Crohn’s Disease: The First Visit

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University of South Alabama
Mobile, Alabama
Adverse Experiences
*Colombel, SONIC N Engl J Med 2010*

<table>
<thead>
<tr>
<th></th>
<th>Any Adverse Event</th>
<th>Serious Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>89.4%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>89.0%</td>
<td>23.9%</td>
</tr>
<tr>
<td>Combination, both</td>
<td>89.9%</td>
<td>15.1%</td>
</tr>
</tbody>
</table>

*TREAT Registry
Lichtenstein, Am J Gastroenterol 2012*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Infliximab</th>
<th>Infliximab + IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>39.9%</td>
<td>49.4%</td>
<td>46.7%</td>
</tr>
<tr>
<td>Serious infection</td>
<td>3.7%</td>
<td>4.7%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Abscess, sepsis, cellulitis, HSV, pneumonia, fungus

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<th>Placebo</th>
<th>Infliximab</th>
<th>Infliximab + IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>0.4%</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>0.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Breast, colon, prostrate, bladder, lung, renal, melanoma, NMSC
Focus

1. Considerations for when we meet an IBD patient new to us
2. Preparation for possible IS or biologic therapy
3. Subsequent care and monitoring

First Visit Checklist

1. Obtain historical information
2. Assess disease activity
3. Obtain serologic markers
4. Vaccinate
5. Prepare for possible IS and biologic therapy
Biologic Indications

1. Failure

2. Disease location and burden
   Gastroduodenal, anorectal, extensive SB, fistula, perineal, SB only, deep ulcerations, extraintestinal disease

3. Predictors of poor prognosis
   Age <40, smoker, weight loss, high ESR and CRP, polyserologies, steroids first flare, >12m disabling symptoms, hospitalizations, resection
1. History

- Age of onset
- IBD family history
- Smoking
- Pregnancies
- Extraintestinal IBD
- Treatments and surgeries
- Hospitalizations
- Active infection
- Work history
- Quality of life

2. Disease activity

- CDAI  [www.ibdjohn.com/cdai](http://www.ibdjohn.com/cdai)
- Harvey-Bradshaw Index
- Short-form IBDQ
- CBC, CRP, CRP, fecal calprotectin or lactoferrin
- Endoscopic and cross-sectional imaging
Crohn’s Disease Activity Index

<table>
<thead>
<tr>
<th>Clinical or laboratory variable</th>
<th>Weighting factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of liquid or soft stools each day for 7 days</td>
<td>× 2</td>
</tr>
<tr>
<td>Abdominal pain (graded from 0 to 3 based on severity) each day for 7 days</td>
<td>× 5</td>
</tr>
<tr>
<td>General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days</td>
<td>× 7</td>
</tr>
<tr>
<td>Complications*</td>
<td>× 20</td>
</tr>
<tr>
<td>Use of diphenoxylate or opiates for diarrhea</td>
<td>× 30</td>
</tr>
<tr>
<td>An abdominal mass (0 for none; 2 for questionable; 5 for definite)</td>
<td>× 10</td>
</tr>
<tr>
<td>Absolute deviation of hematocrit from 47% in men and 42% in women</td>
<td>× 6</td>
</tr>
<tr>
<td>Percentage deviation from standard weight</td>
<td>× 1</td>
</tr>
</tbody>
</table>

Remission score < 150
Moderate disease 230-400

Harvey-Bradshaw Index

- **General well being**
  0 = very well; 1 = slightly below average; 2 = poor; 3 = very poor; 4 = terrible

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

- **Number of liquid stools per day**
  0 = 0–1 stools; 1 = 2–3 stools; 2 = 4–5 stools; 3 = 6–7 stools; 4 = 8–9 stools; 5 = 10+ stools

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

- **Complications**
  Arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissures, new fistulas, abscesses (1 point for each)

- **Total score**

Remission HBI score < 3
Relapse HBI score > 7
**Mayo Scoring System**
**Ulcerative Colitis**

