IBD Module 2: Medication and Patient Management

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Objectives

- Describe current treatment guidelines and practices for managing inflammatory bowel disease (IBD)
- Describe the pharmacology of medication interventions for Crohn’s Disease and Ulcerative Colitis (UC) delineating side effects and relevant drug interactions
- Discuss treatment appropriateness and medication toxicity, including lab values and clinical presentation
- Recognize monitoring tools for disease state progression
- Outline potential special needs/social issues impacting patient’s with IBD
- Discuss the importance of working effectively in collaborative teams to provide patient education and ongoing support to improve access and adherence to therapy
Guidelines

American College of Gastroenterology
– Management of Crohn’s Disease in Adults (2009)
– Ulcerative Colitis in Adults (2010)
– Preventative Care in Inflammatory Bowel Disease (2017)

World Gastroenterology Organisation Global Guidelines
– Inflammatory Bowel Disease (2015)

Guidelines

American Gastroenterology Association
– Drug Therapy for Crohn’s (2014)
– Crohn’s and UC Clinical Care Pathway
– Management of Crohn’s Disease After Surgery Algorithm
– Therapeutic Drug Monitoring (expected summer 2017)
Treatment Goals

• Induction and maintenance
  – Clinical symptoms and improve quality of life
  – Mucosal healing
    • Visually via endoscopy
    • Histologic healing
  – Reduce need for long term corticosteroids, hospital admissions, disease complications, and risk of colon cancer

Assessing the patient

• Ensure cause of symptoms is IBD activity

• Assess symptoms and severity of disease activity
  – review labs
  – clinical symptoms
  – imaging if available
  – colonoscopy if available
Monitoring Efficacy of IBD Therapy

- Evaluate inflammatory markers
  - CRP/hs-CRP, fecal calprotectin, platelets
- Evaluate for anemia
- Trend weight
- Improvement on endoscopy or other imaging
- Evaluate drug toxicity
- Clinical symptom resolution
  - GI related and extraintestinal
- Improved IBD Activity Scores

Treat to Target

1. Active Disease
2. Treatment
3. Add/switch drug and optimize current therapy
4. Target
   - No Mucosal Ulcers
   - Inflammatory markers not elevated
   - No Symptoms
5. Yes
   - 1.2 years
6. No
   - 6 months
   - Continue treatment

Bouguen G et al. CGH 2014.
Benefits of Treat to Target

- Correlate with long term outcomes
  - Surgery, corticosteroid use, hospitalizations, complications, structural damage
- Achievable, feasible
- Cost-effective
- Important to patients
  - Control of symptoms, normalization of function, social participation.

Treatment Plan

Treat alternative causes if related

Adjust modifiable factors
- Discontinue NSAID use
- Encourage smoking cessation

Drugs!!!
Drug Treatment Options

Corticosteroids
Aminosalicylates
Immunomodulators
  – Thiopurines, methotrexate, mycophenolate, cyclosporine, tacrolimus
Biologics
  – Infliximab, adalimumab, certolizumab, golimumab, vedolizumab, natalizumab, ustekinumab
Antibiotics

Corticosteroids

• Used for **induction** of remission
• **Not** recommended for long-term maintenance therapy
• Monitor for acute and chronic adverse effects
• Advance therapy if steroid dependent
• Available in multiple dosage forms
  – Oral, rectal foam, rectal enema, rectal suppository
# Corticosteroids

<table>
<thead>
<tr>
<th><strong>Drugs</strong></th>
<th>Prednisone, Prednisolone, Methylprednisolone, hydrocortisone, Budesonide (Entocort, Uceris)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Anti-inflammatory and immunosuppressive</td>
</tr>
<tr>
<td><strong>Common Adverse Effects</strong></td>
<td>Sleep and mood disturbance, risk of infection, edema, osteoporosis, increased appetite, weight gain, glucose intolerance, hypertension</td>
</tr>
<tr>
<td><strong>Severe Adverse Effects</strong></td>
<td>Adrenal suppression with long term use, Cushing’s syndrome, proximal myopathy, glaucoma, impaired wound healing, growth retardation, psychotic disorder</td>
</tr>
<tr>
<td><strong>Common Drug Interactions</strong></td>
<td>NSAIDs → risk of GI upset and ulcers</td>
</tr>
</tbody>
</table>

