Disclosures

- No disclosures

Objectives:

- Epidemiology
- Etiology
- Diagnosis
- Current therapies
- Health Care Maintenance in the Patient with IBD
Epidemiology of IBD: Overview

- **Time trends in incidence**: Increasing since 1960’s
- **Incidence (per 100,000)**: 3-14
- **Peak age at onset (y)**: 15–30
- **Female-to-male ratio**: 1.1 to 1.8:1
- **Geographic trends**: Developing countries increasing

Clinical Overview and Distribution of IBD

- **IBD**: >1.5 million persons in US
  - **Ulcerative Colitis**: 29%
  - **Indeterminate Colitis**: 10-20% of IBD patients
  - **Crohn’s Disease**: 39%

**Proctitis**: 29%
- **Pancolitis**: 47%
- **Left-sided disease**: 25%
- **Ileitis**: 22%
- **Colitis**: 32%
- **Ileocolitis**: 45%

ETIOLOGY

Current Hypothesis

- Genetic Predisposition
- Mucosal or Innate Immune system
- Environmental Triggers (Diet, antibiotics, infections)

Distribution of UC Disease Severity at Presentation

- Fulminant disease (9%)  
- Moderate to higher activity (71%)  
- Low activity (20%)  

Patients With UC (%)

ETIOLOGY

Current Hypothesis

- Genetic Predisposition
- Mucosal or Innate Immune system
- Environmental Triggers (Diet, antibiotics, infections)
Environmental Risk Factors

- Smoking (OR 1.5-2.0 for CD)
- Appendectomy (OR 0.11-0.38 for UC)
- Dietary factors
- Socioeconomic status, hygiene
- Antibiotic use, effect on microbiota
- Greater environment – Sunlight, temperature, soil?
- * Early childhood immunizations, and isotretinoin exposure is NOT associated with development of IBD

Souradet et al. DDW 2012 abstract 349
Racine et al. DDW 2012 abstract 400

Making A Diagnosis of IBD

Signs and symptoms

- **Crohn's Disease**
  - Abdominal Pain, usu RLQ
  - Weight loss
  - Fevers, night sweats
  - Diarrhea
  - Perianal Disease
  - Anemia, low albumin, elevated ESR, CRP
  - Extraintestinal manifestations (EIM's)
  - Children: Failure to thrive

- **Ulcerative Colitis**
  - Bloody diarrhea
  - Urgency/tenesmus
  - Mucus
  - Abdominal cramping
  - EIM's
Extraintestinal Manifestations of IBD (EIM)

- Ocular Inflammation
- Osteopenia/osteoporosis
- Hepatobiliary tract Inflammation (PSC)
- Cholelithiasis
- Dermatologic Lesions (erythema nodosum pyoderma gangrenosum)
- Nephrolithiasis
- Colorectal cancer
- Thromboembolism
- Ankylosing Spondylitis

Loftus 2004, p 506

Which EIM tends to parallel intestinal inflammatory disease activity?

1. Erythema nodosum
2. Pyoderma gangrenosum
3. Uveitis
4. Primary sclerosing cholangitis

Role of diagnostic testing in IBD

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial diagnosis</th>
<th>Work-up of flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy/ileoscopy</td>
<td>Yes</td>
<td>Yes-selectively, escalation Rx</td>
</tr>
<tr>
<td>CRP</td>
<td>Yes, helps rule out</td>
<td>Yes (if was + initially)</td>
</tr>
<tr>
<td>Fecal tests (calprotectin)</td>
<td>Yes, helps rule out</td>
<td>Yes</td>
</tr>
<tr>
<td>Serologies (ASCA, ANCA, Cib, omp-C)</td>
<td>Rarely</td>
<td>No</td>
</tr>
<tr>
<td>Capsule</td>
<td>Yes, if symptoms CD with neg work-up</td>
<td>Only if inaccessible otherwise</td>
</tr>
<tr>
<td>Double balloon</td>
<td>If known lesion and needs biopsy</td>
<td>Dilation of stricture</td>
</tr>
<tr>
<td>Small bowel imaging (CTE, MRE)</td>
<td>Yes</td>
<td>Yes (CD), especially if concern for complication like abscess, fistula or need for escalation of Rx</td>
</tr>
</tbody>
</table>
Ruling out IBD

- In a systematic review and meta-analysis evaluating the utility of CRP, ESR, fecal calprotectin, and fecal lactoferrin to distinguish between IBS, IBD, and healthy controls (HC)
- None of the biomarkers reliably distinguished IBS vs HC
- ≤1% chance of having IBD with a CRP ≤ 0.5, or fecal calprotectin ≤ 40μg/g