<table>
<thead>
<tr>
<th>Component</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency*</td>
<td>Normal # of stools for the patient</td>
<td>1-2 stools more than normal</td>
<td>3-4 stools more than normal</td>
<td>≥5 stools more than normal</td>
</tr>
<tr>
<td>Rectal bleeding†</td>
<td>No blood seen</td>
<td>Streaks of blood with stool &lt; half the time</td>
<td>Obvious blood with stool most of the time</td>
<td>Blood alone passed</td>
</tr>
<tr>
<td>Endoscopy findings</td>
<td>Normal or inactive disease</td>
<td>Mild disease</td>
<td>Moderate disease</td>
<td>Severe disease</td>
</tr>
<tr>
<td>PGA‡</td>
<td>Normal</td>
<td>Mild disease</td>
<td>Moderate disease</td>
<td>Severe disease</td>
</tr>
</tbody>
</table>

*PGA: Physician’s Global Assessment  

### 3. IBD Serologies

<table>
<thead>
<tr>
<th>Test</th>
<th>Specificity</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>pANCA</td>
<td>Perinuclear antineutrophil cytoplasmic</td>
<td>Distal colitis</td>
</tr>
<tr>
<td>ASCA</td>
<td>Saccharomyces cerevisiae</td>
<td>FS, IP Need for surgery</td>
</tr>
<tr>
<td>OmpC</td>
<td>Outer membrane porin protein C to <em>E. coli</em></td>
<td>FS, IP Need for surgery</td>
</tr>
<tr>
<td>I2</td>
<td>CD-related bacterial sequence</td>
<td>FS SB Disease, Need for surgery</td>
</tr>
<tr>
<td>Cbir1</td>
<td>Flagellin</td>
<td>FS, IP Pouchitis</td>
</tr>
<tr>
<td>NOD2</td>
<td>Nucleotide-binding oligomerization domain 2</td>
<td>FS SB Disease</td>
</tr>
</tbody>
</table>

FS- Fibrostenosing, IP- Internal penetration
Immunosuppressants including steroids, thiopurines and biologics increase the risk of infections, several preventable by vaccination

*Wasan and Farraye, Am J Gastroenterol 2010*

Who’s immunosuppressed?

- Glucocorticoids (Prednisone >20mg daily for 14 days)*
- Immunosuppressives (Azathioprine, 6MP, methotrexate)*
- Biologics*
- Significant protein calorie malnutrition

*Currently or in the last 3 months

*Sands, Inflamm Bowel Dis 2009*
## 4. Vaccinate

<table>
<thead>
<tr>
<th>Inactivated Vaccines</th>
<th>Active Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Influenza (intranasal)</td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)</td>
<td>Varicella</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>Zoster</td>
</tr>
<tr>
<td>Pneumococcal (polysaccharide) vaccine</td>
<td>Mumps. Measles, Rubella (MMR)</td>
</tr>
<tr>
<td>Meningococcal vaccine</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
</tr>
</tbody>
</table>
HBV and Immunosuppressants

- Reactivation common
- Liver dysfunction more frequent and severe

**Recommendations:**

- HBsAg-positive- Anti-viral prophylaxis
- Vaccinate IBD
- Low response; Confirm serology
- Inadequate response- second full series

_Gisbert, APT 2011_

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Human Papilloma Virus

- Increased risk in IBD, worse with IS
- Vaginal HPV, anal HPV, cervical dysplasia

**Recommendations:**

- PAP before immunosuppressants
- Vaccinate females and males <26, including genital warts, abnormal PAP or HPV DNA- positive

_Melhmad, Inflamm Bowel Dis 2009_
Varicella Zoster

- Incidence of zoster higher in IBD
- Live vaccine cautioned to give 1-3 months before immunosuppressants
- May not be contraindicated in short-term steroids, low dose methotrexate or thiopurines
- Some data suggests safety with biologics
- Not contraindicated for household contacts, but avoid localized rash

*Wasan, Am J Gastroenterol 2010*

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Tetanus, diphtheria, pertussis

- Inactivated vaccine
- Td every 10 years; Tdap at least once
Vaccination Outcomes  
Abdallah, DDW 2014

- **Design:**
  Determine influenza and pneumococcal vaccine outcomes

- **Methods:**
  “Explorys” database which integrates patient data from 14 healthcare systems comprising 40 millions patients IBD patients between 1999 and 2012

