Orientation 2009
IBD Overview

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Objectives

• Review the etiology of chronic inflammatory bowel disease

• Discuss diagnosis, differential diagnosis

• Review measures of disease activity

• Discuss IBD therapy
IBD-Background Information

• Inflammation
  – gut’s only response to myriad of potential insults

• Minority of new occurrences of IBD associated with straightforward effort of establishing positive diagnosis
  – No gold standard test exists
  – Casual diagnosis of IBD has many ramifications

• Bottom line:
  – Diagnosing IBD continues to be a challenge!
Environmental Factors Influencing IBD

Medications
- NSAIDs
- Antibiotics

Enteric pathogens

Stress

Smoking

Appendectomy

Family history

Diet
Environmental Triggers of IBD

Alter Flora
- Antibiotics
- Diet

Alter Barrier Function
- Acute infections
- NSAIDs
- Smoking
- Stress
Components of IBD Diagnosis

- Clinical picture
- Endoscopic information/pathologic specimens
- Radiographic evidence
- Chronic course of symptoms
Constructing the Diagnosis of IBD

- Careful process of putting together pieces of a puzzle to accumulate enough evidence to diagnose IBD
Age & Sex Incidence of IBD

Ulcerative Colitis
- Female
- Male

Crohn’s Disease
- Female
- Male

Age of onset (years)

# of PTS
Historical Points Suggestive of IBD

- ↑ stool frequency, ↓ consistency most common presenting sx of UC and CD
  - Altered bowel habits need not be present in either
  - Proctitis, in particular, may present with constipation

- Abdominal pain second most common symptom
  - RLQ pain exacerbated by eating: CD
  - LLQ cramping before BM, relieved by BM: UC
  - Tenesmus: proctitis, most likely UC, occ CD
Historical Points Suggestive of IBD

• Alternating diarrhea and constipation more strongly suggest IBS vs IBD

• Nocturnal diarrhea more common in IBD

• Functional symptoms remaining after bout of enteric infection may be confusing
  – Lingering abdominal pain, loose/urgent stools should prompt objective evaluation by endo/path
Physical Findings in IBD

• Crohn’s Disease
  – Oral lesions
  – Ocular lesions
  – Skeletal manifestations
  – Skin lesions
    • Erythema nodosum
  – Abdominal exam
    • Mass
  – Perianal disease
    • Skin tags
    • Anal fissure
    • Perianal fistula
    • Anal stenosis

• Ulcerative colitis
  – Oral lesions
  – Ocular lesions
  – Skeletal manifestations
  – Skin lesions
    • Pyoderma
  – Abdominal exam
    • Tenderness
  – Perianal disease
    • Rectovaginal fistula
Oral Lesions
Ocular Lesions
Cutaneous Lesions
Perineal Complications of Crohn’s Disease
Common Peri-Anal Conditions

Not to be confused with Crohn’s

- Uncomplicated fistula-in-ano
  - Does not traverse the internal anal sphincter
- Anal fissure (posterior mid-line)
Systemic Complications of Ulcerative Colitis

**Peripheral Arthritis**

- Monoarticular
- Asymmetrical
- Large > small joint
- No synovial destruction
- No subcutaneous nodules
- Seronegative
Systemic Complications of Ulcerative Colitis
Central (Axial) Arthritis

Ankylosing Spondylitis and Sacro-iliitis
Systemic Complications of Ulcerative Colitis

Bile Duct Lesions

Sclerosing cholangitis

Cholangiocarcinoma
Historical Information-Summary

• Presenting signs and symptoms may suggest a particular diagnosis
  – Often not definitive

• Usually requires further investigation!
Useful Laboratory Tests

• Blood work
  – CBC, TSH, ESR, c-RP

• Stool studies
  – Ova and parasites, stool culture, fecal WBC, C. diff toxin A/B
  – Fecal lactoferrin, calprotectin

• Serologic markers
  – ASCA, ANCA, anti-OmpC, anti-CBir1, anti-I2
Diagnostic Tools for IBD

• Endoscopy with pathology
Diagnostic Tools for IBD

- Barium studies (UGI/SBFT, ACBE)
Diagnostic Tools for IBD

- Capsule/wireless endoscopy
Capsule endoscopy

- Not suitable for routine diagnosis
  - best indication is for strong suspicion of Crohn’s despite normal conventional testing (e.g., anemia, weight loss, elevated CRP/ESR, etc)

