s Disease

Moka P et al, J Dig Endosc, 2017
Capsule endoscopy
Pathology

Cheifetz, AD, JAMA 2013
IBD Management

Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee

ACG Clinical Guideline: Management of Crohn's Disease in Adults

Gary R. Lichtenstein, MD, FACG1, Edward V. Loftus Jr, MD, FACG2, Kim L. Isaacs, MD, PhD, FACG3, Miguel D. Regueiro, MD, FACG4, Lauren B. Gerson, MD, MSc, MACG (GRADE Methodologist)5† and Bruce E. Sands, MD, MS, FACG6
Treatment Goals in the IBD patient

- Induce clinical remission (absence of symptoms)
- Steroid-free remission
- Improve quality of life
- Minimize cancer risk (from disease and medications)
- Avoid/minimize surgery and hospitalizations
- “Deep remission” (mucosal healing, biological markers)

Role of PCP in IBD Care

- Early referral to gastroenterologist
- Unexplained diarrhea
- Unexplained Iron Deficiency anemia and markers on inflammation
- Extraintestinal Manifestations
- Unexplained weight loss
New Paradigm: Treat beyond symptoms

OLD
Treat based on symptoms

NEW
Mucosal Healing
Serologic Imaging
Mucosal Healing and Colectomy-free rate

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>MH1 Events</th>
<th>MH1 Total</th>
<th>No MH1 Events</th>
<th>No MH1 Total</th>
<th>Weight</th>
<th>Odds ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arias 2015</td>
<td>105</td>
<td>107</td>
<td>77</td>
<td>97</td>
<td>10.8%</td>
<td>13.64 [3.09, 60.08]</td>
</tr>
<tr>
<td>Armuzzi 2013</td>
<td>41</td>
<td>41</td>
<td>73</td>
<td>85</td>
<td>3.0%</td>
<td>14.12 [0.81, 244.57]</td>
</tr>
<tr>
<td>Cabriada 2010</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>9</td>
<td>2.4%</td>
<td>6.33 [0.26, 152.86]</td>
</tr>
<tr>
<td>Colombel 2011</td>
<td>331</td>
<td>352</td>
<td>243</td>
<td>287</td>
<td>63.9%</td>
<td>2.85 [1.65, 4.92]</td>
</tr>
<tr>
<td>Froslie 2007</td>
<td>175</td>
<td>178</td>
<td>163</td>
<td>176</td>
<td>14.4%</td>
<td>4.65 [1.30, 16.62]</td>
</tr>
<tr>
<td>Gustavsson 2010</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>14</td>
<td>2.7%</td>
<td>17.00 [0.82, 350.60]</td>
</tr>
<tr>
<td>Tursi ADA 2014</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Yamamoto 2010</td>
<td>34</td>
<td>34</td>
<td>63</td>
<td>68</td>
<td>2.8%</td>
<td>5.98 [0.32, 111.32]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>737</td>
<td>743</td>
<td>100.0%</td>
<td></td>
<td>4.15 [2.53, 6.81]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>711</td>
<td>640</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.02; \chi^2 = 6.21, df = 6 \) (\( P < .40 \)); \( I^2 = 3\% \)

Test for overall effect: \( Z = 5.62 \) (\( P < .00001 \))
Mucosal Healing and Long-term remission

Shah et al, Clinical Gastroenterol Hepatol 2016
Step up vs Top Down approach

- Surgery
- Newer biologics
- TNF-α +/- immunomodulators
- Corticosteroids, immunomodulators
- Sulfasalazine, 5-ASA, antibiotics, budesonide
- Biologic Therapy +/- IM
- Corticosteroids

Disease severity

TNF Antagonists

- Infliximab – UC, CD
- Adalimumab – UC, CD
- Golimumab – UC
- Certolizumab - CD
SONIC Study – Crohn’s Disease

(A) Corticosteroid-free Clinical Remission at Wk 26

- Azathioprine Monotherapy: 30.0% (51/170)
- Infliximab Monotherapy: 44.4% (75/169)
- Infliximab-Azathioprine: 56.8% (96/169)