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### Vaccination Outcomes

<table>
<thead>
<tr>
<th>Respiratory Infections</th>
<th>Vaccinated IBD</th>
<th>Non-vacc IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Influenza</td>
<td>Pneumococal</td>
</tr>
<tr>
<td><strong>Influenza/cold</strong></td>
<td>0.03%</td>
<td>0.02%</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td>0.07%</td>
<td>0.16%</td>
</tr>
</tbody>
</table>

- 26.1 million adults
- 107,750 IBD
- 20.7% received influenza and 3.6% pneumococcus
5. Prepare

- CXR
- PPD or Interferon gamma assay (IGRA) quantiFERON gold
- Thiopurine methyltransferase (TPMT)
- Lipase
- B12, iron, vitamin D
- GYN PAP HPV

Tuberculosis

- TNF plays a role in granulomas
- Anti-TNF, thus, interferes with maintenance of latent tbc
- In low incidence countries, tbc 10 fold expected risk
- Case fatality rate 18%

  Keane, N Engl J Med 2001

- PPD conversion rate 22%
- PPD + 37%, IGRA 16%
**Tuberculosis**

- Tuberculin skin test or highly specific whole blood assay (QuantiFeron)
- Chest XRay
- Latent tbc:
  - Isoniazide for 9 months
  - Delay anti-TNF for 2 months

*Targownik, Am J Gastroenterol 2013*
TPMT

- 88% normal homozygous for high enzyme activity
- 11% heterozygous intermediate, require much lower dosage
- 0.3% no enzymatic activity, high risk
- In a Canadian study despite normal TMPT, 5% of 216 developed leukopenia, thus, follow CBC

Chisick, DDW 2012

First Visit Checklist

1. Obtain historical information
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4. Vaccinate
5. Prepare for possible IS and biologic therapy
The Subsequent Visit

1. Clinical status assessment
2. Vaccinations
3. Health maintenance
4. Surveillance

1. Clinical Status Assessment

- Symptoms, CDAI, HBI, IBDQ
- Weight loss
- Complications, hospitalizations, surgeries, work history, quality of life
- Extraintestinal manifestations (eye, skin, joint)
2. Vaccinations
- First visit vaccinations completed
- Subsequent vaccines:
  - Influenza annual
  - Td/Tdap every 10 years
  - Pneumococcal one time revaccination
  - HAV booster at 10 years

3. Health Maintenance
- Annual GYN
- Assess smoking status
- Annual PPD and CXR
- Metabolic bone disease screening (vitamin D and bone density)
- Depression screening
Metabolic Bone Disease

- **Risks:**
  - IBD
  - Steroids
  - Malabsorption

- **Recommendations:**
  - Measure 5-hydroxy-vitamin D
  - Bone density

Vitamin D

- Higher vitamin D correlates with reduced risk of Crohn’s Disease
- Vitamin D <20 associated with higher CRP, hospitalizations and need for surgery
- Restoration of normal D lessens risks of surgery and hospitalizations
  - Annanthakrishnan, DDW 2013
- Low vitamin D associated with cancer risk
  - Annanthakrishnan, Clin Gastro Hepatol 2014
Health Maintenance

- **Smoking** increases:
  - disease activity,
  - severity of disease,
  - frequency of flares,
  - dependence on steroids and immunomodulators
  - venocclusive disease

  Aldhous, Frontline Gastro 2010

- **Depression**
  - 35%
  - Increased with relapses, steroids

Depression Screen

**Effective screening questions:**

1. “Over the past month, have you felt down, depressed or hopeless”
2. “Over the past month, have you felt little interest or pleasure in doing things?”
4. Surveillance

- Skin exam
- Ophthalmology
- Colon dysplasia screening
Skin Cancer

- US risk of melanoma is 20.8/100,000
- Immunosuppressants increase:
  - melanoma risk 3-4 fold
  - non-melanoma skin cancer
  - squamous cancer risk 65-250 times

Recommendations:
Pre-treatment and annual Derm exam

*Long, Gastroenterology 2012*

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EYE

- *Extraintestinal manifestations*
  - Uveitis
  - Panophthalmitis
  - Episcleritis