Therapy for IBD
Evolving Goals of Therapy for IBD: Sustained Deep Remission

<table>
<thead>
<tr>
<th>Goal</th>
<th>Clinical Parameters</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Improved symptoms</td>
<td>Improved QoL</td>
</tr>
<tr>
<td>Remission</td>
<td>No symptoms</td>
<td>Decreased hospitalisation</td>
</tr>
<tr>
<td>Deep remission</td>
<td>Normal endoscopy</td>
<td>Avoidance of surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal/no disability</td>
</tr>
</tbody>
</table>

QoL = Quality of Life
Modified from Panaccione R. Presented at European Crohn’s and Colitis Organization (ECCO) VIII Annual Congress, Prague, Czech Republic, February 2010

Predictors of Poor Response or Colectomy

- Low serum albumin
- ESR > 30 mm/h
- Bandemia
- Prolonged flare
- Active infection
- Hospitalized
- Severe endoscopic lesions
- Disease duration
- Stool frequency
- Percentage of bloody stools
- Body temperature > 37.5°C
- Heart rate > 90 bpm
- Increased CRP
- Toxic megacolon
- Low hemoglobin < 10.5 g/dL

BPM = beats per minute; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.


Serious Potential Adverse Effects From Prolonged Corticosteroid Therapy

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Patients with Adverse Effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.23 (relative risk for beginning insulin)</td>
</tr>
<tr>
<td>Infection</td>
<td>13-20</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>50</td>
</tr>
<tr>
<td>Myopathy</td>
<td>7</td>
</tr>
<tr>
<td>Cataracts</td>
<td>22 (dose-dependent)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>?</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3-5</td>
</tr>
</tbody>
</table>

Aminosalicylates

- Mesalamine (Lialda, Asacol, Rowasa, Canasa), sulfasalazine
- Mainstay of therapy for Ulcerative Colitis, mild to moderate disease
- Induction: 4.8 g daily, Maintenance: 2.4 g daily
- Data suggest improved response of pan-colitis to combination oral, and rectal topical therapies
- Lab monitoring: Annual creatinine required due to risk of interstitial nephritis

UC Biologics Overview:

- Chimeric monoclonal antibody
  - Infliximab (Anti-TNF) Intravenous
- Humanized Fab' fragment
  - Certolizumab Pegol (Anti-TNF) IM
- Human monoclonal antibody
  - Adalimumab (Anti-TNF) IM
- Humanized monoclonal antibody
  - Vedolizumab (Anti-α4 Integrin) Intravenous

Mucosal Healing and Time to Colectomy in Infliximab-treated Patients

Vedolizumab (Entyvio)\textsuperscript{1,2}

- Humanized monoclonal antibody targeting the α4, β7 integrins
- Sister to natalizumab, which targeted α4, β1.7 and is approved for UC, CD, and multiple sclerosis
- FDA approved for adults with moderate to severe UC and CD who were intolerant or did not respond to corticosteroids, IMM, or anti-TNF
- Dosing includes 300 mg IV induction at weeks 0, 2, 6, and then every 8 weeks thereafter
- Check for TB and HBV exposure prior to initiation

Vedolizumab

Which was the most common adverse effect seen in vedolizumab clinical trials?

1. Progressive multifocal leukoencephalopathy (PML)
2. Nasopharyngitis
3. Gastrointestinal perforation
4. Abdominal pain
5. Cytopenias
**Vedolizumab**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=129)</th>
<th>Vedolizumab (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile event</td>
<td>11 (8.5%)</td>
<td>15 (10.4%)</td>
</tr>
<tr>
<td>Cough</td>
<td>27 (21.1%)</td>
<td>23 (16.1%)</td>
</tr>
<tr>
<td>Cough of uncertain cause</td>
<td>3 (2.3%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (8.5%)</td>
<td>14 (9.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (20.4%)</td>
<td>27 (18.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (38.3%)</td>
<td>54 (37.5%)</td>
</tr>
<tr>
<td>Hypertension, new onset</td>
<td>21 (16.5%)</td>
<td>20 (13.8%)</td>
</tr>
<tr>
<td>Serious gastrointestinal infection</td>
<td>3 (2.3%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>25 (19.3%)</td>
<td>26 (17.9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>54 (41.3%)</td>
<td>66 (45.5%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28 (21.6%)</td>
<td>34 (23.5%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16 (12.5%)</td>
<td>21 (14.6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68 (52.2%)</td>
<td>59 (41.1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>51 (39.7%)</td>
<td>78 (54.0%)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>97 (75.2%)</td>
<td>97 (67.1%)</td>
</tr>
<tr>
<td>Any serious infection</td>
<td>8 (6.2%)</td>
<td>13 (9.1%)</td>
</tr>
<tr>
<td>Any cancer</td>
<td>7 (5.4%)</td>
<td>10 (7.0%)</td>
</tr>
</tbody>
</table>


