Evolution of inflammatory bowel diseases in a modern world

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Clinical overview of Inflammatory Bowel Diseases (IBD)

What Is IBD?

- IBD is an autoimmune disease:
  - Chronic inflammation of the GI tract
  - Either progressive or remitting and relapsing course
- Two subtypes of IBD:
  - Ulcerative colitis (UC) contiguous mucosal inflammation limited to the large intestine; typically begins in the rectum and proceeds proximally and may involve the entire colon as well
  - Crohn’s disease (CD) patchy, transmural inflammation affecting any part of the GI tract, but most often the last portion of the ileum and parts of the colon

History of IBD subtypes

- UC
  - first established as a diagnosis in 1985
- CD "regional enteritis"
  - Recognized as a disease entity in 1932 in a paper by Dr. Crohn and colleagues

Clinical Presentation

<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>

How is it diagnosed?

- Laboratory studies
  - CBC, C-Reactive Protein or sedimentation rate, albumin
  - Colonoscopy with intubation of terminal ileum and biopsies
- Small bowel imaging
  - Small Bowel Follow Through or CT enterography
- Stool studies
  - R/O infection
  - Fecal calprotectin or lactoferrin

Differential Diagnosis of IBD

- Infectious colitis (including *Clostridium difficile*)
- Ischemic colitis
- Drug-induced (NSAID) enterocolitis
- Solitary rectal ulcer syndrome
- Radiation enterocolitis
- Diversion colitis
- Endometriosis
- Malignancy
- Functional (IBS)
- Diverticular disease


Endoscopic Severity of UC

- **NORMAL**: Vascular markings present
- **MILD**: Diminished vascular markings, mild erythema, granularity, and friability
- **MODERATE**: Marked erythema, absent vascular markings, contact friability, no ulcers
- **SEVERE**: Spontaneous bleeding, ulcers

Endoscopy in CD

- Sigmoid (normal)
- Transverse
- Ileum
IBD is systemic
“extraintestinal manifestations”

- Hematologic
  - Anemia
  - Pulmonary embolism
  - Venous thromboembolism

- Hepatobiliary
  - Cholelithiasis
  - Primary Sclerosing Cholangitis
  - Autoimmune pancreatitis

- Skin
  - Erythema nodosum
  - Pyoderma gangrenosum

- Musculoskeletal
  - Osteoporosis
  - Peripheral arthralgias and arthritis
  - Spondylarthritis (ankylosing spondylitis, sacroiliitis)

- Eyes
  - Episcleritis
  - Sclerocconjunctivitis
  - Uveitis

- Renal
  - Nephrolithiasis

Causes of IBD

- Immune response
- Microbes
- Genetic susceptibility
- Environmental triggers

Environmental factors

- Smoking
  - ↑CD but ↓ risk for UC
- Hygiene hypothesis
  - Effect of antibiotics, breastfeeding, etc on the microbiota
- Diet-modern day
  - the “WESTERN” diet
    - ↑ animal fat, red meat and processed foods
    - ↓ fruits and vegetables
    - Can have dietary triggers (ie lactose)
Genetics of IBD: 163 Confirmed Loci

- 30 CD specific loci
- 23 UC specific loci
- 110 IBD loci
- Common pathways:
  - Leprosy
  - Mycobacterial susceptibility
  - Other immune-mediated disease
- Genes in common

Microbiome in IBD

- The Human Microbiome Project developed to study the role of microbiota in health and disease
- IBD develops when there is an inappropriate interrelation between the immune responses and the intestinal microbiota.
- Microbiota drive inflammation in genetically susceptible hosts
- Theories suggest may be an abnormality in a single organism (such as Mycobacterium avium paratuberculosis) vs dysbiosis of overall composition and diversity of the microbiome

Landy et al 2013 Gastro 13(6)

Incidence of IBD

- Incidence: 20-100 / 100,000
- 1.4 million in U.S.
- 30% diagnosed each year
- Onset: typically age 15-30
- second peak age 55-65 for UC
- 25% present in childhood
- Frequency similar in males and females

CCFA. The Facts About IBD. 2011.
Prevalence of IBD

Goals of IBD Management

- Early and accurate diagnosis of the disease and its extent
- Rapid and safe INDUCTION OF REMISSION
- Steroid-free durable MAINTENANCE OF REMISSION
- Restoration of growth and development in children; correction of malnutrition
- Avoidance of drug-related and disease related complications (infections, surgery, hospitalization, disability)

Conventional medications

Supportive Agents
- Antidiarrheals
- Bile sequestrants
- Bulk formers
- Antidepressants
- Pain management
- Antispasmodics