- Complications
  - capsule retention
    - in established Crohn’s disease – 5%
    - in suspected Crohn’s disease before obstructive symptoms – less than 1%

_Barkin et al, Am J Gastroenterol 2002; 97: A-83_
Small intestinal Crohn’s disease as seen by wireless capsule endoscopy
Capsule endoscopy in Crohn’s disease

- Detects erosions in suspected Crohn’s disease with negative SBFT / colonoscopy
- Need blinded comparison studies vs other imaging to calculate true sensitivity and specificity
- Need to determine specificity (prevalence of SB erosions in general population)
- Need to clarify safety in stricturing Crohn’s disease – patency capsule may help
CT enterography
Peri-enteric fat stranding

Adapted from Loftus, Oral presentation, ACG 2006
Fistulas

- Tracts
- Usually enhancing (unless perianal)
- ± fluid / air
- Enterocutaneous

Adapted from Loftus, Oral presentation, ACG 2006
Inflammatory stricture with proximal bowel dilation
MR enterography
MR enterography

- No ionizing radiation

- Comprehensive evaluation of bowel and perianal fistula

- Functional evaluation (is narrowing due to stricture or spasm?)
MR enterography: Crohn’s disease findings

- Enhancement
- Wall thickening
- High SI wall / fat
- Deep ulcers
- Comb sign
- Enhancing nodes

Image courtesy of Jeff Fidler, MD
MR enterography: Crohn’s disease findings

- Enhancement
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Image courtesy of Jeff Fidler, MD
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Image courtesy of Jeff Fidler, MD
Small bowel imaging in Crohn’s disease: Prospective blinded 4-way study with consensus reference standard

CTE and CE were equally sensitive but CE was less specific than other 3 modalities

Solem et al, Gastroenterology 2005; 128: A74
Indications for Endoscopy in IBD

- Obtain an accurate diagnosis
- Assess disease activity or possible extension
- Dilate strictures in fibro-stenotic disease
- Detect cancer precursors in long-standing colonic disease

Hommes Gastro 2004;126:1561-1573
Endoscopic Features of IBD

*Ulcerative colitis*

- Edema
- Erythema/Loss of vascularity
- Friability
- Erosions
- Mucopurulent exudate
- Spontaneous bleeding
- Ulceration
Endoscopic Features of IBD

**Crohn’s Disease**

- Patchy edema, erythema
  - Discontinuous
- Apthous ulcerations
- Coalescing ulcerations
- Cobblestoning
Differential Diagnosis of Ileitis
Conditions Mimicking Crohn’s Disease

- Lymphoid hyperplasia
  - Adolescents, young adults
  - Could be clue to hypogammaglobulinemia

- Infections
  - *M. tuberculosis*
  - *Y. entercolitica* (cold-chain hypothesis)
  - *E. histolytica*
  - *Actinomyces* (can cause fistulization)

- Lymphoma

- NSAID induced injury
  - Ulcerations
  - Webs/strictures

- Vasculidities
  - Henoch-Schönlein purpura (GI bleeding, RLQ pain)
  - Spondyloarthropathies

- Eosinophilic gastroenteritis
  - Predominantly eosinophilic infiltrate, sub-mucosal/serosal involvement

- Medications
  - Oral contraceptives
  - Ergot derivatives
  - Digoxin
    - precipitate small vessel thrombosis, ischemic ileitis

- CVID
Intestinal Tuberculosis
Differential Diagnosis of Proctitis

Conditions Mimicking Ulcerative Proctitis

• Crohn’s proctitis
  – Associated with fistulas, fissures, skin tags, anal stricture

• STDs
  – HSV, gonorrhea, chlamydia, LGV, syphilis, whipworm

• Rectal prolapse
  – Inflammation confined to distal 2-3cm of rectum

• Solitary rectal ulcer syndrome
  – Anterior location
  – Fibrosis, muscular hypertrophy on biopsy
Differential Diagnosis of Colitis

- ASLC
- Ischemic colitis
- Beçets syndrome
- Microscopic or collagenous colitis
- SCAD
- Diversion colitis
Acute Self-Limited Colitis (ASLC) vs IBD

- Strongly suspected to be infectious in nature
  - Whether or not an infectious agent is identified

- When enteric pathogen not identified, signs and symptoms distinguish poorly between ASLC and IBD

