Crohn’s Disease

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@IBDMD
Disclosures
(Last 24 months)
• Consultant and Grant Support:
  – Abbvie
  – Amgen
  – Cellgene
  – Janssen
  – Pfizer
  – Prometheus
  – Takeda
  – UCB
Learning Objectives

At the conclusion of this presentation, participants will:

• Recognize the common presentation and progression of Crohn’s disease

• Understand the appropriate treatment options for Crohn’s disease.

• Appreciate the emerging Treat to Target approach to management
Phenotypic Classification of IBD

**Ulcerative Colitis**
Confined to the colon

**Crohn’s Disease**
Any portion of the GI tract

**Frequency of Involvement**
Most
Least
## Clinical Features of IBD: UC vs CD

<table>
<thead>
<tr>
<th>Feature</th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Occasional</td>
<td>Common</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Varies</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Very common</td>
<td>Fairly common</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>Very common</td>
<td>Fairly common</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Fairly common</td>
<td>Common</td>
</tr>
<tr>
<td>Signs of malnutrition</td>
<td>Fairly common</td>
<td>Common</td>
</tr>
<tr>
<td>Perianal disease (skin tags or fistulae)</td>
<td>Absent</td>
<td>Fairly common</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>Absent</td>
<td>May occur</td>
</tr>
<tr>
<td>Growth failure in children/adolescents</td>
<td>Occasional</td>
<td>Common</td>
</tr>
</tbody>
</table>

IBD Today

• More than 1.6 million cases estimated in the United States
  • Ulcerative colitis (UC): 50%
  • Crohn’s disease (CD): 50%
• Frequently young at diagnosis (ages 15-30)
• Most IBD patients do not have a family history
• Affects all ethnicities
  – Most IBD patients are not Jewish
  – Intriguing group of first generation Americans affected

Centers for Disease Control and Prevention. (May 2, 2014) http://www.cdc.gov/ibd
Inflammatory Bowel Disease is now a Global Disease

Incidence & Prevalence of IBD

Before 1960

1980-2006

Temporal Trends of Incidence Rates for Epidemiology of IBD (>10 years)

A  Crohn’s Disease

B  Ulcerative Colitis

New Population of IBD: the elderly patient!

• New onset IBD in those over 60 years old
• Long-standing IBD in those who get older
• Generally milder disease
• Increased risks of therapy-related adverse events in this population

Potential Explanations for Rising IBD Incidence Around the World

• Observational bias
• Hygiene hypothesis
• Infection
• “Westernized” dietary changes
• “Microbiome hypothesis”
The Natural Course of CD

- Health
- Subclinical Inflammation
- Symptomatic Inflammation
- Complications
- Disability
- Death

Cure
Treatment to Stop Progressive Damage in Crohn’s Disease

Treatment to Stop Progressive Damage in Crohn’s Disease

Digestive damage vs. Inflammatory activity

Disease onset, Diagnosis, Early disease

Understanding Prognosis in CD: Which Patients Are at Risk for Worst Outcomes?

- >2 surgeries
- >2 hospitalizations
- Need for rapid induction (eg, hospitalized)
- Intolerance to standard immune modulators (thiopurines, MTX)
- Significant perianal disease
- Significant duodenal disease
- Pyoderma gangrenosum
- Deep ulcers
- Young age of diagnosis
- Smokers

MTX = methotrexate.
Treating Crohn’s Disease
Medical Treatment Options for Patients With CD

- Aminosalicylates
  - Mesalamine
  - Sulfasalazine
- Corticosteroids
  - Budesonide
  - Systemic
- Thiopurines
  - AZA
  - 6-MP
- MTX
- Biologics
  - TNF-α inhibitors
    - Infliximab
    - Adalimumab
    - Certolizumab pegol
  - Anti-integrins
    - Natalizumab
    - Vedolizumab

Mesalamine Maintenance of Remission in Crohn’s Disease

Don’t let comfort with safety affect your interpretation of the efficacy!
If you choose to use 5-ASA in MILD Crohn’s, be sure to monitor for true effect.
Steroids
NCCDS: Response to Therapy for Crohn’s Disease Remission Maintenance

Months After Randomization

- Prednisone 1/4 mg/kg (20 mg)
- Sulfasalazine 1/2 g/kg (2.5 g)
- Azathioprine 1 mg/kg (75 mg)
- Placebo

Not significant

What Is Steroid Dependence?