Aminosalicylates
- Sulfasalazine
- Mesalazine
- Olsalazine
- Balsalazide

Immunomodulators
- 6MP/Azathioprine
- Methotrexate
- Cyclosporine/Tacrolimus

Biologics
- Anti-TNF
- Selective adhesion molecule – Anti-integrin

Antibiotics
- Metronidazole
- Quinolones

Corticosteroids
- Prednisone/Prednisolone
- Budesonide
- ACTH
Aminosalicylates (aka 5-ASA)

- **Colon**
  - Sulfasalazine
  - Olsalazine
  - Balsalazide

- **Terminal Ileum Colon (release at pH ≥7)**
  - Delayed release mesalamine
  - MRCV mesalamine

- **Terminal Ileum Colon (release at pH ≥6)**
  - Granulated mesalamine

- **Duodenum Ileum Colon**
  - Controlled-release mesalamine

5-ASA

**Pros**
- Anti-inflammatory, not immunosuppression
- Well-tolerated
- Usually affordable
- Effective for mild-moderate UC
- May reduce colon cancer risk in patients

**Cons**
- Rare adverse effects of pericarditis, pancreatitis, interstitial nephritis
- Rarely worsens inflammation
- Not effective in CD

Corticosteroids

- Effective in UC and CD
- Systemic corticosteroids demonstrate substantial toxicity at higher doses and for longer periods of time
- A prescription for steroids requires an exit strategy – a steroid-sparing maintenance therapy
- The development of non-systemic steroid formulations provide benefit with less toxicity
Corticosteroids: Risks

- The long-term risks of steroids are significant:
  - Diabetes
  - High blood pressure
  - Increased risk of infection
  - Osteopenia and osteoporosis
  - Avascular necrosis of the hip
  - Water retention/weight gain
  - Cataracts
  - Skin thinning/bruising
  - Hormonal imbalance
  - Anger, anxiety, or other psychiatric effects

Thiopurines: Benefits

- Steroid sparing oral agents
  - 2 medications: azathioprine & 6-mercaptopurine
  - Oral immunosuppressives: effective in maintaining remission in CD and UC in about 50% of patients
  - Usually started when 5-ASAs are not enough to control moderate to severe symptoms or for steroid dependence
  - No role for inducing a remission because it takes 2–4 months to become clinically active
  - Usually combined with a steroid taper when it is started

Thiopurines: Risks

- Potential reactions/adverse events
  - Low white blood cell count
  - Increased risk for infection
  - Increased risk for lymphoma
  - About 4-5 times over the general population
  - Elevated liver function tests
  - Pancreatitis (~3%)
  - Allergic reaction
  - Fatigue

- Need close blood monitoring
  - Especially important when medication is first started
- Overall, about 10% of patients will need to stop the medication because of a reaction or adverse event
Thiopurine methyltransferase (TPMT) and drug monitoring

- TPMT provides information on how drug is metabolized in individual patients
  - Homozygous (90%) dose at 2–2.5 mg/kg AZA or 1–1.5 mg/kg 6-MP
  - Heterozygous (10%) 50% dose reduction
  - No enzyme activity (~3%) DO NOT USE
- Serial CBC and liver enzymes
  - Every 2 weeks for 2 months then every 3–6 months long term
- Metabolite studies
  - 6-TGN target >235 pmol/10(8) to improve response
  - 6-MMP <5700 pmol/10(8) to avoid hepatotoxicity

Methotrexate

- Usually intramuscular/subcutaneous initially, then may switch to oral when stable
- Liver biopsy recommended if liver enzymes are elevated more than 6 months
- Pregnancy category X
- Need folic acid replacement

Biologics: Anti-Tumor Necrosis Factor α...AKA Anti-TNF

- Infliximab
  - Indicated for CD and UC
  - Given via IV infusion x 2 hours
  - Induction at 0, 2, 6 weeks then Q8 weeks
- Adalimumab
  - Indicated for CD and UC
  - Subcutaneous injection every 2 weeks
- Certolizumab
  - Indicated for CD only
  - Subcutaneous injection every 4 weeks
- Golimumab
  - Indicated for UC only
  - Subcutaneous injection every 4 weeks

TNF=tumor necrosis factor.
Anti-TNF

- Contraindications
  - Active cancer
  - Moderate/severe congestive heart failure (NYHA Class III to IV)
  - Active infection or undrained abscess
  - Untreated latent or active tuberculosis
  - Multiple sclerosis/demyelinating disorders