P-values:
- Azathioprine vs Infliximab: P=0.006
- Infliximab vs Infliximab-Azathioprine: P=0.02
- Azathioprine vs Infliximab-Azathioprine: P<0.001

(B) Mucosal Healing at Wk 26

- Azathioprine Monotherapy: 16.5% (18/109)
- Infliximab Monotherapy: 30.1% (28/93)
- Infliximab-Azathioprine: 43.9% (47/107)

P-values:
- Azathioprine vs Infliximab: P=0.02
- Infliximab vs Infliximab-Azathioprine: P=0.06
- Azathioprine vs Infliximab-Azathioprine: P<0.001

SUCCESS Study – Ulcerative Colitis

Panaccione et al, Gastroenterology 2014
Anti-Integrin - Vedolizumab
Vedolizumab – GEMINI I Study (UC)

(A) Mean Partial Mayo Clinic Score

- Placebo (N=149)
- Vedolizumab (N=225)

Week

Placebo vs. vedolizumab at 6 wk, P<0.001

(B) Mean Partial Mayo Clinic Score

- Placebo (N=126)
- Vedolizumab every 8 wk (N=122)
- Vedolizumab every 4 wk (N=125)

Placebo vs. vedolizumab every 8 wk for 52 wk, P<0.001
Placebo vs. vedolizumab every 4 wk for 52 wk, P<0.001

Feagan B, NEJM 2013
Anti-IL12 and IL23 - Ustekinumab

Benson, JM et al, Nature Biotechnology 2011
Ustekinumab – UNITI (Crohn’s)

Feagan BG, NEJM 2016
Approved & Investigational IBD therapies

- TNF Inhibitors – Infliximab (UC,C), Adalimumab (UC,C), Certolizumab (C), Golimumab (UC)
- Anti-Integrin – Vedolizumab (UC,C)
- IL 12/23 – Ustekinumab (C)
- JAK Kinase – Tofacinitib (UC)
- Anti-Integrin – Etrolizumab (UC)
- MadCAM1- PF00547659 (UC,C)
- SP1 – Ozanimod (UC)
- PDE4 – Apremilast (UC)
- SMAD 7/TGF-B1 – Mongersen (C)
Question 3

- Which of the following vaccines is contraindicated on patients on immunosuppression?

- A. Intramuscular Influenza
- B. Intranasal Influenza
- C. Pneumococcal Vaccine
- D. HPV
- E. Hepatitis B
ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease

Francis A. Farraye, MD, MSc, FACG\(^1\), Gil Y. Melmed, MD, MS, FACG\(^2\), Gary R. Lichtenstein, MD, FACG\(^3\) and Sunanda V. Kane, MD, MSPH, FACG\(^4\)
The problem

IBD patients do not receive routine health care maintenance at the same rate compared with the general medical population.
Health Maintenance in the IBD patient

- Bone Health
- Vaccinations
- Colorectal Neoplastic Surveillance
- Cervical Cancer Surveillance
- Skin Surveillance
- Depression Screening
- Smoking Cessation
Who should vaccinate? GI or PCP?

- 50% of gastroenterologists acknowledged not taking an immunization history.

- 2/3 of GI physicians thought the PCP was responsible for administering vaccinations.

- One third of PCP’s felt comfortable administering vaccinations

- Lack of awareness among physicians and patients.
List of Live Vaccines

- Intranasal Influenza
- BCG
- MMR (measles, mumps, rubella)
- Smallpox
- Oral typhoid
- Yellow Fever
- Zoster (Zostavax)
Take home point 3 - Avoid Live Vaccines in Immunosuppressed individuals