- Inability to successfully liberate from corticosteroids and remain in symptomatic (clinical) remission within 30 days
- Inability to avoid *needing* corticosteroids for at least 90 days
  - What does it mean to need steroids?
    - Your need? Or your patient’s need?
    - Don’t confuse steroid withdrawal side effects with need for the bowel!
Remission Rates in Acute Crohn’s: Studies With Budesonide CIR

- Bud CIR 9 mg QD
- Bud CIR 4.5 mg BID*
- Placebo BID
- Mesalamine 2g BID
- Prednisolone 40 mg

*NS vs placebo

Source:
Bone mineral density in relation to budesonide and prednisolone in patients with Crohn’s disease

Choice of first steroid is very important!

Corticosteroids: Short- and Long-Term Efficacy in Crohn’s Disease

### 30-day responses (n=74)
- **Complete response**: 58% (n=43)
- **Partial response**: 26% (n=19)
- **None**: 16% (n=12)

### 1-year responses (n=74)*
- **Prolonged response**: 28% (n=21)
- **Steroid dependent**: 32% (n=24)
- **Surgery**: 38% (n=28)

*1 patient lost to follow-up

Thiopurines

- Azathiporine, 6-MP
- Metabolized by TPMT enzyme
  - If TPMT normal/high activity, titrating dose not needed
- Weight-based dosing usually used
  - AZA 2.5-3.0 mg/kg/d
  - 6-MP 1.5 mg/kg/d
- Metabolite assessment can aid monitoring and understanding of lack of response
  - When used as concomitant therapy, 6-TGn ≥ 125 pmol/8 x 108 RBCs best

Retrospective Correlation of 6-TGN Level to Clinical Response*

*92 pediatric IBD patients receiving 6-MP or AZA ≥4 months.

Toxicity of 6-MP/AZA in IBD
(396 Patients)

- Bone marrow depression 2%
- Pancreatitis 3.3%
- Allergic reactions 2%
- Nausea and vomiting “frequent”
- Hepatitis 0.3%
- CNS Lymphoma 0.3%
- Serious infections 7.4%

Methotrexate

• Effective for induction and maintenance of remission
  – Induction of remission: 25 mg SC/week
  – Maintenance of remission: 15 mg SC/week
  – As concomitant therapy with anti-TNF: ≥12.5 mg/week

• Oral dosing is nearly equivalent to injection dosing up to 15 mg/week.
  – Above 15 mg, use injection (SC, IM)

• Don’t forget folate!

Methotrexate Toxicity

- Rash
- Nausea, Mucositis, Diarrhea
- Bone marrow suppression
- Hypersensitivity pneumonitis (rare in Crohn’s disease dosing)
- Increased liver enzymes
- Hepatic fibrosis/cirrhosis (not reported in Crohn’s disease dosing)

- Liver biopsy not needed/recommended.

**Available Biologic Therapies for Inflammatory Bowel Disease**

<table>
<thead>
<tr>
<th>Biologic Therapy</th>
<th>CD</th>
<th>UC</th>
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</thead>
<tbody>
<tr>
<td>Certolizumab pegol</td>
<td>CD</td>
<td>UC</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>CD</td>
<td>UC</td>
</tr>
<tr>
<td>Golimumab</td>
<td>UC</td>
<td>CD</td>
</tr>
<tr>
<td>Infliximab</td>
<td>CD</td>
<td>UC</td>
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**Anti-integrins**

<table>
<thead>
<tr>
<th>Integrin</th>
<th>CD</th>
<th>UC</th>
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</thead>
<tbody>
<tr>
<td>α₄β₁</td>
<td>CD</td>
<td>UC</td>
</tr>
<tr>
<td>α₄β₇</td>
<td>CD</td>
<td>UC</td>
</tr>
</tbody>
</table>

Anti-TNF Biological Therapy

• Effective for induction and maintenance
  – Differences between agents?
  – Labeled infliximab includes perianal disease
  – Infliximab and adalimumab include pediatric indications

• Parenteral due to size of protein and protein composition

• Test for TB and Hepatitis B before starting therapy
  – Quantiferon reliable
  – Hep B SAb, SAg, core IgM
Earlier Use of Anti-TNF Biologic Therapy in Patients With CD Has Better Outcomes

• Claims data assessment
• >3700 patients all who received anti-TNF at some point
• Three groups: “step-up”, IMM to anti-TNF, early TNF (“top-down”)
• A “top-down” (early) approach to anti-TNF therapy is associated with:
  – A lower risk of concomitant corticosteroid use
  – Less frequent need for dose escalation of anti-TNF agent
  – Less frequent need to discontinue or switch anti-TNF therapy
  – Fewer CD-related surgeries

SONIC: Steroid free remission at week 26

Patients (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Patients (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + PBO</td>
<td>169</td>
<td>30.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFX + PBO</td>
<td>169</td>
<td>44.4</td>
<td>&lt;0.022</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td></td>
<td>56.8</td>
<td>&lt;0.009</td>
</tr>
</tbody>
</table>

Why Is Combination Therapy More Effective?