## Corticosteroid Monitoring

- Blood pressure
- Electrolytes
- Blood glucose
- Bone mineral density
- Weight
- Intraocular pressure (>6 weeks)
- Tolerability
Budesonide

- High first pass effect, only 9-21% bioavailable
- Less systemic absorption
- Less adverse drug reactions vs. systemic corticosteroids

**Site of Action**

Entocort: releases from ileum to ascending colon

Uceris: releases in the colon

Aminosalicylates (5-ASA)

- Used for induction and maintenance
- Used in mild to moderate Ulcerative Colitis or mild Crohn’s colitis
- Various formulations and release sites
  - Suppositories for proctitis
  - Enemas for distal colitis
- Topical + Oral > Oral or Topical monotherapy
- Higher doses for induction
## 5-ASA Formulations

<table>
<thead>
<tr>
<th>Stomach</th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentasa®</td>
<td>Lialda®</td>
<td>balsalazide</td>
<td>balsalazide, olsalazine, sulfasalazine, Apriso®</td>
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</table>

## 5-ASA

<table>
<thead>
<tr>
<th><strong>Drugs</strong></th>
<th>Sulfasalazine, Olsalazine, Balsalazide, Mesalamine (Apriso, Asacol HD, Delzicol, Lialda, Pentasa, Rowasa, Canasa)</th>
</tr>
</thead>
</table>
| **Mechanism** | Unknown  
- Modulator of local chemical mediators  
- Free radical scavenger  
- Inhibitor of tumor necrosis factor (TNF) |
| **Common Adverse Effects** | Headache, diarrhea |
| **Severe and/or Less Common Adverse Effects** | Interstitial nephritis, rash, pancreatitis (<1%), cholestatic hepatitis (<3%), pericarditis |
5-ASA Monitoring

- Renal function
- CBC
- Adverse effects

Sulfasalazine Adverse Effects

**Adverse Effects:** anorexia, dyspepsia, neutropenia, reversible male infertility, agranulocytosis
  
  Anemia → reduced folate absorption, administer with folic acid 1 mg PO q day

**Dose-related toxicities:** nausea, vomiting, diarrhea, headache, arthralgia

**Idiosyncratic reactions:** hepatotoxicity, bone marrow suppression, pancreatitis, pneumonitis, interstitial nephritis
Immunomodulators

- Thiopurines
  - azathioprine and 6-mercaptopurine
- Methotrexate
- Mycophenolate
### Immunomodulators

- Used of maintenance of remission  
  – onset 2-3 months
- Initiated in corticosteroid dependent patients
- Can be added to 5-ASAs or biologics

### Thiopurines

| Drugs & Therapeutic Dose | Azathioprine (Imuran): 2-2.5 mg/kg/day  
6-Mercaptopurine (6-MP, Purinethol): 1-1.5 mg/kg/day |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Inhibits purine nucleotide synthesis and metabolism. Inhibits cell-mediated immunity and suppress T-cell more than B-cell activity.</td>
</tr>
<tr>
<td>Dose-Related Adverse Effects</td>
<td>Nausea, vomiting, malaise, infection, hepatitis, myelosuppression, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Idiosyncratic Adverse Effects</td>
<td>Pancreatitis, fever, rash, arthralgia</td>
</tr>
<tr>
<td>Uncommon Adverse Effects</td>
<td>Non-melanoma skin cancer, lymphoma</td>
</tr>
</tbody>
</table>
## Thiopurines

| Drug Interactions | ACE Inhibitors → increased risk of neutropenia or leukopenia  
|                   | Warfarin → may decrease INR  
|                   | Xanthine oxidase inhibitors → increase risk of myelosuppression  
|                   | • Can use this to obtain therapeutic drug levels |

| Monitoring Drug Toxicity | Thiopurine Methyltransferase (TPMT) prior to therapy  
|                         | CBC & LFTs q 2-4 weeks initially, then every 2-3 months thereafter  
|                         | Thiopurine levels throughout therapy  
|                         | • 6-thioguanine nucleotide (6-TGN)  
|                         | • 6-methyl-mercaptopurine nucleotide (6-MMP) |