- Histopathology takes center stage in guiding accurate diagnosis
ASLC vs IBD

• IBD
  – Architectural distortion
  – Prominent increase in cellularity of lamina propria
  – Basal plasmacytosis
  – Lymphoid aggregates
  – Crypt abscesses
  – Mucin depletion

• ASLD
  – Normal architecture
  – Superficial increase in lamina propria cellularity
  – Intense neutrophilic infiltrate
  – Mucin depletion
  – Discontinuous inflammation
  – Focal cryptitis

Caveat

– Architectural distortion requires time to develop
– May not be identified in first 6-8 weeks of either form of IBD (potentially longer if inflammation is mild)
Differential Diagnosis of Colitis

- ASLC
- Ischemic colitis
- Beçets syndrome
- Microscopic or collagenous colitis
- SCAD
- Diversion colitis
Ischemic Colitis

http://admin.koreahospital.com
Differential Diagnosis of Colitis

- ASLC
- Ischemic colitis
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Differential Diagnosis of Colitis

• ASLC
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Differential Diagnosis of Colitis

- ASLC
- Ischemic colitis
- Beçet’s syndrome
- Microscopic or collagenous colitis
- SCAD
- Diversion colitis
IBD Diagnosis - Summary and Pitfalls

• Inflammation
  – Gut really has limited options for expressing response to myriad of potential insults (one size fits all!)

• Minority of new occurrences of IBD associated with straightforward effort of establishing positive diagnosis
  – No gold standard test exists
  – Casual diagnosis of IBD has many ramifications

• Bottom line:
  – Diagnosing IBD correctly continues to be a challenge!
IBD Treatment Principles

CURE
IBD Treatment Principles

1. Determine underlying cause/location of disease
2. Tailor therapy to patient’s manifestations
3. Achieve and maintain remission
4. Monitor for toxicity/complications
Approach to Crohn’s Disease Therapy
Determine Treatment Plan Based on Underlying Clinical Factors

- Disease behavior (inflammatory, fistulizing, stenotic/obstructing)
- Site/extent
- Presence of extra-intestinal manifestations
- Prior response to specific drugs
- Severity
Disease Behavior

- Inflammatory disease

- Mechanical obstruction (fibro-stenotic)

- Penetrating disease
Provide Therapy Commensurate With Severity of Disease

• Clinical gestalt

• Measurement tools
  – Crohn’s Disease Activity Index
  – Harvey Bradshaw Index
  – Montreal Classification
Crohn’s Disease Activity Index

• Variables
  – Number of liquid or very soft stools
  – Abdominal pain
  – General well-being
  – Number of listed complications
    - Use of antidiarrheal agents
    - Abdominal mass
    - Hematocrit
    - Change in standard body wt

• Measured over a 7-day period
• CDAI ≤ 150: Remission
• CDAI 151–220: Mild disease
• CDAI 220–450: Moderate to severe
• CDAI > 450: Severe disease
Harvey Bradshaw Index

- **General well-being**
  0 = very well, 1 = below par, 2 = poor, 3 = very poor, 4 = terrible

- **Abdominal pain**
  0 = none, 1 = mild, 2 = moderate, 3 = severe

- **Number of liquid stools per day**

- **Abdominal mass**
  0 = none, 1 = dubious, 2 = definite, 3 = definite and tender

- **Complications**
  Arthralgia, uveitis, e. nodosum, p. gangrenosum, fistula, apthous ulcer, abscess (score 1 per item)

### Grading Activity
- <5  remission
- 5-7  mild disease
- 8-16  mod disease
- >16  severe disease

Response = > 3pt drop
Determining Severity
Clinical Gestalt

• Remission
  – Asymptomatic, off systemic steroids
  – No inflammatory sequelae

• Mild to moderate Crohn’s disease
  – Ambulatory
  – Nontoxic
  – No abdominal tenderness, mass or obstruction

• Moderate to severe Crohn’s disease
  – Unresponsive to mild/moderate therapy
  – Prominent fever, weight loss, anemia
  – Abdominal pain/tenderness, obstruction

• Severe Crohn’s disease
  – Persistent symptoms on high dose prednisone
  – High fever
  – Rebound tenderness, abscess
Therapy for Mild Disease

• Oral and topical 5-ASA compounds were first-line agents for patients with mild disease
  – No strong evidence to support therapeutic efficacy in Crohn’s disease