**Tofacitinib**

- Oral, small molecule, Janus-kinase inhibitor, inhibits JAK 1, 2, and 3
- Currently approved for rheumatoid arthritis at a dose of 5 mg twice daily
- Important warnings and adverse effects include:
  - Serious infections, TB reactivation (check for exposure)
  - Lymphoproliferative disorders, Gastrointestinal perforation, Lipid, CBC, and Liver test abnormalities.
  - Live vaccines contraindicated
  - Anticipate FDA approval for UC possibly Fall 2017

Fecal microbiota transplant (FMT)

- Not FDA approved for treatment of C difficile or IBD
- FDA practices "enforcement discretion" for C difficile
- Treatment of IBD requires Investigational New Drug application from FDA (IND)
- RCT data is mixed¹
  - Positive studies evaluated frequent administrations of FMT via enema over several weeks²,³
- Very real risk of flare
  - Particularly for Crohn’s patients
- UCSF has ongoing trial of FMT in IBD
  - Only ulcerative colitis patients being enrolled at this time

Summary of sequential Therapies for UC

Therapy is stepped up according to severity at presentation or failure at prior step.

Disease Severity at Presentation
- Severe
- Moderate
- Mild

Aminosalicylate
- Corticosteroid
- Anti-TNF± 6MP/MTX, Vedolizumab
- Colectomy

SONIC: Corticosteroid-Free Clinical Remission at Week 26 – IFX + IMM

Primary Endpoint

Proportion of Patients (%)

AZA + placebo 52/170
IFX + placebo 75/169
IFX+ AZA* 96/169

Primary Endpoint

AZA + placebo 30.6
IFX + placebo 44.4
IFX + AZA* 56.0

P=0.006
P=0.022
P=0.001

Ustekinumab (Stelara)
- Human Interleukin-12 and 23 antagonist
- FDA approved for plaque psoriasis, psoriatic arthritis, and as of Sept 2016, moderate to severe Crohn’s Disease in those who have failed or were intolerant to IMM, corticosteroid, OR anti-TNF
- Crohn’s induction dosing regimen:
  - **Weight Range (kilogram)**
  - **Recommended Dose**
    - Up to 55 kg
    - Over 55 kg
  - **3 mg/kg (1st week)**
  - **3 mg/kg (1st week)**
  - **520 mg (4 x 130 mg)**
- Maintenance is 90 mg SQ every 8 weeks

3. Likely due to high IFX serum trough levels.
Ustekinumab

Step-up according to severity at presentation or failure at prior step

*Mesalamine does not work for CD, exception may be mild colonic CD
Health Care Maintenance and General Health

Lack of Primary Care
- Many patients with IBD are young and do not have co-morbid illnesses
- The gastroenterologist will often serve as their only physician
- Patients with IBD receive less preventive health services than general primary care patients

1. Selby Inflamm Bowel Dis. 2008;14:253-258

Which vaccine is contraindicated for a 26 yo IBD patient on adalimumab?

1. TDaP booster
2. Inactivated influenza
3. Pneumovax
4. Zoster
5. Hepatitis B

1.
Patients with IBD are under-vaccinated

- 169 patients surveyed
- 146 (86%) reported current or past IS use
- 76 (45%) tetanus vaccine in past 10 yrs
- 41 (28%) received regular influenza shots
- 13 (9%) had pneumococcal vaccine
- 47 (28%) hepatitis B vaccination
- Lack of awareness (49%) most common reason

Vaccines: Who?

- Goal: Prevent infections in a population that is often immunosuppressed
  - Influenza and pneumococcal pneumonia are the most common vaccine preventable illnesses in IBD adults.
- Follow general guideline; exceptions:
  - Early dosing:
    - Pneumovax one-time dose PCV13, followed by PPSV23 in one year, 2nd dose PPSV23 5 yrs later, 3rd at age 65+
  - Zoster
    - Live Vaccines:
      - Contraindicated with immunosuppression (biologics, long term steroid)
  - No increased risk of flares
  - Lack of immunologic response should not discourage vaccination

Human Papilloma Virus

- Multiple studies have shown a higher incidence of abnormal Pap smears in women with IBD
- Increased anal dysplasia with perianal CD
- All women <age 26 with IBD should get HPV vaccination, consider in men as well
Summary

- Patients with IBD should follow the same vaccination guidelines as the general public, except:
  - Patients on biologics should not get live vaccines
  - Newborns born to mothers on anti-TNF should not get live vaccine in first 6 mo
  - Early dosing for pneumococcus, zoster
  - HBV and HAV recommended
- At the time of diagnosis of IBD, vaccinations should be checked and updated prior to starting any immunosuppressant (if possible)

What is correct regarding health maintenance in a 30 yo Crohn's patient on adalimumab, and treated with steroids for > 3 months?