- Multiple mechanisms of disease control
- Reduction in anti-drug antibodies
- Elevation of serum drug levels (greater exposure)
- Other mechanisms/unknown
Anti-TNF Agents: Adverse Events

- Immunogenicity
- Infection
  - Granulomatous (TB, histo, *Listeria*)
  - Viral, fungal
- Autoimmunity
- Lymphoproliferative dx?
- Neoplasm
  - Skin
  - Pediatric tumors
- Psoriaform lesions
- Worsened or de novo congestive heart failure
- Hepatotoxicity (rare)
- Demyelinating disorders

Clinical Assessment of Disease Control

• Routine inquiry regarding stability of disease control (stable maintenance between doses)
• Strict adherence to maintenance regimen
• Ongoing laboratory assessment of clinical stability
• Increasing utilization of surrogate markers of inflammatory activity (fecal calprotectin)
Therapeutic Drug Monitoring
When and How

• Currently only available for infliximab and adalimumab
  – Several different labs can obtain them
• Understanding that higher trough levels are associated with greater likelihood of response, stable remission, mucosal healing
• Mostly used now for assessment of loss of response
  – Is drug present?
  – Are anti-drug antibodies present?
• Soon:
  – Early assessment of levels to predict longer-term outcomes
  – Routine assessment of levels to adjust proactively
Anti-Integrin Therapies

• Mechanism is inhibition of lymphocyte migration from blood vessels to target tissues
• Very stable maintenance
• **Natalizumab** (Gut and CNS (alpha4-beta1 and alpha4-beta7))
  – Induction and maintenance of CD only, 300 mg IV q4w
  – Emergence of brain infection (PML) associated with JC virus reactivation
  – Can measure JC antibody
  – No concomitant therapy
• **Vedolizumab** (Gut only (alpha4-beta7))
  – Induction and maintenance of CD and UC, 300 mg IV 0, 2, 6 weeks then q8w
  – No PML
  – Concomitant therapy allowed
Miscellaneous Pearls
Perianal Disease

• About 25% of patients
• Worst quality of life in Crohn’s disease!
• All IBD patients need a careful perianal examination
  – Exam under anesthesia
  – MRI of pelvis
• Patients with known anal strictures
  – Gentle digital examination every visit
  – Anal cancer screening
• Anti-TNF plus immunomodulator
  – Antibiotics during induction phase
Don’t Ignore Elevated CRP!
‘Silent’ Crohn’s Patients Have 6-Fold Higher Risk of Hospitalizations

- Silent (Asymptomatic) Crohn’s disease (CD) patients feel well but have an elevated CRP
- 178 CD patients with clinical remission (symptom improvement) defined by SIBDQ scores in a prospective registry
- Hospitalization in most cases was due to obstructive disease and surgery was necessary

Majority of hospitalizations in asymptomatic pts with elevated CRP occur within first 12 months of clinic visit when CRP elevation was detected

Chi Square=32.23; P-value<0.001

What is next?
Treat to Target Rheumatology

- Shared decision-making between RA patient and doctor
- Primary goal: maximize health-related quality of life
  - Control of symptoms
  - Normalization of function and social participation
  - Prevention of progressive structural damage
- Abrogation of inflammation is the most important mean to achieve goals
- *Treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA*

Examples of Tight Control and Treat to Target

Hypertension, type 2 diabetes and rheumatoid arthritis

• Treatment algorithms are based on treatment targets
• Frequent monitoring is recommended so that treatment can be optimized
  – HbA$_{1c}$ monitoring every 3 months in patients with diabetes
• Modification of the target for high-risk patient groups
  – lower blood-pressure target of 130/80 mmHg in patients with both hypertension and type 2 diabetes

A Proposed Algorithm for Tight Control of IBD

Baseline assessment of disease activity by endoscopy paired with surrogate marker (Fecal Calprotectin, CRP)

3-6 months

Choice of initial therapy based on severity and prognosis of patient

Re-assessment of disease activity directly or with surrogate marker

3-6 months

Healing Documented?

No

Discussion with patient treatment options

Clinical follow-up that includes assessment of disease stability

Yes

Clinical follow-up that includes assessment of disease stability

6-12 months

Is patient willing to proceed with your recommendations?