• Budesonide: 9mg po daily
  – First choice for mild-moderate ileo-colonic CD
  – More effective than mesalamine
  – Fewer side effects than prednisone
Therapy for Mod to Severe Disease

• Prednisone first-line therapy with Step-up theory of treatment selection
  – Proven efficacy
  – Rapid symptomatic relief
  – Dose as 40-60mg as single AM dose

• Consider early use of biologic therapy

• Immunomodulators
  – Azathioprine/6-mercaptopurine
  – Methotrexate

• Biologics
  – Remicade
  – Humira
  – Cimzia
Therapy for Severe Crohn’s Disease

- IV steroids

- Biologics
  - Remicade
  - Tysabri
  - Humira
  - Cimzia

- Immunomodulators
  - Methotrexate
  - Azathioprine/6-mercaptopurine

- Surgery
# Montreal Classification

- **A=age at dx**
  - A1 <16
  - A2 17-40
  - A3 >40

- **L=location**
  - L1 TI
  - L2 colon
  - L3 ileocecal
  - L4 upper

- **B=behavior**
  - B1 non-stric/pen
  - B2 stricturing
  - B3 penetrating
  - B4 peri-anal dz

- **Risk factors**
  - Age below 40
  - L1, L3
  - Penetrating or stricturing pheno
  - ASCA
  - Anti-OMPc
  - Anti-CBir1
  - Anti-I2
  - Steroid at dx

Beaugerie Gastro 2006
Azathioprine Metabolism

- Initial starting dose 50mg/day
- Can rapidly advance if TPMT testing favorable
- Target dose:
  - 6-MP maximum dose 1.5mg/kg/day
  - AZA maximum dose 2.5-3.0mg/kg/day
- Monitor metabolites:
  - Response maximized when 6-TG level 235-400pg/ml
  - Maintain 6-MMP <5700
- VA:
  - TPMT genetics
  - Thiopurine metabolites
Approach to Ulcerative Colitis Therapy
Selection of Treatment

• Treatment plan designed is based on
  – Severity
  – Extensive vs. distal
  – Presence of complications/extra-intestinal manifestations
  – Prior response to specific drugs

• Therapeutic decisions rarely based on severity of inflammation seen at endoscopy or histology
UC-Clinical Severity

• Severity of disease can be determined by:
  – Truelove and Witt’s criteria
    • mild
    • moderate
    • Severe

• Easy to remember:
  – 2 historical points
  – 2 physical exam points
  – 2 laboratory values
# UC Severity

*Truelove and Witt’s Criteria*

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<th>Variable</th>
<th>Mild</th>
<th>Severe</th>
<th>Fulm</th>
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<td>&gt;6</td>
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<td>ESR</td>
<td>&lt;30mm</td>
<td>&gt;30</td>
<td>&gt;30</td>
</tr>
</tbody>
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- All mild parameters = mild severity
- Fewer than all six severe = moderate
Ulcerative Colitis Activity Index

- **Clinical response**
  - Reduction from baseline \( \geq 3 \) pts
  - Reduction of bleeding \( \geq 1 \) pt
    - or
  - Absolute score \( \leq 1 \)

- **Clinical remission**
  - Score \( \leq 2 \) pts
  - No individual score \( >1 \)
Site of Delivery
Based on 5-ASA Formulation

- Topical therapy’s ability to reduce inflammation directly linked to ability to reach site of inflammation

20% pancolitis
Oral

30-40% beyond sigmoid
Enema

40-50% rectosigmoid
Suppository
5-ASA Therapy

• Best choice for mild to moderate disease

• Sulfasalazine
• Asacol (mesalamine)
• Lialda, (once daily mesalamine)
• Pentasa (mesalamine)
• Dipentum (olsalazine)
• Colazal (balsalazide)

• Rowasa (mesalamine)

• Canasa (mesalamine)
Principles of Topical Therapy

- Treats the rectal/colonic mucosa directly

- Best initial choice for active ulcerative proctitis/sigmoiditis
Topical Therapy Considerations

• Topical mesalamine agents are superior to topical steroids or oral 5-ASA alone for left sided disease
• The combination of oral and topical aminosalicylates are more effective than either alone
• In patients refractory to oral aminosalicylates or topical steroids, mesalamine enemas or suppositories may still be effective (not dose dependent)
• Advantages of topical:
  – Quicker response time
  – Less frequent dosing
  – Fewer side effects than oral