### Health Maintenance Checklist for Adult IBD Patients

<table>
<thead>
<tr>
<th>Vaccine-Preventable Illnesses</th>
<th>Which Patients</th>
<th>How Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (inactive)</td>
<td>All</td>
<td>Annually</td>
</tr>
<tr>
<td>Pneumococcal PCV13</td>
<td>If on/planning immunosuppression</td>
<td>Once¹</td>
</tr>
<tr>
<td>Pneumococcal PPSV23</td>
<td>If on/planning immunosuppression</td>
<td>At baseline, repeat in 5 years and again after age 65</td>
</tr>
<tr>
<td>Tdap</td>
<td>All</td>
<td>Every 10 years</td>
</tr>
<tr>
<td>HPV</td>
<td>All aged 11–26 years</td>
<td>Once¹</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>All adult patients at risk of meningitis</td>
<td>Once¹</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>If non-immune</td>
<td>Once¹</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>If non-immune</td>
<td>Once¹</td>
</tr>
<tr>
<td>MMR (live vaccine)</td>
<td>If non-immune¹</td>
<td>Once¹</td>
</tr>
<tr>
<td>Varicella (live vaccine)</td>
<td>If non-immune¹</td>
<td>Once¹</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>All aged &gt; 50 years</td>
<td>Once¹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer Prevention</th>
<th>Which Patients</th>
<th>How Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical PAP smear</td>
<td>All on systemic immunosuppression¹</td>
<td>Annual</td>
</tr>
<tr>
<td>Skin screen</td>
<td>All on systemic immunosuppression¹</td>
<td>Annual</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>All with colonic disease for &gt; 8 years</td>
<td>Every 1-3 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Screenings</th>
<th>Which Patients</th>
<th>How Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEXA Scan</td>
<td>High risk; women with low BMI, post-menopausal, chronic steroid exposure</td>
<td>At least 2 years apart</td>
</tr>
<tr>
<td>PPD or IGRA</td>
<td>Prior to anti-TNF or anti-IL-12/23</td>
<td>Once (repeat if TB exposure)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>All</td>
<td>Annual</td>
</tr>
<tr>
<td>Depression check</td>
<td>All</td>
<td>Annual</td>
</tr>
</tbody>
</table>

Vaccinate early in disease process – flu, pneumonia, shingles.

Avoid Live Vaccines on IS individuals

Collaborate with GI
Bone Health in the IBD patient

- Risk factors – female, low BMI, older age, smoking chronic steroid use, prolonged inflammatory state.

- Importance – risk of fractures.

- Obtain baseline DEXA Scan, if normal screen every 2-3 years

- Check Vitamin D and supplement accordingly
What about diet?

- Elimination-reintroduction diet
- LOFFLEX
- FODMAP and low residue
- SCD (Carbohydrate Diet)

May improve symptoms, unclear mucosal healing
Dermatology Evaluation

- Patients on IS are 3-4X higher risk of Non Melanoma Skin Cancer (BCC and SCC)
- Yearly skin exams
- SPF 30 skin protection
- Skin protective clothes
- Avoid UV sunlight
- Be vigilant for development of new lesions!
Tobacco Cessation

- Worse clinical course
- Dampens effect of biologic agents
- Increased risk of colonic neoplasia
- Higher risk of post-op complication
- Higher risk of recurrence after surgery
Fecal Transplant in IBD

- Rationale: repopulate the gut with “good bacteria”
- Recommended for refractory C. difficile infection
- Donors undergo extensive serologic, stool testing and medical history.
- Upper (small bowel) or lower administration routes
- Liquid or Capsule formulations
- 3 CD studies with varying rates of clinical remission
- 2 UC RCT with mixed results

Sunkara T, et al J Inflamm Res 2018
Complementary and Alternative Medicine

- **Probiotics**
  - Recommended for pouchitis (VSL #3), OK to use as adjunct to medical therapy in UC.

- **Curcumin**
  - 2 RCTs (UC, C) with clinical improvement/remission when used as adjunct to 5-ASA.

- **Medical Marijuana**
  - 1 RCT (n=21) in Crohn’s with better clinical scores, no change CRP

- **Acupuncture**
  - 1 RCT – improved clinical scores and QoL in mild-moderate Crohn’s.

- **Cupping**
  - low quality studies, insufficient evidence

- **Mind-body**
  - yoga, massage, CBT
Summary

▪ Early recognition of symptoms and referral to gastroenterologist is key.

▪ Vaccinate early and often, remember live vaccine contraindications.

▪ Screen for bone disease, skin/cervical cancer and depression.

▪ Tobacco cessation translates to improved clinical outcomes.

▪ Collaboration between GI and PCP ensures optimization of patient care.
References


References

References


HABLAMOS ESPAÑOL!

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