Anti-TNF drug monitoring
- 10–30% do not respond to therapy
- 40% lose response over the first year
- When is drug monitoring indicated?
  - Loss of response
  - Safeguarding response: Measurable drug level at trough associated with improved response outcomes
  - Reduce adverse events associated with supra therapeutic drug concentrations
  - More cost effective than empiric dose intensification

Biologics: Alpha Integrin Inhibitors
- Vedolizumab
  - Indicated for both CD and UC
  - Given by infusion
  - Induction @ weeks 0, 2, 6
  - Maintenance @ every 8 weeks
- Natalizumab
  - Indicated for CD only
  - Given by infusion monthly
Antibiotics

- Limited role: no use in UC, more effective in small bowel CD
- Treatment of *Clostridium difficile*, fistulas, abscesses, and pouchitis
- Can be effective for managing perianal disease
- Commonly used:
  - Metronidazole
    - Pregnancy class B
  - Ciprofloxacin
    - Pregnancy class C

How do we choose medication strategy?

“Step up” therapy for IBD

<table>
<thead>
<tr>
<th>Disease severity at presentation</th>
<th>Step-up according to severity at presentation or failure at prior step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Natalizumab (CD)</td>
</tr>
<tr>
<td></td>
<td>Vedolizumab (UC/CD)</td>
</tr>
<tr>
<td></td>
<td>Anti-TNF (UC)</td>
</tr>
<tr>
<td></td>
<td>Aminosalicylate/Thiopurine/MTX (CD)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Aminosalicylate</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid</td>
</tr>
<tr>
<td>Mild</td>
<td>Anti-TNF (UC)</td>
</tr>
<tr>
<td></td>
<td>Aminosalicylate/Thiopurine/MTX (CD)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid</td>
</tr>
</tbody>
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Induction

Maintenance
Crohn’s disease is a progressive disease

Benefits of early combined therapy

- Reduced exposure to steroids
- Prevent progression: scarring, strictures, fistulas
- Reduction in surgery and hospitalization rates
- Most benefit in patients with aggressive disease (~25%)

Predicting aggressive disease

**CD**
- Strictures or fistulizing
- Small bowel
- Younger age
- Disease duration > 2 yrs
- Requirement for steroids at diagnosis
- Inflammatory burden (depth of ulcers, ↑ CRP)

**UC**
- Younger age at diagnosis
- Extraintestinal symptoms
- High inflammatory burden (↑ CRP, ↓ albumin, deep ulcers)
- Hospitalized or need for steroids

Dulai et al 2016 IBD(22)4
Surgery in IBD

- Up to 50% of CD patients will require at least one surgery
- Approximately 30% of UC patients will need colectomy

- 7-year cohort study in Denmark
  - 29% CD had resection
  - 12% UC had colectomy


Indications for Surgery

<table>
<thead>
<tr>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrotic obstructing stricture</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td>Cancer</td>
<td>Cancer, high-grade dysplasia, or</td>
</tr>
<tr>
<td>Complex fistulae and abscesses</td>
<td>un resectable low-grade dysplasia</td>
</tr>
<tr>
<td>Perianal complications</td>
<td>Unresponsive, fulminant disease</td>
</tr>
<tr>
<td>Delayed growth (pediatrics)</td>
<td>Steroid dependency</td>
</tr>
<tr>
<td></td>
<td>Delayed growth (pediatrics)</td>
</tr>
</tbody>
</table>
The Cost of IBD

Global Cost

- IBD is a modern disease
- Thrives within industrialized countries
- As people immigrate from developing countries they too assume the same risk (~0.5%)
- Emergence of IBD in newly industrialized countries of Asia, South America and the Middle East

Kaplan 2015 Nat Rev Gastro Hep 12: 720-727
Global Cost

- IBD is not driven by ancestry or ethnicity but by our economic and social environment
  - Migration from rural to urban
  - Agriculture to manufacturing
  - Improved healthcare access (dx of milder diseases)
  - Change in lifestyle behaviors
    - Less fiber, more fat
    - Less breastfeeding
    - Pollution
    - Sedentary

Kaplan 2015

Economic Cost

- One of the top 5 most expensive GI disorders (including reflux, colon cancer, and gallbladder disease) in spite of having the lowest prevalence.
- Studies suggest costs due to pharmaceuticals, office visits & procedures, hospitalizations and surgery


Economic Cost

- Introduction of biologic therapy in 2000
- Annual cost > $25,000 per patient on biologic therapy
- Offset by improvement in quality of life and reduction in surgery
Efforts to improve cost effectiveness while maximizing response