### Thiopurine Metabolism

![Thiopurine Metabolism Diagram](image)

1) EFFECTIVE METABOLITE  
2) LEUKOPENIA

- 6-thiouric acid  
- ALLOPURINOL  
- XO  
- AZA  
- 6-MP  
- HPRT  
- IMPDH  
- 6-thioguanine nucleotides  
- 6-thioguanine  
- 5-monophosphate  
- 6-thiopurine  
- 6-MP  
- 6-MP  
- TPMT  
- ELEVATED LIVER TESTS  
- Purine synthesis

<table>
<thead>
<tr>
<th><strong>Methotrexate (MTX)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical Dose</strong></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
<tr>
<td><strong>Common Adverse Effects</strong></td>
</tr>
<tr>
<td><strong>Severe Adverse Effects</strong></td>
</tr>
</tbody>
</table>
| **Drug Interactions** | • Sulfamethoxazole → risk of MTX toxicity due to synergistic anti-folate effects, decreased MTX clearance, & protein binding displacement  
• Warfarin → may increase INR  
• Penicillins → risk of MTX toxicity due to decreased MTX clearance |
| **Pregnancy** | • Highly teratogenic, contraindicated  
• Avoid pregnancy for at least 1 ovulatory cycle after discontinuation  
• Men – may reversible increase risk of infertility  
• Use not recommended during breastfeeding |
| **Drug Toxicity Monitoring** | CBC, renal function, LFTs at baseline and monthly initially, then every 2-3 months thereafter  
CXR & PFTs at baseline, then periodically (consider) |
Biologic Therapies

**Anti-TNF agents**
- Infliximab (Remicade)
- Adalimumab (Humira)
- Certolizumab (Cimzia)
- Golimumab (Simponi)

**Anti-α4-integrin**
- Natalizumab (Tysabri)
- Vedolizumab (Entyvio)

**Anti-IL 12, IL23**
- Ustekinumab (Stelara)

Anti-TNFα Agents

**Anti-TNFα Therapies**

**Anti-TNFα agents**
- Infliximab (Remicade)
- Adalimumab (Humira)
- Certolizumab (Cimzia)
- Golimumab (Simponi)

Binds and clears soluble TNF.
Binds cell-bound TNF and induces apoptosis of cells expressing membrane TNF.
anti-TNF agents reduce inflammatory infiltrate, but do not block underlying pathogenic triggers.

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**Feldman, M et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 2010.**

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**Anti-TNFα Therapies**

| Infliximab (Remicade®) | Infusion only  
| Load: 5-10 mg/kg on weeks 0, 2, 6  
| Maintenance: 5-10 mg/kg q 8 weeks |  
| Adalimumab (Humira®) | Prefilled syringe and pen  
| Load 4 pens (160 mg) on week 0, then 2 pens (80 mg) on week 2  
| Maintenance is 40 mg q 2 weeks |  
| Certolizumab (Cimzia ®) Crohn's only | Prefilled syringes or Lyophilized vial for SQ  
| Load (2 syringes) 400 mg on week 0, 2, and 4  
| Maintenance 400 mg q 4 weeks |  
| Golimumab (Simponi®) UC only | Prefilled syringe, pen, and solution for IV  
| Load 200 mg on week 0, then 100 mg on week 2  
| Maintenance 100 mg q 4 weeks |
Anti-TNFα Therapies

<table>
<thead>
<tr>
<th>Common Adverse Effects</th>
<th>Injection site reaction, upper respiratory infection, headache, reactivation of hepatitis B or TB, hepatotoxicity (autoimmune) demyelinating disease, infusion reaction, lupus-like reaction (rare), increased mortality in NYHA Class III/IV HF, lymphoma (unclear), non-melanoma skin cancer (unclear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Adverse Effects</td>
<td></td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Live vaccines</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>Days to week</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Obtain Hepatitis B serology and TB test prior to initiation Drug levels and antibody, signs/symptoms of infection</td>
</tr>
</tbody>
</table>