Safdi AJG 1997 1867-71
Green Gastro 1998 15-22
Yang AJG 2001 S311-312
Moderate to Severe UC

- Moderate will often respond to oral prednisone (40-60mg/d)
  - More severe may need admission
  - Outpatient management requires careful monitoring
- May begin steroid taper after patient clinically “well” (2-4 weeks)
  - Decrease prednisone by 5mg/wk until reaching 20mg
  - Below 20mg, taper by 2.5mg to 5mg per week
- Flare during taper should prompt increase to lowest level prior to flare
- Inability to complete taper should prompt consideration of immuno-modulators
Moderate to Severe UC

*Immunomodulators*

- May require use of concomitant immunosuppression
- 6-mp/AZA have been shown to be helpful
- No role for methotrexate
Moderate to Severe UC

Anti-TNF Therapy

- If concomitant immuno-suppression ineffective, maximize therapy

- Consider Remicade for persistently active disease
  - 5mg/kg IV infusion 0, 2, 6 weeks, then q8 weeks
  - Same principles apply
Severe Ulcerative Colitis
General Treatment Guidelines

• Admit to hospital
  – 15% require at some point
• IV fluids/steroids
• GI consultation
• Surgical consultation
• Daily KUB/baseline ESR
• Consider clinical trial
Severe Ulcerative Colitis

Steroid Therapy

• Steroids may be administered in continuous or split dose
  – ACTH 120 units/24 hours as continuous infusion
    • If no steroids within previous 30 days
  – Hydrocortisone 100mg q 8 hours
  – Methylprednisolone 16-20mg q 8 hours*
  – Prednisolone 30mg q 12 hours*

• Continue for 7-10 days, as long as improvement continues
  – If no improvement in 5-7 days, consider other therapy

*Less Na retention, K wasting
Severe Ulcerative Colitis

5-ASA Considerations

• No role for NPO (low residue diet)

• If already on 5-ASA products—STOP!!

• However, if not intolerant, concomitant administration of 5-ASA may improve short and long term response rates
  – 90% response rate when started early
  – 71% response without 5-ASA
Severe Ulcerative Colitis

Predicting Need for Second-Line Therapy

• Much of the morbidity/mortality associated with severe UC comes from delayed surgery

• Need to select patients who will benefit from additional therapy early in course of disease

• Two models predicted medical failure, early surgery:
  – Stool frequency >8/day, or 3-8/day with CRP>45mg/dL after 3 days steroid therapy: 85% require colectomy
  – #BM + 0.14 x CRP (mg/L)>8.0 as optimal cut-off to predict medical failure

Fulminant Colitis

• Medical emergency manifested by
  – high fever
  – abdominal tenderness, abdominal distension
  – hemorrhage

• May or may not have colonic distension

• Morbidity increased by delaying surgical therapy
UC-Indications for Surgery

• Immediate
  – Toxicity and/or perforation
  – Exsanguinating hemorrhage

• Urgent
  – Unresponsive severe colitis
  – Severe/acute complications of disease or therapy
    • Opportunistic infections
    • Steroid psychosis
    • Hemolytic anemia

• Elective
  – Suspected cancer
  – Dysplasia
  – Growth retardation
  – Osteonecrosis or compression fracture
  – Intractability
Cancer Risk from UC/Crohn’s Colitis

- Retrospective study of cancer risk from UC
  - 10 years 2%
  - 20 years 8%
  - 30 years 18%

- Extent AND duration of disease predictive factors

Colorectal Cancer in Ulcerative Colitis

Dysplasia

• Surveillance begins after 8 years
  – 33 biopsies required for 90% confidence of finding dysplasia\(^1\)

• Low grade dysplasia associated with synchronous cancer 19%
  – Debate over need for colectomy

• High grade dysplasia definite indication for colectomy

\(^1\) Rubin et al. Gastro 1992;103:1611-1620
Night Call Scenarios

• Referring physician wants to transfer a 58 year old male with long-standing UC, admitted with a severe flare
  – Hospitalized for five days on IV steroids
    • Minimal relief

• What to do first?
Night Call Scenarios

• ER calls with a 27 year old female with several year history of Crohn’s disease
  – Presents with worsening fevers/chills, abdominal pain in RLQ, and diarrhea
    • Started on left-over Enterocort at home
    • No relief

• What to do?