- Disease stratifying for use of biologics
- Drug level monitoring for optimum dosing of biologics to "personalize" care
- Withdrawing medications that are ineffective.
- Development of biosimilars
- Better understanding of preventive strategies through research on genes, the environment and the microbiome

Kaplan 2015

Biologics to Biosimilars

- Biologic medicines that are developed after a biologic patent expires
- Biosimilar to infliximab approved in Europe
- Biosimilars to infliximab and adalimumab have been developed and are being considered for approval by FDA
- Biologics are costly but made affordable for some patients through copay assistance programs and patient assistance programs.
- The cost of care to government and commercial insurers drives the biosimilar movement

Wolf (2016) IBD:22(4) 994-997

Biosimilars

- Affordable Care Act: The Biologics Price Competition and Innovation Act of 2009
  - Created an abbreviated licensure pathway for biologics shown to be interchangeable with the FDA licensed biologic
  - Meant to be less expensive (~ 40% less)
- Biosimilar ≠ Generic
  - Not interchangeable or therapeutically equivalent
  - Issue of differences in immunogenicity not understood
  - Can patients/providers opt in/out?

Wolf (2016) IBD:22(4) 994-997
Dula et al 2016 IBD 22(4)
Psychosocial Burden

- Increased service utilization and hospital admissions
- Anxiety and depression
- Lack of emotional and psychological support from family, friends and caregivers
- Lack of communication and coordination of care from providers.

Reiss & Sandborn 2015 CGH 13:2219-2224

Psychological distress

- Related to persistent symptoms in quiescent IBD
- ↑ medically unexplained symptoms
- ↑ Disability

Simren et al (2002) AJG (97)

Psychosocial impact in IBD

- "The pathophysiology of IBD is best understood in terms of dysregulation of homeostatic systems (neural, endocrine, immune, inflammatory) in a biologically predisposed host (biopsychosocial model), rather than as conditions caused by a specific etiologic factor"
- Psychosocial factors contribute to clinical expression of disease

Drossman 2004, Kirsner's IBD, 6th edition
Psychosocial Burden

- Effective psychological care can reduce symptoms and service utilization driven by anxiety and not active disease.
- One model: The IBD Support Foundation (IBDSF) uses social workers imbedded in the clinical setting to identify barriers to treatment and wellness through psychosocial assessment and intervention.
  - Identify personal barriers:
    - Anxiety or depression
    - Substance abuse
    - Issues with job or school accommodations
    - Lack of adequate food or housing

Reiss & Sandborn 2015 CGH 13:2219-2224

Personal Burden

- Presenteeism: lost productivity due to chronic illness
  - 440 Employees with IBD
  - 35.6% unemployed
  - 62.9% vs 27.3% presenteeism in IBD vs controls
  - 54.7% vs 27.3% presenteeism even in IBD remission vs controls
  - Only one third of employees with IBD made adjustments for fatigue, irritability and decreased motivation.

Zand et al (2015) IBD 21(7) 1623-1630

Self Reported Disability

- Mainly determined by clinical disease activity and illness perceptions, not severity of disease
- Associated with more service utilization and reduced quality of life.
- May be a target for behavioral intervention to improve self regulation and change illness perception in chronic disease.

Patient Engagement & Activation

- Patient Engagement
  - Interventions designed to increase activation and the resulting behaviors
- Patient Activation
  - Patients understanding their role in the care process and having the knowledge, skills, and confidence to manage their health and health care.
  - Associated with improved health outcomes, enhanced patient experiences, and lower overall health care costs.
  - PA “score” can be calculated and added to EMR to identify patients needing extra support

Shah & Siegel (2015) IBD, 21;12 2975-2978

Chronic disease management

- Strong recommendations
  - Avoid NSAIDs (UC/CD)
  - Quit smoking (CD)
  - Adhere to medications
- Modest recommendation
  - Maintain vitamin D levels
  - Exercise (CD)
- Common sense recommendations
  - Exercise
  - Sleep
  - Reduce stress
  - Meet with a dietician/nutritionist
  - Screen for depression

Herman & Kane (2015) IBD, 21:2979-2984

Treatment Adherence

- Not only adherence to medications but to completing laboratory studies, procedures, office visits
- Can be volitional vs unintentional (not filling prescriptions, missing doses or dose reduction
- Consequences?
  - Worsening disease flares
  - Reduced quality of life
  - Loss of Response (especially biologics)
  - Increased Cost of Care (both inpatient and outpatient)

Treatment Adherence

- Predictors of nonadherence:
  - Young, employed, single
  - Psychiatric disease/stress
  - On multiple medications

- Efforts to improve:
  - Simplified dosing (ie once daily)
  - Electronic reminders
  - Patient engagement in self care
  - Enforcing self efficacy