Anti-TNFα Non-Responders

- **Primary non-responders**
  - Anti-TNFα mechanism not involved
  - Change to different drug class

- **Secondary non-responders**
  - Adherence
  - Drug-Ab formation
  - Increased clearance
  - Anti-TNFα mechanism involved, stay in class
Immunogenicity

Infliximab (Remicade®): 51% after 1 year
  • Appears to be less with higher doses (36%)
Adalimumab (Humira®): 28%
  • Less if given with methotrexate (down to 6%)
Golimumab (Simponi®): 4-7%
  • Less if given with immunomodulators (down to 2%)
Certolizumab (Cimzia®): 11%
  • Less if concomitant immunosuppressant (down to 3%)


Immunogenicity

Prevention
  Limit gaps between therapy
  Consider higher doses in ill IBD patients
Combination therapy
  • Azathioprine
  • Mercaptopurine
  • Methotrexate
### Infliximab, Azathioprine, or Combination Therapy for Crohn’s Disease

#### Objective:
Compare efficacy of azathioprine, infliximab, and combination therapy for induction and maintaining steroid-free remission in patients with moderate to severe Crohn’s disease.

#### Design:
Randomized, double-blind, multicenter trial.

#### Intervention:
| n=508 | Azathioprine 2.5 mg/kg/day (n=170) | Infliximab 5mg/kg 0, 2, 6, q 8 weeks (n=169) | Combination therapy (n=169) *Blood samples collected for presence of antibodies |

#### Primary End Point:
Rate of corticosteroid-free clinical remission after 26 weeks.

#### Secondary End Points:
Mucosal healing in patients with ulcers after 26 weeks.

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### Results:

<table>
<thead>
<tr>
<th>Steroid-free remission at 26 weeks</th>
<th>Azathioprine 30%</th>
<th>Infliximab monotherapy 44.4%</th>
<th>Combination therapy 56%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal healing at 26 weeks in patients with ulcers</td>
<td>Azathioprine 16.5%</td>
<td>Infliximab monotherapy 30.1%</td>
<td>Combination therapy 43.9%</td>
</tr>
<tr>
<td>Antibodies to infliximab</td>
<td>Infliximab 14.6%</td>
<td>Combination 0.9%</td>
<td></td>
</tr>
<tr>
<td>Infliximab trough at week 30</td>
<td>Infliximab 1.6 mcg/mL</td>
<td>Combination 3.5 mcg/mL</td>
<td></td>
</tr>
</tbody>
</table>

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Colombel, J.F., et. al., 2010, NEJM
Anti-α4 Integrin inhibitors

**Anti-α4-integrin**
- **Natalizumab (Tysabri)**
  α4β7, α4β1
- **Vedolizumab (Entyvio)**
  α4β7

Humanized monoclonal antibody against α4 integrin. Inhibits leukocyte adhesion and migration into inflamed tissue.


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**Anti-α4 Integrin inhibitors**

- α4β1 & α4β7 integrins on T cells interact with vascular cell adhesion molecule-1 (VCAM-1) & Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM1) receptors.
  - α4β1 role in CNS lymphocyte trafficking
  - Critical for prevention of John Cunningham (JC virus) infection in brain.
- **Natalizumab**: anti-μ4, risk PML, REMs (TOUCH)
- **Vedolizumab**: μ4β7/MAdCAM-1 binding
Anti-α4 Integrin inhibitors

| Vedolizumab (Entyvio®) | Infusion only  
Load: 300 mg on weeks 0, 2, 6  
Maintenance: 300 mg q 8 weeks |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Interactions</td>
<td>Cautions with live vaccines, weigh benefits TNFα inhibitors</td>
</tr>
<tr>
<td>Common Adverse Effects</td>
<td>Nausea, arthralgia, headache, fatigue, upper respiratory infections</td>
</tr>
<tr>
<td>Severe Adverse Effects</td>
<td>Anaphylaxis, sepsis, infusion reaction, hepatitis, tuberculosis</td>
</tr>
<tr>
<td>Onset of action</td>
<td>3-6 Months</td>
</tr>
</tbody>
</table>
| Monitoring              | Obtain Hepatitis B serology and TB test prior to initiation  
Signs and symptoms of PML, signs of infection |