Yes

Adjust therapy

“Treat to Target”

No

3-6 months

Clinical follow-up

If no other treatment options left

“Disease Monitoring”
How can I remember all this?
Download Cornerstones’ Checklist for IBD Patients by visiting: cornerstoneshealth.org/checklist/

<table>
<thead>
<tr>
<th>Vaccine Preventable Illnesses</th>
<th>Status</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Varicella (chicken pox - Live Vaccine) - Check Variella Zoster Virus IgG. If negative consider vaccination. Can be considered in patients on &quot;low dose&quot; immunosuppression (prednisone ≤20mg/day, MTX, 6-MP, azathioprine), but not on biologics. Can administer 4 weeks prior to starting biologics.</td>
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<tr>
<td>Zoster (Live Vaccine) - Can be administered to patients ≥50 on &quot;low dose&quot; immunosuppression (prednisone ≤20mg/day, MTX, 6-MP, azathioprine), but not on biologics. Can administer 4 weeks prior to starting biologics.</td>
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<tr>
<td>MMR (Live Vaccine) - Controversial in immunosuppressed patients and those planning to start immunosuppressants within 4 weeks.</td>
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<tr>
<td>Diphtheria and Pertussis (Non-Live Vaccine) - Vaccinate with Tdap if not given within last ten years, or if Td ≥2 years.</td>
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<tr>
<td>Influenza (Non-Live Vaccine) - 1 dose annually to all patients during flu season (avoid intranasal live vaccine in immunosuppressed patients)</td>
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<tr>
<td>HPV (Non-Live Vaccine) - Related to cervical and anal cancers: 3 doses approved for females and males ages 9-26 (regardless of immunosuppression).</td>
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<tr>
<td>Hepatitis B (Non-Live Vaccine) - Check hepatitis B surface antigens, hepatitis B surface antibody, hepatitis B core antibody before initiating anti-TNF therapy. If non-immune consider vaccination series with non-live hepatitis B vaccine, 3 doses, if active viral infection or core Ab positive, check PCR and withhold anti-TNF therapy until active infection is excluded or treated appropriately.</td>
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<tr>
<td>Hepatitis A (Non-Live Vaccine) - Safe to administer at-risk patients regardless of immunosuppression.</td>
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<tr>
<td>Meningococcal Meningitis (Non-Live Vaccine) - Vaccinate at-risk patients (college students, military recruits) if not previously vaccinated regardless of immunosuppression.</td>
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</tr>
<tr>
<td>Pneumococcal Pneumonia (Non-Live Vaccine) - Not immunosuppressed: Consider vaccination with PSV23 (Pneumovax®), if immunosuppressed: Vaccinate with PCV13 (Prevnar®) followed by PSV23 (Pneumovax®) 8 weeks later followed by PSV23 booster after 5 years.</td>
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<table>
<thead>
<tr>
<th>Therapy Related Testing</th>
<th>Status</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamines - Annual renal function monitoring.</td>
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<tr>
<td>Thiopurines - TMP/SMX CBC and liver function prior to initiating therapy. Routine CBC and liver function monitoring while on therapy.</td>
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<tr>
<td>Methotrexate - CBC, liver, and renal function prior to initiating therapy. Routine CBC, liver, and renal function monitoring while on therapy.</td>
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<tr>
<td>Anti-TNFα - TNFα screening prior to initiating therapy with PPD skin testing and/or Quantiferon-TB Gold assay: Chest X-Ray if high risk and/or indeterminate PPD or Quantiferon-TB Gold. Perform annual TB risk assessment and consider re-testing if high risk (including travel to endemic region). See Hepatitis B vaccine, CBC, liver, and renal function prior to initiating therapy and periodic monitoring while on therapy.</td>
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</tr>
<tr>
<td>Natalizumab - Exclusion in TOUCH program. Check JCV antibody and treat if negative. Restart JCV antibody q 4-6 months prior to initiating therapy. Routine CBC and liver function monitoring while on therapy.</td>
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<tr>
<td>Vedolizumab - CBC, liver, and renal function prior to initiating therapy and periodic monitoring.</td>
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<thead>
<tr>
<th>Cancer Prevention</th>
<th>Status</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon Cancer - If ulcerative colitis beyond the rectum or Crohn’s is present in at least 1/3 of the colon, perform annual or bi-annual surveillance colonoscopies with targeted mucosal sampling; consider chromoendoscopy if available, to assess for dysplasia after 8-10 years or history of dysplasia.</td>
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</tr>
<tr>
<td>Cervical Cancer - Annual PAP screen if immunocompromised.</td>
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<tr>
<td>Skin Cancer - Annual visual exam of skin by dermatologist if immunocompromised and recommend sunscreen exposure precautions.</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Miscellaneous</th>
<th>Status</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Assessment of anatomic location and activity</td>
<td></td>
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<tr>
<td>Smoking Cessation - Discuss at every visit.</td>
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<tr>
<td>Nutritional Assessment - B12 if ileal disease or resection, iron panel.</td>
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</tbody>
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Summary: Crohn’s Disease

• Assess prognosis of your patient
• Early effective therapy
• Confirm response with biological markers
• Understand pre-therapy testing and monitoring
Thank you