- *Drug effects*
  - Cataracts
  - Glaucoma
Chromoendoscopy

Cancer risk in IBD 2X general population
Duration of disease
1% at 10 years 3% at 20 years 7% at >20 years

Kiesslich, Gastroenterology 2003
Soetikno, Gastroenterology 2013

Concentration of Indigo Carmine used in patients with IBD

<table>
<thead>
<tr>
<th>Purpose of IEE</th>
<th>Mixture</th>
<th>Depth of blue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection</td>
<td>2 Ampules with 250cc of water</td>
<td></td>
</tr>
<tr>
<td>Detailed viewing</td>
<td>1 Ampule with 25cc of water</td>
<td></td>
</tr>
<tr>
<td>Submucosal injection</td>
<td>10 Drops with 100cc of saline</td>
<td></td>
</tr>
</tbody>
</table>
Drug Monitoring

- **ASA**  Periodic renal function
- **Steroids**  Vitamin D, bone density, glucose, CXR, OPTO
- **Thiopurines**  CBC, LFTs
- **Methotrexate**  CBC, LFTs renal function
- **Anti-TNF**  CXR, PPD, vaccines, Derm, PAP, CBC, LFTs
- **Anti-integrins**  JCV q6 months (natalizumab)

Renal Toxicity of Aminosalicylates

- Interstitial nephritis
- Non-specific idiosyncratic reaction
- 46 case reports
- In first 12 months

**Recommendations:**

Avoid ASA in renal disease or advanced diabetes and hypertension

*Katz, Gastroenterology 2007*

*So, DDW 2013*
Hepatic Abnormalities with Immunosuppressants

- FDA Adverse Event Registry System (FAERS)
- 245 hepatic injuries in 142 patients
- Chronic hepatitis in 84 (34%)

**Recommendations:**
Monitor LFTs

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**First Visit Checklist**

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Drug Monitoring

- **ASA** Periodic renal function
- **Steroids** Vitamin D, bone density, glucose, CXR, OPTO
- **Thiopurines** CBC, LFTs
- **Methotrexate** CBC, LFTs renal function
- **Anti-TNF** CXR, PPD, vaccines, Derm, PAP, CBC, LFTs
- **Anti-integrins** JCV q6 months (natalizumab)
Tools
### Checklist for IBD Visits

1. **Clinical Status Assessment**
   - HBI: __________
   - Mayo Score: __________
   - Weight Loss: __________
   - Extraintestinal Dz: __________

2. **Vaccine Preventable Illness**
   - Vaccine Status (date):
     - HAV: _______
     - Influenza: _______
     - Tdap: _______
     - HPV: _______
     - Pneumococcus: _______
     - HBV: _______
     - Meningitis: _______
     - Zoster: _______

3. **Health Maintenance (last date)**
   - PPD: _______
   - GYN: _______
   - Bone Density: _______
   - B12: _______
   - Vitamin D: _______
   - Smoking Cessation discussed: _______
   - Depression Screening: _______

4. **Surveillance**
   - Skin exam, Dermatology referral: _______
   - Ophthalmology referral: _______
   - Dysplasia Screening: _______

5. **Drug Monitoring (last date)**
   - Aminosalicylates: _______
   - CBC, Cr baseline, 1month, periodically: _______
   - Steroids: _______
   - Electrolytes, glucose, CXR, bone density, OPTO: _______
   - Thiopurines: _______
   - TPMT, CBC, LFTs baseline; monitor CBC, LFT: _______
   - Methotrexate: _______
   - CBC, LFT, Cr baseline; monitor CBC, LFT: _______
   - Anti TNFs: _______
   - Baseline TB testing, HBV; monitor CBC, LFT: _______
   - Natalizumab: _______
   - Baseline JCV antibody and monitor q6m: _______

### Quality Indicators for IBD

1. Avoid long-term steroids
2. Tbc testing before anti-TNF
3. CDI testing during flares
4. ASA in mild ulcerative colitis
5. Colectomy in ulcerative colitis
6. Smoking cessation in Crohn’s Disease
7. Vaccinate influenza
8. TPMT before thiopurines
9. Exclude CMV and surgery consult in hospitalized UC
10. Cancer surveillance in longstanding colitis

*Melmed, ACG 2011*
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