IL-12 & IL-23 Antagonist

**Ustekinumab (Stelara)**

IgG1 monoclonal Ab, binds p40 subunit common to cytokines IL12 and IL23. These cytokines signal through JAK/STAT to regulate immune response

JAKs play a role in innate and adaptive immunity. Blocking JAKs modulates the immune response, therefore may plan a role in controlling inflammation in IBD
### IL-12 & IL-23 Antagonist

<table>
<thead>
<tr>
<th><strong>Ustekinumab (Stelara®)</strong></th>
<th>Infusion and prefilled syringe – Crohn’s only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Load:</strong></td>
<td>55kg or less 260 mg IV on weeks 0</td>
</tr>
<tr>
<td></td>
<td>55-85 kg 390 mg IV on week 0</td>
</tr>
<tr>
<td></td>
<td>&gt;85kg 520 mg IV on week 0</td>
</tr>
<tr>
<td><strong>Maintenance:</strong></td>
<td>90 mg q 8 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Drug Interactions</strong></th>
<th>live vaccines</th>
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<tr>
<td><strong>Common Adverse Effects</strong></td>
<td>Injection site reaction, headache, fatigue, upper respiratory infections, urinary tract infection</td>
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<tr>
<td><strong>Severe Adverse Effects</strong></td>
<td>Anaphylaxis, posterior reversible encephalopathy (rare), non-melanoma skin cancer (up to 1.5%), serious infection</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>Weeks to months</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Obtain Hepatitis B serology and TB test prior to initiation</td>
</tr>
<tr>
<td></td>
<td>Signs and symptoms of infection or adverse reactions</td>
</tr>
</tbody>
</table>

### Thiopurine Drug Levels

![Thiopurine Drug Levels](image)

### Drug Trough Assay

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trough</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>5-10</td>
<td>ARUP, Labcorp, Mayo, Miraca, Prometheus</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5-10</td>
<td>ARUP, Labcorp, Mayo, Miraca, Prometheus</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>15*</td>
<td>Miraca</td>
</tr>
<tr>
<td>Golimumab</td>
<td>unknown</td>
<td>Labcorp in 2017?</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>&gt;12*</td>
<td>Miraca, Prometheus, Labcorp in 2017?</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>unknown</td>
<td>Miraca</td>
</tr>
</tbody>
</table>

*More Data Needed, ACG abstracts 2016

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### Anti-TNFα Trough Levels and Mucosal Healing

- Retrospective study, 145 patients: Median trough levels higher in patients with mucosal healing
  - Mucosal healing associated with:
    - Infliximab $> 5.1 \mu g/mL$
    - Adalimumab $> 7.1 \mu g/mL$
    - 85% specificity for mucosal healing
  - Antibodies + infliximab trough $> 3 \mu g/mL$, associated with lower mucosal healing


Biologic Drug Monitoring Concerns

• Not all tests are equal
• Cost
• What to do with the results
  – BRIDGe (Building Research in IBD Globally)
• When to test – timing and frequency

Antibiotics

• Perianal Crohn’s disease
• Fistula
• Pouchitis – inflammation of the pouch created after colectomy in UC
• Metronidazole +/- ciprofloxacin
• Rifaximin
• Augmentin?
• CAUTION: C diff infection
Potential Patient Needs & Impacting Issues

- Patient assistance for medications, visits, labs, and endoscopy
- Assess and support for sexual dysfunction
- Coping skills
- Social participation limits
- Family support and impact
- Post operative complications
- Ostomy issues

Organizations and Resources

Crohn’s Colitis Foundation of America (CCFA)

You and IBD
youandibd.com
IBD Team

Provider – MD, NP, PA
Pharmacist and pharmacy technicians
Social worker and psychologist
IBD nurse
Ostomy and wound nurse
Dietitian
Medical Assistants
Drug programs with nurses
Infusion centers and home health