Herman&Kane (2015) IBD

Health Maintenance in IBD-AGA Quality Measures

- Osteoporosis in steroid users > 600 mg/year
- Avoidance of steroid dependence with steroid sparing tx
- Measurement of Bone Density within past 2 yrs
- Vaccinations: Pneumonia, influenza
- Tobacco screening and cessation counseling
- TB and Hepatitis B screening prior to initial biologic therapy

American Gastroenterologic Association PQRS 2015

Cancer risk due to disease

- Colorectal Cancer risk in colon disease (UC and Crohn's colitis)
- Surveillance colonoscopy recommended every 1-2 years starting 8-10 years after diagnosis
- Risk higher when:
  - dysplasia found in non-polypoid lesions (invisible)
  - Presence of dysplasia in large polyps (> 1 cm)
  - Preceded by histologic findings of “indefinite for dysplasia”
  - Chromoendoscopy (use of dye) is more effective in detecting nonpolypoid lesions than white light

Cancer risk due to immunosuppressive treatment

- Nonmelanoma Skin cancer
  - Increased when treated with immunomodulators for ≥ 3 years
- Cervical dysplasia/cancer
  - Increased risk suggested, due to IBD and/or immunomodulators
- Lymphoma
  - Increased risk reported with use of thiopurines and biologics but results highly variable from study to study

Kane (2008) IBD, 14:8, 1158-1160

Emerging treatments

- Ustekinumab (IV or SQ)
  - Monoclonal antibody antagonist IL-12 & 23 for moderate to severe Crohn's patients who were unresponsive to or intolerant of anti-TNF therapy.
  - Currently under FDA review
- Mongersen (Oral)
  - TGF-β1 a negative T-cell immune response regulator.
  - Phase 3 trials for CD. Releases in Tright colon
- Tofacitinib (Oral)
  - Inhibits Janus kinase family to effect multiple cytokines
  - Phase 2 trials more promising for UC
- Ozanimod (Oral)
  - S1P inhibits lymphocytes from leaving lymphnodes. Phase 2-3 trials in UC

Dulai et al 2016 IBD 22(4) 998-1009

But what about…?

- Low Dose Naltrexone
  - Nonselective opioid receptor antagonist
  - Shown to reduce intestinal inflammation in chemically induced inflammation
  - 2 small studies suggesting improvement in disease activity scores in CD
  - Not commercially available in USA

Segal et al 2014 Cochrane IBD Group
And what about?

- **Fecal Microbial Transplant**
  - Limited to nine case series/case reports & eight where FMT was the treatment for infectious diarrhea in an IBD patient
  - 19/25 had reduced symptoms
  - 13/17 stopped IBD medications
  - 15/24 achieved remission
  - Potential for treatment of IBD if standard medications have failed

  Anderson et al (2012) APT, 36:6, 503-516

And then there is...

- **Diet:**
  - No known diet for IBD
  - Dietary manipulation is common in IBD patients, avoiding “trigger” foods.
  - The Food and Crohn’s Exacerbation Study (FACES) will compare efficacy of the specific carbohydrate diet and a Mediterranean diet in inducing clinical and endoscopic remission in active Crohn’s

  CCFA PCOR Institute

And something about worms?

- Humans evolved with many microorganisms including helminth worms in our GI tracts
- **Hygiene Hypothesis:**
  - Sanitation practices in later 20th century “dewormed” us
- **Trichuris suis:**
  - A type of helminth parasitic worm that can modulate immune response in asthma, allergy, IBD
  - Can cause chronic but asymptomatic infection in host
- Two RCT
  - UC (54 pts)
  - CD (36 pts)
- Early exposure vs primary treatment more beneficial.

  Cochrane Review 2014 Jan 20
**Medical Cannabis?**

- 25 states + DC have legalized medical marijuana
- Approved for medicinal use in Minnesota for CD in 2014 and UC in 2016
- 18% of 313 IBD pts in Canada used and reported relief of symptoms:
  - Abdominal pain (84%)
  - Joint pain (48%)
  - Diarrhea (29%)
- Cannabis associated with increased risk for surgery
- Israeli study reported clinical, steroid free remission in 10/11 pts

Storr (2014) IBD

**Summary**

- IBD are complex immune mediated diseases that present under genetic, environmental and microbial influences.
- Medical and surgical treatment is based on patient factors including severity of disease, age of onset, options available and patient preference.
- Recognition and management of associated psychosocial needs is an integral part of comprehensive IBD care
- The global, economic and personal burden of IBD is significant and efforts are underway to control costs.