1. Delay DEXA screening to age 40
2. Depression screening is not indicated
3. No increased risk of cervical dysplasia
4. Recommend OCP over IUD
5. Screen for hypertension and diabetes

General Health

- Blood Pressure screening
  - Increased risk for secondary hypertension: medications (corticosteroids, cyclosporine)
- Blood Glucose Screening
  - Increased risk due to corticosteroid use
- Ophthalmologic Exam
  - Annual exam
  - Risk of glaucoma on corticosteroids
  - Risk of iritis, optic neuritis, scleritis with IBD
Tobacco Cessation

- Cardiac, pulmonary and oncologic risk
- Active smoking is a risk factor for CD
  - Reduce response to medications
  - Increase rate of post-operative recurrence
  - Shorten duration of remission
- Contributes to increased risk of venous thromboembolism
- Active smoking may benefit UC
- Medical therapy for smoking cessation


Osteoporosis

- IBD pts increased risk for osteoporosis
  - Corticosteroid use
  - Chronic inflammation
  - Low body mass index
- Dual energy x-ray absorptiometry scanning (DXA)
  - IBD men and women over age 50
  - Those with risk factors:
    - Prolonged (>3 months) steroid use
    - History of low trauma fracture
    - Hypogonadism


Cardiovascular disease

- IBD patients are at increased risk of cardiovascular related disease and mortality
- Recent large retrospective database review:
  - HR for MI in IBD patients was 2.22 (1.55-3.2)
  - HR for heart failure was 1.86 (1.22-2.85)
- Therapy reduced CV event rate in this population:
  - Biologics adjusted HR 0.7 (0.59-0.82)
  - IMM adjusted HR 0.68 (0.57-0.81)
- Steroids were associated with increased overall mortality over anti-TNF therapy in both CD and UC
  - Cardiovascular disease and hip fracture contributed

Cancer Screening

- Colon Cancer
  - Every 1-2 years after 8 years of colonic disease
  - Start immediately for those with comorbid PSC, and perform annually

- Cervical and Anal Dysplasia
  - Annual pap smears starting age 21 (per ACOG)\(^2\)
  - May be increased with perianal disease
  - HPV vaccination

1. Allegretti JR et al. IBD. 2015;21(5):1089-97

Cancer screening

- Skin Cancer
  - Increased with immunosuppression, particularly non-melanoma skin cancers with Azathioprine
  - Possible increase of melanoma with anti-TNF\(^1\)
  - Annual skin exam in those on immunosuppression

- Breast Cancer
  - Same as baseline population
  - CD patients may be treated less aggressively and survival is worse\(^2\)

2. Sogaard Inflamm Bowel Dis 2008;14:519-525

General health

- Increased risk of deep vein thrombosis
  - Strongly advocate for tobacco cessation
  - Recommend non-estrogen based contraceptive, or as lowest dose possible, IUD is appropriate
  - Hospitalized patients should be given pharmacologic DVT prophylaxis
Depression

- Higher rates of generalized anxiety, and major depression among IBD patients in the United States\(^1\)
- Depression is associated with increased symptoms, clinical recurrence, poor QoL, and reduced social support\(^2\)
- IBD patients should be screened and treated for depression, which may improve their clinical course\(^3\)


Summary

- Patients with IBD have important general health care needs
- The gastroenterologist should perform:
  - Appropriate laboratory and TB testing
  - Colon cancer surveillance
  - Laboratory drug monitoring
- The gastroenterologist should advise patient and primary care provider:
  - Make sure vaccines are up to date
  - Tobacco cessation
  - Osteoporosis, Htn, Glucose, Ophthalmologic screening
  - Cancer screening
  - Depression screening

Thank you!

UCSF Division of Gastroenterology
Center for Colitis and Crohn’s Disease, Intestinal Rehabilitation Center for Short Bowel Syndrome
1701 Divisadero, Suite 120
Phone: 415-502-4444
Email: kendall.beck@ucsf.edu